

# Cortical Dysfunction in Schizophrenia During Auditory Word and Tone Working Memory Demonstrated by Functional Magnetic Resonance Imaging

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**Background:** Verbal learning and memory deficits are among the most severe cognitive deficits observed in schizophrenia. We have demonstrated that such deficits do not extend to working memory for tones in a substantial number of patients even when verbal working memory is impaired. In this study we used functional magnetic resonance imaging to study the neural basis of this dissociation of auditory verbal and nonverbal working memory in individuals with schizophrenia.

**Methods:** While undergoing functional magnetic resonance imaging, 12 schizophrenic patients and 12 matched control subjects performed auditory Word Serial Position Task and Tone Serial Position Task.

**Results:** Both tasks produced activation in frontal cortex and temporal and parietal lobes of the cerebrum in both groups. While robust activation was observed in the left inferior frontal gyrus (areas 6, 44, and 45) in the

control group during the Word Serial Position Task, activation in the patient group was much reduced in these areas and failed to show the same task-specific activation as in controls. Reduced activation in patients was not confined to the inferior frontal gyrus, but also extended to a medial area during the Tone Serial Position Task and to premotor and anterior temporal lobe areas during both tasks.

**Conclusions:** These findings support the hypothesis that abnormalities in cortical hemodynamic response in the inferior frontal gyrus underlie the verbal working memory deficit in schizophrenia. The relationship of verbal working memory deficits to other cognitive functions suggests that abnormal functioning in the speech-related areas may reflect a critical substrate of a broad range of cognitive dysfunctions associated with schizophrenia.

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**A**LTHOUGH schizophrenia disrupts a broad range of perceptual, sensorimotor, and cognitive functions, tasks assessing verbal learning and memory appear to be particularly disturbed.<sup>1-6</sup> In our companion article,<sup>7</sup> we report that auditory verbal working memory is selectively impaired in schizophrenic patients with basic perceptual and attentional competence while working memory for nonverbal auditory stimuli (ie, tones) remains intact. This suggests that the neural systems for processing auditory verbal and nonverbal material are segregated at some level and that the former can be selectively impaired in schizophrenia.

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Functional imaging studies of verbal working memory tasks consistently report activation in the inferior and middle frontal cortex, and in posterior temporoparietal areas in control subjects,<sup>8-12</sup> re-

sults consistent with reports that verbal deficits are associated with left inferior frontal and posterior temporal lesions.<sup>13</sup> In contrast, imaging work suggests that tonal memory involves cortical and subcortical areas partially lateralized to the right hemisphere,<sup>14</sup> consistent with clinical studies demonstrating right temporal and frontal lobe involvement in pitch discrimination and memory.<sup>15-17</sup>

Although there are no published imaging studies of auditory verbal working memory per se in schizophrenia, a number of studies have reported frontal and temporal lobe abnormalities during word recognition,<sup>18</sup> word generation,<sup>19-22</sup> and auditory selective attention.<sup>23</sup> In addition, several imaging studies have reported decreased frontal lobe activation in schizophrenic patients during performance of neuropsychological tasks sensitive to frontal lobe lesions.<sup>23-26</sup>

The present study sought to examine cortical hemodynamic activity in schizophrenia during a verbal working

## SUBJECTS AND METHODS

### SUBJECTS

All subjects provided informed consent before the study. The patient group consisted of 14 medicated outpatients (8 men) who met Structured Clinical Interview for DSM-III-R<sup>27</sup> criteria for schizophrenia. Symptom scores (mean  $\pm$  SD) on the Positive and Negative Symptom Scale were as follows: positive,  $16.1 \pm 6.0$ ; negative,  $17.2 \pm 4.5$ ; general,  $32.1 \pm 9.0$ ; and total,  $65.0 \pm 18.4$ .

Fourteen subjects (8 men) without history of psychiatric disorder served as controls. None was taking medications that affect the central nervous system. All patients and control subjects were right-hand dominant, as assessed by writing and performing at least 5 of 7 daily activities with their right hand. Subjects with histories of neurologic disorder or trauma, or substance abuse within the last 6 months, were excluded from the study. As assessed by Student *t* test ( $P < .05$ ), the control and schizophrenia groups did not differ in age (controls,  $36.8 \pm 11.8$  years; patients,  $39.6 \pm 8.6$  years), years of education (controls,  $13.9 \pm 1.1$  years; patients,  $14.5 \pm 1.9$  years), or parent education (controls,  $13.5 \pm 2.3$  years; patients,  $13.0 \pm 3.2$  years). All subjects scored at least 90% correct on a screening test of auditory pitch discrimination, described in our companion article,<sup>7</sup> assuring that all subjects could discriminate the tonal stimuli used in the Tone Serial Position Task (TSPT).

### ACTIVATION TASKS

Subjects were trained on the auditory Word Serial Position Task (WSPT) and TSPT before scanning as described in our companion article.<sup>7</sup> In the WSPT, subjects were presented with lists of 4 words followed by a 9-second retention interval. One of the words was then repeated and subjects indicated its position (first, second, third, or fourth) in the list by briefly extending the corresponding number of fingers on their left hand. The TSPT was procedurally identical to the WSPT but consisted of lists of 3 tones instead of 4 words. Tones within each list differed from the next closest tone by a frequency ratio of 0.85 (eg, 500 Hz, 425 Hz, 361 Hz). Fewer tones than words were used in lists to improve the overall level of performance of the task.

### IMAGE ACQUISITION

Scanning took place in a 1.5-T Signa magnetic resonance imaging system (General Electric Corp, Milwaukee, Wis) equipped with echo planar imaging hardware (Advanced NMR

Inc, Wilmington, Mass). Anatomical localizer scans were acquired in the sagittal plane, using conventional T<sub>1</sub>-weighted spin-echo sequence: echo time, 11 milliseconds; repetition time, 667 milliseconds; field of view, 24 cm<sup>2</sup>; slice gap, 0 mm; acquisition matrix, 256  $\times$  128 with 1 excitation; and slice thickness, 5 mm. Ten T<sub>1</sub>-weighted oblique axial slices were acquired with the following imaging sequence: echo time, 13 milliseconds; repetition time, 500 milliseconds; field of view, 40 cm<sup>2</sup>; acquisition matrix, 256  $\times$  192 with 2 excitations; and slice thickness, 9 mm. Slice orientation paralleled the plane transecting the anterior and posterior commissures, and the interslice distance was varied by subject to maintain the same location of slices in all subjects.

Functional images were acquired with an echo planar imaging gradient echo sequence: flip angle, 60°; echo time, 45 milliseconds; repetition time, 1500 milliseconds; field of view, 40  $\times$  20 cm; acquisition matrix, 128  $\times$  64 with 1 excitation; and voxel volume, 9  $\times$  3.125  $\times$  3.125 mm. Eighty images per slice were acquired during each scan.

Image processing was performed with statistical programs written in MATLAB 4.0 (Math Works, Inc, Natick, Mass). All images were screened for motion and other artifacts and contaminated images were eliminated. Subjects were eliminated if movement of the center of mass of activation was greater than 1 pixel across the session, or greater than 0.5 pixel within a scan. Two controls and 2 patients were eliminated because of failure to meet the above criteria, yielding the final sample of 24.

Subjects underwent 2 scans for each task. Computer-generated stimuli were presented via shielded speakers, through air conductance tubes, to headphones, which provided external noise reduction. The volume was adjusted to the comfort of each subject. A WSPT scan consisted of 4 trials each separated from the next by a 14-second baseline interval. The same procedure was used with the TSPT, except that 5 trials were conducted during each TSPT scan separated by 12-second intertrial intervals. The 6 images acquired during the 9-second retention interval preceding the target and the 6 images acquired during the final 9 seconds of the baseline period were compared in the data analysis.

### DEFINITION OF REGIONS OF INTEREST

After coregistration of the anatomical images and echo planar imaging functional maps from individual subjects, the images were transformed into the standard 3-dimensional coordinate system of Talairach and Tournoux.<sup>28,29</sup> Slices were interpolated into the 10 most superior

memory task as well as during a nonverbal working memory task that patients performed normally.

## RESULTS

### TSPT AND WSPT TRAINING PERFORMANCE

The pattern of behavioral deficits on the WSPT and sparing of TSPT performance reported in the larger sample<sup>1</sup> was confirmed in the present sample. On the prescan WSPT test, the patient group performed at a mean of 85% correct, significantly worse than the 94% mean accuracy among the con-

trols ( $F_{1,22} = 5.718$ ;  $P = .03$ ). Performance in the scanner was excellent for both groups on the limited number of WSPT trials, on which the patient group and control group performed at 91% and 95% mean accuracy, respectively ( $F_{1,22} = 0.88$ ;  $P = .36$ ). In training before scanning, the patient group averaged 68% correct on the TSPT compared with 71% for the controls ( $F_{1,22} = 0.217$ ;  $P = .64$ ). During scanning, the groups averaged 69% and 75%, respectively ( $F_{1,22} = 0.33$ ;  $P = .59$ ). Equivalent levels of performance by patients and controls during scanning rule out a failure by the patient group to attend to the stimuli or other extraneous factors as the basis of activation differences between groups.

slices of Talairach space, centered at  $z = +69, +60, +51, +42, +33, +23, +14, +5, -5,$  and  $-16$ . The slices covered the entire cerebrum except for a portion of the anterior and inferior aspect of the temporal pole. Thirty regions of interest (ROIs) in each hemisphere were defined within the Talairach space. The ROIs were constructed from rectangular volumes ( $8 \times 8 \times 9$  mm) and corresponded to Brodmann areas (Figure 1).

#### DATA ANALYSIS

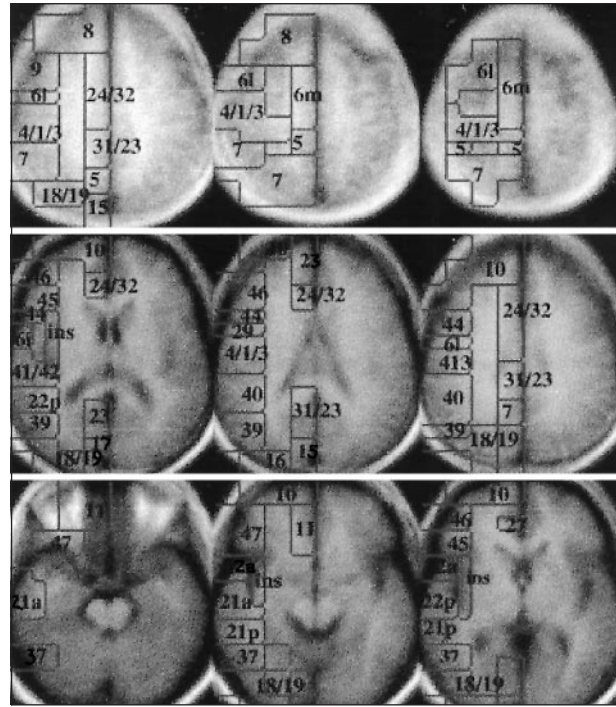
A 2-step analysis was carried out to calculate task-related activation in each individual subject; the values obtained were then used as the dependent measures in repeated-measures analysis of variance. First,  $t$ -values were calculated for each pixel during each task by comparing the 6 images acquired during the retention intervals with the last 6 images acquired during the baseline periods.<sup>28</sup> A criterion for activation was set at a  $t$ -value greater than 1 on both scans of a task, with a minimum cluster size of 4 contiguous pixels meeting this same  $t$ -value threshold. A pixel was assigned the lesser  $t$ -value of the 2 scans for each task. The  $t$ -value criteria were selected because lower thresholds included activation in ventricles and white matter, while higher values eliminated all but a few pixels in some subjects.

Next we calculated the active pixel density in all ROI volumes in each brain for each task. First the number of active pixels in each ROI was divided by the total number of pixels contained in that ROI to adjust for differences in the sizes of the ROIs. Individual differences in global activation were removed by dividing the above ratio by the ratio of the total number of active pixels in the brain to the total number of pixels in the brain. For each ROI, an active pixel density of 1 is equivalent to the mean density of active pixels for the whole brain. To identify regions that showed clear task-related activation, an ROI was retained for further analysis if its mean pixel density was greater than 2 (twice the density of the whole brain) in at least 1 of the groups during 1 of the tasks.

The statistical significance of regional activation differences between groups was evaluated by subjecting pixel density scores for retained ROIs to  $2 \times 2 \times 2$  repeated-measures analysis of variance with group (patients vs controls) as a between-subject factor and task (WSPT vs TSPT) and hemisphere (left vs right) as within-subject factors. A minimum significance value of .05 was used throughout.

#### FRONTAL LOBE

Prescan group differences on the WSPT task were mirrored by cortical hemodynamic differences during WSPT scans. A cluster of ROIs in the left inferior frontal gyrus was preferentially activated by the WSPT task in the controls but not in patients (Figure 2). Analyses of variance confirmed these observations (Table 1). The activation centroids are presented in Table 2. The WSPT produced significantly greater activation than the TSPT in area 44 and inferior lateral area 6. Interactions between group and task in these 2 areas, as well as in area 45, indicated



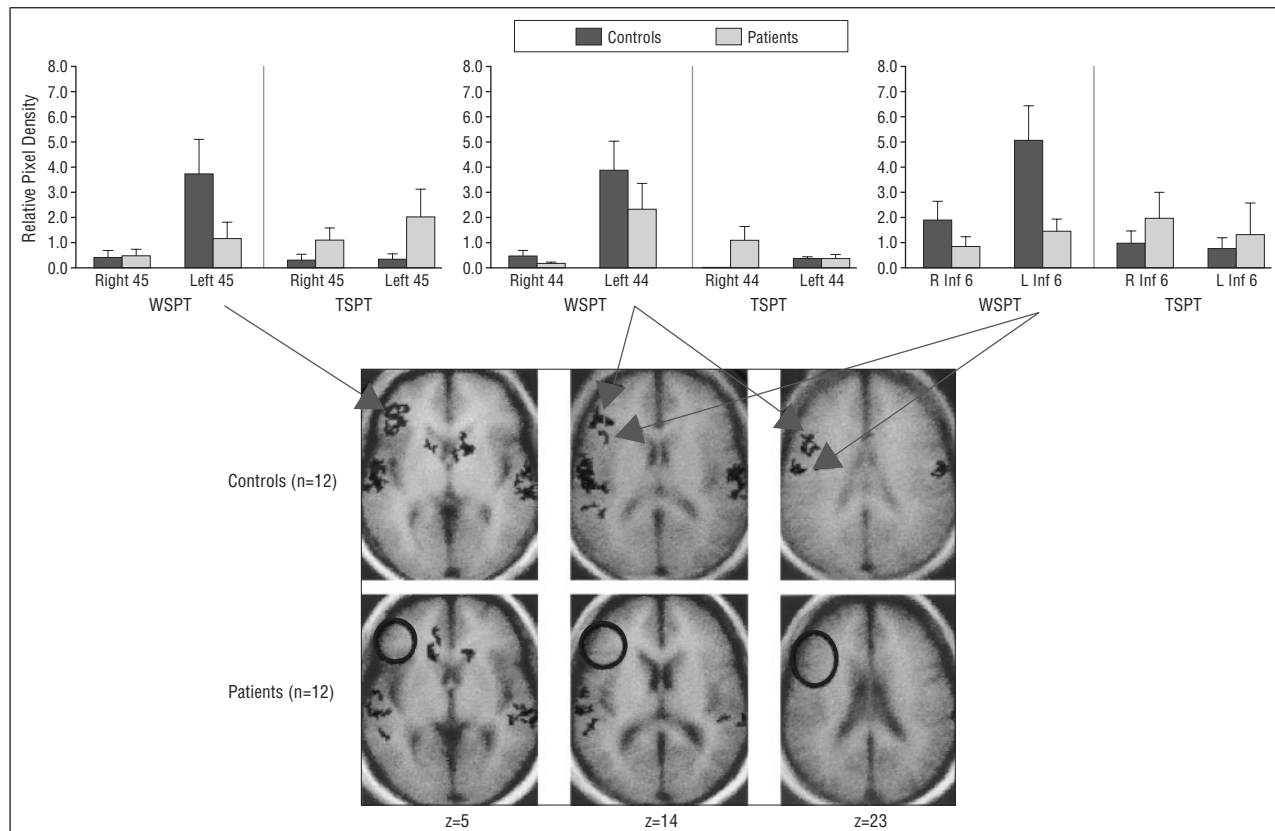
**Figure 1.** Regions of interest in 9 axial slices on the right hemisphere. The analogous regions of interest in the left hemisphere were obtained by applying the mirror image of the map of regions of interest. The number appearing in each region of interest refers to the Brodmann areas of that region in Table 1.

that increased activation was specific to the controls. The WSPT also produced significant effects of hemisphere, reflecting left lateralization of activation in area 44 ( $P < .004$ ) and lateral inferior area 6 ( $P = .03$ ). Similarly, in area 45, a 3-way interaction emerged between group, task, and hemisphere. Follow-up analyses of variance indicated that only the control group produced significantly greater activation during WSPT than during the TSPT in area 44 ( $F_{1,11} = 14.087; P < .004$ ), area 45 ( $F_{1,11} = 7.642; P = .02$ ), and inferior lateral area 6 ( $F_{1,11} = 11.227; P < .007$ ) (Figure 2).

The TSPT task produced significantly greater activation than the WSPT in area 10 and medial area 6 in the frontal lobes, although the greater activation during the TSPT in medial area 6 appeared only in controls (Table 1). Separate analyses of the groups confirmed that controls produced greater activation during the TSPT than during the WSPT ( $F_{1,11} = 8.917; P < .01$ ) in medial area 6, while the patients showed no such increase ( $F_{1,11} = 0.297; P = .59$ ) (Figure 3).

Finally, a main effect of group appeared in lateral area 6, which was activated by both the WSPT and TSPT tasks in the control group to a greater degree than in the patient group.

The correlation between WSPT performance outside the scanner was compared with activation in ROIs that showed task  $\times$  hemisphere interactions reflecting greater activation during the WSPT. Activation in left area 44 correlated with WSPT performance (Pearson  $r = 0.45; P < .02$ ), as did inferior lateral area 6 (Pearson  $r = 0.49; P < .02$ ) in the overall sample. Correlations in patients and controls separately were of equivalent magnitude. The correlation between left medial area 6 activation during



**Figure 2.** Composite activation maps based on median pixel values for the Word Serial Position Task (WSPT) in 3 averaged anatomical slices for the control ( $n = 12$ ) and the patient ( $n = 12$ ) groups, illustrating the hyperfusion in the left inferior frontal gyrus in the schizophrenic group. The bar charts (with SE bars) represent pixel density in the regions of interest corresponding to Brodmann area inferior lateral 6, area 44, and area 45. Reduced activation in the superior temporal gyri is also evident. Threshold for pixels was set at  $t$ -value = 0.2 and a cluster filter of 10 pixels. Approximate Talairach  $z$  coordinate is given for each slice. TSPT indicates Tone Serial Position Task; R Inf, right inferior; and L Inf, left inferior.

**Table 1. Statistical Effects by Regions of Interest for Main Effects and Interactions Detected With ANOVA\***

Region of Interest (Brodmann Area)	Statistical Effect
<b>Frontal Lobe</b>	
Inferior frontal gyrus (BA6)	Group $\times$ task† Group $\times$ hemisphere‡
Lateral frontal cortex (BA6)	Group†
Medial superior frontal gyrus (BA6)	Group $\times$ task† Hemisphere‡
Inferior frontal gyrus (BA44)	Group $\times$ task† Task $\times$ hemisphere‡ Task‡ Hemisphere‡
Inferior frontal gyrus (BA45)	Group $\times$ task $\times$ hemisphere‡ Group $\times$ task‡ Hemisphere‡
Frontal pole (BA10)	Task†
<b>Temporal Lobe</b>	
Anterosuperior temporal gyrus (BA22)	Group† Task†
Posterosuperior temporal gyrus (BA22)	Task‡
Transverse temporal gyrus (BA41/42)	Task $\times$ hemisphere† Task§
<b>Parietal Lobe</b>	
Posterior parietal lobe (BA7)	Task $\times$ hemisphere†

\*Direction of effects and interactions are given in the "Results" section. ANOVA indicates analysis of variance. † $P < .05$ . ‡ $P < .005$ . § $P < .01$ .

the TSPT scan and TSPT behavioral performance was not significant (Pearson  $r = 0.15$ ;  $P = .49$ ).

### TEMPORAL LOBE

Both the WSPT and TSPT produced substantial above-threshold activation throughout the superior temporal gyrus. Unlike the frontal lobe, temporal cortical areas did not show significant group  $\times$  task interactions (Table 1). The WSPT produced significantly greater pixel density than the TSPT throughout the superior temporal gyrus in anterior and posterior area 22 as well as in the primary auditory areas (41/42) (Figure 2). The control group had somewhat higher pixel densities than patients throughout the superior temporal gyrus during both tasks, but group differences reached significance only in anterior area 22. Hemispheric effects of task were confined to area 41/42, reflecting a relative right hemisphere lateralization of activation in this area during the TSPT and a greater pixel density in the left hemisphere during the WSPT. No other effects in the temporal lobe ROIs reached significance.

### PARIETO-OCCIPITAL REGIONS

Group differences failed to appear in the parietal regions, although task-specific activation was present in area 7. A significant interaction of task and hemisphere reflected greater pixel density in the right hemisphere during the TSPT rela-

**Table 2. Center of Mass of Activation for Control and Patient Groups for the WSPT and TSPT Tasks for ROIs Above Threshold\***

ROI	Controls				Patients			
	x	y	z	Density	x	y	z	Density
<b>WSPT Scans</b>								
Frontal								
Inferolateral 6 (L)	-49.9	0.7	22.6	5.05	-52.8	-0.7	20.9	1.43
Medial 6 (L)	-7.2	-7.9	58.3	4.69	-7.4	-8.3	61.1	4.35
Area 44 (L)	-48.8	10.3	24.9	3.97	-48.3	9.0	23.9	2.41
Area 45 (L)	-45.9	24.2	8.1	3.75	-46.9	24.3	10.5	1.17
Medial 6 (R)	7.2	-9.2	59.3	2.84	7.8	-11.7	61.6	2.93
Area 47/11 (L)	-37.2	33.6	-8.3	2.26	-37.4	31.4	-10.6	2.74
Lateral 6 (L)	-38.6	-4.8	50.0	2.26	-28.0	-1.4	55.7	0.91
Temporal								
Area 41/42 (L)	-54.8	-24.4	13.7	9.30	-56.6	-23.3	13.7	4.66
Anterior 22 (R)	56.1	-15.4	3.1	7.52	58.6	-18.8	4.3	2.32
Area 41/42 (R)	59.4	-22.6	13.7	7.00	60.8	-24.5	13.7	2.38
Anterior 22 (L)	-56.9	-12.1	3.3	6.84	-54.9	-13.8	3.2	2.82
Posterior 22 (R)	55.4	-37.0	6.7	4.96	59.9	-37.6	7.2	4.47
Posterior 22 (L)	-54.2	-40.3	9.2	3.46	-54.3	-38.6	9.5	2.35
Anterior 21 (R)	59.1	-17.3	-6.2	1.88	53.8	-17.6	-7.4	2.43
Anterior 21 (L)	-59.0	-15.2	-7.7	1.87	-54.9	-13.4	-11.0	1.77
Parietal								
Area 7 (R)	14.3	-56.8	57.5	1.29	17.5	-53.9	60.3	1.11
Area 7 (L)	-12.1	-55.8	58.0	1.35	-15.3	-57.6	57.7	1.76
Area 5 (R)	10.8	-40.5	57.6	1.43	9.8	-38.9	53.2	3.18
Area 5 (L)	-9.9	-37.4	53.7	2.09	-11.1	-39.4	56.5	4.66
Sensorimotor (R)	38.0	-22.8	46.2	1.79	33.2	-22.1	51.7	1.60
Sensorimotor (L)	-40.5	-20.4	44.3	2.94	-30.2	-26.2	53.4	1.96
<b>TSPT Scans</b>								
Frontal								
Medial 6 (R)	9.4	-15.1	62.7	5.76	8.0	-8.2	63.0	2.85
Medial 6 (L)	-8.0	-12.7	61.8	7.50	-7.9	-10.4	63.3	3.68
Lateral 6 (R)	30.3	-0.1	57.3	2.60	31.9	-4.0	57.9	1.35
Lateral 6 (L)	-26.1	-4.2	62.4	2.82	-32.0	-0.8	53.2	0.68
Area 10 (R)	14.0	56.1	7.3	1.19	11.3	56.1	6.7	2.99
Area 10 (L)	-11.4	55.1	8.4	1.70	-11.5	57.3	3.7	1.74
Medial 11 (R)	8.6	39.4	-16.1	1.94	5.3	43.6	-16.1	2.05
Medial 11 (L)	-6.0	39.2	-16.1	0.56	-6.4	44.2	-16.1	3.41
Lateral 47/11 (R)	32.3	26.6	-12.8	2.74	31.4	30.6	-12.0	2.14
Lateral 47/11 (L)	-32.9	29.1	-10.8	1.85	-33.3	25.9	-12.6	3.74
Temporal								
Posterior 22 (R)	57.8	-36.8	7.1	3.01	59.2	-38.3	9.2	1.60
Posterior 22 (L)	-60.9	-35.1	6.9	1.83	-56.1	-35.4	7.8	0.68
Area 41/42 (R)	57.8	-26.3	13.7	3.92	58.5	-25.2	13.7	2.10
Area 41/42 (L)	-58.1	-22.3	13.7	2.53	-56.9	-23.8	13.7	1.10
Anterior 22 (R)	54.6	-15.0	2.3	3.61	56.9	-12.2	3.2	1.35
Anterior 22 (L)	-54.3	-13.7	3.5	3.60	-53.6	-7.4	1.0	2.64
Parietal								
Area 7 (R)	14.7	-56.5	60.3	2.12	11.9	-57.8	56.5	1.78
Area 7 (L)	-13.7	-55.3	62.1	1.09	-9.2	-59.9	55.2	2.15
Area 5 (R)	7.2	-37.4	55.0	2.54	8.1	-38.5	54.9	2.16
Area 5 (L)	-7.7	-38.8	54.9	4.75	-12.4	-39.4	55.8	2.01
Sensorimotor (R)	20.9	-28.7	56.7	2.37	28.9	-26.1	53.6	1.25
Sensorimotor (L)	-20.7	-31.1	60.8	2.39	-30.6	-25.1	53.7	1.42

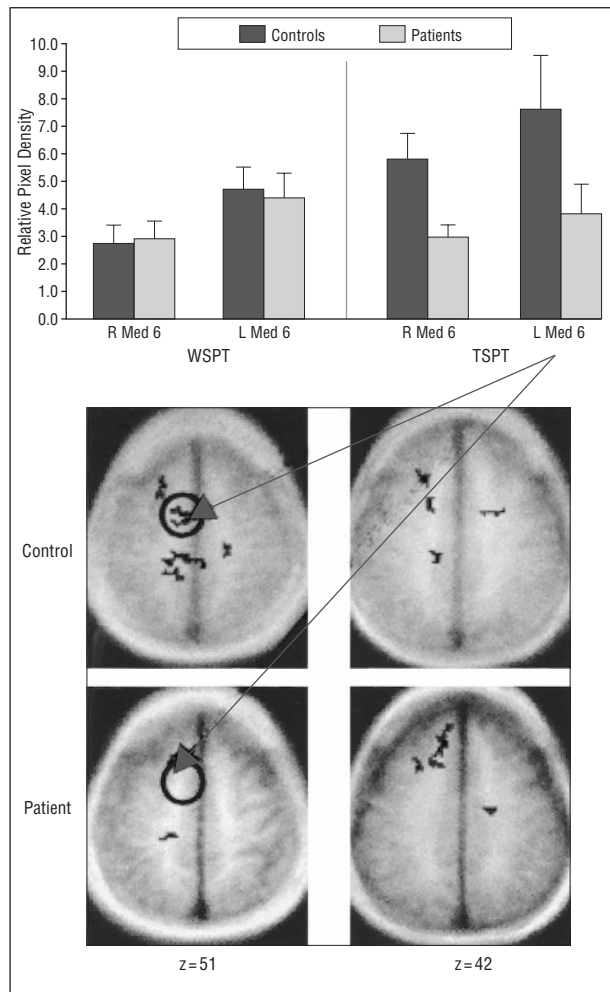
\*WSPT indicates Word Serial Position Task; TSPT, Tone Serial Position Task; and ROI, region of interest.

tive to the WSPT, while there was comparable pixel density in the left hemisphere during both tasks (Table 1). As expected, no ROI in the occipital lobe approached the pixel density threshold of 2 for inclusion in the analyses.

**COMMENT**

The present study indicates that areas in left inferior frontal cortex that are active during verbal working memory

tasks in normal subjects<sup>9,12,30,31</sup> are dysfunctional in schizophrenic patients who have specific performance deficits in verbal but not nonverbal working memory.<sup>1</sup> The WSPT-specific hypoactivity in the left inferior frontal cortex of the schizophrenic group suggests that these language-related regions may be critically related to their verbal working memory deficit. This assertion is supported by the significant correlation between 2 of these ROIs (left areas 44 and inferior lateral 6) and performance on the WSPT assessed



**Figure 3.** Composite activation maps during the Tone Serial Position Task (TSPT) in 2 slices from the control group and schizophrenic group showing the failure of activation in medial area 6. The bar chart (with SE bars) illustrates the hypoactivation in this region that appeared in the patient group only during the TSPT. Both groups showed above-threshold activation in this region during the Word Serial Position Task (WSPT). R Med indicates right medial; L Med, left medial.

before scanning. It is not possible in this study to determine whether the marked failure of activation in the left inferior frontal gyrus during the WSPT scans was caused by abnormalities in the inferior frontal gyrus, failure by patients to engage these areas during the WSPT task because of strategic factors, or a result of failures at earlier stages of processing. Data from previous positron emission tomographic imaging studies of word generation tasks reported comparable activation in patient and control groups in the left inferior frontal gyrus when matched for rate of production, but abnormalities in superior temporal gyrus.<sup>19,20</sup> Thus, under conditions of lexical retrieval, the frontal speech areas appeared normal, but in the present study, which emphasizes encoding and maintenance, these areas appear dysfunctional. It is important that we failed to observe activation in area 46, a site commonly reported active in other studies of working memory. This may reflect differences in stimuli used in the WSPT and other tasks, and, in addition, the heavy reliance on covert rehearsal during the WSPT, which would favor more inferior and spe-

cifically speech-related regions as compared with the more commonly used "N-back" task.<sup>12</sup>

Other cortical areas also showed signs of abnormal function, including areas activated by the behaviorally spared TSPT. The TSPT provided an opportunity to assess cortical hemodynamic abnormalities on a task that is not impaired in these schizophrenic patients.<sup>1</sup> The 2 areas of TSPT-related activation were in the anterior frontal lobe (area 10) and in the supplementary motor and premotor area of the superior frontal gyrus (medial area 6). Connections between area 10 and the superior temporal gyrus have been observed in the rhesus monkey,<sup>32</sup> but activation in area 10 has not been reported in previous functional imaging studies of auditory processing in humans.<sup>33</sup> In medial area 6, the patients failed to produce increased activation during the TSPT scans, as seen in controls, but showed comparable activation during the WSPT scans. Performance of the TSPT task was not impaired either during scanning or on extensive prescan testing. Therefore, the decreased hemodynamic response in the patient group in medial area 6 during the TSPT cannot be attributed to a performance deficit, as appeared to be the case during the WSPT in the inferior frontal gyrus. Similar cases of hypoperfusion and spared behavior have been previously reported in schizophrenia.<sup>34</sup>

The schizophrenia group consistently produced less temporal lobe activation than the controls during both tasks, although a group difference reached statistical significance only in anterior area 22 bilaterally. These results suggest that, while abnormalities are present in temporal lobe regions in schizophrenia,<sup>35-39</sup> they may not compromise auditory perception and memory during processing of relatively simple stimuli (ie, tones), as demonstrated by the sparing of the TSPT task. The verbal memory processes, which are widely considered essential for comprehension and reasoning,<sup>40,41</sup> may rely more heavily on the frontal areas activated in the control subjects of the present study. Given that the WSPT deficit suggests that verbal encoding and maintenance are disrupted in the patients, the inferior frontal areas may also be critical for these processes. However, these patients were selected on the basis of their relatively good attention, and therefore the results must be generalized with caution. In addition, further understanding of the neural systems underlying the distinctions between verbal and auditory processing will be necessary to bear out the present interpretations.

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## REFERENCES

1. Saykin AJ, Gur R, Gur RE, Mozley PD, Mozley LH, Resnick SM, Kester DB, Stafinik P. Neuropsychological function in schizophrenia: selective impairment in memory and learning. *Arch Gen Psychiatry*. 1991;48:618-624.

2. Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P, Gur RC. Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. *Arch Gen Psychiatry*. 1994;51:124-131.
3. Frame CL, Oltmann TF. Serial recall by schizophrenic and affective patients during and after psychotic episodes. *J Abnorm Psychol*. 1982;91:311-318.
4. Calev A, Venebles P, Monk AF. Evidence for distinct verbal memory pathologies in severely and mildly disturbed schizophrenics. *Schizophr Bull*. 1983;9:247-264.
5. Fleming K, Goldberg T, Gold JM, Weinberger DR. Verbal working memory dysfunction in schizophrenia: use of a Brown-Peterson paradigm. *Psychiatry Res*. 1995;56:155-161.
6. Randolph C, Gold J, Carpenter CJ, Goldberg TE, Weinberger DR. Release from proactive interference: determinants of performance neuropsychological correlates. *J Clin Exp Neuropsychol*. 1992;14:785-800.
7. Wexler BE, Stevens AA, Bowers AA, Sernyak MJ, Goldman-Rakic PS. Word and tone working memory deficits in schizophrenia. *Arch Gen Psychiatry*. 1998;55:1093-1096.
8. Awh E, Smith EE, Jonides J. Human rehearsal processes and the frontal lobes: PET evidence. *Ann N Y Acad Sci*. 1995;769:97-117.
9. Cohen JD, Perlstein W, Braver TS, Nystrom LE, Noll DC, Jonides J, Smith EE. Temporal dynamics of brain activation during a working memory task. *Nature*. 1997;386:604-607.
10. Cohen JD, Forman SD, Braver TS, Casey BJ, Servan-Schrieber D, Noll DC. Activation in the prefrontal cortex in a nonspatial working memory task with functional MRI. *Hum Brain Map*. 1994;1:293-304.
11. Kammer T, Belleman M, Guckel F, Brix G, Gass A, Schlemmer H, Spitzer M. Functional MR imaging of the prefrontal cortex: specific activation in a working memory task. *Magn Reson Imaging*. 1998;15:879-889.
12. Smith EE, Jonides J, Koeppe RA. Dissociating verbal and spatial working memory using PET. *Cereb Cortex*. 1996;6:11-20.
13. Damasio AR, Geschwind N. The neural basis of language. *Annu Rev Neurosci*. 1984;7:127-147.
14. Zatorre RJ, Evans A, Meyer E. Neural mechanisms underlying melodic perception and memory for pitch. *J Neurosci*. 1994;14:1908-1919.
15. Robin DA, Tranel D, Damasio H. Auditory perception of temporal and spectral events in patients with focal left and right cerebral lesions. *Brain Lang*. 1990;39:539-555.
16. Zatorre RJ, Samson S. Role of the right temporal neocortex in retention of pitch in auditory short-term memory. *Brain*. 1991;114:2403-2417.
17. Zatorre RJ, Halpern AR. Effect of unilateral temporal lobe excision on perception and imagery of song. *Neuropsychologia*. 1993;31:221-232.
18. Wood FB, Flowers D. Hypofrontal vs. hypo-sylvian blood flow in schizophrenia. *Schizophr Bull*. 1990;16:413-424.
19. Fletcher PC, Frith C, Grasby PM, Friston KJ, Dolan RJ. Local and distributed effects of apomorphine on fronto-temporal function in acute unmedicated schizophrenia. *J Neurosci*. 1996;16:7055-7062.
20. Frith CD, Friston K, Harold S, Silbersweig D, Fletcher P, Cahill C, Dolan RJ, Frackowiak RSJ, Liddle PF. Regional brain activation in chronic schizophrenia patients during the performance of a verbal fluency task. *Br J Psychiatry*. 1995;167:343-349.
21. Dolan RJ, Fletcher PC, Frith CD, Friston KJ, Frackowiak RSJ, Grasby PM. Dopaminergic modulation of impaired cognitive activation in the anterior cingulate cortex in schizophrenia. *Nature*. 1995;378:180-182.
22. Yurgelun-Todd DA, Wasternaux CM, Cohen BM, Gruber BS, English CD, Renshaw PF. Functional magnetic resonance imaging of schizophrenic patients and comparison subjects during word production. *Am J Psychiatry*. 1996;153:200-205.
23. O'Leary DS, Andreasen NC, Hurtig RR, Kesler ML, Rogers M, Arndt S, Cizadlo T, Watkins GL, Boles-Ponto LL, Kirchner PT, Hichwa RD. Auditory attentional deficits in patients with schizophrenia. *Arch Gen Psychiatry*. 1996;53:633-641.
24. Andreasen NC, Rezaei K, Alliger R, Swayze VW, Flaum M, Kirchner P, Cohen G, O'Leary DS. Hypofrontality in neuroleptic-naive patients and in patients with chronic schizophrenia. *Arch Gen Psychiatry*. 1992;49:943-958.
25. Berman KF, Illowsky BP, Weinberger DR. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. *Arch Gen Psychiatry*. 1988;45:616-622.
26. Weinberger DR, Berman KF, Illowsky BP. Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. *Arch Gen Psychiatry*. 1988;45:609-615.
27. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*. Washington, DC: American Psychiatric Association; 1987.
28. Constable RT, Skudlarski P, Mencl E, Pugh RK, Fulbright RK, Lacadie C, Shaywitz SE, Shaywitz BA. Quantifying and comparing region-of-interest activation patterns in functional brain MR imaging: methodology considerations. *Magn Reson Imaging*. In press.
29. Talairach J, Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain: 3-D Proportional System: An Approach to Imaging*. New York, NY: Georg Thieme Verlag; 1988.
30. Paulesu E, Frith CD, Frackowiak RJS. The neural correlates of the verbal component of working memory. *Nature*. 1993;362:342-345.
31. Cohen RM, Semple WE, Gross M, King AC, Nordahl TE. Metabolic brain pattern of sustained auditory discrimination. *Exp Brain Res*. 1992;92:165-172.
32. Petrides M, Pandya DN. Association fiber pathway to the frontal cortex from the superior temporal region in the rhesus monkey. *J Comp Neurol*. 1988;273:52-66.
33. Petrides M, Alivisatos B, Meyer E, Evans AC. Functional activation of the human frontal cortex during the performance of verbal working memory tasks. *Proc Natl Acad Sci U S A*. 1993;90:878-882.
34. Wexler BE. Comments on: Guenther et al [*Eur Arch Psychiatry Clin Neurosci*. 1994;244:115-125]. Diminished cerebral metabolic response to motor stimulation in schizophrenics. *Eur Arch Psychiatry Clin Neurosci*. 1995;246:60.
35. McCarley RW, Shenton ME, O'Donnell BF, Faux SF, Kikinis R, Nestor PG, Jolesz FA. Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. *Arch Gen Psychiatry*. 1993;50:190-197.
36. Chua SE, McKenna P. Schizophrenia—a brain disease? a critical review of structural and functional cerebral abnormality in the disorder. *Br J Psychiatry*. 1995;166:563-582.
37. DeLisi LE, Hoff A, Schwartz JE, Shields GW, Halthore SN, Simhadri GM, Henn FA, Anand AK. Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. *Biol Psychiatry*. 1991;29:159-175.
38. Falkai P, Bogerts B, Schneider T, Greve B, Pfeiffer U, Pilz K, Gonsiorczyk C, Mjtenyi C, Overly I. Disturbed planum temporale asymmetry in schizophrenia: a quantitative post-mortem study. *Schizophr Res*. 1995;14:161-176.
39. Kawasaki Y, Maede Y, Urata K, Higashima M, Yamaguchi N, Suzuki M, Takashima T, Ide Y. A quantitative magnetic resonance imaging study of patients with schizophrenia. *Eur Arch Psychiatry Clin Neurosci*. 1993;242:268-272.
40. Just MA, Carpenter P. A capacity theory of comprehension: individual differences in working memory. *Psychol Rev*. 1992;99:122-149.
41. Baddeley AD. *Working Memory*. New York, NY: Oxford University Press; 1986.