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Brain response abnormalities during verbal learning among patients with schizophrenia

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Abstract

Patients with schizophrenia often show verbal learning deficits that have been linked to the pathophysiology of the disorder and result in functional impairment. This study examined the biological basis of these deficits by comparing the brain response of patients with schizophrenia (n=17) to that of healthy comparison participants (n=14) during a verbal paired-associates learning task using functional magnetic resonance imaging (fMRI). Brain response during new word learning was examined within and between groups in two *a priori* regions of interest, the inferior frontal gyrus and hippocampus, and across the whole brain. In regions of group difference, we also examined the relationship of brain response during learning to later recall of the word pairs. Despite successful matching of levels of word-pair recall, patients' brain response during new learning was abnormal in bilateral regions within the inferior frontal gyrus, a small region in left posterior hippocampus, and other areas within the frontal, parietal and temporal cortex compared to healthy individuals. In some regions, but not in the hippocampus, patients with the most normal brain response also remembered the most word pairs following scanning. Thus, verbal learning deficits found among patients with schizophrenia appear to be related to hypofunction of distributed brain networks.

Keywords

magnetic resonance imaging; functional; hippocampus; inferior frontal gyrus; encoding

1. Introduction

Verbal learning deficits are prevalent in schizophrenia (Saykin et al., 1991), are seen throughout the course of illness (Heaton et al., 2001), have been linked to genetic liability for the disorder (Cannon et al., 1994), and are strongly related to measures of everyday functioning among patients (Green et al., 2000). Understanding the neurobiology of these deficits can help us better understand the pathophysiology of schizophrenia and can perhaps suggest interventions to improve verbal learning and, hence, patients' functional abilities.

Functional neuroimaging studies can be of particular benefit in studying abnormalities during learning because they separate the brain substrate underlying encoding from the substrate

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underlying retrieval, thereby segregating stages that are confounded in most behavioral tests of learning and memory. Previous studies comparing brain response of individuals with schizophrenia to those of healthy participants during the learning stage have shown predominantly frontal and temporal abnormalities (Barch et al., 2002; Eyler Zorrilla et al., 2002b; Jessen et al., 2003; Leube et al., 2003; Ragland et al., 2004; Bonner-Jackson et al., 2005; Ragland et al., 2005; Heinze et al., 2006; Lepage et al., 2006) and a recent meta-analysis confirmed the primary involvement of these regions (Achim and Lepage, 2005).

Hypoactivation of the frontal cortex, especially the inferior prefrontal region, was commonly observed (Hazlett et al., 2000; Nohara et al., 2000; Ragland et al., 2001), although one study found overactivation of this region (Bonner-Jackson et al., 2005). The location and direction of temporal lobe abnormalities have been even less consistent. Despite evidence from lesion and imaging studies linking the hippocampus and parahippocampal cortex to new learning among healthy volunteers and a large literature demonstrating abnormalities of hippocampal size in schizophrenia, this area has not consistently been found to be abnormally activated among schizophrenia patients (Hazlett et al., 2000; Nohara et al., 2000; Ragland et al., 2001; Hofer et al., 2003a, 2003b). Those functional imaging studies that did show differences in medial temporal function between patients and comparison participants generally found underactivation of the hippocampus (Eyler Zorrilla et al., 2000; Barch et al., 2002; Jessen et al., 2003; Leube et al., 2003; Achim and Lepage, 2005; Heinze et al., 2006), but overactivation of the parahippocampal gyrus (Ragland et al., 2004) and hippocampus (Ragland et al., 2005) have also been observed. Level of performance on the learning task may be an important factor to consider in evaluating these discrepancies, as each of these studies accounted for performance issues in a different way.

The purpose of the current study was to replicate and extend our previous findings of functional brain abnormalities during learning (Eyler Zorrilla et al., 2002b) using a verbal, rather than a visual, learning paradigm. In hopes of clarifying discrepant findings in the literature, we first conducted a Region-of-Interest (ROI) analysis that focused on the inferior prefrontal cortex and the hippocampus. We chose these two regions because, among healthy individuals, activation in these areas has been most closely associated with subsequent correct recall and recognition of verbal material (as opposed to less consistent relationships with subsequent memory in other encoding-related regions such as the medial frontal gyrus; (Wagner et al., 1999), and they have been shown to be abnormally activated in previous studies of patients with schizophrenia (Eyler Zorrilla et al., 2000; Hazlett et al., 2000; Nohara et al., 2000; Ragland et al., 2001; Barch et al., 2002; Jessen et al., 2003; Leube et al., 2003; Ragland et al., 2004; Achim and Lepage, 2005; Heinze et al., 2006). ROI analyses yield greater power to detect effects because they reduce the number of voxels examined and, thus, the potential for false positive clusters. We also conducted a less-powerful, exploratory whole brain analysis in order to identify unhypothesized regions of strong difference between groups that could be studied in subsequent work. Given patients' known deficits in new learning, for each of these approaches, we examined brain activity during learning of novel verbal associates in contrast to either further learning of previously-seen associates or to processing of a low-level fixation stimulus. To help interpret observed group differences, we examined the correlation of patient and comparison participant post-scan recall performance with mean activation within the regions of significant group difference. We predicted that patients would show hypoactivation of the inferior prefrontal cortex and the hippocampus compared to healthy individuals, and that those patients with the greatest brain response in these regions would remember the most items on a subsequent cued recall task.

2. Methods

2.1. Participants

Patients were recruited from Board-and-Care homes (assisted living facilities) and outpatient clinics in the San Diego, CA area based on chart diagnoses and were diagnosed with DSM-IV schizophrenia or schizoaffective disorder by means of the Structured Clinical Interview for the DSM-IV (American Psychiatric Association, 1994). Twenty-two patients were scanned; one was excluded due to image artifacts and 4 were excluded due to excessive movement (i.e., met *a priori* criterion of visually noticeable motion on more than 1/3 of time points). The excluded patients were not significantly different from the included patients on age, duration of illness, education, Hopkins Verbal Learning Test immediate recall T-scores, or accuracy of recall of the word pairs presented during scanning (effect sizes ranged from $\eta^2 = 0.0003$ to 0.05). Of the 17 patients included in the study, 2 were women, all were right-handed, and 5 were diagnosed with schizoaffective disorder and 12 with schizophrenia (9 paranoid subtype, 2 disorganized, and 1 residual). Patients' mean (SD) age was 47.2 (11.3) years, mean (SD) education was 13.5 (2.0) years, and mean (SD) duration of illness was 22.9 (12.9) with none having late onset of the disorder (i.e., >40 years old at onset). All patients were stably medicated at the time of the scan (i.e., no change in medication in the past 6 weeks), 16 on atypical antipsychotics (7 olanzapine, 7 risperidone, 1 quetiapine, and 1 ziprasidone) and 1 on trifluoperazine. Two patients also were taking anti-depressant medications (1 paroxetine and 1 bupropion). The patient group was free of current substance dependence or abuse, and had no history of neurologic illness or head injury with loss of consciousness greater than 30 minutes. Based upon neuropsychological testing conducted within 6 weeks of the MRI scan, this group of patients showed mild impairment on measures of delayed verbal list recall as measured by the Hopkins Verbal Learning Test (HVLT; (Brandt, 1991)); mean (SD) *T*-score = 33.2 (13.5)).

Healthy comparison (HC) participants were recruited by word-of-mouth and posted fliers and were free of any self-reported mental or neurologic illness, current substance dependence or abuse, or history of head injury with loss of consciousness. Of the 14 volunteers, 4 were women and all were right handed. The mean (SD) age of the HC group was 45.5 (16.2) years, and the mean (SD) education was 14.1 (2.4) years. There were no significant differences between the patient and HC groups on age ($t = -0.35$, $df = 29$, P (2-tailed) = 0.73), education ($t = 0.78$, $df = 29$, $P = 0.44$), or gender distribution ($\chi^2 = 1.4$, $df = 1$, $P = 0.24$).

The UCSD Human Subjects Committee approved the study, and each participant gave written consent to participate in the experiment. Patients' decisional capacity was assessed with the MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR; (Appelbaum and Grisso, 2001)) and only those with adequate understanding of the protocol were scanned. All participants received monetary compensation (\$25) for participating in the experiment, which took approximately one hour to complete.

2.2. Verbal Paired Associates Task

During scanning, participants viewed 32 pairs of associated nouns and were instructed to "learn which words go together, so that when I show you the first word in the pair, you can tell me the second word in the pair." In an effort to match the performance of schizophrenia patients to that of the healthy participants, patients with schizophrenia were presented with more highly associated target words (as determined by norms provided by Nelson et al (1998)), but saw identical cue words. For example, the HC participants saw Bed-BUG, and the schizophrenia participants saw Bed-SLEEP. The target words shown to HC and schizophrenia participants were not statistically different (range of effect sizes: partial $\eta^2 = 0.001$ to 0.03) on concreteness or imageability (Wilson, 1988), word frequency (Kucera and Francis, 1967), or number of

syllables. The two words in each pair were presented simultaneously, one above and one below the center of the screen, for a duration of 5 seconds, with the cue word always presented on top. In addition to learning the word pairs, participants were asked to indicate which of the two words was capitalized by pressing one of two buttons on a computer mouse, and the position of the capitalized word was counterbalanced. This task served to ensure that each stimulus pair was attended to by the participants. Half of the pairs had been presented prior to scanning, and learned to a criterion of at least 10 out of 16 (63%) pairs recalled successfully (Old pairs), and half had not been seen prior to scanning (New pairs). The 10/16 criterion for Old pairs was chosen based on pilot testing as a level that would likely be achieved by most participants after no more than 3 list exposures and would not result in a ceiling effect of overlearning. Old and New pairs were also matched on mean concreteness, and imageability (Wilson, 1988), word frequency (Kucera and Francis, 1967), number of syllables for both the cue and target word, and mean strength of association (Nelson et al., 1998) between the cue and target. Old and New pairs were interspersed in blocks of 4 trials each. Blocks of visual cross-hair fixation that varied in length between 8 and 16 seconds also were included. The order of blocks was fixed and pseudo-random. After scanning, self-paced cued recall for the word pairs was assessed by recording the participant's verbal response to each cue presented alone. The following measures of performance were assessed: accuracy of recall during pre-scanning exposure, trials to reach pre-scanning criteria, accuracy and reaction time for indicating capitalization during scanning, and recall accuracy following scanning. Each participant completed two runs of the paired associate task, separated by about 12 minutes, during which time a high-resolution anatomical scan was collected. A unique set of words was used for both the Old and New pairs for Run 2, and the order of blocks differed in the two runs. Stimuli were projected onto a screen placed in front of the scanner, and viewed through a small mirror placed above the participant's eyes. The behavioral data were recorded via a fiber optic button box and collected on a Dell Laptop, using MicroExperimental Lab2 software (Psychological Software Tools, Pittsburgh, PA).

2.3. Scanning procedure

Scanning was carried out in a Siemens Vision Magnetom 1.5 Tesla magnet located in Thornton Hospital at UCSD. Foam pads placed at participants' temples limited head movement, and vision was corrected, when necessary, with all-plastic framed glasses. Anatomical images were collected at 1mm³ resolution using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) protocol (TR = 11.4 sec, TE = 4.4, and flip angle = 10 degrees, 180 slices, FOV = 256). During the verbal paired associates learning task, 69 whole brain images were collected with a 4mm slice thickness and a 4 × 4 mm in-plane resolution. Every 4 seconds, 32 axial slices (TR=4000 msec, TE=40, flip angle=90 degrees) were collected, using a gradient-recalled echoplanar imaging sequence to measure the blood oxygenation level dependent (BOLD) signal.

2.4. Image analysis

Structural and functional image analysis was carried out using the Analysis of Functional NeuroImages (AFNI) software package. Each individual's functional time series was examined for artifactual images caused by random scanner noise (present in an average of only 0.4% of images and corrected on a slice-by-slice basis by replacement with an average of the preceding and following time points), and then were corrected for motion by alignment to that base image which necessitated the least interpolation using a three-dimensional iterated, linearized, weighted least-squares method with Fourier interpolation. Following automated motion correction, the time series was examined for uncorrected motion outliers, and time-points with visually-obvious motion were excluded from statistical analysis. Alignment of the functional dataset to the anatomical dataset also was inspected visually and corrected, if necessary, by repositioning the functional data. The association between measured BOLD signal and the

verbal paired associates task was calculated with multiple regression using the program 3dDeconvolve. The following predictors were included in the model: a constant, a linear trend, 6 parameters indicating the degree of motion correction performed in 3 translational planes and 3 rotational angles, and stimulus functions indicating the occurrence of New and Old word pairs. Linear contrasts between New vs. Old pairs and New pairs vs. fixation baseline were calculated. The contrast between New and Old pairs was designed to selectively identify areas of the brain related to novel learning, while controlling for more general cognitive processes such as visual attention, phonemic and semantic processing, and motor response. Initial analyses of this dataset indicated, however, that there was little difference in activation patterns in either group between New and Old words (data available upon request), perhaps because the chosen learning criterion was too lax and further intentional learning of the Old words occurred during scanning. Thus, we chose to use the more robust, but less specific, contrast of New word pairs vs. fixation for the group analyses because it would identify areas important in the processing of novel verbal associations. The fit coefficient for the contrast was averaged across the two runs for each subject and this average brain response value was the dependent variable for subsequent analyses.

2.4.1. Region-of-Interest (ROI) analysis—Based on previous studies of learning-related brain response abnormalities among patients with schizophrenia, group differences were examined in two ROIs: the inferior frontal gyrus (IFG) and the hippocampus. Given the large size of the IFG and likely anatomical and functional heterogeneity of this region, we elected to define the ROI in standard atlas space (Talairach and Tournoux, 1988), as operationalized by the Talairach Daemon (see Figure 1). The statistical images for each participant were blurred with an 8mm Gaussian filter, transformed into standard space and masked with the IFG ROI (volume = 74944 mm³; see Figure 1). We then searched within this region for significant clusters of learning related activity in both patients and comparison participants, and clusters of significant difference between the groups. Clusters were considered significant if each voxel was significant at $P \leq 0.05$ ($t \geq 2.12$, $df = 16$ for patients, $t \geq 2.16$, $df = 13$ for controls, $t \geq 0.950$, $df = 29$ for group comparison) and had a volume of at least 1472 mm³. This threshold/volume combination was determined by Monte Carlo simulation (AlphaSim program) to protect a ROI-wise probability of false positives of $P < 0.05$.

For the hippocampus, we traced each participant's hippocampus in order to increase the specificity of the ROI in this small, but important brain region. For all but one patient participant (due to artifacts in the anatomical image), left and right hippocampal regions of interest were drawn on each participant's high-resolution MPRAGE brain image in sagittal view, rotated into alignment with the anterior commissure - posterior commissure (AC-PC) plane. Following the guidelines of Insausti et al (1998), the tracing began laterally at the appearance of hippocampal tissue in the lateral ventricle. The drawing continued medially, observing the separation between the hippocampal region and the amygdala and including the alveolus. Hippocampal ROIs were re-evaluated in coronal view with special attention paid to the following: (1) the separation between the hippocampus and the posterior aspect of the pulvinar nucleus of thalamus, (2) the separation between the subiculum (which was included in the hippocampal region) and the entorhinal cortex (which was excluded from the hippocampal region measurement), and (3) white matter/grey matter segmentation. Tracing was conducted by two trained technicians who achieved high intraclass correlations (absolute agreement ICC = 0.78 for right hemisphere, 0.72 for left hemisphere) on a set of 5 reliability images. An example of this ROI for a single subject is shown in Figure 1.

Functional activation in the hippocampus was examined for unblurred statistical maps in two ways. First, the mean brain response of each participant across the entire region was calculated on AC-PC aligned images. This analysis uses all the available data within the ROI and can be conducted without warping images into standard space, but differential effects in subregions

might be washed out by the averaging procedure. Thus, in parallel to the IFG analysis, we secondly searched for clusters of task-related activity in both patients and comparison participants, and clusters of significant difference between the groups, within a 6528 mm³ hippocampal region that was created by transforming the hand-drawn ROIs into standard atlas space and classifying a voxel as falling within the hippocampus if it was located in the hippocampus in 9 out of 14 controls and 10 out of 16 patients. These thresholds were used because the resulting region represented >60% of the participants in each group and resulted in a cluster of equal volume across groups; the conjunction of these two masks was then used as the final mask. Clusters were considered significant if each voxel was significant at $P \leq 0.05$ ($t \geq 2.12$, $df = 16$ for patients, $t \geq 2.16$, $df = 13$ for controls, $t \geq 0.950$, $df = 29$ for group comparison) and had a volume of at least 192 mm³, protecting a ROI-wise probability of false positives of $P < 0.05$.

2.4.2. Whole brain analysis—As an exploratory analysis, we also examined task-related brain response in each voxel of the brain using single-sample (for each study group) and independent samples (for the comparison of study groups) t -tests. Regions were considered activated if each voxel was significant at $P \leq 0.05$ ($t \geq 2.12$, $df = 16$ for patients, $t \geq 2.16$, $df = 13$ for controls, $t \geq 0.950$, $df = 29$ for group comparison) and the cluster had a volume of at least 4736 mm³. This threshold/volume combination protected a whole-brain probability of false positives of $P < 0.05$.

2.4.3. Correlations with performance—To aid interpretation of observed group differences, we calculated the Pearson's correlation of mean brain response in clusters of significantly different activation to later cued-recall performance. This addresses the potential criticism that the identified regions could differ between patients and comparison participants for reasons unrelated to the cognitive process of learning. This was done separately for patients and HC participants and then correlations were compared between patients and HC subjects with a z -test. We also examined the relationship of age, duration of illness and capitalization accuracy to both recall accuracy and brain response to see if these variables might moderate any observed relationship between recall accuracy and brain response, or have an informative relationship with brain response that might explain individual differences in activation. Because capitalization accuracy was not normally distributed in either group, we tested for relationships with this variable using Spearman's correlations; all other variables met standard normality assumptions.

2.4.4. Other group comparisons—Performance scores were averaged across the two runs for each subject and these values were compared between patients and HC participants using an independent samples t -test. The degree of correction made by the automated motion correction algorithm in each of 3 translational directions and 3 rotational axes at each time point was squared and summed across the entire functional run for each participant, averaged across runs, and the mean of these averages calculated separately for translation and rotation. An independent samples t -test was used to compare the indices between patients and HC participants. To evaluate the degree to which motion indices may have been correlated with the occurrence of either stimulus type (word pairs vs. fixation) or change in stimulus type (block onset), we calculated the Pearson correlations between each participant's degree of motion correction needed in each translational direction and rotational axis with both a reference vector indicating stimulus type and one indicating the start of new blocks of trials. These correlations were converted to Fisher's Z scores, averaged across runs, and then compared with independent samples t -tests between patients and comparison participants. All comparisons were considered significant at $P \leq 0.05$ two-tailed.

3. Results

3.1. Task performance

Despite the fact that patients were impaired on a clinical measure of delayed verbal recall, our manipulation of associative strength was successful in matching performance levels during scanning between schizophrenia and HC participants (Table 1). Both groups were actively engaged in the task during scanning (approximately 90% accuracy of judging which word was capitalized), had similar time on task (so-called “duty cycle”) as indicated by reaction time, and were able to recall about 60% of the New word pairs when presented with a cue following scanning.

3.2. Motion

After excluding participants with high levels of motion from the schizophrenia group (as described above), there were no remaining significant group differences in overall degree of motion, as indexed by the mean translational (schizophrenia mean (SD): 1.21 (0.9) mm; HC: 1.05 (0.8) mm; $t = -0.52$, $df = 29$, $P = 0.61$) or rotational (schizophrenia: 1.0 (0.7) degrees; HC: 0.72 (0.4) degrees; $t = -1.13$, $df = 29$, $P = 0.27$) motion correction made by the automated algorithm. There were also no differences between the groups in degree of task-related motion, which was minimal in both groups (schizophrenia range of r 's: 0.05 to 0.14; HC: 0.04 to 0.07).

3.3. Inferior Frontal Gyrus ROI

Significant clusters of task-related brain response within the IFG search region were found in both the HC participants and in patients with schizophrenia (Table 2; Figure 3). Both groups strongly activated bilateral regions in more dorsolateral parts of the IFG. Schizophrenia patients, however, showed aberrant response bilaterally in more ventrolateral regions, in which their brain response was greater during fixation than during learning, significantly so on the right side. Correspondingly, bilateral areas of significant difference between the two groups (primarily in ventrolateral regions, Brodmann's areas 45 and 47) were observed that were mainly due to the existence of a strong task-related response among the healthy individuals and either no response or a contrasting fixation-related response among patients with schizophrenia. When the relationship of later cued-recall performance to mean brain response in these clusters of differential activation was examined, we found that brain response in these clusters of differential IFG activation was not significantly related to New word recall performance in either group, although there were moderate, non-significant positive correlations among the schizophrenia group for Left IFG BA45 and Right IFG BA47 (Table 5). Capitalization accuracy, duration of illness and age were not significantly related to brain response in any of the clusters, and all of the effect sizes were small.

3.4. Hippocampal ROI

There were no significant differences between groups in the average brain response across all voxels within each hemisphere of the hippocampus, with both groups showing a small and highly variable response (Left hemisphere: HC mean (SD) percent signal change: 0.33 (0.8), schizophrenia patients: 0.21 (1.1); $t = 0.34$, $df = 28$, $P = 0.73$; Right hemisphere: HC participants: -0.10 (0.8); schizophrenia patients: 0.02 (1.4); $t = -0.275$, $df = 28$, $P = 0.78$). In the search-region approach comparable to that used for the IFG, we found small clusters of significant hippocampal brain response within each of the study groups and an area of significant differential activation in the left hemisphere (Table 3; Figure 3). Specifically, the task-related hippocampal brain response of patients with schizophrenia occurred more anteriorly, with a significant response in the right hemisphere, whereas the response of HC individuals occurred more posteriorly in the left hemisphere. The left posterior cluster was significantly more active in HC than schizophrenia patients. The relationship of brain response

within this cluster to later recall performance in both groups was small and non-significant (Table 5). Similarly, capitalization accuracy, age, and duration of illness showed no relationship to activity of this region among either group.

3.5. Whole brain analysis

Whole brain analysis revealed several areas of task-related brain response outside of the *a priori* regions of interest and confirmed the IFG ROI findings (Table 4; Figure 4). Specifically, healthy individuals activated a large bilateral region that spanned cerebellum, temporo-occipital areas, parahippocampus, and areas of the lateral prefrontal cortex during novel word-pair learning compared to fixation. Schizophrenia patients showed somewhat similar temporo-occipital brain response bilaterally, but had more areas that were preferentially engaged during fixation, including: midline precuneus, medial frontal gyrus, and right middle and superior temporal gyrus. When the two groups were statistically compared, the regions of greatest difference between them were: midline precuneus/posterior cingulate/cerebellum, left IFG and basal ganglia, left fusiform and middle temporal gyrus, and midline superior and medial frontal gyrus. As can be inferred by these verbal labels and from the Figure, many of the clusters were broad and spanned several distinct regions. It should be noted that the subcomponents of these large clusters are not necessarily protected individually from false positives. In the parietal and frontal clusters, the healthy individuals showed a positive task-related response; whereas, the patients' mean response was near zero. In the left fusiform / medial temporal gyrus cluster, both groups showed a positive brain response, with the HC group showing a greater magnitude of response. Within the patient group, those with greater recall accuracy had greater mean activation within the three frontal and temporal clusters, but not within the cuneus / posterior cingulate / cerebellum cluster (Table 5). Within the comparison group, there was a trend for mean activation within the fusiform / medial temporal gyrus cluster to relate positively to recall accuracy ($r = 0.49$, $df = 14$, $P = 0.07$), but response in the other clusters was not significantly associated. The recall correlations were not significantly different between groups, although there was a trend for the correlation to be larger among patients in the midline middle and superior frontal gyrus cluster ($z = 1.8$, $P = 0.08$). Capitalization accuracy, age, and duration of illness were not significantly related to activity within any of the clusters of differential activity, and all the effect sizes were small.

4. Discussion

During encoding of verbal paired associates, patients with schizophrenia had diminished brain response to study words compared to healthy individuals in bilateral IFG and a small area within the left hippocampus. These abnormalities were observed despite evidence that our experimental manipulation resulted in equivalent average recall performance in the study groups. Our hypotheses regarding the relationship between activation and recall performance were only partially supported. Within the IFG clusters of differential brain response, there were non-significant positive associations for two regions, such that patients with diminished brain response within the left IFG BA45 and right IFG BA47 clusters were less able to remember word pairs after scanning. Furthermore, there was a significant positive association between activation within an IFG cluster identified in the whole brain analysis, suggesting that ventrolateral prefrontal cortex underactivation may be important for explaining the well-documented verbal learning deficits associated with schizophrenia. Within the small cluster of differential activation in the hippocampus, there was no significant relationship with later recall performance in either group.

Our results in the ventrolateral IFG region are consistent with most previous neuroimaging studies of verbal learning that compared patients with schizophrenia to healthy individuals (Hazlett et al., 2000; Nohara et al., 2000; Ragland et al., 2001). Given that this region appears

to be sensitive to encoding strategy (e.g., deep vs. shallow processing) among healthy individuals (Demb et al., 1995; Otten et al., 2001) and among patients with schizophrenia (Bonner-Jackson et al., 2005; Ragland et al., 2005), it seems likely that our finding of hypoactivation of this region reflects less use of semantic elaboration strategies during learning among the patients in the current study. Although the word pairs were semantically related, responses to them were made based on orthographic features (i.e., capitalization). In contrast to Bonner-Jackson et al.'s (2005) finding of greater involvement of BA45 and BA10 and Ragland et al.'s (2005) finding of no abnormality in ventrolateral activation among patients compared to healthy individuals when a semantic vs. phonemic strategy was encouraged, the present findings of underactivation suggest that hypofrontality is likely to be found when strategy is not constrained or the directions encourage shallow processing, whereas normalized function or even hyperfrontality is more likely to be observed under conditions in which deep semantic encoding is encouraged and necessary for the response. In regard to material specificity, we had not observed similar IFG deficits in our previous study of picture encoding (Eyler Zorrilla et al., 2002b), suggesting that this prefrontal region may be more involved in verbal than visual learning deficits among patients.

Our hypothesis of hippocampal abnormalities during encoding of word pairs among patients was partly supported. Although mean hippocampal brain response did not distinguish the study groups, examination of the voxel-wise results suggested differential anterior/posterior patterns of activation, and we did find a small region of the left posterior hippocampus that was more active among healthy individuals than patients with schizophrenia. This is consistent with our previous picture encoding study (Eyler Zorrilla et al., 2000) and the results of other word encoding studies (Barch et al., 2002; Jessen et al., 2003), but in contrast to overactivation of hippocampus during deep vs. shallow encoding seen by Ragland et al (2005). It has been suggested (Ragland et al., 2004) that temporal lobe overactivation is related to frontal hypoactivity due to reciprocal functional connections between the two regions, but the current study found underactivation in both hippocampus and ventrolateral prefrontal cortex. Hippocampal overactivity has also been postulated to relate to abnormalities of lexical processing and increased semantic spread of activation among patients (Ragland et al., 2005). In the current study, the use of strong associates and shallow encoding processes in the patient group may have minimized these effects and thus revealed a deficit in activity. It should be emphasized that, just as functional imaging studies of frontal lobe response during working memory tasks have clearly shown (Van Snellenberg et al., 2006), the direction of functional abnormality in schizophrenia during learning is likely to be a complex function of task demands. Contrary to our expectation and to our previous findings with a picture learning task (Eyler Zorrilla et al., 2002a), we did not find a relationship between brain response in this left hippocampal region and later recall performance among either patients or healthy individuals. Nor were there associations between left hippocampal brain response and other task or demographic factors. This suggests that the observed hippocampal deficits may be related to aspects of the complex verbal learning task that do not directly support later recall performance.

Based on a whole brain analysis, we observed group differences in several unhypothesized regions including cuneus/posterior cingulate/cerebellum, fusiform gyrus / middle temporal gyrus, and midline medial and superior frontal gyrus. Consistent with the region of interest analysis, brain response in the whole brain cluster that included the left IFG was lower among patients than comparison subjects and positively related to later recall performance. Similar positive correlations were seen in the midline cluster that spanned both medial frontal and superior frontal gyrus and in the fusiform gyrus / middle temporal gyrus region. Within the medial prefrontal cluster the low-performing patients showed a fixation-related response or deactivation, whereas higher-performing patients and comparison subjects generally did not engage this region. In contrast, in the temporal lobe cluster, low performing patients showed little brain response while higher performing patients showed more normal, positive response.

The positive association between later recall and brain response in these regions suggests that they are also important for understanding novel learning deficits among schizophrenia patients and deserve further, more focused investigation.

Some potential limitations of the present study should be considered when interpreting our findings. First, we chose to contrast novel word pair learning to a fixation condition because of the lack of strong brain response differences when novel word learning was directly compared to further learning of previously-learned pairs. Use of the New pairs vs. fixation contrast was advantageous because it strongly activated multiple brain areas in both study groups, but also raises the issue of whether group differences in brain response were truly related to the cognitive process of learning or to some other aspect of the task (e.g., phonemic decoding, semantic recall of word meaning, capitalization judgments, or motor output). These concerns are mitigated to some degree by our finding that, in some of the regions of significant difference between patients and comparison participants, patients with diminished brain response remembered fewer word-pairs after scanning, suggesting that these areas of abnormality play some role in the verbal learning deficits often seen among patients with schizophrenia. Second, we chose to use more highly-associated target words for the patients than the HC participants, while maintaining equivalence on other word attributes such as frequency, concreteness, imageability, and number of syllables. This had the desired effect of matching the difficulty level of the task and variability in task performance between the two groups, but may have resulted in un-matching of the information processing stream involved in learning the pairs. It could thus be argued that the observed hypoactivation was related to greater automaticity of encoding the strong associates seen by the patients. Although this possibility cannot be ruled out, our instructions did encourage both patients and controls to use intentional associative strategies and pairs were viewed for 5 seconds, thus potentially minimizing any benefit of quicker automatic processing of the strongly associated words that might have led to a reduced IFG response not related to schizophrenia learning pathology. Furthermore, because schizophrenia patients are known to have learning deficits, any method of performance matching is likely to result in unmatching of at least one other factor. Thus, although the results of this study must be interpreted in the context of other studies that have controlled for other potential confounds, we have shown that deficits in activation are not completely driven by motivation or reaction time differences. Other potential limitations include a relatively small sample size, which would decrease our power to detect small effects, and the use of multiple statistical tests, which might increase our rate of Type I error.

A strength of this study is the fact that task performance was equivalent between the two study groups, thus arguing against the criticism that hypoactivation in the observed regions was due to differences in timing of responses or lack of engagement in the task by patients. In addition, we carefully ruled-out group differences in several types of motion that might have led to apparent, but non-cognitive, brain response differences. Finally, we took advantage of the intra-group heterogeneity of word-pair recall accuracy to examine the relationship of brain response during encoding to later recall performance. The observation that hypothesized ventrolateral prefrontal regions and unhypothesized midline frontal and left temporal regions were more active among patients who later remembered more words increased our confidence in the validity of these observed differences in activation between patients and healthy individuals. Thus, this study adds to the body of knowledge that suggests that abnormality of ventrolateral prefrontal brain systems likely contributes to cognitive and functional deficits among patients with schizophrenia. Other regions, such as the hippocampus, medial and superior frontal gyrus, and left fusiform gyrus may also be functionally impaired, but the nature of these impairments and their association with learning deficits deserves further study. Specifically, multivariate analyses that emphasize the inter-relationships among these brain regions may prove more illuminating in the search for the underlying pathophysiology of learning deficits in schizophrenia.

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Figure 1.

Regions of interest (ROIs) examined in the study, shown in standard Talairach & Tournoux atlas space. Blue = inferior frontal gyrus, Red = hand-drawn hippocampal ROI of a representative participant transformed into standard space and resampled to 4mm^3 resolution. ROIs are superimposed on axial slices that span from 25 Inferior to 31 Superior, in 4mm increments.

Figure 2.

Brain response to All pairs vs. Fixation in the inferior frontal gyrus ROI.

Unthresholded signed effect sizes for a single-sample t -test are presented in the top panel for the HC participants and the middle panel for patients with schizophrenia. Warm colors represent areas more active during word pair learning than fixation and cool colors represent areas more active during fixation than during word pair learning. Results are overlaid onto axial slices of a high-resolution anatomical that span from 21 Inferior to 35 Superior in 4mm increments. The bottom panel shows the thresholded and clustered results (protecting an ROI-wise $P \leq 0.05$) of the independent-sample t -test comparing HC participants to those with schizophrenia, with warm colors representing areas of greater task-related brain response

among healthy individuals. Results are overlaid onto axial slices of a high-resolution anatomical that span from 17 Inferior to 15 Superior in 4 mm increments.

Figure 3.

Brain response to All pairs vs. Fixation in the hippocampal ROI.

Unthresholded signed effect sizes for a single-sample *t*-test are presented in the top panel for the HC participants and the middle panel for patients with schizophrenia. Warm colors represent areas more active during word pair learning than fixation and cool colors represent areas more active during fixation than during word pair learning. Results are overlaid onto coronal slices of a high-resolution anatomical that span from 7 Posterior to 35 Posterior in 4 mm increments. The bottom panel shows the thresholded and clustered results (protecting an ROI-wise $P \leq 0.05$) of the independent-sample *t*-test comparing HC participants to those with schizophrenia, with warm colors representing areas of greater task-related brain response

among healthy individuals. Results are overlaid onto two coronal slices of a high-resolution anatomical at 27 Posterior and 31 Posterior.

Figure 4.

Whole brain response to All pairs vs. Fixation in the HC participants (top left) and patients with schizophrenia (top right) displayed as signed effect sizes and overlaid onto axial slices of a high-resolution anatomical image spanning the whole brain in 8 mm increments. Warm colors represent areas more active during word pair learning than fixation and cool colors represent areas more active during fixation than during word pair learning. The bottom panel shows the independent-sample *t*-test comparison of HC participants to schizophrenia patients, with warm colors representing areas of greater task-related brain response among healthy individuals, overlaid onto a 3-dimensionally rendered image with sagittal slices cut out at 42 Left, 30 Left, 4 Left (midline), and 25 Right. Images have been clustered and thresholded so as to protect a whole-brain probability of false positives less than or equal to 0.05.

Table 1
Task Performance in Patients with Schizophrenia (n = 17) and HC Participants (n = 14)

Measure	HC Participants			Schizophrenia Patients			t	P
	N	Mean	SD	N	Mean	SD		
Pre-scan Recall (Proportion Correct)	14	0.67	0.12	17	0.70	0.15	-0.57	0.57
Trials to Reach Pre-scan Criterion	14	1.75	0.99	17	1.97	1.1	-0.58	0.56
Capitalization Identification During Scan (Proportion Correct)	14	0.97	0.04	16	0.89	0.18	1.7	0.10
Capitalization Identification During Scan (Reaction Time in ms)	13	1429	449	16	1714	657	-1.3	0.19
Post-scan Recall - All Pairs (Proportion Correct)	14	0.72	0.17	17	0.71	0.18	0.24	0.81
Post-scan Recall - Old Pairs (Proportion Correct)	14	0.85	0.13	17	0.84	0.14	0.32	0.75
Post-scan Recall - New Pairs (Proportion Correct)	14	0.60	0.22	17	0.56	0.25	0.40	0.69

Table 2
Clusters of significant brain response within the inferior frontal gyrus search region for the contrast of New pairs vs. fixation

Direction of Response	Hemisphere	Subregion (Brodmann's Area)	Volume (in μ l)	Coordinates of Maximum Intensity Voxel	T-score for Maximum Intensity Voxel	η^2 (Mean $\pm$ SEM)
HC Participants Learn > Fixation	L	Dorso- and ventro-lateral (9,44,45 & 47)	17664	47L, 19A, 14S	7.6	0.46 $\pm$ 0.01
	R		4032	49R, 5A, 26S	5.9	0.48 $\pm$ 0.02
Schizophrenia Patients Learn > Fixation	L	Dorsolateral (9 & 44)	4928	49L, 9A, 26s	5.1	0.37 $\pm$ 0.01
	R		1472	46R, 3A, 27S	3.2	0.29 $\pm$ 0.01
	R	Dorsolateral (9 & 44)	1728	34L, 17A, 13I	-5.9	-0.38 $\pm$ 0.02
	*L		4480	46L, 30A, 7S	3.9	0.21 $\pm$ 0.01
	L	Ventrolateral (45)	2432	31L, 24A, 9I	4.0	0.23 $\pm$ 0.01
	*R	Ventrolateral (47)	1920	35R, 17A, 13I	3.8	0.20 $\pm$ 0.01

Note: L = Left, R = Right, A = Anterior, P = Posterior, S = Superior, I = Inferior,

* = Brain response correlated with recall performance among patients at trend level (r 's = 0.38)

Table 3
Clusters of significant brain response within the hippocampal search region for the contrast of New pairs vs. fixation

Direction of Response	Hemisphere	Volume (in μ l)	Coordinates of Maximum Intensity Voxel	T-score of Maximum Intensity Voxel	Eta ² (Mean $\pm$ SEM)
HC Participants					
Learn > Fixation	L	384	22L, 32P, 1I	3.4	0.38 $\pm$ 0.03
Schizophrenia Patients					
Learn > Fixation	R	448	28R, 12P, 18I	3.2	0.29 $\pm$ 0.03
HC > Schizophrenia	L	384	22L, 32P, 2I	3.2	0.21 $\pm$ 0.02

Note: L = Left, R = Right, A = Anterior, P = Posterior, S = Superior, I = Inferior

Table 4
Clusters of significant brain response across the whole brain for the contrast of New pairs vs. fixation

Direction of	Hemisphere	Region	Volume (in μ l)	Coordinates of Maximum Intensity Voxel	T-score of Maximum Intensity Voxel	η^2 (Mean $\pm$ SEM)
HC Participants Learn > Fixation	L&R	Cerebellum/occipital lobe/fusiform gyrus/precuneus/cuneus/pre & post-central gyrus/middle & inferior prefrontal gyrus/basal ganglia	594368	6L, 35P, 18S	13.2	0.49 $\pm$ 0.002
Schizophrenia Patients Learn > Fixation	L&R	Cerebellum/fusiform gyrus/precuneus/cuneus/medial frontal gyrus/pre & post-central gyrus, inferior frontal gyrus/thalamus	255360	11L, 45P, 16S	9.5	0.42 $\pm$ 0.002
Fixation > Learn	R R Midline Midline	Superior and inferior parietal lobule Parahippocampal gyrus / uncus Precuneus	18304 5888 12992	32R, 42P, 50S 32R, 7P, 27A 1R, 55P, 36S	5.3 4.3 -4.5	0.37 $\pm$ 0.006 0.33 $\pm$ 0.008 0.33 $\pm$ 0.005
HC > Schizophrenia	R Midline/R *L *L *Midline	Medial frontal gyrus Middle and superior temporal gyrus Precuneus/posterior cingulate/cerebellum Inferior frontal gyrus/basal ganglia Fusiform and middle temporal gyrus Superior and medial frontal gyrus	4928 34944 28672 10368 9152	48R, 59P, 22S 8R, 71P, 14S 34L, 15A, 13S 44L, 48P, 9I 4L, 18A, 54S	-5.0 -4.6 4.3 5.3 4.2 4.1	0.33 $\pm$ 0.006 0.36 $\pm$ 0.01 0.20 $\pm$ 0.002 0.21 $\pm$ 0.003 0.23 $\pm$ 0.006 0.20 $\pm$ 0.004

Note: L = Left, R = Right, A = Anterior, P = Posterior, S = Superior, I = Inferior,

* = Brain response significantly correlated with recall performance among patients, $P > 0.05$

Table 5
Pearson's correlations of brain response in clusters of significant difference with performance and demographic variables among both schizophrenia and HC groups

Cluster	Recall Accuracy		Capitalization Accuracy ^a		Age		Illness Duration	
	Schizophrenia (n=17)	HC (n=14)	Schizophrenia (n=16)	HC (n=14)	Schizophrenia (n=17)	HC (n=14)	Schizophrenia (n=17)	HC (n=14)
L Hippocampus	0.17	0.10	-0.05	0.30	0.05	0.04	-0.11	0.04
L IFG BA 45 (ROI)	0.38	0.33	0.17	0.32	-0.07	-0.13	-0.02	-0.13
L IFG BA 47 (ROI)	-0.08	0.17	0.24	0.26	0.09	0.07	0.20	0.07
R IFG BA 47 (ROI)	0.37	-0.14	0.20	-0.33	-0.07	0.48	0.09	0.48
Midline Cuneus / Posterior	0.09	0.28	-0.06	0.33	0.03	0.12	-0.09	0.12
Cingulate / Cerebellum								
L IFG / Basal Ganglia (Whole Brain)	0.48 *	0.11	0.04	0.26	0.20	0.08	-0.03	0.08
L Fusiform / Middle Temporal Gyrus	0.58 *	0.49	0.19	-0.03	0.01	-0.04	-0.18	-0.04
Midline Superior and Medial Frontal Gyrus	0.54 *	-0.11	0.06	0.21	-0.27	0.28	-0.30	0.28

^a Spearman's correlation used

* p < 0.05