# A Functional Magnetic Resonance Imaging Study of Working Memory Abnormalities in Schizophrenia

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***Background:*** *Previous neuroimaging studies of working memory (WM) in schizophrenia, typically focusing on dorsolateral prefrontal cortex, yield conflicting results, possibly because of varied choice of tasks and analysis techniques. We examined neural function changes at several WM loads to derive a more complete picture of WM dysfunction in schizophrenia.*

***Methods:*** *We used a version of the Sternberg Item Recognition Paradigm to test WM function at five distinct loads. Eighteen schizophrenia patients and 18 matched healthy controls were scanned with functional magnetic resonance imaging at 3 Tesla.*

***Results:*** *Patterns of both overactivation and underactivation in patients were observed depending on WM load. Patients' activation was generally less responsive to load changes than control subjects', and different patterns of between-group differences were observed for memory encoding and retrieval. In the specific case of successful retrieval, patients recruited additional neural circuits unused by control subjects. Behavioral effects were generally consistent with these imaging results.*

***Conclusions:*** *Differential findings of overactivation and underactivation may be attributable to patients' decreased ability to focus and allocate neural resources at task-appropriate levels. Additionally, differences between encoding and retrieval suggest that WM dysfunction may be manifested differently during the distinct phases of encoding, maintenance, and retrieval.*

**Key Words:** Dorsolateral prefrontal cortex, fMRI, memory load, schizophrenia, Sternberg task, working memory

Against a general background of cognitive deficits in schizophrenia, working memory (WM) difficulties are particularly noteworthy (Cohen et al 1996; Goldman-Rakic 1991; Weinberger et al 1986). Working memory, a critical building block of cognition, has been defined as the "temporary storage and manipulation" of information (Baddeley 1992). Individuals with schizophrenia show deficits on many different WM tasks (Goldberg et al 1998; Park and Holzman 1992; Park et al 1999; Perlstein et al 2001; Wexler et al 1998).

Although the exact neural substrates of WM are not fully known, nonhuman primate studies (Friedman and Goldman-Rakic 1994; Miller et al 1996; Petrides 1995) suggest that the lateral prefrontal cortex (PFC), particularly dorsolateral prefrontal cortex (DLPFC, Brodmann areas 9/46), plays a leading role. Neuroimaging studies replicate this finding in humans (D'Esposito et al 1999; Manoach et al 2003; Rypma and D'Esposito 1999; Veltman et al 2003). Furthermore, DLPFC activation is load-dependent and positively correlated with load in healthy subjects (Jansma et al 2000; Manoach et al 1997; Rypma and D'Esposito 1999; Veltman et al 2003) when performance is well above chance. Studies of PFC activation in healthy subjects beyond their WM capacity disagree, reporting both increases (Jaeggi et al 2003) and diminutions (Callicott et al 1999).

Neuroimaging studies investigating schizophrenia report aberrant DLPFC activation, with controversy over whether patients under- or overactivate during WM tasks. Earlier studies demonstrated reduced DLPFC activation in schizophrenia (Callicott et al 1998; Menon et al 2001; Yurgelun-Todd et al 1996). Several recent studies report increased regional activation (Callicott et al 2003; Manoach et al 1999, 2000). The discrepancy may be related to task performance and task difficulty. In one study, when patients' WM performance was matched to control subjects', patients showed relative DLPFC overactivation (Callicott et al 2003, but see Manoach et al 2000, in which activation at matched performance was similar between groups). Thus, under conditions of equivalent task performance, schizophrenia patients may activate "inefficiently" and show greater WM-related activation than control subjects (Callicott et al 2000). However, as task difficulty increases, patients may disengage or begin performing poorly, resulting in relative underactivation (Callicott et al 2003). Methodologic questions also remain; though most studies rely on group-averaged analysis techniques, one study demonstrating increased DLPFC activation on an individual level reports different results using group averages (Manoach et al 2000).

One can address these questions by examining activation at multiple levels of increasing memory load. Many recent studies have done this using an *N*-back WM task. One such report demonstrated increased right PFC activation in schizophrenia as load increased and hypothesized that activity may decrease when WM capacity is exceeded (Callicott et al 2000), as previously shown in healthy control subjects (Callicott et al 1999); however, this study used a limited range of loads, which precluded testing schizophrenia patients beyond capacity. Another group also used a limited WM load range but showed a drop in right DLPFC activation at the highest load in patients compared with control subjects (Perlstein et al 2001). Recently, a third group was able to exceed WM capacity in patients using a 3-back load (Jansma et al 2004). Despite increasingly poor performance, they reported increasing DLPFC activity with increasing load until capacity was reached at the 3-back level, when activity dropped compared with control subjects.

The steep difficulty gradient of the *N*-back task, however, limits studies of WM load response to three WM load levels because it is relatively easy at the 1-back level but exceeds WM capacity in many patients and some healthy control subjects by the 3-back level. This may explain downward spikes in activation from the 2- to the 3-back condition. In addition, *N*-back tasks tend to incorporate target stimuli as probes, conflating the theoretically distinct WM subprocesses of encoding, mainte-

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**Table 1.** Summary of Demographic Data

| | *n* (*n* male) | Mean Age (SD) | Mean Years Education[a] (SD) | Mean IQ[b] (SD) | Mean Laterality Quotient (SD) | Mean Parental Occupation Score[c] (SD) |
|---|---|---|---|---|---|---|
| Patients | 18 (16) | 36.9 (11.2) | 12.7 (2.1) | 103.2 (10.9) | 73.4 (39.3) | 3.72 (1.80) |
| Controls | 18 (15) | 37.4 (11.5) | 15.6 (1.9) | 110.0 (4.8)[d] | 63.4 (36.3)[e] | 3.06 (1.59) |

[a]Significant between-groups difference, $p < .001$.
[b]Significant between-groups difference, $p < .05$.
[c]Lower scores = higher occupational status. When subjects reported both parents' occupations, their scores were averaged for that subject. Parental occupation data were not available for one control subject and two patients. No significant difference between groups ($p = .27$, two-tailed).
[d]Three control subjects' IQs could not be estimated because of familiarity with the test.
[e]One control did not return to complete the handedness questionnaire.

nance, and retrieval (Manoach et al 2003), which could be important to study separately.

Complementing the *N*-back reports, some neuroimaging studies have employed versions of the Sternberg Item Recognition Paradigm (Sternberg 1966) to examine WM (Manoach et al 1999, 2000, 2003; Veltman et al 2003). When matching task performance to control subjects, Manoach et al (2000) found activation of the basal ganglia and thalamus unique to patients but found similar results between groups in DLPFC, although the ability to detect differences at matched performance may have been limited by a small sample size. Their task was not conducive to studying load effects because it incorporated only two WM loads.

Our study had several purposes. First, we hoped to replicate the findings of Callicott et al (2003), in detecting DLPFC overactivation in schizophrenia patients matched for performance with healthy control subjects. We also expected basal ganglia and thalamus activations only in schizophrenia, replicating Manoach et al (2000). Our second goal was to improve on prior work investigating load effects by using a multiload Sternberg task with a relatively gentle difficulty gradient. Like Jansma et al (2000, 2004) and others on the *N*-back task, we anticipated positive correlations between PFC activation and load until WM capacity was reached, when we predicted decreased activation. Thus, we designed a version of the Sternberg task that incorporated five distinct loads spread over two conditions and that was well equipped to represent encoding, maintenance, and retrieval as distinct task phases.

## Methods and Materials

### Subjects

Eighteen patients (16 men) with chronic schizophrenia or schizoaffective disorder ($n = 2$) were recruited from a local rehabilitation center, through radio and newspaper advertisements and with flyers in various hospitals' psychiatric wards. All were on stable doses of antipsychotic medication. Eighteen healthy control subjects, consisting of hospital employees and their friends and family members, were recruited via e-mail and word of mouth. Healthy control subjects were matched individually to patients for age and handedness; groups were matched for gender (1 additional female in the healthy group). Patients and control subjects were all administered the Structured Clinical Interviews for DSM-IV (SCID-IV; First et al 2002) to verify the presence and absence of psychotic illness, respectively. Exclusion criteria for healthy control subjects included any present or past Axis I disorder and first-degree relatives with a psychotic disorder. Exclusion criteria for both groups included significant medical or neurologic illness at the time of participation, past major head injury, and history of alcohol or drug abuse within a 6-month period before participation. Subjects' years of education, laterality quotient (Oldfield 1971) as a measure of handedness, parental occupations as a measure of developmental socioeconomic status (using Hollingshead occupational scores; Hollingshead 1975), and an estimate of IQ (using a modified version of the National Adult Reading Test; Nelson 1982) were also collected; these data are summarized in Table 1. All subjects gave written informed consent before participation in the study, which was approved by the local institutional review board.

### Task

Our task was a modified Sternberg Item Recognition Paradigm (Sternberg 1966) that required subjects to memorize a list of alphabetic letters (consonants only), maintain them in memory for several seconds, and then recognize whether probe letters were members of this list. During each encoding phase, subjects saw a list of consonants, displayed sequentially for 1.5 sec each with a 1 sec interstimulus interval (ISI). After a 9-sec maintenance period, in the retrieval phase, subjects saw a sequential series of probe letters (onscreen for 2.5 sec with a 500 msec ISI) and were instructed to press one button with their dominant-hand index fingers for letters in the list (targets) and another button with the middle finger of the same hand for other letters (foils). The task was organized into conditions of medium and high difficulty according to the distribution of memory loads described in Table 2. An additional practice condition contained blocks of all possible memory loads. Each task condition lasted approximately 7 min. The task was implemented on standard desktop PCs running custom presentation software (VAPP, http://nilab.psychiatry.ubc.ca/vapp).

Before entering the scanner, all subjects were given complete task instructions and the practice condition. Practice and instructions were repeated if necessary until subjects achieved a high rate of correct responses on at least the blocks with lower memory loads. In the scanner, all subjects received the medium-difficulty condition. All eighteen control subjects and 11 of the patients also performed the high-difficulty condition; six patients did not receive the high-difficulty condition because of study protocol changes and one due to near-chance performance on the medium condition. In the scanner, stimulus display was achieved with a rear-projection screen and a mirror mounted on the head coil; subjects made their responses with a fiber-optic response box (Photon Control, Burnaby, Canada).

### Data Acquisition

Functional magnetic resonance images (fMRIs) were collected at the Olin Neuropsychiatry Research Center in the Institute of Living/Hartford Hospital using a Siemens Allegra 3-Tesla scanner (Siemens, Erlangen, Germany) with a two-channel head coil. A custom head cushion was used for head stabilization, and magnetic field homogeneity was handled by the scanner's built-in shimming program. The T2*-weighted images were acquired with a gradient-echo

**Table 2.** Distribution of Memory Loads in Task Conditions

| Condition | Load (Letters in Memory Set) | Total Probes[a] | Targets per Probe Set | Occurrences of Load per Condition |
|---|---|---|---|---|
| Medium | 4 | 4 | 2 | 3 |
| | 5 | 4 | 2 | 4 |
| | 6[b] | 5 | 2 or 3 | 3 |
| Difficult | 6[b] | 5 | 2 or 3 | 3 |
| | 7 | 6 | 3 | 3 |
| | 8 | 6 | 3 | 2 |

[a]The number of probes was varied across working memory (WM) loads to achieve rough equality between the number of functional images acquired during encoding and retrieval (because the duration of the encoding period necessarily increases with growing WM load). In this way, we hoped to gain equal power to detect activation in both epochs with a fairly limited number of trials per subject.

[b]Note that the parameters of the six-item WM load incorporated into the medium condition ("medium 6") are identical to those of the six-item load in the difficult condition ("difficult 6"). "Medium 6" and "difficult 6" differ only in context, that is "medium 6" is interspersed during a given scan run with four- and five-item loads, whereas "difficult 6" is interspersed during its own scan run with seven- and eight-item loads.

planar sequence (repetition time = 1.86 sec, echo time = 27 msec, flip = 70°). The images consisted of whole-brain volumes of 36 sequentially acquired 3-mm slices parallel to the anterior commissure–posterior commissure line (voxel size 3.44 × 3.44 × 3 mm with a 1-mm slice gap). Behavioral data were acquired by the stimulus presentation software.

### Data Analysis

Functional images were analyzed with SPM2 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, University College London, United Kingdom), running in Matlab 6.5 (MathWorks, Natick, Massachusetts). The first five images of each time series were removed to compensate for saturation effects, and each time series was manually reoriented (i.e., affine transformations were applied) to bring all images into approximately the same space as the SPM template image. Motion correction was achieved using INRIAlign (Freire and Mangin 2001; Freire et al 2002); images were then spatially normalized to the echoplanar image (EPI) template image in SPM. After normalization, images were spatially smoothed with a 12-mm isotropic Gaussian kernel and temporally filtered with a fifth-order low-pass Butterworth filter (cut-off frequency = .25 Hz) to reduce any high-frequency noise.

First-level fMRI statistics were computed using SPM to create statistical parametric maps and contrast images containing weighted parameter estimates of each subject's activation. Regressors were defined separately for encoding and retrieval at each load level (the maintenance epoch was not included in the SPM model as it was highly collinear with both the encoding and retrieval epochs). These values were fed into SPM and SPSS 11.5 for Windows (SPSS, Chicago, Illinois) to compute group statistics. To report activation regions, the Montreal Neurological Institute coordinate system used by SPM was first converted into Talairach and Tournoux space (Talairach and Tournoux 1988) with a Matlab program (Brett 2002), and the converted coordinates were then fed into the Talairach Daemon Database (Lancaster et al 2000) for anatomic labeling, verified by visual inspection. All coordinates reported are in Talairach space.

We subsequently performed several random-effects analyses. We first used SPM to perform independent two-sample *t* tests between the patient and control groups. Six such analyses were performed, comparing control subjects' difficult condition to patients' medium condition, control subjects' medium condition to patients' medium condition, and control subjects' difficult condition to patients' difficult condition, for both encoding and retrieval.

We next used independent-sample *t* tests to compare control subjects and patients in the medium condition, examining only epochs with perfect performance accuracy. To do this, we grouped patients and control subjects pairwise by age and handedness and only analyzed epochs in which each patient and the corresponding control subject both had perfect performance (approximately half of all epochs; all patient–control pairs shared at least one epoch, and thus all subjects were included in the random-effects analysis). In this way, performance was exactly matched without differences in statistical power between groups.

To examine WM load effects, we performed a within-subjects analysis of variance (ANOVA) design in SPM for each group during each epoch type (encoding/retrieval). To detect linear increases according to load, we used one-sample *t* contrasts to examine the trend effect [−2 −1 0 1 2] across memory loads of 4, 5, 6, 7, and 8 within each group. Because six-item memory loads occurred both in the medium and difficult conditions, the contrast images for "medium 6" and "difficult 6" were averaged for inclusion in this design.

Finally, to address effects of memory load in context, we used four paired *t* tests in SPM to compare the "medium 6" load to the "difficult 6" load for each group (control/patient) and epoch type (encoding/retrieval). Note that the "medium 6" and the "difficult 6" differ only in context; they are the same six-item WM load, where the "medium 6" is intermixed with the easier WM loads (4 and 5 items) of the medium condition and the "difficult 6" is intermixed with the more difficult WM loads (7 and 8 items) of the difficult condition. To verify between-group differences, two difference images were created for each subject by subtracting the contrast image for "medium 6" from that of "difficult 6" for both encoding and retrieval; these difference images were entered into two independent-samples *t* tests in SPM (one each for encoding and retrieval) to find regions with significantly greater contextual differences in control subjects than in patients.

Unless otherwise specified, all analyses of fMRI data used a significance threshold of $p < .001$, uncorrected, and an extent threshold of .2 cc (8 voxels).

## Results

### Task Performance

In the medium condition, control subjects responded with significantly greater accuracy than patients (97.4% correct, SD = 3.2%, vs. 81.0%, SD = 14.1%), as revealed by an independent samples *t* test ($t = 4.8$, $df = 18.7$, $p < .0005$; all performance analyses two-tailed, equal variances not assumed). By the same

**Table 3.** Summary of Performance Data

| Condition | Group | Mean % Correct (SD) | *t*/*p* Value | Mean Reaction Time (SD) | *t*/*p* Value |
|---|---|---|---|---|---|
| Medium | SZ | 81.0 (14.1) | $t = 4.8$ | 1.11s (.24) | $t = 2.8$ |
| Medium | HC | 97.4 (3.2) | $p < .0005$ | .93s (.12) | $p < .01$ |
| Difficult | SZ | 75.8 (14.9) | $t = 2.4$ | 1.16s (.25) | $t = 1.4$ |
| Difficult | HC | 87.5 (7.5) | $p < .05$ | 1.06s (.12) | $p = .17$ |
| Medium | SZ | 81.0 (14.1) | $t = 1.7$ | 1.11s (.24) | $t = .8$ |
| Difficult | HC | 87.5 (7.5) | $p = .096$ | 1.06s (.12) | $p = .42$ |

HC, healthy control group; SZ, Schizophrenia group.

metric, control subjects also performed more accurately in the difficult condition (87.5% correct, SD = 7.5%, vs. 75.8%, SD = 14.9%, $t = 2.4$, $df = 13.1$, $p < .05$, as above). The closest performance comparison was between control subjects in the difficult condition and patients in the medium condition (87.5% correct, SD = 7.5%, vs. 81.0%, SD = 14.1%); the difference was not statistically significant ($t = 1.7$, $df = 25.8$, $p = .096$, as above).

Repeated-measures ANOVAs revealed a significant effect of WM load on accuracy for both control subjects ($F = 9.5$, $df = 2.2,36.6$, $p < .0005$, Greenhouse–Geisser correction) and patients ($F = 3.9$, $df = 4,40$, $p < .01$); contrast tests showed a significant linear trend (control subjects: $F = 23.5$, $df = 1,17$, $p < .0005$, patients: $F = 7.8$, $df = 1,10$, $p < .05$). A similar mixed ANOVA with combined data from both groups and diagnosis as a between-subjects factor revealed no significant interaction of diagnosis with load ($F = .8$, $df = 4,108$, $p = .49$, Greenhouse–Geisser correction).

Independent-sample *t* tests also showed control subjects responding significantly faster than patients in the medium condition (.93 sec, SD = .12 sec, vs. 1.11 sec, SD = .24 sec, $t = 2.8$, $df = 24.8$, $p < .01$, two-tailed, equal variances not assumed), but the difference was not significant in the difficult condition (1.06 sec, SD = .12 sec, vs. 1.16 sec, SD = .25 sec, $t = 1.4$, $df = 27$, $p = .17$, two-tailed). There was also no significant difference in reaction time between control subjects in the difficult condition and patients in the medium condition (1.06 sec, SD = .12 sec, vs. 1.11 sec, SD = .24 sec, $t = .8$, $df = 25.6$, $p = .42$, two-tailed, equal variances not assumed). These performance data are summarized in Table 3.

To discover whether probe stimulus type (target/foil) might affect reaction time, probe type was added as a factor in ANOVA analysis of reaction time. Repeated-measures ANOVA showed significant effects of both load ($F = 16.6$, $df = 2.3,39.9$, $p < .0001$, Greenhouse–Geisser correction) and probe type ($F = 8.7$, $df = 1,17$, $p < .01$) on reaction time for control subjects, with the effect of load having both linear ($F = 32.2$, $df = 1,17$, $p < .0001$) and quadratic ($F = 6.4$, $df = 1,17$, $p < .05$) components. Control subjects also showed significant interactions between load and probe type ($F = 3.1$, $df = 4,68$, $p < .05$, Greenhouse–Geisser correction), but the interaction had no significant trends of linear or quadratic order. Although patients also showed a significant load effect ($F = 8.9$, $df = 4,40$, $p < .0001$) of linear order ($F = 70.2$, $df = 1,10$, $p < .0001$), the effect of probe type was not significant ($F = 1.8$, $df = 1,10$, $p = .21$); however, there was a significant interaction between load and probe type ($F = 3.9$, $df = 4,40$, $p < .01$) of linear order ($F = 8.9$, $df = 1,10$, $p < .05$), with greater WM loads causing greater increases in reaction time for foils than targets.

### Between-Group fMRI Analyses

The closest approximation to equal task performance was between patients in the medium and control subjects in the difficult condition; a two-sample *t* test design in SPM between these conditions revealed several substantial clusters, including the left DLPFC, thalamus, and basal ganglia, that were more active in control subjects than in patients during encoding (Table 4A). Similar clusters of greater control activation were found by another two-sample *t* test for retrieval (Table 4B). (To account for any remaining between-groups performance difference, these analyses were also performed using analysis of covariance [ANCOVA] with performance as a nuisance variable; this did not substantially alter the findings.) Examining clusters more active in patients, the only areas surviving the extent threshold were small clusters near the left lingual gyrus (approximately 20 voxels for encoding, 10 for retrieval) and the medial frontal gyrus (approximately 10 voxels, encoding only).

A between-group comparison of activation during the medium condition revealed smaller discrepancies during encoding; still, control subjects had significantly greater activation in two small clusters in the left DLPFC area (Table 4C), whereas no areas were significantly greater for patients. During retrieval, however, the converse was true; control subjects showed no significant activations greater than patients, but patients showed greater activation in a number of areas including lateral PFC and basal ganglia (Table 4D).

Comparing both groups' activations during the difficult condition revealed similarly small differences; for encoding, control subjects showed a small (approximately .1 cc) region in the left DLPFC that was activated significantly more than in patients (Table 4E), although patients showed no areas of significantly greater activation. During retrieval, control subjects again activated more in PFC and thalamus (Table 4F); patients again showed no voxels of greater activation.

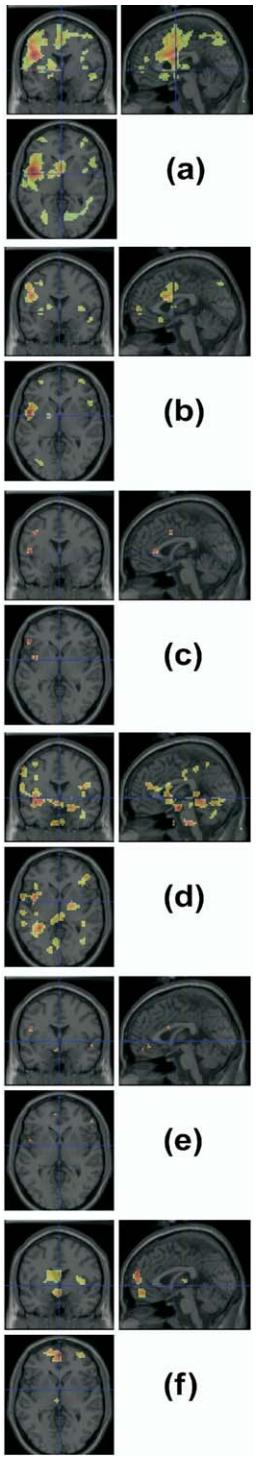
Because the groups differed slightly in IQ, the analyses just described were also performed using ANCOVA with IQ as a nuisance variable; results were not substantially different from those presented.

Finally, a two-sample between-group *t* test in the medium condition, using only epochs that contained all correct responses, yielded a striking drop in between-group differences: no differences in either direction for encoding, and no areas of greater activation in control subjects during retrieval. During retrieval, however, patients exhibited significantly greater activation in left hippocampus and right amygdala (Table 5A) and may have exhibited additional subthreshold overactivations; a more liberal threshold of $p < .01$, uncorrected, revealed several other regions more active in patients during successful retrieval, including bilateral hippocampus and amygdala, basal ganglia, and portions of bilateral DLPFC (Table 5B).

COLOR

**Table 4.** Results of Two-Sample *t*-Tests in SPM, Medium and Difficult Conditions, By Cluster[a]

| R/L | Anatomical Label | Brodmann Area(s) | Vol. (cc) | Max. T (x,y,z) | Figure |
|---|---|---|---|---|---|
| a. HC difficult > SZ medium, encoding | | | | | |
| L | Inferior/Middle Frontal, Precentral, Postcentral, Superior Temporal Gyri, Insula | 1, 3, 6, 8, 9, 13, 22, 44, 45, 46 | 22.6 | 7.9 (−45,10,22) | |
| L+R | Medial/Superior Frontal, Cingulate Gyri | 6, 8, 24, 32 | 5.8 | 5.4 (0,11,49) | |
| R | Inferior/Superior Parietal Lobule, Precuneus | 7, 40 | 2.2 | 4.1 (15,−64,56) | |
| L | Putamen, Lateral/Medial Globus Pallidus, Thalamus, Caudate | n/a | 2.1 | 5.3 (−18,0,8) | |
| L | Superior Parietal Lobule, Precuneus | 7, 19 | 1.6 | 4.2 (−27,−68,45) | |
| R | Inferior Frontal, Superior Temporal Gyri | 22, 38, 47 | 1.3 | 4.8 (50,20,−11) | |
| L | Middle/Superior Frontal Gyri | 10 | 0.8 | 4.1 (−36,55,0) | |
| L | Superior/Transverse Temporal Gyri | 22, 41, 42 | 0.8 | 3.9 (−62,−14,3) | |
| L | Lateral/Medial Globus Pallidus, Putamen, Parahippocampal Gyrus, Amygdala | 34 | 0.3 | 4.0 (−18,0,−8) | |
| R | Inferior/Middle Frontal Gyri | 10 | 0.3 | 3.9 (39,55,0) | |
| R | Middle/Superior Frontal Gyri | 10 | 0.3 | 3.7 (33,47,14) | |
| R | Inferior/Middle Frontal, Precentral Gyri | 6, 9 | 0.2 | 3.6 (39,7,27) | |
| b. HC difficult > SZ medium, retrieval | | | | | |
| L | Inferior/Middle Frontal, Precentral Gyri, Insula | 6, 8, 9, 13, 44, 46 | 5 | 5.2 (−45,10,22) | |
| R | Inferior/Middle/Superior Frontal Gyri | 10 | 0.7 | 4.2 (39,55,3) | |
| L | Middle/Superior Frontal Gyri | 10 | 0.4 | 3.8 (−30,55,0) | |
| L | Precuneus, Superior Parietal Lobule | 7 | 0.4 | 3.6 (−27,−76,48) | |
| R | Superior Temporal, Inferior Frontal Gyri | 38, 47 | 0.3 | 4.2 (50,20,−14) | |
| L | Putamen, Lateral Globus Pallidus, Thalamus | n/a | 0.3 | 3.8 (−18,0,8) | |
| c. HC medium > SZ medium, encoding | | | | | |
| L | Inferior Frontal Gyrus | 45, 46 | 0.5 | 3.7 (−48,29,7) | |
| L | Precentral, Middle Frontal Gyri | 6, 9 | 0.4 | 3.7 (−39,5,36) | |
| d. SZ medium > HC medium, retrieval | | | | | |
| L | Parahippocampal, Fusiform, Superior/Transverse Temporal Gyri, Hippocampus, Caudate | 19, 36, 37, 41 | 3.3 | 4.4 (−36,−44,−5) | |
| L | Inferior Frontal, Precentral Gyri, Insula, Claustrum | 6, 13, 44, 45, 47 | 3 | 4.2 (−59,10,16) | |
| R | Parahippocampal Gyrus, Amygdala, Hippocampus | 28, 34, 37 | 1.6 | 4.3 (21,−7,−15) | |
| R | Inferior/Middle Frontal Gyri | 10, 13, 46 | 1.4 | 4.0 (45,39,15) | |
| L | Lingual Gyrus, Cuneus | 17, 18 | 0.6 | 3.6 (−15,−76,1) | |
| L | Precentral, Postcentral Gyri | 3, 4, 6 | 0.6 | 3.8 (−59,−16,37) | |
| L | Inferior Parietal Lobule, Postcentral Gyrus | 40 | 0.5 | 4.0 (−59,−33,46) | |
| R | Superior/Transverse Temporal Gyri | 41 | 0.4 | 4.0 (42,−35,7) | |
| L | Inferior/Superior Parietal Lobules | 7, 40 | 0.3 | 3.6 (−39,−53,55) | |
| L | Insula, Inferior/Middle Frontal Gyri | 13, 46 | 0.2 | 3.6 (−39,24,13) | |
| L | Precentral Gyrus | 4, 6 | 0.2 | 3.6 (−36,−16,31) | |
| R | Substania Nigra, Red Nucleus | n/a | 0.1 | 3.5 (6,−27,−9) | |
| e. HC difficult > SZ difficult, encoding[b] | | | | | |
| L | Medial Frontal Gyrus | 10, 11 | 0.1 | 3.6 (−3,50,−15) | |
| R | Middle Frontal Gyrus | 47 | 0.1 | 3.6 (53,42,−9) | |
| L | Inferior Frontal, Precentral Gyri, Insula | 9, 13, 44 | 0.1 | 3.8 (−45,10,19) | |
| f. HC difficult > SZ difficult, retrieval | | | | | |
| L+R | Medial/Superior Frontal Gyri | 9, 10 | 2.6 | 4.1 (−15,59,16) | |
| L+R | Medial Frontal, Orbital Gyri | 10, 11 | 1.7 | 4.5 (−3,49,−15) | |
| R | Inferior/Middle/Superior Frontal Gyri | 10 | 0.9 | 4.2 (39,55,3) | |
| L+R | Thalamus | n/a | 0.2 | 3.7 (−3,−17,9) | |



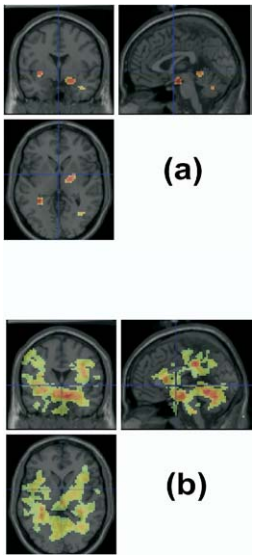

[a]Voxels are 3 mm × 3 mm × 3 mm, so 1 voxel = 0.027 cc. All comparisons are thresholded at $p < .001$, uncorrected, extent threshold 0.2 cc (8 voxels), unless otherwise specified. Figures are "glass brain" sums of total activation per plane, overlaid on slices from a template T1 scan at Talairach co-ordinate (0,0,0).

[b]Extent threshold 0.08 cc (3 voxels; clusters in this analysis became more substantial at more liberal probability thresholds).

COLOR

**Table 5.** Results of Two-Sample *t*-Test in SPM, Medium Condition, Perfect Epochs Only, By Cluster[a]

| R/L | Anatomical Label | Brodmann Area(s) | Vol. (cc) | Max. T (x,y,z) | Figure |
|---|---|---|---|---|---|
| a. SZ medium > HC medium, retrieval, perfect epochs[b] | | | | | |
| R | Parahippocampal Gyrus, Amygdala | 28, 34, 37 | 1.6 | 4.1 (18,−9,−15) | |
| L | Hippocampus, Parahippocampal Gyrus, Caudate | 19, 37 | 0.9 | 3.9 (−30,−41,0) | |
| b. SZ medium > HC medium, retrieval, perfect epochs[c] | | | | | |
| L+R | Lingual, Parahippocampal, Fusiform, Superior Temporal Gyri, Hippocampus, Caudate, Culmen, Cuneus | 17, 18, 19, 27, 30, 36, 37, 41 | 20.5 | 3.9 (−30,−41,0) | |
| L+R | Parahippocampal, Superior Temporal, Inferior Frontal, Subcallosal Gyri, Amygdala, Hippocampus, Subthalamic, Red Nuclei, Substania Nigra, Hypothalamus, Mammillary Body, Lateral/Medial Globus Pallidus, Putamen, Claustrum, Uncus | 13, 21, 28, 34, 35, 37, 38, 47 | 9.4 | 4.1 (18,−9,−15) | |
| L | Insula, Precentral, Superior Temporal, Inferior Frontal Gyri, Claustrum | 6, 13, 22, 38, 44, 46, 47 | 7.4 | 2.9 (−36,15,5) | |
| R | Insula, Inferior/Middle Frontal, Precentral Gyri, Claustrum, Putamen | 9, 10, 13, 44, 45, 46 | 5.2 | 3.0 (33,18,10) | |
| L | Inferior Parietal Lobule, Precentral, Postcentral Gyri, Insula, Precuneus | 2, 3, 4, 7, 13, 29, 40 | 4.5 | 3.0 (−56,−35,49) | |
| R | Inferior/Superior Parietal Lobules, Precentral, Postcentral, Superior Temporal, Supramarginal, Angular, Cingulate Gyri, Insula, Precuneus | 2, 3, 6, 7, 13, 22, 31, 39, 40 | 2.6 | 3.3 (33,−54,36) | |
| L | Precentral, Postcentral Gyri | 1, 2, 3, 4, 6 | 2.6 | 3.1 (−59,−15,42) | |
| L | Uncus, Parahippocampal Gyrus, Amygdala, Hippocampus, Lateral/Medial Globus Pallidus, Putamen | 20, 28, 35, 36, 37 | 1.9 | 2.8 (−21,−1,−25) | |
| R | Hippocampus, Caudate, Parahippocampal, Superior Temporal Gyri | 41 | 0.5 | 2.6 (30,−32,−1) | |
| R | Precentral, Postcentral Gyri | 4, 6, 43 | 0.5 | 2.6 (59,−2,14) | |
| L | Claustrum, Insula | 13 | 0.5 | 2.5 (−30,−2,19) | |
| R | Cingulate Gyrus | 24, 32 | 0.2 | 2.5 (18,4,30) | |




[a]Voxels are 3 mm × 3 mm × 3 mm, so 1 voxel = 0.027 cc. Figures are "glass brain" sums of total activation per plane, overlaid on slices from a template T1 scan at Talairach co-ordinate (0,0,0).
[b]Thresholded at $p < .001$, uncorrected, extent threshold 0.2 cc (8 voxels).
[c]Same analysis thresholded at $p < .01$, uncorrected, extent threshold 0.2 cc (8 voxels).

These clusters were somewhat similar to the patterns seen when comparing both groups during retrieval in the medium condition without taking accuracy into account, but because of differences in number of epochs analyzed, it is difficult to compare the two designs directly.

### Modulation of Activation by WM Load

A within-subjects ANOVA analysis in SPM revealed significant effects of load on activation for both groups. During encoding, control subjects showed several large clusters for which increased task load caused a linear increase in activation, including one in left DLPFC (Table 6A). Patients also showed several clusters for the same effect, although less extensively, including a small part of left DLPFC (Table 6B).

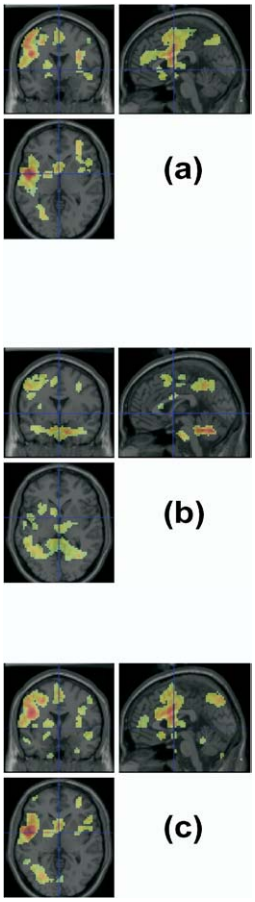
A similar within-subjects ANOVA design for retrieval, however, differed between the two groups. Control subjects still showed several clusters of linear increase, including left DLPFC (Table 6C). During retrieval, however, patients showed no voxels with a linear effect at the same significance threshold, and, even at a threshold of $p < .01$, uncorrected, the only suprathreshold clusters were small and located well outside any regions of interest. Plots of both groups' activation response to WM load at the most responsive voxel in lateral PFC are shown in Figure 1A (encoding) and Figure 1B (retrieval).

Finally, an SPM paired *t* test design comparing the "medium 6" load to the "difficult 6" load revealed similar results to the ANOVA analyses. Again, both control subjects and patients showed areas of significantly greater activation for the "difficult 6" than for the "medium 6" during encoding. As before, the results for both groups included clusters in lateral PFC, and control subjects had more extensive areas of difference than patients (Table 7A and 7B for control subjects and patients, respectively). During retrieval, however, control subjects again showed a pattern of significant differences similar to those found during encoding (Table 7C), whereas patients showed no such effect. Patients may have exhibited some context effect at subthreshold levels during retrieval, however; at a more liberal threshold of $p < .01$, uncorrected, patients showed some small context-sensitive clusters including one near left DLPFC (Table 7D), but these clusters were still smaller than those of control subjects at the stricter threshold. A two-sample *t* test, comparing the difference between "medium 6" and "difficult 6" at the lateral PFC voxel of greatest effect for each group and epoch type, showed that control subjects had a significantly greater context

COLOR

**Table 6.** Results of ANOVAs in SPM, By Cluster[a]

| R/L | Anatomical Label | Brodmann Area(s) | Vol. (cc) | Max. T (x,y,z) | Figure |
|---|---|---|---|---|---|
| a. HC, activation modulated by load, encoding | | | | | |
| L | Precentral, Postcentral, Inferior/Middle/Superior Frontal, Superior/Transverse Temporal Gyri, Insula | 1, 2, 3, 6, 8, 9, 13, 22, 41, 42, 43, 44, 45, 46 | 21.2 | 4.9 (−50,2,44) | |
| R | Inferior/Middle/Superior Frontal Gyri | 9, 10, 46 | 3.7 | 4.3 (33,47,14) | |
| L+R | Medial/Superior Frontal, Cingulate Gyri | 6, 8, 32 | 3.6 | 4.1 (0,11,52) | |
| L | Inferior/Superior Parietal Lobules, Precuneus | 7, 40 | 3 | 3.9 (−27,−56,44) | |
| R | Superior Temporal, Inferior Frontal Gyri, Insula | 13, 38, 45, 47 | 1.8 | 3.8 (48,17,−11) | |
| L | Putamen, Lateral Globus Pallidus, Thalamus, Caudate | n/a | 1.6 | 4.3 (−18,0,8) | |
| R | Inferior/Middle Frontal Gyri, Precentral | 6, 9 | 0.7 | 3.8 (36,7,25) | |
| L | Lateral/Medial Globus Pallidus, Putamen, Parahippocampal Gyrus, Amygdala | 34 | 0.4 | 3.7 (−18,−3,−7) | |
| R | Middle Frontal Gyrus | 6, 8, 9 | 0.3 | 3.4 (50,8,44) | |
| b. SZ, activation modulated by load, encoding | | | | | |
| L | Inferior/Superior Parietal Lobules, Precuneus, Postcentral Gyrus | 2, 7, 40 | 7.3 | 4.7 (−48,−47,44) | |
| L | Medial/Superior Frontal, Cingulate Gyri | 6, 8, 24, 32 | 1.5 | 4.6 (−9,11,46) | |
| L | Middle/Superior Frontal Gyri | 6 | 1.4 | 4.5 (−27,17,54) | |
| L | Precentral, Inferior Frontal Gyri | 6, 9 | 1.1 | 4.2 (−45,1,28) | |
| R | Inferior/Superior Parietal Lobules, Precuneus, Angular Gyrus | 7, 19, 39, 40 | 1 | 3.9 (33,−62,42) | |
| R | Uncus, Parahippocampal Gyrus | 28, 34, 35, 36 | 0.8 | 4.0 (9,−13,−27) | |
| L | Precentral Gyrus | 4, 6 | 0.5 | 3.8 (−39,−12,56) | |
| L | Insula, Claustrum | 13 | 0.3 | 4.1 (−30,21,10) | |
| L | Precentral/Postcentral Gyri | 1, 3, 4, 6 | 0.3 | 3.7 (−53,−7,45) | |
| c. HC, activation modulated by load, retrieval | | | | | |
| L | Inferior/Middle Frontal, Superior/Transverse Temporal, Precentral, Postcentral Gyri, Insula | 3, 6, 8, 9, 13, 22, 41, 42, 43, 44, 45, 46 | 22.2 | 5.3 (−42,7,22) | |
| L | Inferior/Superior Parietal Lobules, Precuneus | 7, 19, 40 | 6.8 | 4.7 (−30,−71,45) | |
| L+R | Medial/Superior Frontal, Cingulate Gyri | 6, 8, 32 | 4.4 | 4.3 (0,11,52) | |
| R | Middle/Superior Frontal Gyri | 10 | 1.7 | 3.6 (33,50,3) | |
| L | Lateral/Medial Globus Pallidus, Putamen, Thalamus, Caudate | n/a | 1.7 | 4.0 (−18,−2,8) | |
| R | Inferior Frontal, Superior Temporal Gyri | 38, 47 | 1.5 | 3.9 (50,20,−11) | |
| R | Inferior/Middle Frontal, Precentral Gyri | 6, 9 | 1.2 | 4.4 (36,7,25) | |
| L | Parahippocampal Gyrus, Amygdala, Lateral/Medial Globus Pallidus, Putamen | 34, 37 | 0.6 | 3.8 (−21,−1,−10) | |
| R | Middle Frontal, Precentral Gyri | 6, 8, 9 | 0.5 | 3.5 (50,8,44) | |
| R | Uncus, Inferior Temporal Gyrus | 20, 36 | 0.4 | 3.6 (30,−2,−30) | |
| L | Fusiform, Inferior/Middle Temporal Gyri | 20, 37 | 0.4 | 4.0 (−56,−50,−13) | |
| R | Precuneus, Superior Parietal Lobule | 7 | 0.3 | 3.4 (0,−76,48) | |
| L | Inferior/Middle/Superior Frontal Gyri | 10 | 0.2 | 3.5 (−39,55,0) | |




[a]Voxels are 3 mm × 3 mm × 3 mm, so 1 voxel = 0.027 cc. All comparisons are thresholded at $p < .001$, uncorrected, extent threshold 0.2 cc (8 voxels). Figures are "glass brain" sums of total activation per plane, overlaid on slices from a template T1 scan at Talairach co-ordinate (0,0,0).

effect for both encoding ($t = 2.9$, $df = 25.6$, $p < .005$, one-tailed, equal variances not assumed) and retrieval ($t = 3.0$, $df = 27$, $p < .005$, one-tailed). An interesting behavioral effect mirrored these results. Although both groups experienced a small reduction in accuracy for "difficult 6" compared with "medium 6," the between-group difference was not significant ($t = .4$, $df = 12.5$, $p = .72$, two-tailed, equal variances not assumed), and neither group showed a significant difference in reaction time for encoded (target) probe stimuli. For nonencoded (foil) probes, however, control subjects had a mean .16 sec (SD = .22 sec) increase in reaction time for "difficult 6" compared with "medium 6," whereas patients actually had a mean .06 sec (SD = .17 sec) decrease; the between-group difference was significant ($t = 2.9$, $df = 27$, $p < .01$, two-tailed).

## Discussion

In this study, we aimed to replicate and extend previous fMRI studies of WM and PFC abnormalities in schizophrenia by using a task more conducive to examining activation at different WM loads. We predicted greater activation in patients when matched for performance with control subjects, as well as load-based increases in activation for both groups up to the point where memory capacity was exceeded. As previously suggested (Calli-

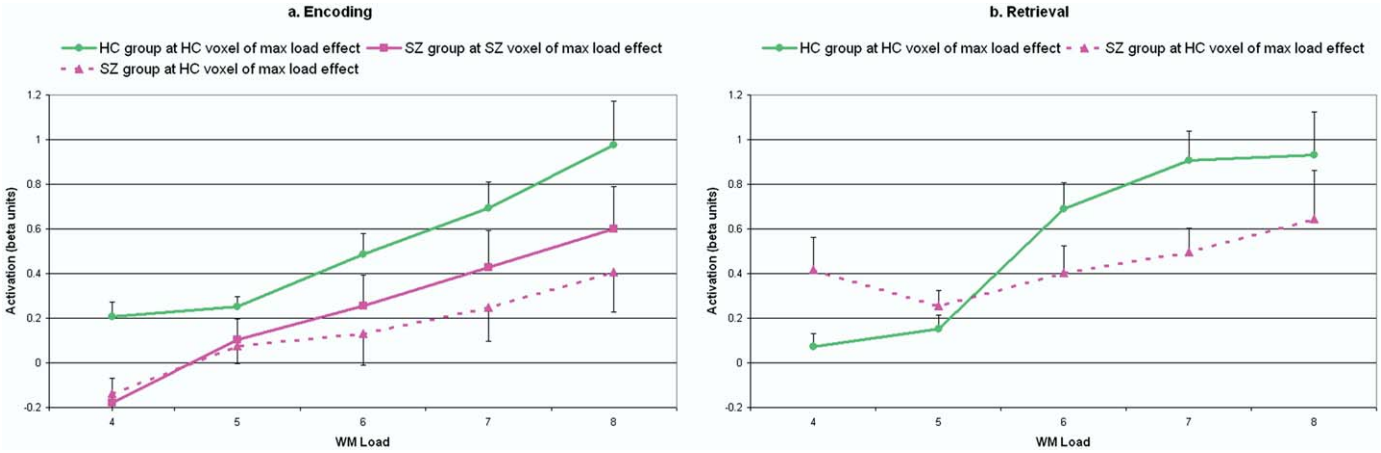



**Figure 1.** Plots of activation by WM load in voxels of maximum load dependence in lateral PFC**.**Values are averaged measures of activation extracted in a 6mm radius around the voxel of interest. Voxels of interest were isolated using an "effects of interest" contrast in a repeated-measures ANOVA model across 5 WM loads to find the lateral PFC voxel for each subject group with the strongest differential response to changes in load. (a) During encoding, controls (HC: solid green line) and patients (SZ: solid pink line) show relatively similar load-response curves in each group's respective region of maximum load effect (HC: centered at Talairach coordinate −48, 4, 19; SZ: −48, 4, 25). SZ patients' response at the HC group's voxel of maximum load effect (−48, 4, 19) is also shown (dotted pink line); not surprisingly, the plot is quite similar as the two groups' centers of maximum effect are only 6mm apart. (b) During retrieval, controls (HC: solid green line) again showed an effect of increasing activation with increasing WM load around their voxel of maximum load effect (centered at Talairach coordinate −45, 7, 22). Patients during retrieval, however, did not show any load effects in lateral PFC at $p$ values up to $p < .05$, uncorrected; thus, for comparison purposes, the SZ patients' response is plotted only at the HC group's voxel of maximum load effect (dotted pink line), showing little response to changes in WM load.

cott et al 2003), however, the nature of WM dysfunction in schizophrenia is more complex than simple over- or underactivation of specific neural circuits, and our findings of both hyper- and hypoactivation in patients depending on WM load support this viewpoint.

Several findings were not predicted by our initial hypotheses. Although comparable accuracy rates were achieved between control subjects in the difficult condition and patients in the medium condition, we found underactivations in patients rather than the overactivations predicted by Callicott et al (2003). We found substantial activation of the thalamus and basal ganglia in healthy control subjects, which Manoach et al (2000) found only in patients; generally, our results suggested that these subcortical regions tend to activate similarly to cortical areas in the WM network, both in terms of normal patterns in control subjects and the over- and underactivations found in patients. We also partially refuted our hypothesis about load effects based on Jansma et al (2004); although we found a significant linear effect of load on activation in control subjects (for both encoding and retrieval) and patients (for encoding only), we did not find a decrease in activation at higher WM loads, possibly because our task did not become sufficiently difficult to produce discouragement or disengagement.

We also uncovered several unexpected effects that warrant further study. Investigating effects of WM load on activation, we found control subjects' activations to be consistently more load-dependent than patients'. Although it is hypothesized that alternating findings of overactivation and underactivation in schizophrenia could be accounted for by shifting the inverted-U shape of activation plotted by WM load to the left (Callicott et al 2003, Manoach 2003), as in Figure 2A, our findings of reduced load sensitivity in schizophrenia (particularly for retrieval) suggest that the plot for patients is also somewhat flatter, perhaps as illustrated in Figure 2B.

Our related finding of differential responses to a six-item WM load depending on the surrounding load context warrants further investigation in both patients and healthy control subjects. These preliminary results suggest that a difficulty context affects control subjects' WM network more than patients', supporting the idea that schizophrenia patients have decreased neural responsiveness to WM load differences; this converges with several lines of evidence suggesting that schizophrenia is associated with deficits in the ability to use context to guide task performance (Barch et al 2001; Cohen et al 1999; Ford et al 2004; Henik et al 2002; Servan-Schreiber et al 1996). This study was not designed to examine this effect, however, and thus further study will be necessary to rule out potential confounds. For example, all our subjects performed the medium-difficulty task before the high-difficulty version, leading to potential practice or habituation effects. It is also possible that greater activation for WM loads of seven and eight resulted in a difference in the calculated baseline signal or that residual blood oxygenation level–dependent (BOLD) response from preceding seven- or eight-item loads resulted in overlap that artificially heightened the apparent activation for the "difficult 6" condition. Although it would seem that most of these potential confounds would, if anything, lead to artificially decreased activation in the "difficult 6" condition and that the general linear model (GLM) employed by SPM would deal with possible BOLD overlap, further investigation using counterbalanced conditions and a close examination of BOLD signal change patterns is necessary to establish this effect conclusively.

Also unexpected were the differences between patients' activations during encoding and retrieval. Generally, control subjects activated similarly during encoding and retrieval, whereas patients failed to show load-sensitive effects during retrieval that were present during encoding. To reframe this, patients' activation patterns appeared more "normal" during encoding than during retrieval. This suggests that further study of the maintenance period between encoding and retrieval could be highly fruitful in isolating the exact nature and progression of WM breakdown in schizophrenia.

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**Table 7.** Results of Paired *t*-Tests in SPM, "Difficult 6" vs. "Medium 6," By Cluster[a]

| R/L | Anatomical Label | Brodmann Area(s) | Vol. (cc) | Max. T (x,y,z) | Figure |
|---|---|---|---|---|---|
| a. HC, "difficult 6" > "medium 6," encoding | | | | | |
| L | Inferior/Middle Frontal, Precentral Gyri, Insula | 6, 9, 13, 44, 45, 46 | 9.5 | 6.8 (−45,7,22) | |
| L+R | Medial/Superior Frontal, Cingulate Gyri | 6, 8, 32 | 3 | 6.0 (0,14,49) | |
| L | Inferior/Middle/Superior Frontal Gyri | 10 | 0.9 | 4.5 (−33,55,3) | |
| R | Inferior Frontal Gyrus, Insula | 13, 47 | 0.4 | 4.4 (33,26,−4) | |
| L | Putamen, Lateral Globus Pallidus | n/a | 0.4 | 4.5 (−18,1,11) | |
| R | Inferior Frontal, Superior Temporal Gyri | 38, 47 | 0.3 | 4.2 (50,20,−11) | (a) |
| L | Precuneus | 7 | 0.3 | 4.2 (−9,−76,45) | |
| R | Inferior/Middle/Superior Frontal Gyri | 10, 46 | | 5.7 (36,55,3) | |
| b. SZ, "difficult 6" > "medium 6," encoding | | | | | |
| L | Inferior Frontal Gyrus, Insula, Claustrum | 13, 45, 46 | 1 | 5.7 (−33,27,10) | |
| R | Inferior Parietal Lobule, Supramarginal Gyrus | 40 | 0.7 | 6.0 (53,−36,38) | |
| L | Inferior Parietal Lobule | 40 | 0.5 | 5.7 (−45,−50,41) | |
| R | Inferior Frontal Gyrus | 45, 47 | 0.2 | 5.1 (30,32,1) | (b) |
| c. HC, "difficult 6" > "medium 6," retrieval | | | | | |
| L | Inferior/Middle Frontal, Superior Temporal, Precentral Gyri, Insula | 6, 8, 9, 13, 22, 44, 45, 46 | 12.4 | 7.7 (−45,10,22) | |
| L | Inferior/Superior Parietal Lobules, Precuneus | 7, 40 | 3.5 | 5.3 (−33,−70,50) | |
| L+R | Medial/Superior Frontal, Cingulate Gyri | 6, 8, 32 | 2.3 | 5.0 (0,14,49) | |
| R | Inferior/Middle/Superior Frontal Gyri | 10, 46 | 2.2 | 5.2 (33,55,0) | |
| L | Inferior/Middle/Superior Frontal Gyri | 10, 11 | 1.2 | 5.7 (−33,52,−3) | (c) |
| R | Superior Temporal, Inferior Frontal Gyri | 38, 47 | 0.7 | 5.1 (50,20,−16) | |
| L | Superior Temporal Gyrus | 22 | 0.3 | 4.3 (−62,−9,0) | |
| L | Putamen, Lateral Globus Pallidus | n/a | 0.3 | 4.1 (−18,1,11) | |
| d. SZ, "difficult 6" > "medium 6," retrieval[b] | | | | | |
| R | Inferior/Middle Temporal, Fusiform Gyri | 20, 37 | 0.8 | 5.5 (50,−36,−16) | |
| L | Insula, Claustrum | 13 | 0.4 | 3.9 (−30,21,10) | |
| L | Precentral, Inferior Frontal Gyri | 6, 9 | 0.6 | 3.5 (−45,−2,28) | (d) |
| R | Inferior/Superior Parietal Lobules, Precuneus, Angular Gyrus | 7, 19, 39, 40 | 1.1 | 4.1 (30,−59,42) | |
| L | Inferior/Superior Parietal Lobules, Precuneus | 7, 40 | 3.0 | 3.7 (−48,−47,44) | |

[a]Voxels are 3 mm × 3 mm × 3 mm, so 1 voxel = 0.027 cc. All comparisons are thresholded at $p < .001$, uncorrected, extent threshold 0.2 cc (8 voxels), unless otherwise specified. Figures are "glass brain" sums of total activation per plane, overlaid on slices from a template T1 scan at Talairach co-ordinate (0,0,0).

[b]Thresholded at $p < .01$, uncorrected, extent threshold 0.2 cc (8 voxels).

A limitation of this study is the difficulty in determining what other cognitive events may have coincided with memory error in patients. Subjects were not interviewed to determine which factors contributed to their incorrect responses. Because subjects received no extra compensation according to performance, disengagement due to lack of motivation was possible, as was simple inattention. Several patients had substantial positive symptoms, which may have also contributed to distractibility. Although some studies provided performance-based bonuses to increase motivation (Manoach et al 1999, 2000, 2003), few have reported on or controlled for the additional confounds discussed here. This makes it difficult to separate primary breakdowns in the WM circuitry from motivational or attentional deficits, particularly when attempting to explain hypoactivation.

To help unravel this issue, we analyzed only blocks in which both patients and control subjects provided all correct responses, which yielded a surprising reduction in between-group differences (replicating, to some extent, Manoach et al 2000). Although some of this reduction could be attributed to fewer epochs being compared (approximately half of all epochs), leading to potential losses in measurement sensitivity, it nevertheless suggests that *successful* WM function in schizophrenia patients is not strikingly different from that of healthy control subjects. The most robust between-groups difference in this analysis—greater amygdala and hippocampal activation in patients during retrieval—could indicate that patients recruit a more extensive network to achieve successful WM retrieval or could be due to other factors (e.g., greater cognitive and emotional stress imposed by the patients' increased difficulty in responding correctly). Additional areas of hyperactivation in patients, only present below our a priori statistical threshold, suggest that, if anything, patients may slightly overactivate the WM network during successful retrieval at moderate loads (mirroring Callicott et al 2003). Even at the lower

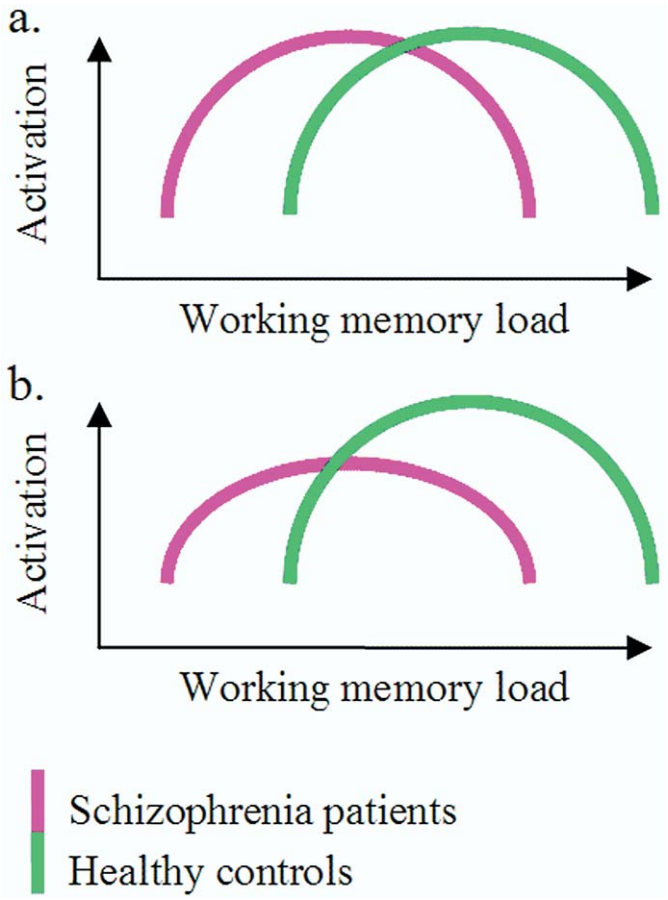


**Figure 2.** Models describing the hypothesized shape of neural response to increasing load in the working memory network. (a) Predicts that patients and controls have similar load-response curves when dealing with increasing working memory load, but that patients' curves are shifted to the left, thus resulting in apparent overactivations at low loads and underactivations at high loads. Similar models and figures have been previously presented and discussed in (Manoach 2003) and (Callicott et al 2003). (b) Similar, but modified to show a flatter response curve for patients that reflects a decreased ability to modulate neural response in accordance with increasing task difficulty.

threshold, however, the DLPFC was implicated less than we expected.

One advantage of our study is our ability to examine WM performance separately during encoding and retrieval at a variety of loads. Prior studies using the Sternberg paradigm have often had limited loads (e.g., Manoach et al 1999, 2000), which used loads of only two and five items; considering the rule-of-thumb $7 \pm 2$ items that define the limit of most individuals' working memories (Miller 1956), such loads may have been insufficiently challenging to engage WM fully in control subjects or high-performing patients. Our findings regarding load-dependent activation, as well as previous studies (Jansma et al 2004), demonstrate the benefits of studying WM function at a variety of load levels, including loads that are challenging to participants. Additionally, our finding of greater WM network abnormalities during retrieval than encoding supports the use of similar tasks to further investigate the progression of WM breakdown during maintenance and retrieval.

One problem intrinsic to WM studies in schizophrenia is patient heterogeneity. Previous studies report that WM activation patterns are less consistent among patients than control subjects (Manoach et al 2000), making it difficult to assess the validity of averaged group results. In other words, do findings of "underactivations" truly reflect a uniform characteristic of the patient group, or are they an artifact of more widely distributed loci of activity, leading to lower group averages in the specific areas activated more consistently in control subjects? Because performance is hypothesized to affect findings of hyper- versus hypoactivation and our own findings revealed a smaller-than-expected between-group difference when only epochs of perfect performance were compared, the wide range of cognitive abilities among people with schizophrenia is important to consider in future studies. Future investigations with a greater number of subjects should provide a clearer picture of the overall activation response in various loci of the WM network varying by both performance and WM load.

Other limitations of our study include some patients' not performing the high-difficulty condition, leading to a lower $n$ at the higher WM loads. Order effects are also possible because all subjects performed the medium condition before the difficult, although this should not affect between-group differences unless a group-by-order interaction is predicted.

In summary, our results imply that abnormal WM network response in schizophrenia is affected by several factors. Activation during retrieval was generally more abnormal than during encoding, indicating the need to study the maintenance period of WM to discover where and when the WM process begins to break down. Additionally, we found the WM network in patients to be less responsive to context and changing load demands, suggesting that both hyper- and hypoactivation could be caused by an inability to muster and allocate neural resources at context-appropriate levels. Finally, our analyses of correct-response epochs suggest that patients' activation during successful WM function differs from control subjects less than during unsuccessful WM function. This argues for the need for future studies to analyze performance at the trial rather than the group level to characterize fully the relationship between neural activity and successful WM performance.

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