# Three-Dimensional Mapping of Temporo-Limbic Regions and the Lateral Ventricles in Schizophrenia: Gender Effects

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**Background:** *Local alterations in morphological parameters are poorly characterized in several brain regions widely implicated in schizophrenia neuropathology.*

**Methods:** *Surface-based anatomical modeling was applied to magnetic resonance data to obtain three-dimensional (3D) average anatomical maps and measures of location, shape, asymmetry, and volume for the lateral ventricles, hippocampus, amygdala, and superior temporal gyrus in schizophrenic (*n *= 25; 15 male) and normal subjects (*n *= 28; 15 male) matched for demographic variables. For all regions, intra-group variability was visualized and group differences assessed statistically to discriminate local alterations in anatomy across sex and diagnosis.*

**Results:** *Posterior hippocampal volumes, lengths, and widths were reduced in patients. The right amygdala showed volume increases in schizophrenia patients versus controls. Ventricular enlargements, pronounced in the left hemisphere, occurred in the superior and lateral dimensions in patients, and these effects interacted with gender. Superior horn anterior extremes, inferior horn volumes, and hippocampal asymmetries exhibited gender effects. Significant group differences were absent in superior temporal gyrus parameters. Finally, regional variability profiles differed across groups.*

**Conclusions:** *Clear morphometric differences of the lateral ventricles, hippocampus, and amygdala indicate regional displacements and shape distortions in several functional systems in schizophrenia. Alterations in these structures as mapped in 3D may provide the foundation for establishing brain abnormalities not previously defined at such a local level.* Biol Psychiatry 2001;50: 84–97 © *2001 Society of Biological Psychiatry*

**Key Words:** MRI, hippocampus, ventricles, amygdala, asymmetry, morphometry

## Introduction

Decades of imaging research confirm the presence of structural brain abnormalities in schizophrenia. Morphometric findings however, frequently lack consensus, and the regional specificity of cerebral anomalies are difficult to pinpoint, problems that are further complicated by clinical heterogeneity. Structural brain abnormalities reported in schizophrenia appear to include several functional systems, suggesting that different neurobiological mechanisms are involved, resulting from polygenetic influences, as well as environmental factors during neurodevelopment. Furthermore, gender differences are present in both the phenomenology and neurobiology of schizophrenia (Cowell et al 1996; DeLisi et al 1989; Narr et al 2000), suggesting that the mechanisms underlying schizophrenia involve sexually dimorphic developmental processes and that gender influences differences in brain morphology across diagnosis. Moreover, it has been suggested that schizophrenia may involve processes that compromise the specialization of association areas, resulting in alterations in normal structural and functional asymmetries (Nasrallah 1986). Finally, the large interindividual variability present in normal neuroanatomic structure makes it difficult to isolate regionally and disease-specific brain alterations in schizophrenia.

Until recently, morphometric studies have employed mostly volumetric analyses when comparing the structure of cortical and subcortical regions and/or alterations in asymmetry across diagnostic groups (Harrison 1999; Lawrie and Abukmeil 1998). These studies have, in part, been limited by the current resolution of in vivo imaging data, labor-intensive manual delineation methods, and the unavailability of sophisticated image analysis techniques. Notwithstanding, the most prominent morphological abnormalities reported in schizophrenia include ventricular

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enlargement and decreases in cortical and hippocampal volumes (Harrison 1999; Lawrie and Abukmeil 1998; Nelson et al 1998; Velakoulis et al 1999). Regions of frontal and temporal cortices, including the superior temporal gyrus, are also widely implicated in schizophrenia structural neuropathology (Gur et al 1998; Harrison 1999; Petty 1999; Rapoport et al 1999) although these cerebral abnormalities appear in other psychiatric populations. Finer image analysis strategies are therefore needed to isolate structural pathology specific to schizophrenia. For example, ventricular enlargement in schizophrenic patients remaining after brain size corrections implies that brain tissue is lost in specific regions after brain development is complete (Stevens 1997; Rapoport et al 1997). Yet little is known about how ventricular enlargement relates to distortions in surrounding anatomy that could help identify disease-specific differences in morphology.

Probabilistic atlasing approaches retain information about neuroanatomic complexity and variability in individual subjects. They may also reveal alterations in brain morphology in diseased populations by comparisons with imaging databases of normal anatomy (Mazziotta et al 1995; Thompson et al 1998). These methods are well suited for isolating pathology in diseased brains that manifests as subtle differences in regions of interest in linked functional systems across populations. These techniques can 1) preserve information on individual variability across many complex regions in three dimensions; 2) detect fine details in gross morphology, including very local shape differences and asymmetries; 3) provide maps of anatomic differences in a common stereotaxic coordinate system; 4) point to pathophysiological mechanisms that target different functional systems in schizophrenia, and that may implicate specific abnormal neurodevelopmental or degenerative processes (Gur et al 1998; Nopoulos et al 1995; Rapoport et al 1999); and 5) allow direct comparison of functional and structural data that can be combined across studies.

In this study we used a probabilistic atlasing approach (Mazziotta et al 1995; Thompson et al 1998) and methods that generate average surface models of internal anatomy obtained from magnetic resonance (MR) images (Thompson et al 1996a,b), to analyze cortical and subcortical regions widely implicated in schizophrenia neuropathology. We hypothesized, based on the work of others, that the lateral ventricles would show volume enlargements preponderantly in the left hemisphere (Lawrie and Abukmeil 1998) and that the superior temporal gyrus, hippocampus, and amygdala would show volume decreases in patients with schizophrenia versus controls (Nelson et al 1998). Furthermore, morphometric parameters, including location, variability, and cerebral asymmetries, as mapped in three dimensional (3D) stereotaxic space, were expected to show regional differences that would further discriminate diagnostic groups. The direction and extent of these morphometric differences however, were not known *a priori*, given that this study is among the first to assess fine alterations in morphology at such a local level. Statistical procedures were thus used to isolate regionally specific and potentially disease-specific differences in anatomy obtained from the stereotaxic parameters. Furthermore, given that gender differences are reported in brain morphology, and that schizophrenic patients have exhibited different patterns of neuroanatomic abnormalities across gender (e.g., Cowell et al 1996; DeLisi et al 1989; Narr et al 2000), we hypothesized that morphometric diagnostic effects would be modulated by gender. Analyses were thus performed to isolate any potential gender effects and interactions between gender and diagnosis for all regions of interest.

Table 1. Sample Characteristics (Mean ± SD)

| | SZ male ($n$ = 15) | NC male ($n$ = 15) | SZ female ($n$ = 10) | NC female ($n$ = 13) |
|---|---|---|---|---|
| Age (years) | 32.4 ± 7.9 | 33.0 ± 10.1 | 39.9 ± 10.2 | 35.2 ± 9.0 |
| Education (years) | 12.5 ± 2.3 | 14.1 ± 5.3 | 12.4 ± 2.5 | 13.6 ± 3.4 |
| Parental SES | 2.9 ± 1.5 | 3.1 ± 0.9 | 2.9 ± 0.6 | 2.7 ± 0.6 |
| Height (inches) | 69.9 ± 2.2 | 70.7 ± 3.3 | 65.5 ± 2.9 | 65.5 ± 2.9 |
| Age of onset (years) | 20.4 ± 3.9 | — | 19.9 ± 2.7 | — |
| Illness duration (years) | 12.0 ± 7.8 | — | 20.0 ± 9.8 | — |
| Left handedness | ($n$ = 1) | ($n$ = 1) | ($n$ = 1) | ($n$ = 1) |

Patients with schizophrenia (SZ) and normal control subjects (NC) were group matched for the demographic and clinical variables listed above. Significant gender effects were present for height ($p < .0001$) and for illness duration between male and female patients ($p < .03$).

SES, socioeconomic status.

## Methods and Materials

### *Subjects*

All schizophrenic patients ($n$ = 25; 15 male, 10 female) met DSM-III-R (American Psychiatric Association 1987) criteria and were not diagnosed with any other psychiatric illnesses. Two patients were receiving clozapine. All other patients were receiving conventional antipsychotic medication. Control subjects ($n$ = 28; 15 male, 13 female) were screened for any personal or family history of psychiatric illness. Male and female patient and control groups did not differ significantly in age, years of education, height, or parental socio-economic class (Table 1). Socio-economic status was obtained from the Office of Population Censuses and Surveys *Standard Occupational Classification* (1991) using details of "best-ever" parental occupation and handedness was defined using the Annett Handedness scale (Annett 1970). Exclusion criteria for all subjects included head trauma, drug abuse, and hereditary neurological disorders. Subjects gave informed written consent for participation with ethical

Table 2. Neuroanatomic Delineation of Subcortical Regions

| Region | Surfaces | Anterior | Posterior |
|---|---|---|---|
| Superior horn | lateral, medial, and superior | Frontal lobes where first discernible | Joining of superior and inferior horns (atrium) |
| Posterior horn | lateral and medial | Superior horn termination point | Last appearance in occipital lobe |
| Inferior horn | superior, inferior | Appearance in temporal lobes | Superior horn termination point |
| Anterior hippocampus | superior, inferior | Discrimination of pes hippocampi | Crus cerebri separates from the pons |
| Posterior hippocampus | superior, inferior | Termination level of anterior hippocampus | Crus of the fornix |
| Amygdala | superior, inferior | Where gray matter thickness is $>1.5\times$ larger than adjacent temporal cortex | When the pyramidal shape above inferior horn disappears (near the anterior commissure) |

The lateral ventricles were contoured in coronal slices by following cerebrospinal fluid–tissue interfaces with a mouse-driven cursor. Ventricular surfaces were digitized separately in each hemisphere according to neuroanatomic landmarks defining the superior, inferior, and posterior horns. The hippocampus and amygdala were contoured in oblique coronal sections using the anatomic boundaries summarized above.

permission obtained from the Bethlem & Maudsley Ethical Committee (Research).

## *Image Analysis Procedures*

High-resolution 3D spoiled gradient recalled (SPGR) MR images were acquired on a GE Signa 1.5T scanner as series of 124 contiguous 1.5 mm coronal slices ($256\times256$ matrix; 20 cm field of view (FOV)). Brain volumes were corrected for signal intensity inhomogeneities (Sled et al 1998), aligned, and linearly scaled in each axis by placing the anterior commissure (AC) at the origin (0, 0, 0) and the posterior commissure (PC) at coordinate position ($-23.5$, 0, 0) in *x, y,* and *z* co-ordinates in the midsagittal plane (Talairach and Tournoux 1988). This procedure is used to correct for differences in head position and orientation and places data in a common co-ordinate space that is specifically used for inter-individual and group comparisons.

## *Regions of Interest*

The lateral ventricles, hippocampus, amygdala, and the superior temporal gyrus were contoured in brain volumes resliced at 0.5 mm by the same technician blind to diagnosis. Previously developed neuroanatomic delineation protocols were followed (Bartzokis et al 1993; Jack et al 1995; Thompson et al 1996b; Thompson and Toga 1998; and Levitt et al 2000, in preparation, see Pruessner et al 2000 for review). Landmarks defining boundaries for each region of interest are summarized in Table 2. The lateral ventricles were divided into superior, posterior, and inferior horns and contoured on coronal slices. Cerebrospinal fluid (CSF)/tissue interfaces were digitized separately using a mouse-driven cursor and included superior, lateral, and medial CSF/tissue interfaces for the superior horns, and the lateral and medial surfaces for the inferior and posterior horns (boundaries shown in color in Figure 1).

The hippocampus was separated into anterior and posterior regions (Table 2). Superior and inferior connecting surfaces were digitized separately on oblique coronal slices (i.e., resliced orthogonal to the axis connecting the superior and inferior limits of the hippocampus). The superior temporal gyrus was contoured in coronal slices from the superior temporal sulcus (inferior boundary) to the anterior limit of the Sylvian fissure, at the temporal pole. The model was continued posteriorly to the crus of the fornix and/or the appearance of the angular gyrus.

## *Surface Mesh Averaging*

Surface meshes were constructed for each region of interest using a surface-based anatomical modeling approach as previously detailed (Thompson et al 1996a,b, 1997). Briefly, digitized points representing the tissue boundaries from each region are resampled and made spatially uniform by stretching a regular parametric grid over each surface. Homologous grid-points from corresponding surfaces from subjects in each group are then matched in all three dimensions to obtain average parametric meshes. The variation between these sets of points is calculated, and average surface representations for each region are created in 3D stereotaxic space that index the amount of intra-group variability present at each grid point (Figure 1). Maps of regional displacements between groups are similarly obtained as 3D displacement vectors between corresponding grid points from the group averaged surface meshes. Finally, length, width, volume, and the 3D extremes of brain regions are measured in stereotaxic co-ordinates and included as dependent variables in statistical analyses.

## *Reliability*

Intra- and inter-rater reliability was assessed for region of interest measures. For intra-rater reliability, one brain was randomly chosen and each region of interest contoured six times. For inter-rater reliability, six different randomly selected brains were contoured by two independent investigators who were trained on delineation protocols. To assess intra-rater reliability, the six ($n = 6$) drawings from the same brain were averaged and the 3D root mean square distance (r.m.s.) between equivalent points calculated. For inter-rater reliability, the surface contours from the six different brains are averaged separately for each investigator, and the averages are compared on a point-by-point basis to again establish the r.m.s. distances between equivalent points. Contouring error was $<1.5$ mm (3D r.m.s. distance) for each region in intra and $<2.0$ mm in inter-rater tests. Finally, intraclass correlation coefficients were obtained for volume measures and ranged between .89 and .96 for regions of interest.

Total brain volumes (raw and after AC-PC normalization) were obtained for all tissue types. Reliability in selecting representative tissue type intensity values for each tissue class (gray and white matter and CSF) from each brain volume was evaluated in 10 different test brains, $r > .94$ for all tissue types

(Sowell et al 1999). Finally, to cross-validate volume measurements of the lateral ventricles obtained from the surface contouring approach that were acquired in AC-PC scaled space with volume measurements obtained from the tissue-classified brain volumes in native space, lateral ventricle CSF voxels were isolated in tissue classified volumes. Correlations between tissue-classified lateral ventricular CSF (both hemispheres) were highly correlated with volume measurements obtained from the surface modeling protocol ($r = .89$, $p < .0001$ left hemisphere volume and $r = .91$, $p < .0001$ right hemisphere).

### *Statistical Analyses*

Volume and morphometric parameters obtained in 3D stereotaxic space (mm or $mm^3$) were compared using multivariate analyses of covariance (MANCOVAs), and followed by univariate analyses and tests of simple effects when appropriate. There is some argument in the statistical literature over whether MANOVAs protect against inflated Type I error (e.g., Bray and Maxwell 1982; Tabachnick and Fidel 1996). We did not employ a Bonferroni correction however, because it is overly conservative and several of the individual ANOVAs were conducted on dependent measures, such as group differences in regional volumes and asymmetries that are established in the literature. Nevertheless, only parameters of regions of interest considered as source variables and that were hypothesized to best characterize group differences in anatomy were included as dependent variables (see Results). Furthermore, univariate analyses involving a given factor were undertaken only when that factor was found to be significant in the omnibus multivariate analysis, or to interact significantly with the different dependent variables in this same analysis.

### *Covariates*

To compensate for linear AC-PC scaling, native AC-PC distances were cubed and assessed, along with brain volumes, as possible covariates by examining significant associations with the dependent variables. Only native AC-PC distances correlated significantly with dependent measures and were included as covariates when shown to significantly contribute to the variance (see Results). To examine whether the groups defined by sex and diagnosis differed in average native AC-PC distances or raw brain volume, separate two (Gender) by two (Diagnosis) ANOVAs were performed. Significant Gender effects were found for AC-PC distance, with men > women ($p < .006$; $26.84 \pm 0.24$ and $25.72 \pm 0.29$ mm, respectively, mean/SEM) and for brain volume ($p < .0005$; men = $1270.9 \pm 21.5$ $cm^3$; women = $1161.5 \pm 14.8$ $cm^3$). Finally, the effects of AC-PC scaling on brain volume were assessed, showing that a significant Gender effect remained in AC-PC scaled brain volumes, ($p < .04$; men = $945.8 \pm 41.7$ $cm^3$; women = $949.0 \pm 30.8$ $cm^3$). The highly significant effect of the covariate ($p < .00001$) suggests AC-PC scaling largely controls for head size differences across gender, although here its main goal is to allow group comparisons of anatomical maps in stereotaxic space. There were no significant effects of Diagnosis for either covariate.

## Results

### *Summary*

Subcortical regions revealed shape distortions and variability profiles that differed across diagnostic groups. Significant asymmetries in ventricular parameters including length, volume, and posterior extremes were seen in patients and normal control subjects. Ventricular volumes however, were bilaterally larger in male schizophrenic patients versus controls, although more prominently so in the left hemisphere (LH). Enlargements were shown to reflect significant superior and lateral displacements of superior and posterior horn ventricular surfaces. Conversely, posterior hippocampal volumes were reduced bilaterally in patients versus control subjects indexing reductions in hippocampal lengths and widths. Volumes of the right amygdala, however, were greater in patients compared to control subjects. Significant asymmetries were present in anterior hippocampal volumes in male groups (right hemisphere [RH] > LH). No significant differences were found in superior temporal gyrus parameters in groups defined by gender and diagnosis.

### *Lateral Ventricles*

**VARIABILITY AND DISPLACEMENT MAPS.** Ventricular enlargement, mapped in 3D, can be observed in the superior horns where the average surface representations from each of the four groups defined by gender and diagnosis are shown in color (Figure 2). Variability maps, however, revealed similar profiles in both diagnostic groups with greatest variability in the caudal posterior horns (14 mm) (Figure 3). Inferior horn variability was increased on the medial surfaces anteriorly (~6 mm) (Figure 3). Maps of regional displacements between groups show ventricular enlargement in the superior/vertical and lateral axes in schizophrenia. This feature is especially clear in the LH superior and posterior horns (Figures 4 and 5a). Furthermore, differences between the group averaged ventricular surface models are noticeable in the vicinity of the caudate head. Finally, displacements of the superior horn are found mirrored by surrounding neuroanatomic regions. This is shown by including a displacement map of the midsagittal corpus callosum (Narr et al 2000; Figure 5).

**STATISTICAL ANALYSES.** Morphometric variables from each hemisphere were used as repeated measures in two (Gender) by two (Diagnosis) by two (Hemisphere) analyses of covariance (ANCOVAs) for each lateral ventricle subregion. Dependent variables included 1) volume; 2) lateral; 3) superior; 4) inferior; 5) anterior; or 6) posterior extremes of the lateral ventricles in 3D stereo-

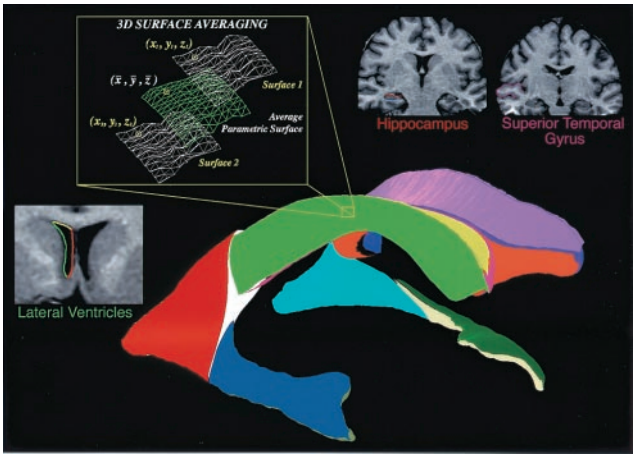


Figure 1. Parametric mesh construction. Contours of the lateral ventricles and other regions of interest were outlined in image volumes by following tissue interfaces with a mouse-driven cursor (see insets). Region of interest were further divided into subregions to isolate between group differences in specific neuroanatomic regions. For example, the lateral ventricles were divided into the superior, inferior, and posterior horns. Cerebrospinal fluid–tissue boundaries representing superior, medial, and lateral connecting surfaces of the superior horn; lateral and medial connecting surfaces of the posterior horn; and superior and inferior surfaces of the inferior horn were digitized separately (shown in different colors). **Inset:** For each surface the digitized points from the manual contours were regularized and a parametric grid overlaid. To create average surface meshes, equivalent grid points from each subject are matched. Geometric information about the deviations between individual surfaces are retained and can be viewed as the root mean square magnitude of displacement vectors required for mapping each individual onto the group average mesh.

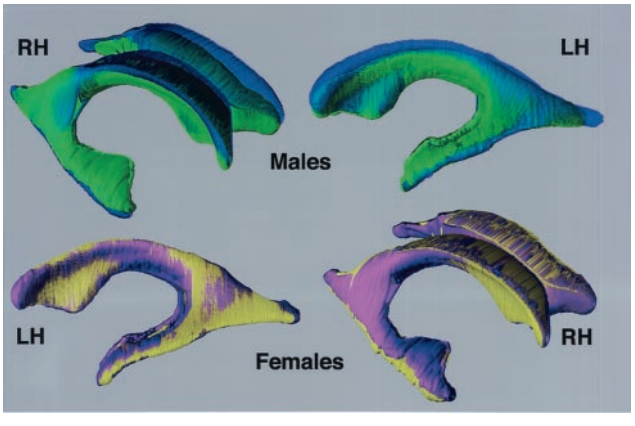


Figure 2. Color averages of the lateral ventricles in groups defined by sex and diagnosis. Average surface representations of the lateral ventricles are superimposed in different colors from each of the four groups defined by gender and diagnosis (male groups mapped above). Maps show locally distinct enlargements of the superior and posterior horns in male schizophrenic patients compared to control subjects (blue: male schizophrenic patients; green: male normal control subjects; purple: female patients; yellow: female control subjects; RH, right hemisphere; LH, left hemisphere).

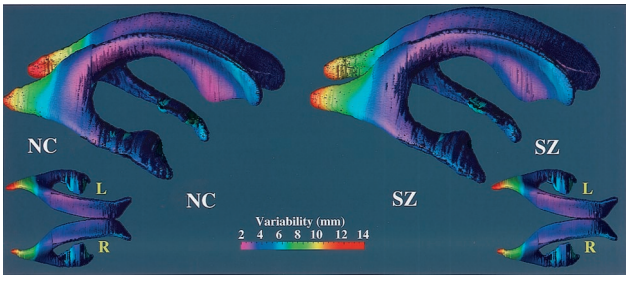


Figure 3. Three-dimensional average surface representation and variability map of the lateral ventricles. A diagonal view of the lateral ventricles in schizophrenic patients ($n = 25$, SZ) and normal control subjects ($n = 28$, NC) in both hemispheres. **Inset:** top view. The color bar represents the root mean square magnitude of variability in millimeters (mm). In both groups, variability increases toward caudal tip of the posterior horn (highest variability shown in red). In the inferior horn increased variability can be discriminated on anterior medial surfaces in both patient and control groups. L, left; R, right.

taxic space (mm); and 7) inferior length (rostral inferior horn to caudal posterior horn) and 8) superior length (rostral superior horn to caudal occipital horn). Only native AC-PC distances were significantly associated with the dependent measures (average $r = .25$, compared to $r = .08$ for raw brain volume) and were included in omnibus multivariate and appropriate univariate analyses.

Table 3 summarizes results showing highly significant

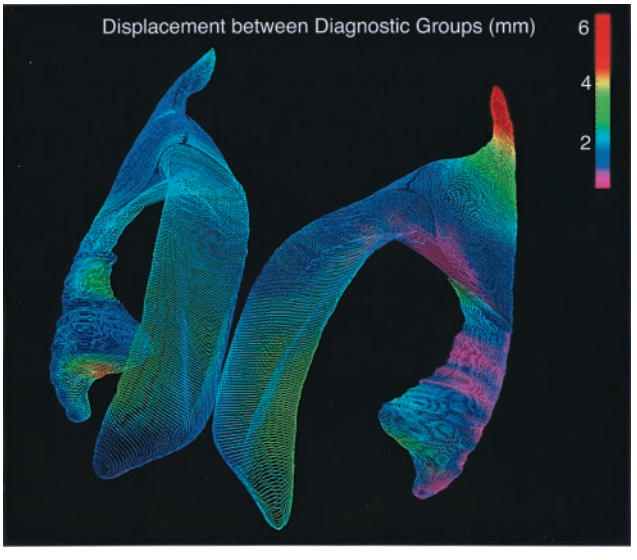


Figure 4. Three-dimensional displacement maps of the lateral ventricles. Top view of the lateral ventricles showing regional differences from average surface models between schizophrenic patients ($n = 25$, SZ) and normal control subjects ($n = 28$, NC) mapped across gender in both hemispheres. The color bar represents the root mean square magnitude of displacements in millimeters (mm). Diagnostic group displacements can be seen in the left posterior horn, on superior ventricular surfaces, and in the vicinity of the caudate nucleus (highest displacement shown in red).

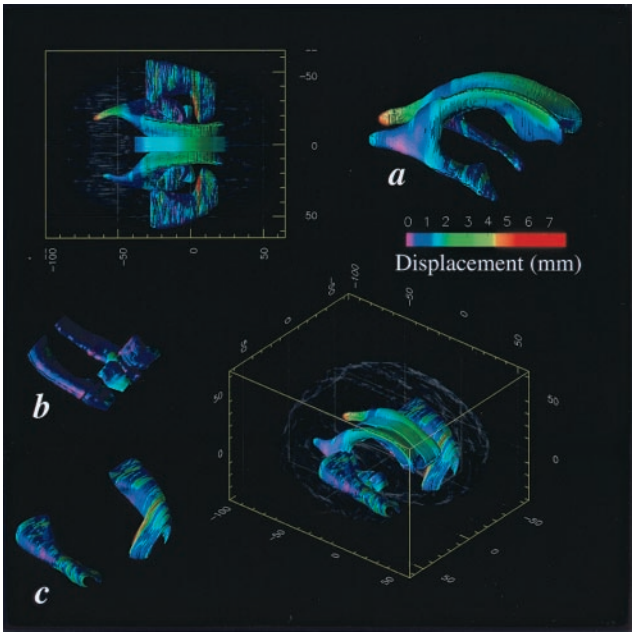


Figure 5. Three-dimensional (3D) displacement maps. Average surface representations of the lateral ventricles; the hippocampus and amygdala; the superior temporal gyrus and the corpus callosum that show the displacement (mm) between normal ($n$ = 28) and schizophrenic groups ($n$ = 25) mapped across gender in the same stereotaxic space. The magnitude of the 3D displacement vectors required to match the average surface models between diagnostic groups are encoded by the color bar (red = maximal displacement for these regions). **Insets: (a)** The lateral ventricles: Displacement is greatest in the posterior tip of the left posterior horn. Enlargement of the lateral ventricles in schizophrenic patients can clearly be discriminated in superior and lateral dimensions in stereotaxic space. A complementary displacement can be observed in the corpus callosum (composite) that is also found to exhibit different shape profiles in schizophrenic patients. **(b)** The hippocampus and amygdala: Displacement is reflected between group surface meshes in the anterior amygdala and medial and superior surfaces of the anterior and posterior hippocampus. **(c)** The superior temporal gyrus: Displacement is highest between groups in anterior regions and continues along the superior bank of the gyrus.

ventricular enlargements in the superior and posterior horns in male patients, more prominently in the LH, as well as superior and lateral stereotaxic displacements of ventricular extremes. Significant hemispheric asymmetries in both diagnostic groups included increased LH lengths, with LH extremes extending further posteriorly in stereotaxic space. Finally, gender differences were identified in superior horn anterior extremes (more rostral in men) and inferior horn volumes (larger in men).

### *Hippocampus/Amygdala*

**VARIABILITY AND DISPLACEMENT MAPS.** Hippocampal variability maps show an increase in overall variability in schizophrenic patients (6.1 mm) versus control subjects (5.3 mm) (Figure 6). Increased variability is present in the amygdala, with localized increases anteriorly. This feature occurs bilaterally in patients. Furthermore, variability is increased on the superior surfaces in anterior and posterior hippocampal regions in both diagnostic groups. Displacement maps (Figure 5b) show local stereotaxic displacements between diagnostic groups most prominently in RH and between the medial and superior surfaces of groups defined by diagnosis.

**STATISTICAL ANALYSES.** The same multivariate design above was used to assess group differences in morphometric parameters from anterior and posterior hippocampal regions and the amygdala. Dependent measures included 1) volume; 2) width; 3) length; and 4) superior and 5) inferior extremes. Again, raw brain volume and AC-PC distance were examined as possible covariates. Only AC-PC distance correlated significantly with dependent measures (average $r = .34$, $p < .05$, vs. raw brain volume, $r = .19$, $p > .05$).

Table 4 summarizes significant results from these statistical analyses. Significant bilateral decreases in posterior hippocampal volumes, lengths, and widths were present in patients versus control subjects. The right amygdala, however, was significantly larger in volume and extended more inferiorly in stereotaxic space in schizophrenic patients. The anterior hippocampus exhibited significant hemispheric asymmetries, which interacted with gender and diagnosis. Significant RH > LH anterior hippocampal volumes were seen in male subjects only.

### *Superior Temporal Gyrus*

**VARIABILITY AND DISPLACEMENT MAPS.** Variability was increased, and regions of high variability were more diffuse in patients with schizophrenia (14 mm+) compared to control subjects (12.5 mm) (Figure 7). Variability was greatest on dorsomedial surfaces in anterior and posterior gyral regions in the vicinity of the anterior planum temporale. Group displacement maps (Figure 5c) show distributed patterns of displacement. These group displacements were highest in the vicinity of the medial junction of the temporal and frontal lobes (limen insula). Multivariate analyses of superior temporal gyrus measures did not indicate significant group or hemispheric effects.

## Discussion

Advances in imaging analysis techniques have allowed us to map in three-dimensional space, complex and detailed morphometric differences in subjects with schizophrenia. Statistical differences show ventricular enlargements, abnormalities in limbic structures, and alterations in struc-

Table 3. Lateral Ventricles—Summary of Significant Results

| Region | Effect | | Mean ± SEM | | df | *F* | *p*-value |
|---|---|---|---|---|---|---|---|
| Superior horn | | | | | | | |
| Multivariate effects | Asymmetry | | | | (1,48) | 5.06 | $p < .02$ |
| | Gender × Diagnosis | | | | (1,48) | 8.18 | $p < .006$ |
| | Asymmetry × Diagnosis | | | | (1,48) | 10.05 | $p < .002$ |
| | Gender × Diagnosis × Dependent Variables | | | | (7,336) | 8.26 | $p < .0001$ |
| | Asymmetry × Dependent Variables | | | | (7,336) | 10.06 | $p < .0001$ |
| | Asymmetry × Diagnosis × Dependent Variables | | | | (7,336) | 3.33 | $p < .001$ |
| | Asymmetry × Gender × Dependent Variables | | | | (7,336) | 2.82 | $p < .007$ |
| | Asymmetry × Gender × Diagnosis × Dependent Variables | | | | (7,336) | 2.74 | $p < .009$ |
| Volume (univariate effects) | Gender × Diagnosis | | | | (1,48) | 8.06 | $p < .006$ |
| | Males | | | | (1,27) | 10.60 | $p < .003$ |
| | LH | SZ M > NC M | SZ M: 6305 ± 915.4 | NC M: 2639.5 ± 380.3 | (1,28) | 8.24 | $p < .006$ |
| | RH | SZ M > NC M | SZ M: 4742.1 ± 769.8 | NC M: 2588.3 ± 424.2 | (1,28) | 5.80 | $p < .02$ |
| | Asymmetry × Diagnosis | | | | (1,48) | 9.94 | $p < .002$ |
| | Patients | LH > RH | RH: 3879.7 ± 524.8 | LH: 5051.6 ± 663.2 | (1,24) | 16.46 | $p < .004$ |
| Superior extreme | Gender × Diagnosis | | | | (1,48) | 9.96 | $p < .002$ |
| | Males | | | | (1,27) | 24.57 | $p < .0001$ |
| | LH | SZ M > NC M | SZ M: 26.64 ± 0.61 | NC M: 22.96 ± 0.46 | (1,28) | 29.92 | $p < .0001$ |
| | RH | SZ M > NC M | SZ M: 26.23 ± 0.68 | NC M: 23.12 ± 0.47 | (1,28) | 17.01 | $p < .001$ |
| Superior length | Asymmetry | LH > RH | RH: 80.15 ± 1.56 | LH: 85.45 ± 1.69 | (1,48) | 11.35 | $p < .001$ |
| LH anterior extreme | Gender | M > F | M: 22.16 ± 0.47 | F: 22.04 ± 0.59 | (1,48) | 4.70 | $p < .03$ |
| LH lateral extreme | Gender × Diagnosis | | | | (1,48) | 5.80 | $p < .01$ |
| | Males | SZ M > NC M | SZ M: −20.80 ± 0.58 | NC M: −19.70 ± 0.32 | (1,28) | 6.32 | $p < .01$ |
| Posterior horn | | | | | | | |
| Multivariate effects | Asymmetry | | | | (1,48) | 5.76 | $p < .02$ |
| | Gender × Diagnosis × Dependent Variables | | | | (7,336) | 2.35 | $p < .03$ |
| | Asymmetry × Dependent Variables | | | | (7,336) | 5.59 | $p < .0001$ |
| | Asymmetry × Diagnosis × Dependent Variables | | | | (7,336) | 4.24 | $p < .0004$ |
| Volume (univariate effects) | Asymmetry | LH > RH | RH: 1873.8 ± 145.1 | LH: 2156.9 ± 156.1 | (1,49) | 11.50 | $p < .001$ |
| | Asymmetry × Diagnosis | | | | (1,49) | 3.52 | $p < .06$ |
| | Patients | LH > RH | RH: 1950.0 ± 198.8 | LH: 2418.5 ± 227.4 | (1,24) | 13.55 | $p < .001$ |
| LH volume | Gender × Diagnosis | | | | (1,48) | 4.09 | $p < .04$ |
| | Males | SZ M > NC M | SZ M: 2701.1 ± 311.1 | NC M: 1677.5 ± 248.5 | (1,28) | 6.60 | $p < .01$ |
| Posterior extreme | Asymmetry | LH > RH | RH: −58.49 ± 1.36 | LH: −63.36 ± 1.48 | (1,49) | 9.80 | $p < .002$ |
| Inferior horn | | | | | | | |
| Multivariate effects | Gender | | | | (1,48) | 5.00 | $p < .03$ |
| | Gender × Dependent Variables | | | | (7,336) | 5.59 | $p < .0001$ |
| LH volume (univariate effects) | Gender | M > F | M: 481.84 ± 38.54 | F: 451.42 ± 31.40 | (1,48) | 5.57 | $p < .02$ |

Multivariate analyses using Gender, Diagnosis, and Hemisphere as independent factors were performed for subdivisions of the lateral ventricles: 1) the superior; 2) inferior; and 3) posterior horns, in each hemisphere. Shape variables included: 1) volume; 2) lateral; 3) superior; 4) inferior; 5) anterior; or 6) posterior extremes of the lateral ventricles in three-dimensional stereotaxic space (mm); and 7) inferior length and 8) superior length. Anterior commissure–posterior commissure distance showed significant correlations with the dependent measures and was included as a covariate in omnibus analyses and univariate tests. M, male subjects; F, female subjects; NC, normal control subjects; SZ, schizophrenic patients; LH, left hemisphere; RH, right hemisphere.

tural asymmetries, in patients versus control subjects. Results indicated that gender interacts with disease processes. Female patients are less vulnerable to ventricular enlargement and to alterations in surrounding neuroanatomic regions compared to male patients (Narr et al 2000). Morphometric abnormalities in limbic regions, however, were present in both male and female patients, suggesting that disturbances in sexually dimorphic developmental processes influence different functional systems in schizophrenia. Results also provide information about the ranges of extremely local normal neuroanatomic variation, thus helping to generate more refined hypotheses concerning alterations of brain morphology in disease. Moreover, potentially disease-specific regional structural abnormalities, such as displacements and local distortions in anatomy that may not be detected with volumetric analyses, were isolated using the image analysis techniques described here. Specifically, displacements of the corpus callosum are shown to be associated with lateral ventricular enlargements. The callosum also exhibits shape pro-

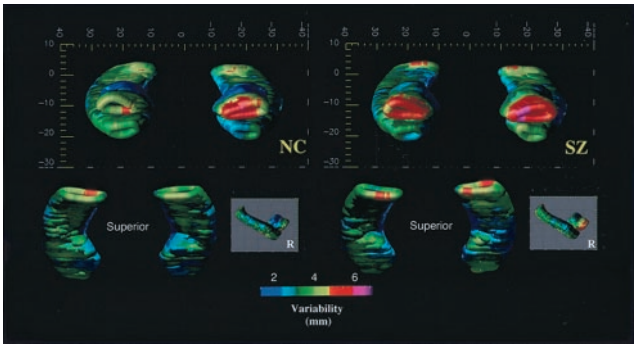


Figure 6. Three-dimensional variability maps of the hippocampus and amygdala. Average surface representations and variability profiles of hippocampus and amygdala are shown (front superior and inferior views; **inset:** right view) in each diagnostic group in stereotaxic co-ordinates (NC, normal control subjects, $n = 28$; SZ, schizophrenic patients, $n = 25$). The color bar represents the root mean square magnitude of variability in millimeters (mm) within each group. Variability is greatest in the anterior amygdala (left in NC, and bilaterally in SZ) and more pronounced in the anterior hippocampus (more diffuse in the RH in both groups) and extends along the superior and inferior surfaces of the posterior body.

files that are different in patients with schizophrenia compared to other patient populations that also show ventricular volume increases (Narr et al 2000). Our results add to this earlier work by showing that enlargements of the lateral ventricles in schizophrenia include significant displacements in the superior and lateral axes, away from midline. Finally, these results support the hypothesis that different functional systems are structurally altered in schizophrenia simultaneously. Cortical and subcortical regions should therefore be studied in concert when trying to distinguish patterns of morphology that may be population specific.

In spite of the power of the anatomical mesh modeling approach used in this study, there are some methodological limitations that primarily concern the linear scaling methods used to align and register AC and PC points in each brain volume for the purposes of describing group differences in anatomy. Nevertheless, these problems are inherent to many techniques that rely on anatomical averaging to describe morphological differences across populations. For instance, nonlinear registration approaches that become increasingly complex as local size and shape differences in morphology are eliminated may use an average or individual target templates to control for the enormous variability in brain size and shape across individuals. Results are often more difficult to interpret, however, especially given that typically the complex relationships between pathological deformations at the

Table 4. Hippocampus and Amygdala–Summary of Significant Results

| Region | Effect | | Mean ± SEM | | df | *F* | *p*-value |
|---|---|---|---|---|---|---|---|
| Posterior hippocampus | | | | | | | |
| Multivariate effects | Diagnosis | | | | (1,48) | 7.76 | $p < .007$ |
| | Diagnosis × Dependent Variables | | | | (4,192) | 7.51 | $p < .0001$ |
| RH volume (univariate) | Diagnosis | NC > SZ | SZ: 1163.36 ± 56.27 | NC: 1346.37 ± 50.32 | (1,48) | 7.73 | $p < .007$ |
| RH length | Diagnosis | NC > SZ | SZ: 23.49 ± 0.36 | NC: 24.76 ± 0.33 | (1,48) | 5.54 | $p < .02$ |
| RH width | Diagnosis | NC > SZ | SZ: 21.39 ± 0.36 | NC: 22.82 ± 0.45 | (1,48) | 4.61 | $p < .03$ |
| LH volume | Diagnosis | NC > SZ | SZ: 1202.44 ± 49.60 | NC: 1374.51 ± 53.12 | (1,48) | 6.40 | $p < .01$ |
| LH length | Diagnosis | NC > SZ | SZ: 24.30 ± 0.31 | NC: 25.56 ± 0.34 | (1,48) | 6.46 | $p < .01$ |
| LH width | Diagnosis | NC > SZ | SZ: 20.86 ± 0.46 | NC: 22.32 ± 0.40 | (1,48) | 9.68 | $p < .02$ |
| Anterior hippocampus | | | | | | | |
| Multivariate effects | Asymmetry × Gender × Diagnosis | | | | (4,192) | 4.64 | $p < .03$ |
| | Asymmetry × Gender × Diagnosis × Dependent Variables | | | | (4,192) | 4.88 | $p < .0009$ |
| Volume (univariate) | Asymmetry × Gender × Diagnosis | | | | (1,48) | 4.84 | $p < .03$ |
| | Males | RH > LH | LH: 336.85 ± 26.91 | RH: 429.47 ± 23.98 | (1,25) | 6.18 | $p < .01$ |
| Amygdala | | | | | | | |
| Multivariate effects | Diagnosis | | | | (1,48) | 4.91 | $p < .03$ |
| | Diagnosis × Dependent Variables | | | | (4,192) | 5.23 | $p < .0005$ |
| RH volume (univariate) | Diagnosis | SZ > NC | SZ: 687.68 ± 43.49 | NC: 588.28 ± 29.71 | (1,48) | 5.80 | $p < .01$ |
| RH inferior extreme | Diagnosis | SZ > NC | SZ: −15.01 ± 0.55 | NC: −13.20 ± 0.28 | (1,48) | 9.61 | $p < .003$ |
| RH width | Diagnosis | NC > SZ | SZ: 17.83 ± 0.38 | NC: 18.91 ± 0.37 | (1,48) | 4.12 | $p < .04$ |

Multivariate analyses were performed on shape parameters from the anterior and posterior hippocampus and amygdala in each hemisphere, with dependent measures including 1) volume ($mm^3$); 2) width; 3) length; and 4) superior and 5) inferior extremes in stereotaxic co-ordinates (mm). Independent measures included Hemisphere, Gender, and Diagnosis. Raw brain volume and anterior commissure–posterior commissure (AC-PC) distance (cubed) were examined as possible covariates. Only AC-PC distance was significantly correlated with the dependent measures and included as a covariate. Univariate tests were performed only when justified by the omnibus analysis. NC, normal control subjects; SZ, schizophrenic patients; LH, left hemisphere; RH, right hemisphere.

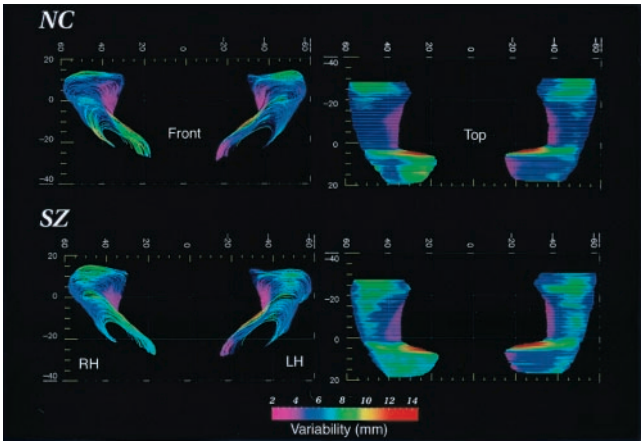


Figure 7. Three-dimensional variability maps of the superior temporal gyrus. Average surface representations and within-group variability profiles of the anterior superior temporal gyrus (NC, normal control subjects, $n = 28$; SZ, schizophrenic patients, $n = 28$). The color bar represents the root mean square magnitude of variability in millimeters (mm) within each group. **Left:** front view of superior temporal gyrus; **right:** top view of superior temporal gyrus. Variability is highest in anterior regions (more in right hemisphere) and posterior regions both groups, although more diffuse along the superior surface in schizophrenic patients.

cortex and of subcortical structures are not known. Nevertheless, many sophisticated techniques are available in the literature that have been validated for deciphering shape variations of cortical and subcortical structures between diseased populations (e.g., Bookstein 1989; Martin et al 1998; Toga and Thompson 2000; Thompson et al 2000b). Detailed descriptions and comparisons of these techniques, however, are beyond the scope of this discussion. For the purposes of this study we chose to use a two-point AC-PC registration given 1) that these points are measured with relatively little error; 2) clinical heterogeneity in schizophrenic populations complicates the issue of using an average anatomical template; 3) linear AC-PC scaling can be statistically removed from the data; 4) results are easily interpreted; and 5) widely used digital atlases rely on linear scaling to map composite MR data into stereotaxic space (Collins et al 1994). Notwithstanding, AC-PC scaling may influence results such that displacements in AC-PC scaled space may not represent the same displacements in real world co-ordinates, but this is nevertheless not expected to compromise the integrity of statistical differences in stereotaxic parameters between groups. The main objective of this study was to assess group differences in neuroanatomic parameters between populations and to implement a relatively simple and interpretable method to control for individual differences in brain size and head orientation. Finally, these methods have been validated for isolating structural pathology in other patient populations and for comparing morphometry and cognition (Thompson et al 1996a,b, 1997, 1998; Mega et al 1998; Thompson and Toga 1998).

## Ventricular Enlargements

Although ventricular enlargement is well established in schizophrenia (e.g., Lawrie and Abukmeil 1998; Raz and Raz 1990), the local profiles of ventricular enlargement and the relationships with surrounding neuroanatomic abnormalities have not previously been mapped. For example, regions related to specific limbic and forebrain circuitry are in close proximity to the lateral ventricles and include the corpus callosum, cingulate cortex, prefrontal regions, hippocampus, amygdala, thalamus, and the striatum. Male patients in this study were shown to exhibit significantly larger volumes of LH superior and posterior horns and RH superior horns. Furthermore, shape parameters obtained in stereotaxic space suggest that ventricular enlargement results from local displacements superiorly (vertical axis) and laterally (horizontal axis) in each hemisphere, as reflected in displacement maps between groups where relationships between the lateral ventricle and midsagittal callosal displacements can be discriminated (Figure 5). Decreased volumes of the posterior hippocampus in schizophrenic patients however, do not appear to reflect volume enlargements of the inferior horn, although medial inferior horn surfaces show increased patterns of variability. Furthermore, large displacements between diagnostic groups are present in the posterior tip of the occipital horns (Figure 3). Diagnostic effects, however, were not present for posterior ventricular extremes, but as the variability maps show, enormous variation exists in the caudal tips of the occipital horns, perhaps masking diagnostic differences.

### *Lateral Ventricle Asymmetry*

Asymmetries of the lateral ventricles are present early in development and appear to be a normal brain variant (Achiron et al 1997; Lodin 1968). In normal adults the left lateral ventricle is reported as wider than the right, and the left posterior horn as longer (Petty 1999). Nevertheless, ventricular asymmetries are extremely variable across individuals (Shapiro et al 1986), as shown in our variability maps of ventricular morphology (Figure 3). Earlier studies in schizophrenia report that LH ventricular volume asymmetries are typically greater in patients (Crow et al 1989; DeLisi 1991; Lawrie and Abukmeil 1998), and relate to age of onset (Aso et al 1995). Significant LH $>$ RH superior and posterior horn volume asymmetries and LH increases in ventricular lengths and posterior extremes confirm and complement previous findings. Volume

asymmetry, however, was shown to interact with diagnosis such that superior and posterior horn volumes were larger (23% and 20%, respectively) in LH versus RH in patients compared to control subjects (4% and 7% LH larger). Ventricular volume asymmetries are therefore more pronounced in LH in schizophrenic patients. This finding is compatible with views of increased left hemisphere vulnerability in schizophrenia, at least at the subcortical level (Crow 1997). Relationships between ventricular and cortical asymmetries, especially in perisylvian regions, remain to be determined.

### *Hippocampus and Amygdala*

The hippocampus is implicated in schizophrenia neuropathology, showing both microscopic and macroscopic alterations. Microscopic findings from postmortem studies report 1) reduced neuronal size (Arnold et al 1995; Benes et al 1991; Zaidel et al 1997); 2) abnormalities in neuronal orientation (Conrad et al 1991; Kovelman and Scheibel 1984); and 3) altered neuronal density (Falkai and Bogerts 1986; Jeste and Lohr 1989; Zaidel et al 1997) although negative reports are present (see Dwork et al 1997 for review). Furthermore, many (e.g., Bogerts et al 1993; Breier et al 1992; Gur et al 2000; Rossi et al 1994b; Shenton et al 1992), though not all macroscopic studies using imaging techniques have reported decreased volumes of the hippocampus (~4%) and amygdala (~4–5%) in schizophrenia (see Nelson et al 1998 for review). Confounds, however, have included using low resolution imaging data, sampling only parts of hippocampal and amygdala regions, clinical heterogeneity (Bogerts 1997), and positive publication biases. Notwithstanding, the majority of studies report effects in the same direction (Lawrie and Abukmeil 1998; Nelson et al 1998), indicating a bilateral decrease in hippocampal volume in patients with schizophrenia, regardless of head size corrections. Fewer studies have investigated hippocampal shape alterations in schizophrenia (Csernansky et al 1998; Haller et al 1996), but suggest finer morphological distortions are present that implicate specific hippocampal-cortical connections.

In this study the hippocampus and amygdala were modeled separately from high resolution MR data. Results support that hippocampal volume is bilaterally reduced in schizophrenia (Nelson et al 1998), although this effect was seen in posterior regions as opposed to anterior regions, where volume reductions have been reported in the minority of studies that separate the hippocampus into anterior (including some amygdala) and posterior sections (Bilder et al 1995; Shenton et al 1992; Suddath et al 1990; Wienberger et al 1992). Finally, results indicate that hippocampal lengths and widths are similarly reduced in schizophrenia. Other studies have reported reduced hippocampal length in patients, suggesting that this contributes to volume reductions (Bogerts et al 1990; Fukuzako et al 1996), although different neuroanatomic criteria for posterior boundaries were used. In general, posterior determination points of the hippocampus could compromise results and complicate cross-study comparisons.

Morphometry of the amygdala proper is less widely studied in schizophrenia. Increased volumes (although not statistically significant) have been observed in patients (Bogerts et al 1990). Significant increases in amygdala volumes, however, have been reported in female patients versus female control subjects (Gur et al 2000), as have significant amygdala volume decreases in schizophrenia (e.g., Breier et al 1992; Rossi et al 1994b). When included with hippocampal measurements however, the amygdala may contribute to decreased volume of the hippocampus/amygdala complex in schizophrenia (Nelson et al 1998). We report, however, that amygdala volume is significantly increased in patients versus control subjects, with inferior extremes lower (vertical axis) in patients and widths diminished. Interestingly, amygdala volumes were also increased in childhood-onset patients versus control subjects (Levitt et al 2000, unpublished data), although decreases in amygdala volume are also reported in children with schizophrenia-spectrum disorders (Yeo et al 1997). These findings, however, may not be relevant to the current study, given that subjects differed in several clinical and demographic arenas. Childhood onset studies may nevertheless provide some special clues to understanding the underlying neurobiology of schizophrenia. The amygdala, potentially involved in alterations of mood, affect, and perception of emotion in schizophrenia, connects to several regions that show structural abnormalities in patients including the hippocampus, cingulate and frontal cortex. Moreover, the amygdala receives moderate dopaminergic input from mesolimbic pathways, and enlargements in amygdala volume may be related to medication effects (Yeo et al 1997), or alternatively to a lack of pruning.

Variability maps of the hippocampus and amygdala are complementary to those of Csernansky and colleagues (Csernansky et al 1998). In their study a different approach involving the principles of general pattern matching and a template of hippocampal neuroanatomy was used to compare shape deformations in schizophrenic subjects. With this technique, information is obtained by warping an anatomical template to individual anatomy and details about the warp are preserved for analysis. Although this sophisticated approach has many advantages, the eigenvectors obtained from each individual warp are not precise in terms of stereotaxics and are therefore more difficult to comprehend than shape measurements obtained in stereo-

taxic space. Nevertheless, Csernansky and co-investigators (Csernansky et al 1998) implicated the lateral aspect of the head of the hippocampus and the medial aspect of the body. In our study (Figure 5), we contrasted displacement between average 3D surfaces between diagnostic groups rather than from an individual anatomical template. We saw differences on the superior and medial surfaces of the anterior hippocampus and a slightly smaller bilateral difference between the medial/superior surfaces of the posterior hippocampus. Distortions between groups, however, were most pronounced on the lateral surface of the right amygdala and less so on the lateral surface in LH. Furthermore, if variability may be interpreted as indicative of pathology or vulnerability, given that schizophrenic patients exhibit diffuse and an increased number of cerebral structural abnormalities, maps showing within-group differences implicate increased heterogeneity in patients. Nevertheless, methodological differences are a potential confound when comparing studies (Figure 6).

### *Hippocampus and Amygdala Asymmetry*

Many studies have reported decreases in hippocampal and amygdala volume in LH in schizophrenia (e.g., Bogerts et al 1990; Breier et al 1992; Rossi et al 1994a), and recently RH hippocampal volumes have been associated with age and illness duration in chronic schizophrenic patients (Velakoulis et al 1999). Moreover, subtle RH greater than LH hippocampal volume asymmetries are seen in normal populations (e.g., Pruessner et al 2000). Our results suggest anterior hippocampal regions in male subjects carry these asymmetries. When assessing percent difference in volume across hemispheres between the two diagnostic groups, means for the left and right amygdala were 7% different in control subjects, and 1% different in patients (larger in RH). The anterior hippocampus was 21% and 18% larger (RH) and the posterior hippocampus was 3% and 4% larger (LH) in control subjects and patients, respectively. These differences suggest volume asymmetries are pronounced in the anterior hippocampus in both diagnostic groups, although only significant in males.

### *Superior Temporal Gyrus*

The planum temporale is situated on the superior surface of the superior temporal gyrus caudal to the anterior transverse gyrus of Heschl. This region, associated with hemispheric specialization for language, is known to exhibit leftward asymmetries in humans (e.g., Geschwind and Levitsky 1968; Steinmetz et al 1990). Furthermore, language disorders and other neuropsychological deficits implicating temporal lobe function are common in schizophrenia (Crow 1997). Several studies (e.g., Barta et al 1997; DeLisi et al 1994; Flaum et al 1995; Kikinis et al 1994; Marsh et al 1997; Menon et al 1995; Shenton et al 1992) have implicated the superior temporal gyrus in schizophrenia, and studies have reported altered asymmetries of the planum (e.g., Barta et al 1997; Falkai et al 1995). Our results, however, fail to replicate those reported in the literature, which could in part be due to the landmarks chosen for defining gyral termination points. These points were at the level of the medial appearance of the supramarginal gyrus. Asymmetries or interactions with diagnosis in posterior temporal regions would thus not be detected (Ide et al 1996; Narr et al 2001; Witelson and Kigar 1992). Furthermore, because the superior temporal gyrus was measured as a whole, results regarding alterations in asymmetry of the planum temporale are obscured. Previous results imply that although this area may be larger in LH, there are increases in surrounding areas in RH (Steinmetz et al 1990). No conclusion regarding alterations of asymmetry for the planum temporale can thus be determined between diagnostic groups from this study. Nevertheless, differences in the patterns of variability on the superior surface of the superior temporal gyrus at least indicate a bilateral increase in variability and some regional displacement in the vicinity of the planum in patients versus control subjects (Figures 5 and 7).

The sensitive surface-based anatomical modeling techniques employed in this study were able to detect morphometric distortions and the direction of anatomical displacements in 3D stereotaxic space in schizophrenic patients as compared to control subjects. Ventricular enlargement revealed displacements that indexed specific shape alterations in surrounding anatomic regions. These changes are not thought to reflect decreases in brain volume, given that brain volume did not differ significantly between diagnostic groups. Further studies may elucidate whether parameters reflecting ventricular enlargement reflect displacements, volume reductions, or shape distortion of cingulate cortices, the thalamus, and the striatum. Furthermore, pronounced LH ventricular enlargement in patients supports the view that the left hemisphere is more vulnerable in schizophrenia neuropathology. Volume reductions of the hippocampus were accompanied by decreases in width and length. These findings may be assessed in relation to other regions that are connected via intricate limbic circuitry, such as prefrontal and entorhinal cortex and the thalamus. Furthermore, brain atlasing applications should incorporate clinical variables to further define alterations in structural parameters and facilitate a better understanding of neuropathological processes that are detected at the macroscopic level. Finally, these novel findings indicate specific morphometric arrangements of cerebral structures in schizophrenia. Future replications of these findings may ultimately serve, with the aid of sophisticated statistical

techniques, such as principal components or discriminant functions analyses, to characterize morphometric abnormalities that are indeed disease specific.

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## References

Achiron R, Yagel S, Rotstein Z, et al (1997): Cerebral lateral ventricular asymmetry: Is this a normal ultrasonographic finding in the fetal brain? *Obstet Gynecol* 89:233–237.

American Psychiatric Association (1987): Diagnostic Criteria from DSM-III-R. Washington, DC: American Psychiatric Association.

Annett M (1970): A classification of hand preference by association analysis. *Br J Psychol* 61:303–321.

Arnold SE, Franz BR, Gur RC, et al (1995): Smaller neuron size in schizophrenia in hippocampal subfields that mediate cortical-hippocampal interactions. *Am J Psychiatry* 152:738–748.

Aso M, Kurachi M, Suzuki M, et al (1995): Asymmetry of the ventricle and age at the onset of schizophrenia. *Eur Arch Psychiatry Clin Neurosci* 245:142–144.

Barta PE, Pearlson GD, Brill LB, et al (1997): Planum temporale asymmetry reversal in schizophrenia: Replication and relationship to gray matter abnormalities. *Am J Psychiatry* 154:661–667.

Bartzokis G, Mintz J, Marx P, et al (1993): Reliability of in vivo volume measures of hippocampus and other brain structures using MRI. *Magn Reson Imaging* 11:993–1006.

Benes FM, Sorensen I, Bird ED (1991): Reduced neuronal size in posterior hippocampus of schizophrenic patients. *Schizophr Bull* 17:597–608.

Bilder RM, Bogerts B, Ashtari M, et al (1995): Anterior hippocampal volume reductions predict frontal lobe dysfunction in first episode schizophrenia. *Schizophr Res* 17:1:47–58.

Bogerts B (1997): The temporolimbic system theory of positive schizophrenic symptoms. *Schizophr Bull* 23:423–435.

Bogerts B, Ashtari M, Degreef G, et al (1990): Reduced temporal limbic structure volumes on magnetic resonance images in first episode schizophrenia. *Psychiatry Res Neuroimaging* 35:1–13.

Bogerts B, Lieberman JA, Ashtari M, et al (1993): Hippocampus-amygdala volumes and psychopathology in chronic schizophrenia. *Biol Psychiatry* 33:236–246.

Bookstein FL (1989): Principal warps: Thin-plate splines and the decomposition of deformations. *IEEE Trans Pattern Analysis Machine Intelligence* 11:567–585.

Bray JH, Maxwell SE (1992): Analyzing and interpreting significant MANOVAs. *Rev Educ Res* 52:340–367.

Breier A, Buchanan RW, Elkashef A, et al (1992): Brain morphology and schizophrenia: A magnetic resonance imaging study of limbic, prefrontal cortex, and caudate structures. *Arch Gen Psychiatry* 49:921–926.

Collins DL, Neelin P, Peters TM, et al (1994): Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *J Comput Assist Tomogr* 18:192–205.

Conrad AJ, Abebe T, Austin R, et al (1991): Hippocampal pyramidal cell disarray in schizophrenia as a bilateral phenomenon. *Arch Gen Psychiatry* 48:413–417.

Cowell PE, Kostianovsky DJ, Gur RC, et al (1996): Sex differences in neuroanatomical and clinical correlations in schizophrenia. *Am J Psychiatry* 153:799–805.

Crow TJ (1997): Schizophrenia as failure of hemispheric dominance for language. *Trends Neurosci* 20:339–343.

Crow TJ, Colter N, Frith CD, et al (1989): Developmental arrest of cerebral asymmetries in early onset schizophrenia. *Psychiatry Res* 29:247–253.

Csernansky JG, Joshi S, Wang L, et al (1998): Hippocampal morphometry in schizophrenia by high dimensional brain mapping. *Proc Natl Acad Sci USA* 95:11406–11411.

DeLisi LE (1991): Brain imaging studies of cerebral morphology and activation in schizophrenia. In: Stuart E, Steinhauer R, Gruzelier EJH, et al, editors. *Neuropsychology, Psychophysiology, and Information Processing.* Amsterdam: New York: Elsevier.

DeLisi LE, Dauphinais ID, Hauser P (1989): Gender differences in the brain: Are they relevant to the pathogenesis of schizophrenia? *Compr Psychiatry* 30:197–208.

DeLisi LE, Hoff AL, Neale C, et al (1994): Asymmetries in the superior temporal lobe in male and female first-episode schizophrenic patients: Measures of the planum temporale and superior temporal gyrus by MRI. *Schizophr Res* 12:19–28.

Dwork A (1997): Postmortem studies of the hippocampal formation in schizophrenia. *Schizophr Bull* 155:385–402.

Falkai P, Bogerts B (1986): Cell loss in the hippocampus of schizophrenics. *Eur Arch Psychiatry Neurol Sci* 236:154–161.

Falkai P, Bogerts B, Schneider T, et al (1995): Disturbed planum temporale asymmetry in schizophrenia: A quantitative postmortem study. *Schizophr Res* 14:161–176.

Flaum M, Swayze VW 2nd, O'Leary DS, et al (1995): Effects of diagnosis, laterality, and gender on brain morphology in schizophrenia. *Am J Psychiatry* 152:704–714.

Fukuzako H, Fukazako T, Hashiguchi T, et al (1996): Reduction in hippocampal formation volume is caused mainly by its shortening in chronic schizophrenia: Assessment by MRI. *Biol Psychiatry* 39:938–945.

Geschwind N, Levitsky W (1968): Human brain: Left-right asymmetries in temporal speech region. *Science* 161:186–187.

Gur RE, Cowell P, Turetsky BI, et al (1998): A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Arch Gen Psychiatry* 55:145–152.

Gur RE, Turetsky BI, Cowell P, et al (2000): Temporolimbic volume reductions in schizophrenia. *Arch Gen Psychiatry* 57:769–775.

Haller JW, Christensen GE, Joshi SC, et al (1996): Hippocampal MR imaging morphometry by means of general pattern matching. *Radiology* 199:787–791.

Harrison PJ (1999): The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain* 122:593–624.

Ide A, Rodríguez E, Zaidel E, et al (1996): Bifurcation patterns in the human sylvian fissure: Hemispheric and sex differences. *Cereb Cortex* 6:717–725.

Jack CR Jr, Theodore WH, Cook M, McCarthy G (1995): MRI-based hippocampal volumetrics: Data acquisition, normal ranges, and optimal protocol. *Magnetic Resonance Imaging* 13:1057–1064.

Jeste DV, Lohr JB (1989): Hippocampal pathologic findings in schizophrenia. A morphometric study. *Arch Gen Psychiatry* 46:1019–1024.

Kikinis R, Shenton ME, Gerig G, et al (1994): Temporal lobe sulco-gyral pattern anomalies in schizophrenia: An in vivo MR three-dimensional surface rendering study. *Neurosci Lett* 182:7–12.

Kovelman JA, Scheibel AB (1984): A neurohistological correlate of schizophrenia. *Biol Psychiatry* 19:1601–1621.

Lawrie SM, Abukmeil SS (1998): Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. *Br J Psychiatry* 172: 110–120.

Lodin H (1968): Normal topography of the cerebral ventricular system in childhood. *Acta Radiol Diagnosis* 7:512–520.

Marsh L, Harris D, Lim KO, et al (1997): Structural magnetic resonance imaging abnormalities in men with severe chronic schizophrenia and an early age at clinical onset. *Arch Gen Psychiatry* 54:1104–1112.

Martin J, Pentland A, Sclaroff S, et al (1998): Characterization of neuropathological shape deformations. *IEEE Trans Pattern Analysis Machine Intelligence* 20:97–112.

Mazziotta JC, Toga AW, Evans A, et al (1995): A probabilistic atlas of the human brain: Theory and rationale for its development (The International Consortium for Brain Mapping; ICBM). *Neuroimage* 2:89–101.

Mega MS, Thompson PM, Cummings JL, et al (1998): Sulcal variability in the Alzheimer's brain: Correlations with cognition. *Neurology* 50:145–151.

Menon RR, Barta PE, Aylward EH, et al (1995): Posterior superior temporal gyrus in schizophrenia: Grey matter changes and clinical correlates. *Schizophr Res* 16:127–135.

Narr KL, Thompson PM, Sharma T, et al (2000): Mapping morphology of the corpus callosum in schizophrenia. *Cereb Cortex* 10:40–49.

Narr KL, Thompson PM, Sharma T, et al (2001): Three-dimensional mapping of gyral shape and cortical surface asymmetries in schizophrenia: Gender effects. *Am J Psychiatry* 158:244–255.

Nasrallah HA (1986): A controlled magnetic resonance imaging study of corpus callosum thickness in schizophrenia. *Biol Psychiatry* 21:274–282.

Nelson MD, Saykin AJ, Flashman LA, et al (1998): Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: A meta-analytic study. *Arch Gen Psychiatry* 55:443–440.

Nopoulos P, Torres I, Flaum M, et al (1995): Brain morphology in first-episode schizophrenia. *Am J Psychiatry* 152:1721–1723.

Petty RG (1999): Structural asymmetries of the human brain and their disturbance in schizophrenia. *Schizophr Bull* 25:121–139.

Pruessner JC, Li LM, Pruessner M, et al (2000): Volumetry of hippocampus and amygdala with high-resolution MRI and three dimensional analysis software: Minimizing the discrepancies between laboratories. *Cereb Cortex* 10:433–442.

Rapoport JL, Giedd J, Kumra S, et al (1997): Childhood-onset schizophrenia. Progressive ventricular change during adolescence. *Arch Gen Psychiatry* 54:897–903.

Rapoport JL, Giedd JN, Blumenthal J, et al (1999): Progressive cortical change during adolescence in childhood-onset schizophrenia. A longitudinal magnetic resonance imaging study. *Arch Gen Psychiatry* 56:649–654.

Raz S, Raz N (1990): Structural brain abnormalities in the major psychoses: A quantitative review of the evidence from computerized imaging. *Psychol Bull* 108:93–108.

Rossi A, Stratta P, Mancini F, et al (1994a): Magnetic resonance imaging findings of amygdala-anterior hippocampus shrinkage in male patients with schizophrenia. *Psychiatry Res* 52:43–53.

Rossi A, Stratta P, Mancini F, et al (1994b): Magnetic resonance imaging findings of amygdala-anterior hippocampus shrinkage in male patients with schizophrenia. *Psychiatry Res* 52:43–53.

Shapiro R, Galloway SJ, Shapiro MD (1986): Minimal asymmetry of the brain: A normal variant. *Am J Roentgenol* 147:753–756.

Shenton ME, Kikinis R, Jolesz FA, et al (1992): Abnormalities of the left temporal lobe and thought disorder in schizophrenia. *N Engl J Med* 327:604–612.

Sled JG, Pike GB (1998): Standing-wave and RF penetration artifacts caused by elliptic geometry: An electrodynamic analysis of MRI. *IEEE Trans Med Imaging* 17:653–662.

Sowell ER, Thompson PM, Holmes CJ, et al (1999): Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *Neuroimage* 9:587–597.

Steinmetz H, Rademacher J, Jäncke L, et al (1990): Total surface of temporoparietal intrasylvian cortex: diverging left-right asymmetries. *Brain Lang* 39:357–372.

Stevens JR (1997): Anatomy of schizophrenia revisited. *Schizophr Bull* 23:373–383.

Suddath RL, Christison GW, Torrey EF, et al (1990): Anatomical abnormalities in the brains of monozygotic twins discordant for schizophrenia. *N Engl J Med* 322:789–794.

Tabachnick BG, Fidell LS (1996): *Using Multivariate Statistics,* 3rd ed. New York: HarperCollins College Publishers.

Talairach J, Tournoux P (1988): *Co-Planar Stereotaxic Atlas of the Human Brain: A 3-Dimensional Proportional System, an Approach to Cerebral Imaging.* Stuttgart, New York: G. Thieme Medical Publishers.

Thompson PM, MacDonald D, Mega MS, et al (1997): Detection and mapping of abnormal brain structure with a probabilistic atlas of cortical surfaces. *J Comput Assist Tomogr* 21:567–581.

Thompson PM, Mega MS, Narr KL, et al (2000a): Brain image analysis and atlas construction. In: Fitzpatrick M, Sonka M, editors. *SPIE of Medical Image Processing and Analysis.* Bellingham, Washington: SPIE Press (In press).

Thompson PM, Moussai J, Zohoori S, et al (1998): Cortical variability and asymmetry in normal aging and Alzheimer's disease. *Cereb Cortex* 8:492–509.

Thompson PM, Schwartz C, Lin RT, et al (1996a): Three-dimensional statistical analysis of sulcal variability in the human brain. *J Neurosci* 16:4261–4274.

Thompson PM, Schwartz C, Toga AW (1996b): High-resolution random mesh algorithms for creating a probabilistic 3D surface atlas of the human brain. *Neuroimage* 3:19–34.

Thompson PM, Toga AW (1998): Anatomically-driven strategies for high-dimensional brain image warping and pathology detection. In: Toga AW, editor. *Brain Warping.* San Diego: Academic Press, 1998.

Thompson PM, Woods RP, Mega MS, et al (2000b): Mathematical/computational challenges in creating deformable and probabilistic brain atlases. *Hum Brain Mapping* 9:81–92.

Toga AW, Thompson PM (2000): An introduction to maps and atlases of the brain. In: Toga AW, Mazziotta JC, editors. *Brain Mapping: The Systems.* San Diego: Academic Press.

Velakoulis D, Pantelis C, McGorry PD, et al (1999): Hippocampal volume in first-episode psychoses and chronic schizophrenia: A high-resolution magnetic resonance imaging study. *Arch Gen Psychiatry* 56:133–141.

Weinberger DR, Berman KF, Suddath R, Torrey EF (1992): Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: A magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. *Am J Psychiatry* 149:890–897.

Witelson SF, Kigar DL (1992): Sylvian fissure morphology and asymmetry in men and women: Bilateral differences in relation to handedness in men. *J Comp Neurol* 323:326–340.

Yeo RA, Hodde-Vargas J, Hendren RL, et al (1997): Brain abnormalities in schizophrenia-spectrum children: Implications for a neurodevelopmental perspective. *Psychiatry Res Neuroimaging* 76:1–13.

Zaidel DW, Esiri MM, Harrison PJ (1997): Size, shape, and orientation of neurons in the left and right hippocampus: Investigation of normal asymmetries and alterations in schizophrenia. *Am J Psychiatry* 154:812–818.