Temporolimbic Volume Reductions in Schizophrenia

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**Background:** Neuroanatomic studies of schizophrenia have reported temporolimbic abnormalities. Most magnetic resonance imaging studies have evaluated small samples of primarily men with chronic schizophrenia. Our goal was to evaluate sex differences in segmented temporal lobe subregions with reliable parcellation methods, relating volume with clinical and neurocognitive parameters.

**Methods:** Magnetic resonance imaging was performed in 100 patients with schizophrenia (58 men, 42 women; 39 neuroleptic naive, 61 previously treated) and 110 healthy controls (51 men, 59 women). Gray and white matter volumes of temporolimbic (hippocampus and amygdala) and neocortical regions (superior temporal gyrus and temporal pole) were examined. Symptoms, functioning, and neurocognition were assessed concurrently.

**Results:** Hippocampal gray matter volume was reduced in men (7%) and women (8.5%) with schizophrenia. In the amygdala, however, decreased volume was evident for men (8%) whereas women (10.5%) had increased volume. Magnetic resonance imaging of the temporal pole showed decreased gray matter in men (10%) and women (8.5%). For the superior temporal gyrus, the decrease exceeded that of whole-brain only in men (11.5%). Volumes were largely uncorrelated with clinical measures, but higher hippocampal volumes were associated with better memory performance for all groups. Cortical volumes were associated with better memory performance in healthy women.

**Conclusions:** Schizophrenia is associated with reduced gray matter volume in temporolimbic structures. In men, reduction was manifested in all regions, whereas women showed decreased hippocampal volumes but increased amygdala volumes. The abnormalities are evident in patients with first-episode schizophrenia and correlate more strongly with cognitive performance than with symptom severity.

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TEMPORAL LOBE structures and circuitry modulate cognition and emotion, prompting their neuroanatomic examination in schizophrenia. Investigations with magnetic resonance imaging (MRI) have evaluated lobar volumes and specific subregions implicated in neurobehavioral domains aberrant in schizophrenia, such as memory. Regional volumes have also been linked to clinical features, including thought disorder and auditory hallucinations. This research complements neuropathological findings documenting abnormal morphometry, cytoarchitecture, and neuroreceptors in temporolimbic structures.

Studies have reported volume reduction in the global temporal lobe, gray matter (GM), but not white matter (WM), with lateralization to the left hemisphere. Regional analysis revealed decreased volume in temporolimbic structures including the hippocampus, parahippocampal gyrus, and amygdala. However, some studies did not find differences in these regions. A meta-analysis examined 18 studies measuring hippocampal volumes, sometimes combined with amygdala. Bilateral hippocampal reduction had a significant effect on size, and adding amygdala further increased it. Laterality effects were inconclusive.

Cortical temporal regions, especially the superior temporal gyrus (STG), have also been examined. Reduced volume has been observed in anterior, posterior, and total STG and is related to the severity of auditory hallucinations and thought disorder. However, other studies have not noted STG decrease. It is also unclear whether STG reduction is differential compared with other temporal lobe association cortices.
SUBJECTS AND METHODS

SUBJECTS

The sample included 100 patients with schizophrenia (58 men, 42 women) and 110 healthy controls (51 men, 59 women) from the Schizophrenia Research Center (Philadelphia, Pa). Participants were right-handed and aged 18 to 45 years. They represented a subsample for whom we reported whole-brain data and an expanded sample of participants in the prefrontal study. The current sample does not differ from the other samples in demographic or clinical characteristics (Table 1 and Table 2). Patients had a DSM-IV diagnosis of schizophrenia established by research psychiatrists as previously detailed. The healthy controls also underwent comprehensive assessment including medical, neurological, and psychiatric evaluations with laboratory tests. Participants had no history of a disorder or event that might affect brain function (eg, substance use or dependence, hypertension, cerebrovascular disease, seizure disorder, head trauma with loss of consciousness, or endocrine disorder). After complete description of the study, written informed consent was obtained prior to participation. Clinical assessments, neurocognitive testing, and MRI studies were conducted within a week.

ASSESSMENT

Clinical

Assessments, conducted by research psychiatrists with established procedures, included the Scale for Assessment of Positive Symptoms (SAPS), the Hamilton Depression Scale (HAM-D), Premorbid Adjustment Scale (PAS), and Quality of Life Scale. The sample was mildly to moderately impaired (Table 3).

Neurocognitive

A standardized battery and procedures provided measures of abstraction-flexibility, attention, verbal memory, spatial memory, verbal abilities, and spatial abilities. Testing was done by trained fellows supervised by investigators.

Conclusions are limited by variation in imaging parameters affecting resolution, variation in regional boundary definitions, and small sample sizes that include primarily men. Sex differences have been noted clinically, with women having later onset, milder course, and more affective symptoms. Neurocognitively, however, reports vary. Our goal was to evaluate GM and WM volumes of temporolimbic and neocortical areas in men and women with schizophrenia. We hypothesized that: (1) schizophrenia is associated with lower GM volumes across temporolimbic regions; (2) the reduction is more evident in men than women; (3) volume reduction is observed at initial clinical presentation; (4) higher volume is associated with better memory performance in patients and controls; and (5) no directional hypothesis is offered relating volume with symptom severity, but we expect higher volumes to be associated with better functioning.

MRI MEASUREMENTS

Magnetic resonance imaging scans were acquired as detailed: a GE Signa (General Electric Co, Milwaukee, Wis) 1.5-T system was used, along with a spoiled gradient-recalled echo sequence; we used a 35° flip angle; repetition time was 35 milliseconds; echo time was 6 milliseconds; field of view was 24 cm; there was 1 repetition, a 1-mm slice thickness, no gaps, transaxial images, and 0.9375×0.9375-mm resolution. Images were realigned as in the prefrontal analyses, resliced along the anterior commissure–posterior commissure axis for head tilt, and none had parenchymal lesions or skull abnormalities. The brain volume was extracted semiautomatically and segmented into GM and WM using the optimal thresholding and morphological operations previously detailed.

Temporal Subregions

The temporal lobe was divided into limbic (hippocampus and amygdala) and cortical regions (STG and temporal pole). Regions were drawn on the realigned sagittal series with the exception of the medial aspect of STG, which uses the realigned coronal series (Figure 1).

Hippocampus

The GM structure lying on the lateral ventricle is bounded inferiorly by the WM, separating it from the parahippocampal cortex. Laterally and posteriorly it is bounded by a WM region, the alveus, which separates the tail of the hippocampus from the atrium of the lateral ventricle, thus excluding the choroid plexus. On the more lateral slices, the anterior border is defined by the temporal horn of the lateral ventricle. On the more medial slices, a small strip of WM separates the hippocampus from the amygdala. The coordinates of the border established by the WM are maintained on those slices where there is no white strip present. The outline of the hippocampus is traced as it appears on each slice.

Amygdala

The drawing for the amygdala is performed on the sagittal plane but all 3 planes are used to determine the borders. The superior border is determined in 2 steps. First, the coronal slice cutting through the most inferior-anterior point of the temporal horn of the lateral ventricle is chosen from

RESULTS

MAGNETIC RESONANCE IMAGING

The ANCOVA for the hippocampus showed a main group effect of diagnosis (F1,191=3.53; P=.03), indicating that patients had overall smaller hippocampal volumes (Table 4). No other main effects or interactions were significant. The ANCOVA for amygdala showed no main effects of diagnosis or sex, but a diagnosis×sex interaction was significant (F1,192=4.21; P=.04). This reflected

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the sagittal plane. Then, on the coronal plane, the most lateral point of cerebrospinal fluid (CSF) where the chiasmatic cistern meets the amygdala provides the linear superior border on the sagittal plane. The anterior border is determined by the caudal coronal slice in which the anterior commissure disappears and the third ventricle becomes continuous. This coronal slice is used as the anterior border on the sagittal plane. The inferior border of the amygdala is determined by the axial slice on which the tip of the inferior horn of the lateral ventricle first appears. The posterior border of the amygdala is drawn adjacent to the anterior border of the hippocampus.

Superior Temporal Gyrus

The anterior border is defined by a vertical line representing the most posterior CSF pixel in front of the limen insula. This anterior point remains consistent on the sagittal slices cutting through the insular cortex. The posterior border is determined by a vertical line where the lateral fissure is capped by the supramarginal gyrus at the slice lateral to the appearance of the insular gyri. The superior and inferior borders are determined by the CSF of the lateral fissure and the superior temporal sulcus, respectively. Tracing of the region on the sagittal plane ends when the inferior temporal gyrus becomes discontinuous. The drawings from the sagittal plane are displayed on the coronal plane using 3-dimensional imaging software, whereupon the remaining medial portion of the gyrus is drawn. The gyrus is still bounded inferiorly by the superior temporal sulcus and superiorly by the CSF of the lateral fissure. The medial border is defined by a line connecting the most inferior point of the insular cortex to the most medial point of the superior temporal sulcus.

Temporal Pole

The posterior border of this region is defined as the anterior border of STG. Anteriorly it is bounded by the sphenoid bone, inferorly by the temporal bone (articual tubercle), and superiorly by the lateral fissure. The region is then drawn in both the lateral and medial directions until there is no longer brain anterior to the established posterior border. Based on the defining boundaries, the TP includes the anterior middle and inferior temporal gyri. It may also include the most anterior segment of STG that is difficult to separate reliably.

Reliability

Two raters independently completed the temporal region drawings on the same 10 randomly selected cases of 3 controls and 5 patients. The intraclass correlations for the 4 subfields in each hemisphere for GM and WM ranged from 0.90 to 0.96.

DATA ANALYSIS

Brain volumes in milliliters were the dependent measures in the analyses. Since only GM was present for the hippocampus and amygdala, they were each analyzed using univariate analyses of covariance (ANCOVA), with diagnosis and sex grouping factors, hemisphere as a repeated-measures (within-group) factor, and total cranial, brain, GM volumes, and age as sequential covariates. For temporal cortex (STG and TP), where both GM and WM were measured, a multivariate analysis of covariance (MANCOVA) was conducted where a compartment (GM, WM) was added as a repeated-measures factor. These analyses tested hypotheses 1 and 2. Because covariates other than total cranial volume, necessary for equating men and women, did not alter the effects, we report the results of the MANCOVAs with cranial volume covaried. Analyses of variance were performed within the patient group, contrasting first-episode neuroleptic-naive to previously treated patients (hypothesis 3) and comparing deficit with nondeficit subtypes.57 As these analyses did not show group effects or interactions, these results are not detailed.

To examine the relationship between volumes and neurocognitive functioning, we computed the correlations between GM volume in the above subregions and performance on the 6 neurocognitive domains. Two domains, verbal and spatial memory, are hypothesized to relate to temporal lobe functioning (hypothesis 4). This was tested with a Pearson correlation coefficient with a level set at 0.05. The other 4 correlations were considered exploratory and the P value was Bonferroni adjusted so that a P value of .01 (0.05/4) was considered significant at P = .05. Similarly, the possible link between volumes and clinical variables was examined by correlating the temporal subregions’ GM with global measures of function (PAS and Quality of Life Scale), where positive correlations are expected with volumes (hypothesis 3) and severity of symptoms (SANS, SAPS, HAM-D), where we make no directional hypothesis. Here P values were Bonferroni adjusted using the 5 measures in the denominator, so that a P value of .01 was considered significant at P = .05. All P values were 2 tailed.

Reduced volume in men relative to increased volume in women with schizophrenia, compared with their healthy counterparts (Figure 2). The MANCOVA for STG showed a main effect of diagnosis (F[1,189] = 5.47; P = .03), with patients having lower volumes than controls. There was a main effect of compartment (F[1,192] = 4.12; P = .04) showing overall higher GM than WM, and a diagnosis \times compartment interaction (F[1,192] = 21.70; P = .001), indicating that the reduction in STG volume seen in patients was specific to GM. No other main effects or interactions involving diagnosis were significant. For TP, the MANCOVA showed a main effect of diagnosis (F[1,189] = 2.78; P = .03) with patients having lower volumes than controls. A compartment \times diagnosis interaction (F[1,192] = 9.50; P = .002) reflected that the reduced parenchymal volume in patients was specific to GM. Again, no other effects or interactions were significant.

Covarying age in the data analyses was justified by volume correlations with age, within the limited range. These correlations were significant only for cortical GM, and not for WM or subcortical regions (amygdala and hippocampus). For healthy men, increased age was associated with decreased GM volume in STG (t[39] = −.39; P = .01). In healthy women, the corresponding correlations were t[39] = −.26; P = .05 and r = −.30, P = .03, respectively. In men with schizophrenia, only TP volume correlated with age (t[39] = −.35; P = .008) and for women with schizophrenia the correlation was significant only for STG (r[40] = −.31, P = .05). Correla-
CORRELATION OF MRI
WITH ASSESSMENT MEASURES

Clinical

Because the differences between patients and controls were in GM, only GM volumes were correlated with the clinical symptoms. In men with schizophrenia, lower hippocampus volume correlated with poorer PAS ($r_{39} = -0.34$; $P = .02$). No other correlations were significant after Bonferroni adjustment. There were no correlations between volumes and illness duration.

Neurocognitive

The hypothesized correlations between volumes and memory were significant for the hippocampus in healthy men (verbal, $r_{39} = 0.30$; $P = .05$; spatial, $r = 0.37$; $P = .02$),...
healthy women (spatial, $r_{54}=0.35; P=.007$), men with schizophrenia (verbal, $r_{56}=0.35; P=.02$), and women with schizophrenia (verbal, $r_{40}=0.26; P=.05$; spatial, $r=0.29; P=.05$). Amygdala volume did not correlate significantly with performance on any neurocognitive domain. Superior temporal gyrus volume correlated significantly with spatial memory in healthy women ($r=0.36; P=.005$). Temporal pole volume correlated with verbal and spatial memory in healthy women ($r=0.27; P=.04$ and $r=0.36; P=.005$, respectively). Other correlations that withstood Bonferroni adjustment included STG with attention in healthy men ($r=0.38; P=.05$) and TP with abstraction ($r=0.45; P=.009$) and spatial abilities ($r=0.38; P=.004$) in healthy women.

**Table 4. Mean Temporal Volumes for Patients With Schizophrenia and Healthy Controls**

<table>
<thead>
<tr>
<th>Subregion</th>
<th>Patients Mean (SD)</th>
<th>Controls Mean (SD)</th>
<th>Effect Size Men/Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td><strong>Hippocampus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left GM</td>
<td>4.2 (1.0)</td>
<td>3.6 (0.6)</td>
<td>4.4 (0.6)</td>
</tr>
<tr>
<td>Right GM</td>
<td>4.3 (0.8)</td>
<td>4.1 (0.5)</td>
<td>4.7 (1.0)</td>
</tr>
<tr>
<td><strong>Amygdala</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left GM</td>
<td>1.8 (0.5)</td>
<td>1.6 (0.5)</td>
<td>2.0 (0.6)</td>
</tr>
<tr>
<td>Right GM</td>
<td>1.7 (0.4)</td>
<td>1.6 (0.5)</td>
<td>1.8 (0.6)</td>
</tr>
<tr>
<td><strong>Superior temporal left</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM</td>
<td>10.7 (2.1)</td>
<td>10.0 (1.8)</td>
<td>12.1 (2.2)</td>
</tr>
<tr>
<td>WM</td>
<td>4.2 (1.2)</td>
<td>4.4 (1.2)</td>
<td>4.5 (1.4)</td>
</tr>
<tr>
<td><strong>Superior temporal right</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM</td>
<td>10.2 (1.6)</td>
<td>9.7 (1.7)</td>
<td>11.4 (2.0)</td>
</tr>
<tr>
<td>WM</td>
<td>5.5 (1.3)</td>
<td>4.8 (1.1)</td>
<td>5.6 (1.4)</td>
</tr>
<tr>
<td><strong>Temporal pole left</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM</td>
<td>8.1 (2.1)</td>
<td>7.0 (1.4)</td>
<td>8.8 (1.9)</td>
</tr>
<tr>
<td>WM</td>
<td>1.4 (0.8)</td>
<td>1.3 (0.5)</td>
<td>1.5 (0.8)</td>
</tr>
<tr>
<td><strong>Temporal pole right</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM</td>
<td>7.4 (1.8)</td>
<td>6.8 (1.4)</td>
<td>8.4 (2.1)</td>
</tr>
<tr>
<td>WM</td>
<td>1.8 (0.7)</td>
<td>1.7 (0.5)</td>
<td>2.1 (0.8)</td>
</tr>
</tbody>
</table>

*Values are presented in milliliters unless otherwise indicated. GM indicates gray matter; WM, white matter.

Examination of cortical and subcortical temporal regions supported the hypothesized volume reduction in schizophrenia and its specificity to GM. This is consistent with findings of whole-brain and temporal subregion volume decrease. We previously reported an average decrease in GM volume of 6% for men and 3% for women with schizophrenia, relative to healthy controls. By evaluating both neocortical and temporolimbic structures, we could assess the nature and extent of volume change for specific temporal regions. The decreased volume is evident across the sample for the hippocampus, where both men (7%) and women (8.5%) with schizophrenia manifest comparable decrease in volume. For the amygdala, however, sex differences were observed. While men (8%) with schizophrenia show decrease in volume, women (10.5%) display increased volume. For the cortical regions, STG was substantially decreased in men (11.5%) but for women (4%), the decrease did not exceed that seen for the whole brain. Both patient groups showed decreased volume of TP (10% for men, 8.5% for women). Thus, it appears that hippocampal and TP volume are reduced in both men and women with schizophrenia. However, consistent with the hypothesis, volume reduction was more diffuse in men. Our finding on the hippocampus supports the conclusion of the meta-analysis of Nelson et al that hippocampal volume is reduced in schizophrenia. However, we did not find generalized reduction in amygdala volume as implied by their observation that the inclusion of amygdala enhanced the effect size. Most patients in previous studies were men. Our results indicate that the hippocampal finding is also evident in women, but reduced amygdala volume is seen only in men with schizo-
phrenia. Our results also support the hypothesis that temporal lobe abnormalities are not correlated with duration of illness and are observed in neuroleptic-naive patients. Therefore, they do not reflect treatment effects or chronicity.

An association between hippocampal volume and clinical measures was noted only in men, where lower volume was related to poorer premorbid functioning. The sparse and modest correlations between volumes and clinical measures are noteworthy and consistent with other studies that suggest that the neuroanatomic abnormalities may underlie more enduring disease features than those reflected in cross-sectional clinical ratings.

The hypothesized association between temporal volumes and memory was confirmed for the hippocampus, where volume correlated with better performance in all groups. In healthy women, volume was associated with better memory also for cortical temporal regions. Patients overall showed similar correlations to controls, as they did for the prefrontal regions. This may suggest that while volume reduction is associated with poorer neurocognitive abilities, it does not alter the association between neuronal integrity and performance. It is noteworthy that amygdala volume did not correlate with neurocognitive measures in any group. This supports the notion that hippocampal and cortical temporal regions have a greater role in cognition than the amygdala that has been associated with emotions. In the prefrontal subregions we observed correlations with cognitive measures for dorsal and not orbital cortex. There is corroborative evidence that the amygdala and the orbitofrontal cortex play a role in mediating emotion processing.

The connectivity among regions can be examined by correlating anatomic and physiologic features with combined use of structural and functional imaging.

No laterality effects were observed for temporal subregions. Some studies have reported laterализed volume reduction in subcortical and cortical areas. However, this has not been a consistent finding. We noted relative increase in glucose metabolism for the left medial temporal structures in affective disorder and schizophrenia: a magnetic resonance imaging study. Cereb Cortex. 1998;8:117-124.

The study has several limitations. Our sample included young adult patients with mild to moderate symptoms and without comorbidity. The generalizability of findings to older adults with a broader range of symptoms merits further investigation. The neuroanatomic sectors contain functionally distinct subdivisions, which could be differentially affected. More advanced procedures for automated feature analysis are needed. Given the sex differences in the amygdala, measures of emotion processing are lacking.

The anatomic data on frontal and temporal subregions indicate volume reductions in GM that generally exceed whole-brain changes. Lower volumes are evident at first presentation and are unrelated to illness duration. However, the effects in some regions are moderated by sex. The main difference between men and women with schizophrenia is that in men regions related to cognitive processing are predominantly reduced, whereas in women the abnormalities include parts of the neural system related to emotion processing. We also noted that neuroanatomic measures were unrelated to symptom severity assessed cross-sectionally. However, modest associations were established with neurocognitive performance, and these showed some specificity. Thus, prefrontal volumes correlated with attention and abstraction performance, while temporolimbic volume correlated with memory measures. These correlations were seen in patients and controls, suggesting similar coupling between brain volume and performance.

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