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Functional abnormalities of medial temporal cortex during novel picture learning among patients with chronic schizophrenia

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Abstract

Background: Learning deficits are prominent among patients with chronic schizophrenia and are associated with poor everyday functioning. Little is known, however, about the brain physiology underlying these difficulties with encoding new information. **Purpose:** The purpose of the current study was to compare the brain response during novel picture encoding between patients with chronic schizophrenia and healthy individuals using functional magnetic resonance imaging (fMRI). **Methods:** Nine middle-aged patients with DSM-III-R or DSM-IV schizophrenia and 10 age- and education-comparable healthy individuals were studied. Using fMRI, the blood oxygenation level dependent (BOLD) signal was measured during novel picture encoding (experimental condition) and during presentation of a repeated picture (control condition). Encoding-related brain response was examined in both groups and compared between the patient and comparison groups in each voxel within four bilateral search regions (fusiform gyrus, parahippocampal gyrus, hippocampus, and inferior frontal gyrus). **Results:** Despite comparable subsequent ability to recognize the presented pictures, patients with schizophrenia showed abnormal encoding-related brain response in regions of the hippocampus and parahippocampal and fusiform gyri compared to healthy individuals. In medial temporal regions, patients showed greater BOLD response during the control condition (repeated picture) than during the experimental condition (novel pictures). **Conclusion:** Abnormalities of the medial temporal brain systems examined in this study may underlie learning deficits in schizophrenia. Further research is needed to illuminate the role of these brain dysfunctions in poor everyday functioning and their amenability to treatment.

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1. Introduction

Deficits in learning and memory are among the most prominent neuropsychological dysfunctions in

schizophrenia (Saykin et al., 1991). Patients with schizophrenia have difficulty learning new information in both visual and verbal modalities, and such deficits are strongly related to poor functional outcome (Green et al., 2000). Poor learning has been correlated with the size of medial temporal and frontal cortical regions, as well as with resting blood flow and metabolism in these regions (Maher et al., 1995; Nestor et al., 1993; Seidman et al., 1994;

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DeLisi et al., 1991). Such correlative designs, while suggestive, do not provide direct evidence that functional deficits of temporal and frontal regions are responsible for impaired learning among patients with schizophrenia.

Functional neuroimaging studies have directly compared brain activation between patients with schizophrenia and comparison subjects during recall or recognition memory. Although these studies, using a variety of tasks, have been fairly consistent in demonstrating abnormalities among the patients, they have shown divergent patterns of regional deficits that include frontal, temporal, hippocampal, thalamic, cerebellar, and parietal abnormalities (Andreasen et al., 1996; Busatto et al., 1994, 1995; Crespo-Facorro et al., 1999; Ganguli et al., 1997; Gur et al., 1994; Heckers et al., 1998, 1999; Ragland et al., 1998; Wood and Flowers, 1990). Studies combining encoding and retrieval have more consistently found abnormal striatal, frontal, and temporal metabolism (Shihabuddin et al., 1998; Hazlett et al., 2000) and abnormal frontal, temporal, and parietal blood flow (Fletcher et al., 1998) among patients with schizophrenia.

To our knowledge, no published study has examined differences in brain activation between patients with schizophrenia and healthy individuals specifically during encoding of new information. Neuroimaging studies of encoding-related activation in healthy individuals have implicated the prefrontal cortex and parahippocampal and hippocampal cortices (Nyberg et al., 2000). Medial temporal activation has been especially apparent during encoding of complex, novel pictures in contrast to encoding of a repeated picture (Stern et al., 1996; Gabrieli et al., 1997; Constable et al., 2000). Thus, encoding tasks, particularly those involving picture stimuli, appear to be useful behavioral assays of brain activity in regions that are hypothesized to be impaired in schizophrenia. The present study compared the brain activation of patients with chronic schizophrenia to healthy comparison subjects of similar age during a picture-encoding task using functional magnetic resonance imaging (fMRI). We hypothesized that patients would have less activation than healthy subjects in both medial temporal and prefrontal cortical regions, whereas brain response in visual processing areas (e.g., the fusiform gyrus) would be equivalent between the groups.

2. Methods

2.1. Subjects

Patients were recruited from the Intervention Research Center on Psychosis in Older Adults (IRC) at UCSD. Thirteen patients with DSM-III-R or DSM-IV schizophrenia (SZ), as determined by the SCID (Spitzer et al., 1990, 1994) and diagnostic consensus by staff psychiatrists, were studied. Subjects had no history of major neurologic illness or head injury, no current substance abuse or dependence, and no abnormalities on structural magnetic resonance imaging as rated by a neuroradiologist. Four patients with schizophrenia were excluded from further analysis due to excessive motion (i.e., motion parameters greater than 2.5 standard deviations (S.D.) of the comparison subject distribution). Of the nine remaining subjects, five were women and all were right-handed with a mean (standard deviation) age of 54.5 (5.9) years, mean education of 12.8 (1.3) years, and a mean duration of illness of 27.3 (10.6) years. All were stable outpatients at the time of study, with a mean score of 29.8 (7.8) on the Brief Psychiatric Rating Scale (Overall and Gorham, 1962). All patients were medicated; five on atypical antipsychotic medications, two on both atypical and typical medications, and two on only typical antipsychotics.

Ten healthy comparison subjects, recruited from the IRC and from hospital staff, met the same exclusion criteria as the patients and had normal structural magnetic resonance imaging scans [mean age: 61.9 (12.9) years; mean education 13.4 (1.0)]. Two of the HC subjects were women and all were right-handed. There were no significant differences between the patient and HC groups on gender ($\chi^2(1) = 3.25$, NS), age ($t(17) = -1.56$, NS), or education ($t(17) = -1.19$, NS).

All subjects were paid for their participation and gave written informed consent to participate in the study, which had been approved by the UCSD Human Subjects Committee.

2.2. Behavioral task

The task involved an alternating control (“REPEAT”) and experimental (“ENCODE”) block design based on the Stern et al. (1996) task. Each block

consisted of six trials, composed of picture presentation (2500 ms) and an intertrial interval (500 ms). A 3-s warning screen reminded the subject of which type of block was to follow. During eight ENCODE blocks, subjects memorized novel, colored, complex photographs. To ensure that subjects remained oriented to the stimuli, subjects pressed a response key as quickly as possible when each picture appeared and held the key until the picture disappeared. During 10 REPEAT blocks, subjects saw the same complex picture (a photograph of autumn leaves) on every trial. Subjects pressed a response key each time this picture was presented, but were told that their memory for this picture would not be tested. Thus, both the REPEAT and ENCODE blocks were designed to involve motor responses and visual processing, whereas the ENCODE blocks also involved encoding processes. Additionally, four blocks of fixation baseline trials were presented (“FIXATE”). The picture stimuli were presented to the subjects using an LCD projector, back-projected onto a screen at the subjects’ feet. Motor responses were made using a fiber-optic button box and were recorded by the MicroExperimental Lab2 software package (Psychological Software Tools, Pittsburgh, PA).

2.3. Scanning procedure

High-resolution anatomical images were collected in a Siemens Magnetom 1.5 T magnet using the magnetization-prepared rapid acquisition gradient echo (MPRAGE) protocol (180 sagittal slices, 1 mm thickness, 1×1 mm in-plane resolution, TR = 11.4 ms, TE = 4.4 ms, flip angle = 10°). One hundred fifty-six whole brain images of blood oxygen level dependent (BOLD) signal intensity were collected during performance of the picture-encoding task using a gradient-recalled echoplanar imaging (EPI) sequence (20 axial slices, 7 mm thickness, 3.44×3.44 mm in-plane resolution, TR = 3000 ms, TE = 40 ms, flip angle = 90°).

2.4. Performance measures

The percentage of picture stimuli to which subjects responded with a button press and their response times were recorded during scanning for 15 of the 19 subjects (6 SZ and 9 HC). Approximately 10 min after

completion of the imaging task, all subjects participated in a forced-choice recognition memory task in which the 48 presented stimuli were each paired with a visually dissimilar foil. Recognition data were lost for one SZ patient due to equipment failure.

2.5. Image analysis

Images were analyzed using the Analysis of Functional NeuroImages (AFNI) software package. Each individual’s image time series was motion-corrected using a three-dimensional iterated, linearized, weighted least-squares method with Fourier interpolation. The images were aligned to the image for which the median amount of translation (in three planes) and rotation (around three axes) required across time points to correct for motion was minimized. The translation and rotation indices at each time point were saved for use as covariates in the individual-subject statistical analysis. In addition, each subject’s data were assessed for the degree of stimulus-correlated motion by examining the correlation between the stimulus reference function and the six motion indices.

At each voxel in the motion-corrected image, a regression model was tested with signal intensity across the image time series as the dependent variable. The predictor variables were (1) a set of shifted trapezoidal reference functions representing the contrast between the ENCODE and REPEAT conditions, (2) the degree of in-plane and rotational motion, and (3) a linear trend. The fit coefficient for the best-fit, shifted (up to 6 s) trapezoidal reference function was the measure of functional contrast used in subsequent analyses.

In order to constrain the number of within- and between-group comparisons, encoding-related brain response was examined in both groups and compared between SZ and HC in each voxel of four bilateral search regions: hippocampus, parahippocampal gyrus, inferior prefrontal cortex (Brodmann’s Area [BA] 44/45), and fusiform gyrus. These search regions were selected based on previous studies of healthy individuals demonstrating their involvement in encoding of novel information (Nyberg et al., 2000; Stern et al., 1996; Gabrieli et al., 1997; Constable et al., 2000). Coordinates for and the extent of each search region were determined using the Talairach Daemon software (Lancaster et al., 2000). The search regions were used to mask each subject’s three-dimensional dataset of fit

coefficients which had been transformed into standardized atlas space (Talairach and Tournoux, 1988), resampled into $4 \times 4 \times 4$ mm cubic voxels, and blurred with a 7-mm FWHM Gaussian filter. To test hypotheses about group differences, we compared the mean fit coefficient between groups in all voxels within each search region (two-sample *t*-test). Clusters of brain response were considered reliably different from zero within groups or reliably different between the two groups if they consisted of at least seven contiguous voxels, each with a *t*-value ≥ 2.459 ($p \leq 0.025$). This threshold and cluster volume combination was found to protect a search-region-wise $p = 0.059$ in a Monte Carlo simulation (AlphaSim, AFNI software package). The inter-subject variability at each voxel within the search regions also was examined and compared between groups, using an *F*-test of the ratio of the variances (Ferguson, 1981). To help interpret between group effects, we identified areas of significant BOLD response within each group by comparing the fit coefficients at voxels within each search region to zero (single-sample *t*-test). For the statistical maps of brain response presented in the figures, the magnitude of between or within group effect was expressed as η^2 and given a valence based on the directionality of the effect (range = -1.0 to $+1.0$). η^2 was chosen as the measure of effect size over other measures because its values are easily interpreted as the proportion of variance accounted for by the factor of interest. η^2 is the ratio of the sums of squares of the factor of interest (e.g., group membership) over the total sums of squares and is easily transformed to other common statistics such as the Student's *t*-test ($\eta^2 = t^2 / (t^2 + (n_a + n_b - 2))$), where

n_a and n_b are the number of subjects in groups a and b, respectively).

Several analyses were conducted post hoc in order to aid interpretation of the observed group differences. First, the task-related response of every voxel in the brain was compared between groups. Clusters were considered significant if they contained 13 contiguous (within a 4-mm radius) voxels (832 mm^3 volume) that each exceeded a threshold of $t = 2.462$ ($p \leq 0.025$). Second, the contrast of ENCODE vs. FIXATE was compared between groups in a control region (primary visual cortex, BA 17) in order to explore the specificity of observed differences to encoding-related brain regions and to address the potential concern that methodological or broad physiological factors influenced the between-group findings (Callicott et al., 1998). Third, within the clusters found to be significantly different between patients and controls, the magnitude of the contrast between the FIXATE condition and the ENCODE and REPEAT conditions was examined. Finally, correlations between brain response and recognition memory task performance also were computed for each voxel in the search regions. A full discussion of the correlation findings is presented elsewhere (Eyler Zorrilla et al., 2002).

3. Results

3.1. Behavioral performance

During scanning, schizophrenia patients and healthy comparison subjects were equivalent in their perform-

Table 1
Areas of significant brain response in healthy comparison subjects during picture encoding

| Direction of response | Cluster | Hemisphere | Brain region | Subregion | Volume (in μl) | Coordinates ^a of maximum intensity voxel | η^2 mean (S.E.M.) |
|-----------------------|---------|------------|-----------------------|--------------|----------------------------|---|------------------------|
| ENCODE > REPEAT | 1 | L | Fusiform gyrus | BA 19 and 37 | 12 608 | 30L, 49P, 16I | 0.72 (0.01) |
| | 2 | L | | BA 18 | 704 | 22L, 89P, 16I | 0.59 (0.03) |
| | 3 | R | Fusiform gyrus | BA 19 and 37 | 11 776 | 30R, 57P, 12I | 0.70 (0.01) |
| | 4 | L | Parahippocampal gyrus | BA 36 | 5952 | 26L, 45P, 8I | 0.62 (0.01) |
| | 5 | R | Parahippocampal gyrus | BA 30 and 36 | 7744 | 18R, 37P, 0I | 0.67 (0.01) |
| | 6 | L | Hippocampus | Anterior | 1088 | 34L, 21P, 16I | 0.60 (0.02) |
| | 7 | R | Hippocampus | Posterior | 640 | 26R, 33P, 4I | 0.67 (0.03) |
| | 8 | R | Brodman's Areas 44/45 | BA 45 | 576 | 50R, 19A, 12S | 0.60 (0.04) |

S.E.M. = standard error of the mean; BA = Brodmann's Area; L = left, R = right, A = anterior, P = posterior, I = inferior, S = superior.

^a From Talairach and Tournoux (1988).

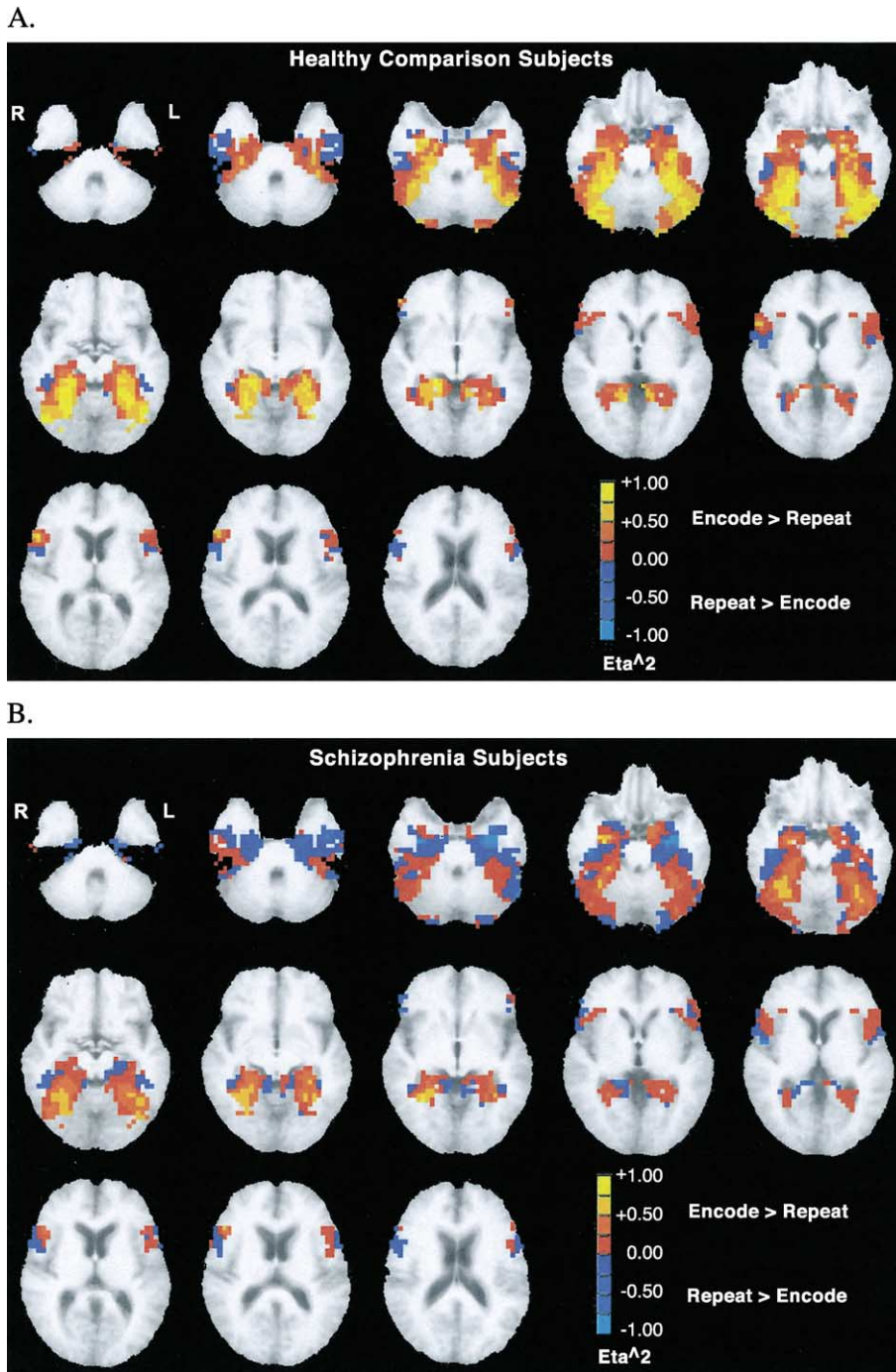


Fig. 1. Magnitude and direction of brain response to the task in all voxels within the search regions overlaid onto axial slices of an average anatomical image in Talairach and Tournoux (1988) space (slices span from 27 inferior to 21 superior in 4-mm increments). Color scale represents effect sizes for the group-wise difference between conditions (Encode vs. Repeat) as measured by η^2 (signed to reflect the direction of the contrast). Images are not thresholded; see Tables 1 and 2 for areas of significant activation. (A) Healthy control participants. (B) Schizophrenia patients.

Table 2

Areas of significant brain response in schizophrenia patients during picture encoding

| Direction of response | Cluster | Hemisphere | Brain Region | Sub Region | Volume (in μ l) | Coordinates ^a of maximum intensity voxel | Eta ² mean (S.E.M.) |
|-----------------------|---------|------------|-----------------------|--------------|---------------------|---|--------------------------------|
| ENCODE > REPEAT | 1 | L | Fusiform gyrus | BA 37 | 832 | 38L, 53P, 8I | 0.54 (0.01) |
| | 2 | R | Fusiform gyrus | BA 19 and 37 | 2112 | 30R, 49P, 8I | 0.57 (0.01) |
| | 3 | L | Parahippocampal gyrus | BA 19 | 448 | 26L, 49P, 4I | 0.52 (0.01) |
| | 4 | R | Parahippocampal gyrus | BA 19 | 1600 | 30R, 49P, 0I | 0.61 (0.01) |

S.E.M. = standard error of the mean; BA = Brodmann's Area; L = left, R = right, A = anterior, P = posterior, I = inferior, S = superior.

^a From Talairach and Tournoux (1988).

ance of the orientation task, as indexed by the percentage of picture stimuli to which they pressed the button [mean (standard deviation): SZ 94.8% (8.6); HC 86.1% (25.1); $t(13) = -0.80$, NS], and by the mean reaction time for the button presses [SZ: 609 (175) ms; HC: 576 (192) ms; $t(13) = -0.34$, NS]. After scanning, no significant difference was found between SZ and HC groups in subjects' ability to recognize picture items presented during scanning [mean percent correct: SZ 72.9% (17.1); HC 76.8% (11.1); $t(16) = 0.59$, NS].

3.2. Brain response to the encoding task

Within the search regions, HC showed several areas of significant positive response (Table 1; Fig. 1A). The BOLD response was greater during encoding of novel pictures than during presentation of a repeated picture in large, bilateral regions of the fusiform gyrus (BA 18, 19, and 37), extending to the parahippocampal gyrus bilaterally, and into the hippocampus. Encoding-related response was observed in a small region of BA 45 on the right in the frontal lobe as well.

Like the HC subjects, SZ patients showed several areas with greater brain response to novel than repeated pictures (Table 2; Fig. 1B). Bilateral regions of the fusiform gyrus (BA 19 and 37) were observed to be active, as were bilateral regions in the parahippocampal gyrus.

3.3. Differential brain response to the encoding task in SZ vs. HC

No significant group differences in stimulus-correlated motion were observed (HC median correlations = -0.07 to 0.03 ; SZ median correlations = -0.04 to 0.05 ; Mann-Whitney U 's ranged from 25 to 38, all $p > 0.05$). Likewise, the 9 SZ patients and 10 HC subjects studied did not significantly differ in the amount of in-plane or rotational motion during the scan as measured by the sum of squared deviations of each image from the base image.

Within the search regions examined, the encoding-related brain response of HC subjects was greater than that of SZ whenever a group difference was found (Table 3; Figs. 2 and 3). In clusters within the fusiform gyrus search region, HC showed a large positive re-

Table 3

Areas of significant differential brain response in patients vs. comparison subjects during picture encoding

| Cluster | Hemisphere | Brain Region | Sub Region | Volume (in μ l) | Coordinates ^a of maximum intensity voxel | Eta ² for HC – SZ contrast mean (S.E.M.) |
|---------|------------|-----------------------|------------|---------------------|---|---|
| 1 | L | Fusiform gyrus | BA 37 | 1216 | 54L, 61P, 20I | 0.38 (0.02) |
| 2 | L | Fusiform gyrus | BA 20 | 640 | 34L, 45P, 20I | 0.30 (0.01) |
| 3 | R | Fusiform gyrus | BA 20 | 640 | 34R, 41P, 16I | 0.30 (0.01) |
| 4 | L | Parahippocampal gyrus | BA 20 | 1472 | 34L, 9P, 20I | 0.32 (0.01) |
| 5 | R | Parahippocampal gyrus | BA 30 | 448 | 14R, 37P, 4S | 0.34 (0.03) |
| 6 | L | Hippocampus | Anterior | 704 | 34L, 9P, 20I | 0.33 (0.02) |

S.E.M. = standard error of the mean; BA = Brodmann's Area; L = left, R = right, A = anterior, P = posterior, I = inferior, S = superior.

^a From Talairach and Tournoux (1988).

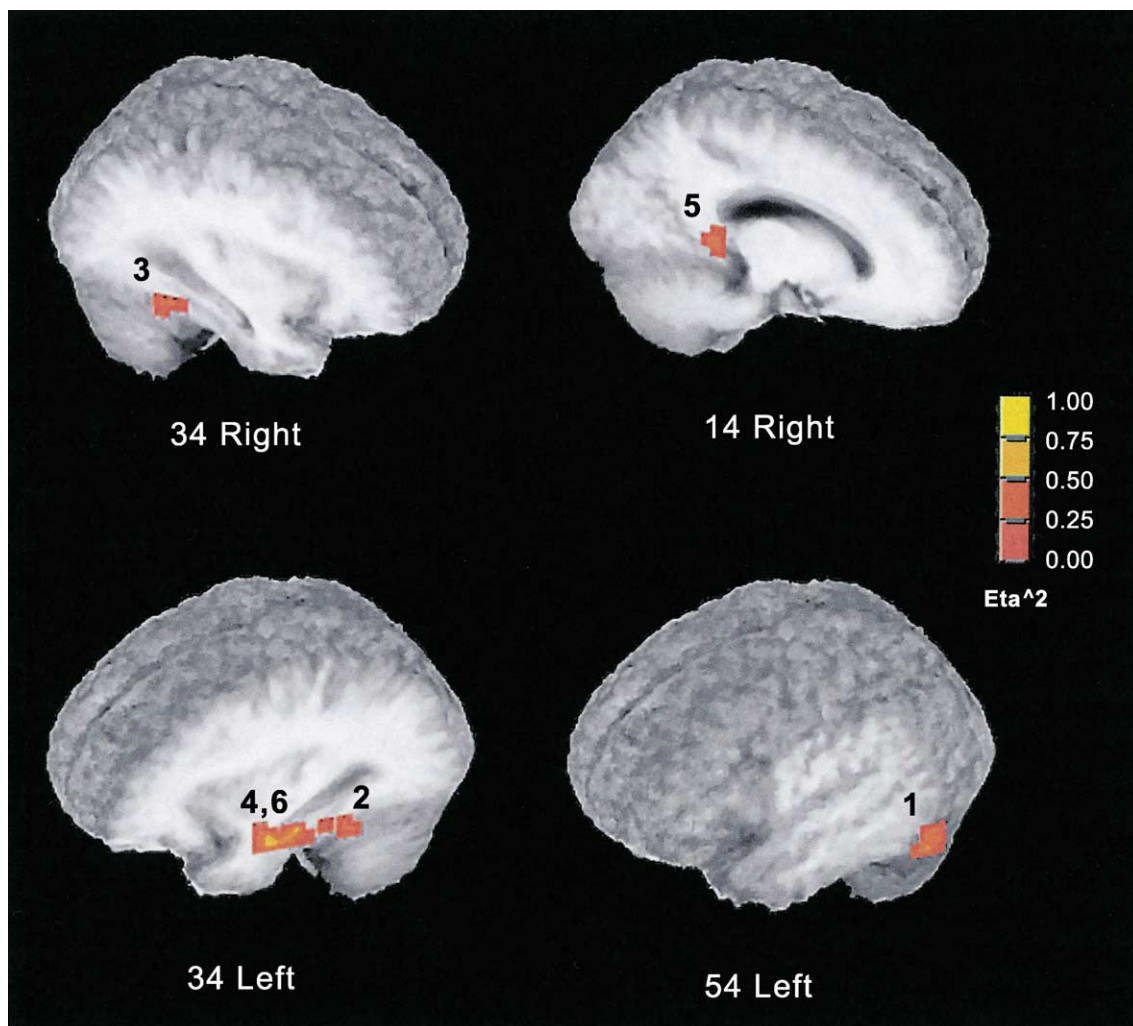


Fig. 2. Clusters of significant difference between healthy comparison subjects and schizophrenia patients for encoding-related brain response overlaid on rendered mean anatomical images sliced in the sagittal plane at the left or right Talairach coordinates indicated below each image. Numerals correspond to the cluster number indicated in Table 3. Color scale represents effect sizes for the control – schizophrenia difference in fit coefficient as measured by η^2 (signed to reflect the direction of the contrast).

sponse (i.e., greater signal intensity during novel pictures than during repeated pictures), whereas SZ showed either a small positive response or no difference in signal intensity between the two conditions. In the hippocampus and parahippocampus, the brain response of SZ and HC was different in direction. Whereas HC showed a positive response, SZ showed a negative response (i.e., lower signal intensity during novel pictures than during repeated pictures). No group differences in magnitude of brain response were

observed within the BA 44/45 search region. In addition, there were no significant differences in inter-subject variability of BOLD response between the groups in any of the search regions. All F -values to test ratios of variances were less than the critical values required for a two-tailed test at $p=0.05$.

Compared to a whole brain analysis, the a priori search region approach has greater power to detect small between-group differences because it decreases the number of voxels compared. A limitation of this

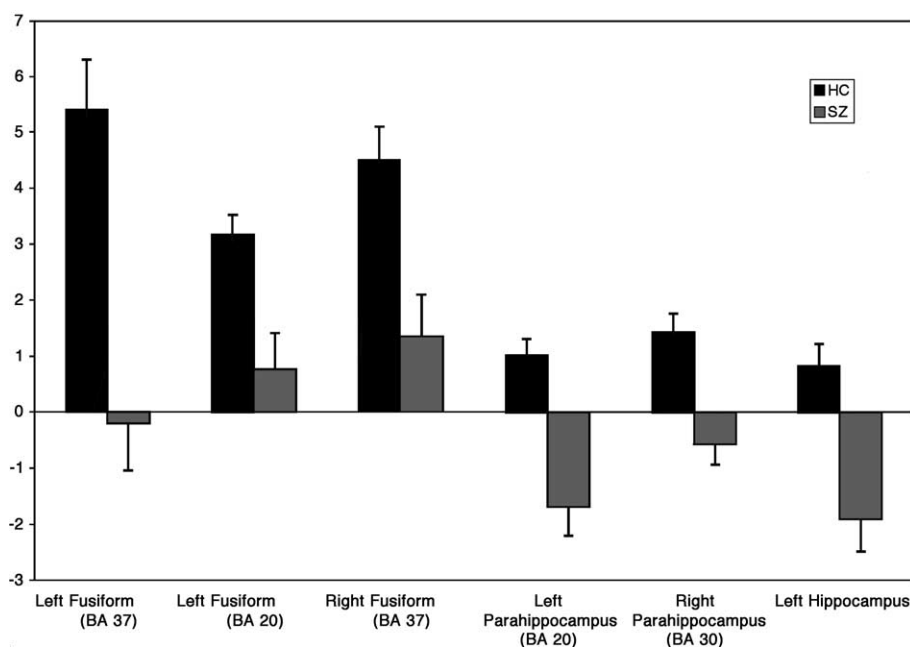


Fig. 3. Mean \pm S.E.M. fit coefficient of schizophrenia patients (SZ) and healthy comparison subjects (HC) in each cluster found to differ significantly between groups (see Table 3). BA = Brodmann's Area.

approach is that other brain regions in which large differences between groups exist may be overlooked. Thus, we conducted a post hoc whole brain analysis to explore other potential areas of difference between HC subjects and SZ patients. This revealed several areas outside of our a priori search regions in which HC subjects showed greater encoding-related brain response than SZ subjects. Specifically, significant between-group differences were found in temporal lobe (bilateral BA 20 and left BA 37), medial frontal gyrus (right BA 8), anterior cingulate (left BA 32), bilateral middle frontal gyrus (BA 6), left inferior parietal lobule (BA 40), and left occipital lobe (BA 18). As in the search region analysis, these differences arose primarily due to strong negative brain responses among SZ patients in the frontal and temporal clusters. No regions were found in which the brain response of SZ patients was significantly greater than that of HC subjects (full data available upon request).

In both the search region and whole brain analyses, large portions of the temporo-occipital cortex and smaller areas within the parahippocampal cortex were found to show significant encoding-related positive

response in both HC and SZ subjects to a statistically equivalent degree. As a more stringent test of the hypothesis that group differences were specific to regions thought to be dysfunctional in schizophrenia and to address the potential concern that methodological factors led to the findings of group differences, we conducted additional between-group comparisons in primary visual cortex (BA 17)—an area whose contribution to the encoding task should not differ between groups. Analysis of the response of voxels within BA 17 revealed a strong positive bilateral response to the ENCODE condition compared with the FIXATE condition for both the HC and SZ groups, with no significant clusters of group difference observed (data available upon request).

In order to understand more fully the finding of a positive brain response among HC subjects and a negative brain response among SZ subjects in the medial temporal search regions, the mean fit coefficients for the contrasts between the FIXATE condition and the ENCODE and REPEAT conditions were examined in these clusters. In each of the clusters, the pattern of positive brain response in HC subjects and

negative response in SZ subjects also was seen when the ENCODE condition was compared to the more unstructured baseline task. Specifically, SZ patients had smaller signal change in the ENCODE condition when compared to the FIXATE condition while HC subjects generally had positive fit coefficients for the ENCODE vs. FIXATE contrast. The magnitude of the contrast between the REPEAT and FIXATE conditions, however, was small and generally similar between the two groups.

The importance of group differences in brain response to cognitive differences between the groups was explored by examining the correlation between individual differences in encoding-related brain response and subsequent recognition memory performance (Eyler Zorrilla et al., 2002). In medial temporal regions, the SZ patients with the most negative contrast between the ENCODE and REPEAT conditions performed the most poorly on the subsequent recognition memory test. Surprisingly, the opposite relationship was seen in HC subjects. The HC subjects with the largest positive hippocampal and parahippocampal response during encoding were those who later remembered the fewest number of items (see Eyler Zorrilla et al., 2002, for a full discussion).

4. Discussion

Patients with schizophrenia showed abnormal brain response during the encoding of novel pictures compared to HC subjects, even though SZ patients were attending to the task to the same degree as HC subjects (as evidenced by equivalent latency and accuracy of button-presses to the stimuli in the scanner) and later were able to recognize the pictures just as well. Within the regions examined, group differences in brain response were found in the medial temporal lobe and in areas of the fusiform gyrus. In parahippocampal and hippocampal search regions, clusters were identified in which SZ had a lower brain response compared to HC subjects because of a smaller response to novel than repeated pictures. Such negative responses also were observed when the signal during novel picture encoding was contrasted to that during a fixation baseline. Similar results were seen in other frontal and temporal lobe clusters in a post hoc whole brain analysis.

The interpretation of negative brain responses (sometimes called deactivations) in fMRI studies is difficult, and these findings are therefore often ignored. Because the BOLD signal is a relative measure, a negative correlation with the stimulus input function has two possible explanations: a decrease in blood flow to the region during the experimental condition compared to the baseline condition, or an increase in blood flow to the region during the baseline condition compared to the experimental condition. We consider the latter possibility first. Increased blood flow during a baseline task compared to an experimental task is likely to be the result of imperfect cognitive subtraction, that is, unique information processing demands in the baseline task that are not present in the experimental task. In the present study, a negative brain response was observed among SZ patients compared to two different baseline tasks. If the negative response was the result of a failure of cognitive subtraction, it would mean that patients were engaging in cognitive processes that required both frontal and temporal lobe regions while viewing a repeated picture and a fixation point, but not while encoding novel pictures. While some have argued that memory processes are active during resting or undemanding baseline conditions (Andreassen et al., 1996; Binder et al., 1999), it seems unlikely that these systems would be *more* engaged than during an explicit encoding condition, even in patients with learning dysfunction. Still, further research is needed to rule out such an explanation completely.

The negative brain response among SZ patients is more likely the result of a true decrease of the hemodynamic response during the experimental task, perhaps as a result of decreased metabolic requirements due to inhibitory influences. This apparent underactivity of medial temporal regions was not accompanied by significant overactivity in other brain regions, however. Still, the areas exerting such influences may have been distributed and thus difficult to detect with the powerful, but spatially limited search region analysis, or with the less powerful whole brain approach. The negative response may thus reflect aberrant functional connectivity of the medial temporal lobes with other regions that resulted in dampening of the normal response in these areas among SZ patients.

Brain activation in medial temporal regions among HC has been attributed to binding of associated features to facilitate storage and later retrieval (Cohen et

al., 1999). The aberrant brain response of SZ patients in this region may therefore reflect a dysfunction of these binding mechanisms. The hippocampus also is known to be involved in novelty detection (Dolan and Fletcher, 1997). Underactivity of this region among SZ thus might be related to decreased novelty processing compared to healthy individuals. Contrary to our hypothesis, SZ also showed decreased brain response to novel pictures compared to HC in some areas of the fusiform gyrus search region, perhaps indicating a failure of SZ to process the visual features of the stimuli as richly as HC. BOLD response was not different between groups in primary visual cortex, however, suggesting that SZ abnormalities were specific to higher cognitive processes involved in novel picture encoding. Finally, no significant between group differences were found in the BA 44/45 search regions, but other frontal areas of difference were seen in a post hoc whole brain analysis. This suggests that frontal abnormalities in schizophrenia are less prominent in encoding-related inferior regions than in regions (such as BA 6, 8, and anterior cingulate) that have been implicated in working memory and attentional processes.

In the face of aberrant brain responses in regions known to be important for learning new information, how were patients able to perform adequately on the subsequent recognition memory test? It is unlikely that they did so through compensation by other neural systems since no regions were found to be more active among SZ patients than HC subjects. More likely, SZ patients encoded the items at a superficial level that was adequate for familiarity judgments but would not have supported more demanding recall or recognition tasks. The idea that the SZ patients in this study had unrevealed visual encoding deficits is supported by the fact that they were impaired as a group on a clinical test of visual recognition memory (Heaton et al., 1991) both compared to age- and education-matched norms and to a subset of the HC subjects (data not shown). Moreover, patients' scores on the post-scan recognition memory test correlated highly with their scores on the more difficult clinical test ($r=0.66$). Thus, while our simple recognition test apparently was sensitive to stable individual differences in visual recognition abilities and showed that patients were attending to the pictures at least to a minimal degree, it may not have been adequate to

explore the depth of subjects' encoding. A more difficult recognition memory test with visually similar foils might have demonstrated a group deficit.

Our findings of medial temporal dysfunction among SZ patients are consistent with previous studies that examined correlations between cognitive functioning and both resting metabolism and structural abnormalities (Maher et al., 1995; Seidman et al., 1994; Goldberg et al., 1994; DeLisi et al., 1991; Nestor et al., 1993). The locations of between-group differences in the present study also are similar to those found with previous neuroimaging tasks that examined encoding and retrieval at the same time (Shihabuddin et al., 1998; Fletcher et al., 1998; Hazlett et al., 2000). Fletcher et al. (1998) reported abnormalities of fronto-temporal connectivity, in which SZ patients showed lower frontal brain response but abnormally high temporal response. While our finding of a negative brain response among patients compared to HC subjects may suggest abnormal functional connectivity during encoding, we did not observe overactivation of the temporal cortex. This discrepancy may be due to task differences, as we imaged only during learning and used pictures rather than verbal stimuli.

Though typical of many neuroimaging studies, the sample size within each group was relatively small, limiting power to detect small differences between the two groups. We attempted to mitigate this problem by restricting the search areas in the a priori analyses to those regions hypothesized to be important for learning new information, but caution is still warranted in interpreting the lack of significant differences in any of the areas examined. In addition, although post hoc whole brain analyses and examination of a control region suggest that group differences were most prominent in fusiform, temporal and frontal regions, our study cannot rule out important group differences in additional brain regions. The conclusions of the present study are limited to currently medicated, middle-aged, chronic schizophrenia patients who have a long history of psychotropic drug use. Further, such patients are known to have decreased volume of temporal and frontal cortices, which could have influenced the magnitude of the observed BOLD response in our search regions. It seems unlikely, however, that volumetric differences could completely explain the negative brain response found among SZ patients or

the altered patterns of correlation with later performance. Keeping these limitations in mind, our results suggest that abnormal functioning of medial temporal regions underlies encoding performance in some patients with schizophrenia. However, future research is needed to confirm and generalize these findings and to understand their implications for patients' everyday functioning.

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References

- Andreasen, N.C., O'Leary, D.S., Cizadlo, T., Arndt, S., Rezai, K., Ponto, L.L., Watkins, G.L., Hichwa, R.D., 1996. Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal–thalamic–cerebellar circuitry. *Proceedings of the National Academy of Sciences of the United States of America* 93, 9985–9990.
- Binder, J.R., Frost, J.A., Hammeke, T.A., Bellgowan, P.S.F., Rao, S.M., Cox, R.W., 1999. Conceptual processing during the conscious resting state: a functional MRI study. *Journal of Cognitive Neuroscience* 11, 80–95.
- Busatto, G.F., Costa, D.C., Ell, P.J., Pilowsky, L.S., David, A.S., Kerwin, R.W., 1994. Regional cerebral blood flow (rCBF) in schizophrenia during verbal memory activation: a 99 mTc HMPAO single photon emission tomography (SPET) study. *Psychological Medicine* 24, 463–472.
- Busatto, G.F., David, A.S., Costa, D.C., Ell, P.J., Pilowsky, L.S., Lucey, J.V., Kerwin, R.W., 1995. Schizophrenic auditory hallucinations are associated with increased regional cerebral blood flow during verbal memory activation in a study using single photon emission computed tomography. *Psychiatry Research* 61, 255–264.
- Callicott, J.H., Ramsey, N.F., Tallent, K., Bertoline, A., Knable, M.B., Coppola, R., Goldberg, T., van Gelderen, P., 1998. Functional magnetic resonance imaging brain mapping in psychiatry: methodological issues illustrated in a study of working memory in schizophrenia. *Neuropsychopharmacology* 18, 186–196.
- Cohen, N.J., Ryan, J., Hunt, C., Romine, L., Wszalek, T., Nash, C., 1999. Hippocampal system and declarative (relational) memory: summarizing the data from functional neuroimaging studies. *Hippocampus* 9, 83–98.
- Constable, R.T., Carpentier, A., Pugh, K., Westerveld, M., Oszunar, Y., Spencer, D.D., 2000. Investigation of the human hippocampal formation using a randomized event-related paradigm and Z-shimmed functional MRI. *NeuroImage* 12, 55–62.
- Crespo-Facorro, B., Paradiso, S., Andreasen, N.C., O'Leary, D.S., Watkins, G.L., Boles Ponto, L.L., Hichwa, R.D., 1999. Recalling world lists reveals “cognitive dysmetria” in schizophrenia: a positron emission tomography study. *American Journal of Psychiatry* 156, 386–392.
- DeLisi, L.E., Hoff, A.L., Schwartz, J.E., Shields, G.W., Halthore, S.N., Gupta, S.M., Henn, F.A., Anand, A.K., 1991. Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study [published erratum appears in *Biol. Psychiatry* 1991, Mar 1; 29 5:519]. *Biological Psychiatry* 29, 159–175.
- Dolan, R.J., Fletcher, P.C., 1997. Dissociating prefrontal and hippocampal function in episodic memory encoding. *Nature* 388, 582–585.
- Eyler Zorrilla, L.T., Jeste, D.V., Brown, G.G., 2002. Functional MRI and novel picture learning among older patients with chronic schizophrenia: abnormal correlations between recognition memory and medial temporal brain response. *Am. J. Geriatric Psych.* 10, 52–61.
- Ferguson, G.A., 1981. *Statistical Analysis in Psychology and Education*, 5th ed. McGraw-Hill, New York, NY, pp. 189–192.
- Fletcher, P.C., McKenna, P.J., Frith, C.D., Grasby, P.M., Friston, K.J., Dolan, R.J., 1998. Brain activation in schizophrenia during a graded memory task studied with functional neuroimaging. *Archives of General Psychiatry* 55, 1001–1008.
- Gabrieli, J.D.E., Brewer, J.B., Desmond, J.E., Glover, G.H., 1997. Separate neural bases of two fundamental memory processes in the human medial temporal lobe. *Science* 276, 264–266.
- Ganguli, R., Carter, C., Mintun, M., Brar, J., Becker, J., Sarma, R., Nichols, T., Bennington, E., 1997. PET brain mapping study of auditory verbal supraspan memory versus visual fixation in schizophrenia. *Biological Psychiatry* 41, 33–42.
- Goldberg, T.E., Torrey, E.F., Berman, K.F., Weinberger, D.R., 1994. Relations between neuropsychological performance and brain morphological and physiological measures in monozygotic twins discordant for schizophrenia. *Psychiatry Research: Neuroimaging* 55, 51–61.
- Green, M.F., Kern, R.S., Braff, D.L., Mintz, J., 2000. Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the “right stuff”? *Schizophrenia Bulletin* 26, 119–136.
- Gur, R.E., Jaggi, J.L., Shtasel, D.L., Ragland, D., Gur, R.C., 1994. Cerebral blood flow in schizophrenia: Effects of memory processing on regional activity. *Biological Psychiatry* 35, 3–15.
- Hazlett, E.A., Buchsbaum, M.S., Jee, L.A., Nenadic, I., Fleischman, M.B., Shihabuddin, L., Haznedar, M.M., Harvey, P.D., 2000. Hypofrontality in unmedicated schizophrenia patients studied with PET during performance of a serial verbal learning task. *Schizophrenia Research* 43, 33–46.
- Heaton, R.K., Grant, I., Matthews, C.G., 1991. *Comprehensive Norms for Expanded Halstead–Reitan Battery: Demographic Corrections, Research Findings, and Clinical Applications Psychological Assessment Resources*, Odessa, FL.
- Heckers, S., Rauch, S.L., Goff, D., Savage, C.R., Schacter, D.L., Fischman, A.J., Alpert, N.M., 1998. Impaired recruitment of the hippocampus during conscious recollection in schizophrenia. *Nature Neuroscience* 1, 318–323.

- Heckers, S., Goff, D., Schacter, D.L., Savage, C.R., Fischman, A.J., Alpert, N.M., Rauch, S.L., 1999. Functional imaging of memory retrieval in deficit vs. nondeficit schizophrenia. *Archives of General Psychiatry* 56, 1117–1123.
- Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Frietas, C.S., Rainey, L., Kochunov, P.V., Nickerson, D., Mikiten, S.A., Fox, P.T., 2000. Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping* 10, 120–131.
- Maher, B.A., Manschreck, T.C., Woods, B.T., Yurgelun-Todd, D.A., Tsuang, M.T., 1995. Frontal brain volume and context effects in short-term recall in schizophrenia. *Biological Psychiatry* 37, 144–150.
- Nestor, P.G., Shenton, M.E., McCarley, R.W., Haimson, J., Smith, R.S., O'Donnell, B., Kimble, M., Kikinis, R., Jolesz, F.A., 1993. Neuropsychological correlates of MRI temporal lobe abnormalities in schizophrenia. *American Journal of Psychiatry* 150, 1849–1855.
- Nyberg, L., Persson, J., Habib, R., Tulving, E., McIntosh, A.R., Cabeza, R., Houle, S., 2000. Large scale neurocognitive networks underlying episodic memory. *Journal of Cognitive Neuroscience* 12, 163–173.
- Overall, J.E., Gorham, D.R., 1962. The brief psychiatric rating scale. *Psychological Reports* 10, 799–812.
- Ragland, J.D., Gur, R.C., Glahn, D.C., Censits, D.M., Smith, R.J., Lazarev, M.G., Alavi, A., Gur, R.E., 1998. Frontotemporal cerebral blood flow change during executive and declarative memory tasks in schizophrenia: a positron emission tomography study. *Neuropsychology* 12, 399–413.
- Saykin, A.J., Gur, R.C., Gur, R.E., Mozley, P.D., Mozley, L.H., Resnick, S.M., Kester, B., Stafiniak, P., 1991. Neuropsychological function in schizophrenia: selective impairment in memory and learning. *Archives of General Psychiatry* 48, 618–624.
- Seidman, L.J., Yurgelun-Todd, D., Kremen, W.S., Woods, B.T., Goldstein, J.M., Faraone, S.V., Tsuang, M.T., 1994. Relationship of prefrontal and temporal lobe MRI measures to neuropsychological performance in chronic schizophrenia. *Biological Psychiatry* 35, 235–246.
- Shihabuddin, L., Buchsbaum, M.S., Hazlett, E.A., Haznedar, M.M., Harvey, P.D., Newman, A., Schnur, D.B., Spiegel-Cohen, J., Wei, T., Machac, J., Knesarek, K., Vallabhajosula, S., Biren, M.A., Ciaravolo, T.M., Luu-Hsia, C., 1998. Dorsal striatal size, shape, and metabolic rate in never-medicated and previously medicated schizophrenics performing a verbal learning task. *Archives of General Psychiatry* 55, 235–243.
- Spitzer, R.L., Williams, J.B.W., Gibbon, M., First, M.B., 1990. *User's Guide for the Structured Clinical Interview for DSM-III-R*. American Psychiatric Press, Washington, DC.
- Spitzer, R.L., Williams, J.B., Gibbon, M., First, M.B., 1994. *Structured Clinical Interview for the DSM-IV*. American Psychiatric Association, Washington, DC.
- Stern, C.E., Corkin, S., Gonzalez, R.G., Guimaraes, A.R., Baker, J.R., Jennings, P.J., Carr, C.A., Sugiura, R.M., Vedantham, V., Rosen, B.R., 1996. The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences of the United States of America* 93, 8660–8665.
- Talairach, J., Tournoux, P., 1988. *A Coplanar Stereotaxic Atlas of the Human Brain*. New York, NY.
- Wood, F.B., Flowers, D.L., 1990. Hypofrontal vs. hypo-sylvian blood flow in schizophrenia. *Schizophrenia Bulletin* 16, 413–424.