Mapping Cortical Thickness and Gray Matter Concentration in First Episode Schizophrenia

We mapped regional changes in cortical thickness and intensity-based cortical gray matter concentration in first episode schizophrenia. High-resolution magnetic resonance images were obtained from 72 (51 male, 21 female) first episode patients and 78 (37 male, 41 female) healthy subjects similar in age. Cortical pattern matching allowed comparisons of cortical thickness and gray matter concentration at thousands of homologous cortical locations between subjects in three dimensions. Principal components analyses reduced measures obtained across the cortex to identify global differences in cortical thickness/gray matter concentration. First principal component factor scores showed significant effects of diagnosis, sex and age for both cortical measures. Diagnosis and age effects remained significant after brain size correction. Cortical thickness and gray matter concentration values were highly correlated. Statistical maps showed significant regional gray matter thinning in frontal, temporal and parietal heteromodal association cortices bilaterally in first episode patients. Regional reductions in cortical gray matter concentration were similar but pronounced in the superior temporal lobe. Regional reductions in cortical thickness and gray matter concentration are present at disease onset in brain regions linked with functional disturbances in schizophrenia. Cortical thickness and gray matter concentration mapping produce similar results, although the concentration metric may be influenced by diagnostic differences in extra-cortical cerebrospinal fluid and surface curvature/complexity.

Keywords: brain structure, heteromodal association cortices, imaging, prefrontal cortices, superior temporal gyrus

Introduction

A dialectic of hypotheses focusing on discrete cortical, limbic, striatal or diencephalic regional or system abnormalities [e.g. left superior temporal gyrus (Shenton et al., 1992), thalamus (Andreasen et al., 1994), fronto-striatal (Robbins, 1990), fronto-limbic (Weinberger et al., 1992, Bilder et al., 1995), cortico-striatal-pallido-thalamic (Braff et al., 1995), corticostriatal-thalamo-cerebellar (Andreasen et al., 1999),] versus hypotheses of widespread cortical gray matter abnormalities (Pfefferbaum et al., 1994; Lim et al., 1996a) perhaps maximal in heteromodal cortex (Pearlson et al., 1996), have been proposed to explain the underlying neurobiology of schizophrenia. These hypotheses are supported to degree by evidence from in vitro imaging studies. That is, existing imaging data confirms that multiple brain regions are affected in schizophrenia (Pearlson, 2000; Shenton et al., 2001). However, disease effects appear subtle

(Ward et al., 1996; Lawrie and Abukmeil, 1998) and regional inconsistencies in findings are common. Despite mixed results that may stem from small effect sizes in the presence of large inter-individual differences in brain structure, reductions in tissue volumes have been reported in some cortical and subcortical regions with relative consistency. Notably, gray matter deficits in lateral and medial temporal cortices, principally the superior temporal gyrus (and hippocampus subcortically), are reported in the majority of studies (Lawrie and Abukmeil, 1998; Wright et al., 1999b, 2000; Shenton et al., 2001). Gray matter deficits in other neocortical regions, including frontal cortices, particularly prefrontal and orbitofrontal regions, and parietal cortices, are also observed, although less frequently replicated (Shenton et al., 2001).

In humans, the majority of the cerebral cortex consists of association areas that form functional circuits reciprocally linking different cortical and subcortical centers to support higher cognitive functions. During prenatal development, migrating cells from the marginal zone of the telencephalic vesicle cause the cortex to thicken. The thickness of the cerebral cortex (ranging between 1.5 to 4.5 mm) thus reflects the density and arrangement of cells (neurons and neuroglia and nerve fibers) (Parent and Carpenter, 1995). Disturbances in neurogenesis, neuronal migration, differentiation and synaptogenesis and in mechanisms that involve neuronal and synaptic pruning have been implicated in schizophrenia (Jakob and Beckmann, 1986; Arnold, 1999). These factors may selectively affect the lamination of specific cortical regions and may prove a more sensitive measure by which to identify alterations in brain structure that form the basis of functional disturbances characterizing individuals with schizophrenia. However, to identify regional changes in cortical gray matter, magnetic resonance imaging (MRI) studies have traditionally compared volumes from discrete cortical regions of interest. More recently, a number of studies have also used sophisticated computational image analysis techniques that allow voxel-wise comparisons of gray matter distributions to be made throughout the entire brain volume (Wright et al., 1999a, Sigmundsson et al., 2001; Wilke et al., 2001; Ananth et al., 2002) or across the cortex exclusively (Thompson et al., 2001b; Sowell et al., 2002; Narr et al., 2003). Studies using voxel-based morphometry (VBM) methods (Ashburner and Friston, 2000) and/or using search regions exclusively at the cortex (Thompson et al., 2001b) sometimes refer to differences observed in the proportion of gray matter voxels, which are defined based on signal intensity thresholds, compared with voxels representing other
tissue types as gray matter density differences. However, to avoid confusion with the cell packing density measured cytoarchitectonically, in this study we will refer to changes in the proportion of gray matter voxels with respect to voxels representing other tissue types, as differences in intensity-based gray matter concentration. The relationships between intensity-based gray matter concentration and cortical thickness, which has been associated with neuronal packing density (Selemon et al., 1995, 1998), remain to be characterized.

A few studies have assessed cortical thickness in schizophrenia using postmortem data. These studies, focusing mainly on frontal regions, have shown that neuronal density is increased and that neuronal somal sizes are smaller in patients with schizophrenia compared with control groups (Selemon et al., 1995, 1998, 2003; Rajkowska, 1997). Importantly, increased neuronal packing density and smaller somal sizes appear to correspond with small reductions in cortical thickness. Increased neuronal density has also been observed in the anterior cingulate (Bouras et al., 2001) and in occipital regions (Selemon et al., 1995), while increases in the density of microglia has been reported in both frontal and temporal cortical regions (Radewicz et al., 2000). Post-mortem studies, however, are limited by the labor intensiveness of measurement methods, rendering it impractical to measure cellular density and thickness in all cortical regions. Furthermore, post-mortem specimens are less commonly available and sample sizes have been comparatively small in these investigations. Thus, at present, post-mortem studies may not be able to adequately address the regional specificity of cortical thickness changes in schizophrenia. In contrast, in vivo imaging data together with improvements in computational image analysis methods may allow differences in cortical thickness across the cortex to be estimated at high resolution using automated or semi-automated procedures.

To our knowledge, only three prior studies have examined cortical thickness in schizophrenia using imaging data. Of these, only one has assessed cortical thinning across the entire cortex at relatively high spatial resolution (Kuperberg et al., 2003). Results showed significant thinning in distributed areas of the cortex, but most prominently in frontal and temporal regions, in chronic schizophrenia patients relative to demographically similar healthy comparison subjects. A second study examined sulcal and gyral cortical thickness separately collapsed over each lobar region in patients with childhood and adolescent onset schizophrenia compared with age equivalent healthy controls (White et al., 2003). Significant thinning was observed in the cortex underlying the sulci in frontal, temporal and parietal regions in schizophrenia patients. Significant cortical thinning beneath the gyri was observed in the temporal lobe only. Another study examining exclusively prefrontal regions in first episode schizophrenia (Wiegand et al., 2004), however, did not detect cortical thinning averaged across the entire prefrontal lobe. Notwithstanding, patients showed significant reductions in prefrontal gray matter volume and cortical thickness and volume were significantly correlated. Interestingly, both age and age at first medication were negatively correlated with prefrontal cortical thickness in first episode patients but not in healthy control subjects, or in patients with first episode affective psychosis.

Despite mixed findings, prior evidence suggests that the pathophysiological mechanisms underlying schizophrenia affect cortical regions linked by functional circuitry and may manifest as abnormalities in cortical thickness and/or lamina thickness. Advanced image analysis methods and large sample sizes, however, may be necessary to isolate small and regionally specific differences in cortical thickness, given that effect sizes for global and regional gray matter abnormalities in volumetric studies are reported as small (Ward et al., 1996; Lawrie and Abukmeil, 1998). In this investigation, we therefore set out to examine cortical thickness at sub-voxel resolution across the entire cortex in a large sample of first episode patients, who had received little or no prior medication exposure, compared with demographically similar healthy subjects. To increase the likelihood of isolating regional changes cortical thickness, we used cortical pattern matching methods that control for individual differences in anatomy by matching homologous cortical regions between subjects (Thompson et al., 2000, 2001a). We hypothesized that cortical thinning would occur predominantly in association cortices (prefrontal, temporal and parietal regions), as implicated in earlier investigations of cortical thickness in schizophrenia (Selemon et al., 1998; Kuperberg et al., 2003; White et al., 2003). The modulating influences of sex and age were also examined, given that these variables have not been assessed in association with cortical thickness in schizophrenia. As a secondary goal, we aimed to determine whether intensity-based cortical gray matter concentration (the distribution of voxels segmenting as gray matter), as measured in VBM (Wright et al., 1999a; Sigmundsson et al., 2001; Wilke et al., 2001; Ananth et al., 2002) and earlier cortical pattern matching studies (Thompson et al., 2001b; Narr et al., 2003), indexes similar disease-related processes in schizophrenia. Principal components analyses were used to reduce cortical thickness and gray matter concentration values obtained at thousands of homologous cortical locations to examine overall effects of diagnosis and hemisphere. To identify the regional specificity of cortical thinning and/or reduced intensity-based gray matter concentration, statistical comparisons were performed at each cortical location. Relationships between cortical thickness and intensity-based gray matter concentration were compared at both the global and regional levels.

Materials and Methods

Subjects

Subjects included 72 (51 male, 21 female) patients experiencing their first episode of schizophrenia and 78 (37 male, 41 female) healthy comparison subjects, similar in age (patients: mean ± SD = 25.1 ± 4.7 years; controls: 27.5 ± 6.6 years). A structured diagnostic interview, the Schedule for Affective Disorders and Schizophrenia (Endicott and Spitzer, 1978) and the Structured Clinical Interview for Axis I DSM-IV Disorders (First et al., 1997) were performed to determine diagnostic status of patients. Patients were assessed longitudinally to confirm diagnoses made at the initial episode. Psychopathology was assessed using the Schedule for Affective Disorders and Schizophrenia Change Version with Psychosis and Disorganization Items rating scale and the Scale for the Assessment of Negative Symptoms (Andreasen, 1984). Thirty-nine patients (54%) were drug-naive at the time of the scan. The median number of days of antipsychotic medication received by the remaining first episode patients prior to scanning was 8 days (range = 1-187 days).

Healthy comparison subjects were recruited through local newspaper advertisements and community word of mouth. Healthy controls had no history of psychiatric illness as determined by clinical interview using the Structured Clinical Interview, nonpatient edition. Exclusion criteria for all subjects included serious neurological or endocrine disorders, any medical condition or treatment known to affect the brain, or meeting DSM-IV criteria for mental retardation. The North
Cortical Pattern Matching
Cortical pattern matching methods were used to spatially relate homologous regions of cortex between subjects. These matching algorithms are employed to ensure that gray matter measures (cortical thickness and intensity-based gray matter concentration) are obtained from equivalent cortical locations in each individual (Narr et al., 2001; Thompson et al., 2001b; Sowell et al., 2002). For cortical pattern matching, a cortical surface extractor is first used to obtain parametric models of the cortex from each MR volume (MacDonald et al., 1994). The cortical surface parameter space coordinates are made up of 65 536 surface points, but do not yet index the same anatomy across all subjects. In order to match equivalent cortical regions between subjects, the cortical surface models from each individual were used to outline 38 primary cortical sulci and fissures employing previously validated anatomic delineation protocols (www.loni.ucla.edu/~esowell/new_sulcvar.html). The manually derived sulcal landmarks were then used as anchors to drive the surrounding cortical surface anatomy of each individual into correspondence. That is, during the surface-warping procedures, the algorithm computes a 3-D vector deformation field that records the amount of x, y and z coordinate shift (or deformation), associating the same cortical surface locations in each subject with reference to the average anatomical pattern of the entire study group (Thompson et al., 2000, 2001a,b). In this study, the cortical pattern matching algorithms were used only to associate the same parameter space coordinates across subjects without actually warping each cortical surface model to the average. Cortical models thus remain in native space but are reparameterized such that the same anatomy bears the same coordinate locations in each subject. Reliability for the manual outlining of sulcal landmarks was established on six test brains, where the 3-D root mean square distance was <2 mm for all landmarks within and between raters as previously described (Narr et al., 2003).

Intensity-based Gray Matter Concentration
The 3-D deformation vector fields obtained from the cortical pattern matching methods allow a local measurement of gray matter to be made at spatially homologous cortical surface locations in each subject, referencing corresponding point locations in spatially registered tissue classified scalp-edited brain volumes. Tissue classified brain volumes were obtained using the partial volume correction method described above (Shattuck et al., 2001). To quantify cortical gray matter, we measured the proportion (or concentration) of voxels segmenting as gray matter based on signal intensity information, relative to all other tissue types, within a sphere with a fixed radius of 15 mm at homologous cortical surface locations in each individual. For each point on the cortical surface, gray matter concentration ratios (ranging between 0.00 and 1.00) can be compared statistically to provide maps indexing very local differences in tissue proportions across the entire cortex within or across groups (Thompson et al., 2001b; Sowell et al., 2002; Narr et al., 2003).

Cortical Thickness
To quantify cortical gray matter thickness, the 3-D deformation fields obtained from the cortical pattern matching algorithms were again used to equate homologous cortical locations between individuals. Cortical thickness was defined as the 3-D distance measured from the cortical white-gray matter boundary in the tissue classified brain volumes (Shattuck et al., 2001) to the cortical surface (gray–CSF boundary) in each subject using the 3-D Eikonal equation (Sapiro, 2001). Tissue classified brain volumes were resampled at 0.33 mm cubic voxels to obtain distance measures indexing gray matter thickness at sub-voxel spatial resolution. Gray matter thickness was then measured at thousands of homologous cortical locations in each subject. Importantly, while the gray matter concentration measure estimates the ratio of gray matter within the cortical mantle relative to other tissue types, gray matter thickness quantifies only the distance of the cortical ribbon across white matter and cerebrospinal fluid (CSF) as based on signal intensity thresholds using a partial volume correction method (Shattuck et al., 2001).

Statistical Analyses
To circumvent the need to correct for statistical comparisons made at each cortical surface location (surface points) and to examine global effects of cortical gray matter, Principal Component Analysis (PCA) was first used to reduce (i) intensity-based gray matter concentration and (ii) cortical thickness values, measured at the 65 536 spatially homologous cortical surface locations in each individual, into principal components. PCA was performed for each hemisphere separately to allow the examination of hemispheric asymmetries and potential interactions between Hemisphere and Diagnosis in statistical analyses. The scree plots in Figure 1 show that the first components for gray matter concentration explained 28 and 29% of the total variance for the left and right hemispheres respectively. For cortical thickness, 33% of the total variance was explained by the first PCA component for both hemispheres. Only components falling above the elbow (or bend) of the scree plots were examined statistically. Figure 1 shows that approximately four components fall above the elbow of the scree plots for all measures. Figure 1 also shows the variance accounted for by additional principal components where no factor beyond the fourth component accounts for >4% of the total variance. Factor scores from the first four PCA components were thus included as dependent variables in statistical analyses using the General Linear Model (GLM). Factor scores from the left and right hemisphere were included as repeated measures. Diagnostic group (Schizophrenia patients; Normal controls) was included as a categorical predictor variable. Sex was included as a covariate, given that different ratios of males and females were present within each diagnostic group. Interactions between Diagnosis and the covariate, Sex, were also examined. Age was included as a second covariate. All interactions with the within subjects variable, Hemisphere, were included in the model. To confirm that total brain size did not contribute to any observed schizophrenia effects, statistical analyses were performed both with and without covarying for total brain volume. A similar statistical model was used to examine group differences in total brain volume and total gray matter, white matter and CSF volumes, although Hemisphere was not included as a variable.

To follow up significant omnibus results from analyses of PCA factor scores, statistical comparisons were performed at each cortical surface location in 3-D to reveal the regional specificity of intensity-based gray matter concentration and cortical thickness abnormalities in first episode schizophrenia. Main effects of Diagnosis were again examined after covarying for Sex. Interactions between Diagnostic group and the covariate, Sex, were also examined. Regional effects of Age were not examined given that diagnostic groups were similar in age and showed
similar aging effects for the PCA factor scores as shown in Figure 2. Finally, Diagnostic group differences were examined within male and female groups separately to confirm that sex-related differences in global brain size did not influence any observed disease-related effects. The results of these tests, performed at 65 536 cortical locations in 3-D, were mapped onto the group-averaged cortical surface model where statistically significant results are indexed in color. For all analyses, a two-tailed alpha level of 0.05 (uncorrected) was used as the threshold for statistical significance.

Finally, Pearson’s correlation coefficients were used to examine relationships between cortical intensity-based gray matter concentration and cortical thickness for the same PCA components. Correlations between gray matter concentration and cortical thickness measures were also performed at each cortical location in 3-D to show the extent of statistical relationships at the regional level. The average and variability distributions of cortical thickness and gray matter concentration were examined within each group.

Results

Total Brain and Brain Tissue Volumes

Main effects of Diagnosis were absent for total brain volume although the effect of the covariate, Sex, was highly significant $F(1,145) = 48.13, P < 0.00001$. For total gray matter volume, significant main effects of Diagnosis $F(1,145) = 4.81, P < 0.02$, Sex $F(1,145) = 35.20, P < 0.00001$ and Age $F(1,145) = 9.14, P < 0.002$ were detected. After correcting for total brain volume, effects of Diagnosis $F(1,144) = 14.06, P < 0.0002$ and Age $F(1,144) = 42.54, P < 0.00001$ remained significant. White matter volumes showed only main effects of Sex $F(1,145) = 32.90, P < 0.00001$ and Age $F(1,145) = 4.01, P < 0.05$. After covarying for total brain volume, only main effects of Age remained significant $F(1,144) = 12.23, P < 0.0006$. CSF volumes showed main effects of Diagnosis $F(1,145) = 3.93, P < 0.049$, Sex $F(1,145) = 14.77, P < 0.0002$ and Age $F(1,145) = 7.64, P < 0.006$. After brain size correction, main effects of Diagnosis $F(1,144) = 6.58, P < 0.01$ and Age $F(1,144) = 10.10, P < 0.00001$ were significant. Means and standard deviations for total brain and brain tissue volumes are provided in Table 1 in groups defined by Sex and Diagnosis. To show relative group differences after correcting for total brain volume, tissue volumes were residualized for brain volume and residuals were added to the means obtained from the entire sample for each tissue compartment.

Intensity-based Gray Matter Concentration PCA Scores

Factor scores from the first principal component, accounting for ~28% of the variance, showed significant main effects of Diagnosis $F(1,145) = 15.79, P < 0.0001$, Sex $F(1,145) = 4.23, P < 0.01$ and Age $F(1,145) = 6.11, P < 0.01$ for gray matter concentration. No effects of Hemisphere or interactions between the predictor variable and any of the covariates were observed. Effects of Diagnosis $F(1,144) = 16.35, P < 0.0001$ and Age $F(1,144) = 6.15, P < 0.01$ remained significant after covarying for total brain volume. Figure 2 (top panel) shows factor scores from the first PCA component plotted by age in groups defined by Sex and Diagnosis. Factor scores from the second principal component (~8% of the total variance) showed main effects of Age $F(1,145) = 4.01, P < 0.04$ and Hemisphere $F(1,145) = 11.39, P < 0.001$ and a significant interaction between Age and Hemisphere $F(1,145) = 11.94, P < 0.001$. These results were similar after covarying total for brain volume, showing significant Age $F(1,144) = 7.46, P < 0.02$ and Hemisphere $F(1,144) = 9.88, P < 0.002$ effects, as well as a significant Age by Hemisphere interaction $F(1,144) = 12.18, P < 0.0006$. Factor scores from the third principal component (~6% of the variance), only showed a main effect of Sex both before $F(1,145) = 7.83, P < 0.006$ and after brain size correction $F(1,144) = 5.60, P < 0.02$. Finally, factor scores from the fourth principal component (~4% of the variance)
revealed main effects of Sex \( F(1,145) = 3.87, P < 0.05 \) and Age \( F(1,145) = 6.90, P < 0.01 \) that remained significant after brain size correction. Sex: \( F(1,144) = 6.99, P < 0.01 \); Age: \( F(1,144) = 7.03, P < 0.009 \).

**Cortical Thickness PCA Scores**

Factor scores from the first principal component for cortical gray matter thickness, accounting for 33% of the total variance, showed main effects of Diagnosis \( F(1,145) = 6.37, P < 0.01 \), Sex \( F(1,145) = 10.24, P < 0.001 \) and Age \( F(1,145) = 6.97, P < 0.009 \). Effects of Diagnosis \( F(1,144) = 7.22, P < 0.008 \) and Age \( F(1,144) = 7.21, P < 0.008 \) remained significant after covarying for total brain volume. No interactions between the predictor variable, Diagnosis, and any of the covariates were observed. Figure 2 (bottom panel) shows factor scores from the first PCA component plotted by age in groups defined by sex and diagnosis. Factor scores from the second principal component (~9% of the variance) showed main effects of Age only \( F(1,145) = 7.35, P < 0.008 \) that were also significant after brain size correction \( F(1,144) = 8.51, P < 0.004 \). Third component factor scores (~4% of the variance) showed a main effect of Hemisphere \( F(1,145) = 5.78, P < 0.02 \) that was no longer significant after taking brain volume into account. Factor scores from the fourth principal component (also ~4% of the variance) showed main effects of Sex \( F(1,145) = 9.49, P < 0.002 \) and Age \( F(1,145) = 4.09, P < 0.05 \), and a significant Hemisphere by Diagnostic group interaction \( F(1,145) = 4.37, P < 0.04 \).
same effects were significant after covarying for total brain volume; Sex: \( F(1,144) = 6.06, P < 0.01 \); Age: \( F(1,144) = 4.10, P < 0.04 \); Hemisphere by Diagnostic group, \( F(1,144) = 4.37 \), \( P < 0.04 \).

### Regional Effects of Intensity-based Gray Matter Concentration

To isolate regional differences in intensity-based gray matter concentration across the cortex, we compared gray matter concentration ratios at all cortical surface locations in 3-D. Probability values, indexed in color, were mapped back onto an averaged cortical surface model from the entire group at each 3-D point location. Probability values showing positive and negative effects were mapped separately to determine whether group differences reflect increased or decreased gray matter concentration. Figure 3 shows statistical mapping results for (i) comparisons between schizophrenia patients and healthy subjects after covarying for sex (top row); (ii) between groups defined by sex (second row); (iii) interactions between sex and diagnosis (third row); and (ii) effects of diagnosis mapped within male and female groups separately (last row).

The top row of Figure 3 shows that first episode patients possess significant decreases in intensity-based gray matter concentration in dorsolateral prefrontal cortex, most prominently in the middle frontal gyrus, and in the temporal lobe, particularly the superior temporal gyrus bilaterally. Further decreases are visible in inferior parietal regions, and in occipital regions in the left hemisphere. No significant increases in intensity-based gray matter concentration were observed in schizophrenia patients compared with controls. The second row shows regional increases in gray matter concentration in superior parietal regions in females compared with males (right). Males fail to show any significant regional increases in gray matter concentration compared with females (left). Statistical maps in the third row show that sex by diagnosis interactions were absent for local gray matter concentration measures as consistent with the PCA factor score comparisons. Finally, in the last row, effects of diagnosis compared separately within male (right) and female (left) groups show that decreases in intensity-based gray matter concentration are more pronounced in the pre- and post-central gyrus in males, although the spatial profiles possess many similarities between males and females overall.

### Regional Effects of Cortical Thickness

Statistical maps in Figure 4 show the same statistical comparisons described above, but include cortical thickness values obtained at homologous cortical locations in 3-D as the dependent measure. The top row of Figure 4 shows schizophrenia effects after covarying for biological sex. Cortical thinning is evident in dorsolateral prefrontal and lateral temporal cortices, consistent with the pattern of results observed for gray matter concentration (Fig. 3). Cortical thinning, however, appears more spatially diffuse in the left hemisphere in temporal and inferior parietal regions when compared with the regional gray matter concentration results. No significant regional increases in cortical thickness were observed in first episode patients (top left). Overall, females possessed thicker cortices in parietal regions (second row) even without brain size correction. Males, however, exhibited thicker cortex in frontal regions proximal to the interhemicpheric fissure. The statistical maps in the third row show interactions between sex and diagnosis: they suggest that left anterior temporal and medial frontal regions are more affected in female schizophrenia patients. In the last row, gray matter thinning appears most prominent in temporal and dorsolateral prefrontal regions in female patients compared with female comparison subjects. Male patients, however, appear to exhibit regional decreases in gray matter thickness most prominently in the vicinity of the pre and postcentral sulcus bilaterally, although some gray matter thinning is also evident in temporal and frontal regions.

### Associations between Intensity-based Gray Matter Concentration and Cortical Thickness

Pearson’s correlation coefficients showing relationships between factor scores from the first four principal components for intensity-based cortical gray matter concentration and thickness are presented in Table 2. Factor scores were highly correlated for the same components in each hemisphere with all probability values of <0.001. Figure 5 shows average cortical gray matter thickness (top) and gray matter concentration (middle) distributions across all subjects. Average cortical thickness ranged between 2 and 4.5 mm, and intensity-based gray matter concentration ratios ranged between 0.25 and 0.65 across the cortex. Average and variability profiles for both measures were similar within each group (figures not shown). The bottom panel of Figure 5 shows the statistical relationships between gray matter concentration and cortical thickness at
each cortical location in 3-D. Cortical gray matter indices were significantly (positively) correlated across all cortical locations with the exception of the temporal poles.

**Discussion**

**Total Brain and Brain Tissue Volumes**

Patients experiencing their first episode of schizophrenia failed to show significant differences in brain volume compared with healthy comparison subjects. On average male patients possessed slightly larger mean brain volumes than male controls (Table 1). These mean increases, however, were attributable to the significantly larger CSF volumes observed across both male and female schizophrenia patients. Importantly, patients exhibited significant reductions in global gray matter, with respect to comparison subjects, that were more pronounced after taking total brain volume into account. No diagnostic differences were observed for white matter tissue volumes and no interactions between diagnostic group and sex or age were detected for any brain tissue compartment. The presence of global CSF increases and gray matter decreases match many previous observations in schizophrenia (Lawrie and Abukmeil, 1998; Harrison, 1999; Wright et al., 2000; Shenton et al., 2001). Moreover, these abnormalities have been identified in first episode patients (Lim et al., 1996b; Zipursky et al., 1998). Many previous studies, however, have failed to detect significant global differences in gray matter in schizophrenia (Ward et al., 1996; Lawrie and Abukmeil, 1998). Our findings thus illustrate the importance of using large sample sizes to detect small differences in brain tissue volumes as appear present in individuals with schizophrenia. Although some evidence suggests that gray matter loss in schizophrenia is progressive, at least in the early stages of the illness and may influenced by antipsychotic medication exposure (Cahn et al., 2002), our data supports the idea that gray matter abnormalities are present near disease onset in patients with little or no prior medication treatment.

**PCA Analyses of Cortical Gray Matter Changes**

PCA analyses of intensity-based gray matter concentration and cortical thickness values obtained from homologous cortical regions, confirm the presence of cortical (as opposed to whole brain) gray matter changes in first episode schizophrenia. The first principal components, accounting for 27–33% of the total variance for both cortical gray matter indices (concentration and thickness) sampled at high resolution across the entire cortex, showed significant disease-related effects. Although cortical thickness values represent the distance between the cortical white–gray matter boundary and the external gray matter–CSF boundary, and gray matter concentration measures reflect the proportion of gray matter within the cortical mantle with respect to other tissue types, results showed that these measures are highly correlated. That is, intensity-based gray matter concentration and cortical thickness values appear to index the same or similar disease-related processes both at the global (i.e. when measures are reduced using PCA) and at the

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**Figure 3.** Statistical maps showing significant regional differences in cortical gray matter concentration (i) in patients with first episode schizophrenia (sz) compared with healthy subjects (nc) after covarying for sex (top row); (ii) between male and female subjects across diagnostic groups (second row); (iii) for interactions between sex and diagnosis (third row); and (iv) between diagnostic groups with in males (right) and females (left). Probability values, indexed in color, show positive and negative effects.
regional level (Table 2, Fig. 5). Differences in cortical gray matter concentration reduced using PCA, however, were not detected previously in chronic schizophrenia even in the presence of significant extra-cortical (sulcal and subarachnoid) CSF increases (Narr et al., 2003). The sample size of the prior investigation, however, was only one-third of the current sample size. Thus, in the presence of small effect sizes, global intensity-based gray matter concentration findings may have remained undetected.

Regional Effects of Intensity-Based Gray Matter Concentration

Some cortical regions, such as lateral and medial temporal cortices and, to a lesser extent, frontal and parietal cortices, appear most implicated in the structural neuropathology of schizophrenia (Lawrie and Abukmeil, 1998; Shenton et al., 2001). Results from volumetric studies (Goldstein et al., 1999; Gur et al., 2000; Sanfilipo et al., 2000) and investigations of gray matter concentration throughout the brain using VBM (Wright et al., 1999a; Sigmundsson et al., 2001; Wilke et al., 2001; Ananth et al., 2002), however, frequently disagree concerning the spatial localization of cortical gray matter changes. In our investigation, cortical gray matter concentration and thickness measures showed similar regional effects when comparisons were performed at thousands of homologous cortical locations in 3-D. Regional changes in intensity-based gray matter concentration showed that patients exhibit decreased cortical gray matter proportions in heteromodal association areas, particularly in superior temporal and lateral prefrontal cortices (Fig. 3). Reduced gray matter proportions were also apparent in the inferior parietal lobules bilaterally and in left hemisphere occipital regions. These spatial patterns appeared similar when comparing female diagnostic groups separately. However, comparisons of men with schizophrenia to healthy male controls also showed reductions of gray matter concentration in and around the pre and postcentral gyri. In spite of some differences in the spatial profiles of gray matter reductions within male and female groups, significant interactions between sex and diagnosis were not observed at the regional (or global) level. Thus, we do not believe the independent interpretation of these gray matter maps among men alone merits separate interpretation, but could serve as a focus for a replication study to determine the generality of this finding.

Uncorrected statistical maps of regional intensity-based gray matter concentration showed similar regional effects in our earlier study of chronic schizophrenia patients and...
demographically similar healthy comparison subjects, even though cortical gray matter concentration values reduced using PCA were not significant (Narr et al., 2003). Specifically, regional reductions in gray matter concentration were distributed through heteromodal association areas and within the pre- and post-central gyrus, although they were less notable in the superior temporal cortex. Extra-cortical CSF increases, however, were pronounced surrounding temporal regions. Reciprocal relationships between gray matter decreases and extra-cortical CSF increases have been shown to occur during normal aging (Jernigan et al., 1991; Coffey et al., 1998; Courchesne et al., 2000). Thus, it is possible that regional increases in extra-cortical CSF may serve to predict more subtle regional reductions in cortical gray matter. Our findings are also compatible with at least two VBM studies of first episode schizophrenia (Job et al., 2002; Kubicki et al., 2002). Specifically, Kubicki et al. (2002) showed differences in intensity-based gray matter concentrations within the superior temporal gyrus and parietal lobe. Job et al. (2002) similarly observed gray matter concentration reductions in the left middle temporal and postcentral gyri in first episode patients compared with controls.

**Regional Effects of Gray Matter Thickness**

Our statistical maps of cortical thickness showed similar spatial profiles as those for intensity-based cortical gray matter concentration. Patients with first episode schizophrenia exhibited cortical thinning in heteromodal lateral prefrontal and temporal cortices, as well as in parietal and occipital regions (Fig. 4). Comparisons between exclusively female diagnostic groups showed similar regional effects. Males, however, showed thinning within the pre and postcentral gyrus regions that were largely above the threshold of statistical significance in female patients, while regional effects appeared more pronounced in temporal regions in female patients. Interactions between sex and diagnostic group showed that female patients also possess some cortical thinning in anterior temporal regions and adjacent to the interhemispheric fissure (medial frontal) that did not appear present in male patients. Sex by diagnosis interactions were not observed for cortical gray matter concentration.

Our cortical thickness findings are in line with results from an earlier imaging study of cortical thickness in chronic schizophrenia (Kuperberg et al., 2003). Using a similar methodological approach, Kuperberg et al. (2003) measured cortical thickness in twelve cortical regions in 33 schizophrenia patients compared with 32 demographically similar healthy subjects. Cortical thickness was also approximated across cerebral cortex after smoothing with a kernel of radius 60 mm. Results showed that cortical thinning was most prominent in prefrontal and temporal cortices. However, cortical thinning was also observed in orbitofrontal and inferior frontal regions, local effects that were marginal or absent in our study. Cortical thinning was also identified in right medial frontal cortices, a region that was not examined in our investigation. Another study examined prefrontal cortical thickness in first episode schizophrenia (Wieband et al., 2004), where cortical thickness was defined as the shortest distance from the white-gray matter boundary to voxels on the 3-D cortical surface. Significant reductions in prefrontal gray matter volume were observed in first episode patients \((n = 17)\) compared with healthy subjects \((n = 17)\), but reductions in cortical thickness averaged across the region were not detected, even though thickness and volume measures were positively correlated. These results may suggest cortical thinning was below the threshold of significance for the entire prefrontal lobe, and that more regional effects may have remained undetected.

A third study used a slightly different approach to examine differences in cortical thickness between early and adolescent onset schizophrenia patients compared with healthy comparison subjects (White et al., 2003). Cortical thickness was estimated by creating an iso-surface from the midpoint of voxels segmenting 'purely' as gray matter within the cortical ribbon. Cortical thickness was then defined as the minimum distance from the iso-surface to voxels segmenting 50% as gray matter and 50% as white matter and these distances were doubled to approximate actual thickness. Cortical thickness was then compared for gyral and sulcal regions separately collapsed across the four lobes. Results showed that the thickness of the cortex was reduced in sulcal regions in the frontal, parietal and temporal lobes and reduced in gyral regions only in the temporal lobes in patients compared with controls. These findings are partially compatible with our results, although our statistical maps did not reveal pronounced effects in the sulcal folds.

**Sex Effects**

Males exhibited larger total brain volumes and individual brain tissue volumes compared with females, as universally documented in the normative literature. Factor scores from PCA analyses also showed main effects of sex for both cortical gray matter indices. Sex effects, however, were no longer significant after covarying for total brain volume, with the exception of comparisons between factor scores from the third and fourth
principal component for intensity-based gray matter concentration values. These results suggest that there are some sex differences in cortical gray matter that are independent of brain size. Importantly, the removal of brain size differences may also serve to obscure potential sex effects since sex and brain size are strongly associated. Statistical maps of regional effects of sex showed similar patterns as reported by other groups (Nopoulos et al., 2000; Good et al., 2001). That is, although males possess larger brain tissue volumes than females, females show some focal increases in gray matter concentration compared with males in absolute terms. These differences, measured across both diagnostic groups, were present in posterior parietal regions (Nopoulos et al., 2000; Good et al., 2001). Statistical maps showing sex differences in cortical thickness were similar to those observed for gray matter concentration values. However, small increases in cortical thickness were shown in anterior medial frontal regions and towards the temporal poles in male compared with female subjects whereas male subjects showed no local increases in gray matter concentration.

Age and Hemispheric Effects

Significant effects of age were also observed for the three major tissue compartments. Subtle gray matter decreases and white matter and CSF increases occurred with age, as consistent with previous findings in this age range (Coffey et al., 1998; Magnotta et al., 1999; Symonds et al., 1999; Good et al., 2001). Diagnostic groups showed similar age effects for all brain tissue compartments and for PCA factor scores from the first principal components of both cortical gray matter indices, irrespective of brain size corrections. These results demonstrate that age is a strong predictor of cortical gray matter differences between individuals even in early adulthood. Previously, whole brain gray matter volumes and regional changes in intensity-based gray matter concentration were shown to occur prematurely in male patients with chronic schizophrenia (Narr et al., 2003). That is, male patients showed early gray matter reductions that remained relatively static from disease onset into the fifth decade, while demographically similar healthy comparison subjects and female patients showed a gradual decline in gray matter volume over the same time period. These results do not contradict our current findings given that our study groups were of a relatively narrow age range and on average a decade younger that the chronic schizophrenia patients previously examined. Furthermore, differences in aging effects between groups were only examined cross-sectionally in the chronic schizophrenia study, and remain to be confirmed longitudinally. Hemispheric differences between diagnostic groups were only detected in factor scores from the fourth PCA component cortical thickness values. Statistical maps, however, show some small hemispheric differences when comparisons of cortical thickness and concentration are made locally.

Methodological Limitations

Although intensity-based gray matter concentration and thickness measures are strongly associated over the majority of the cortex, these measures were not significantly correlated in the temporal poles and in medial frontal regions (Fig. 5). These small discrepancies in results illustrate some important methodological differences between the two measures. Specifically, gray matter concentration measures may be more susceptible to artifacts stemming from differences in the curvature of the cortical surface where increased curvature may cause less gray matter to be sampled within the kernel of a fixed radius. Interestingly, the temporal poles and interhemispheric folds are among the most curved regions of the cortex perhaps accounting for the lack of significant correlations in these regions only. Intensity-based concentration measures may in part also reflect differences in the surrounding tissue. For example, prior data suggest that disease effects are larger when CSF to whole brain ratios are examined compared with when brain tissue volumes are examined alone (Gur et al., 1991; Woods et al., 1996; Cannon et al., 1998). This may also apply at the regional level. The gray matter concentration ratio may also be influenced by sulcal widening as has been previously documented in schizophrenia (Shenton et al., 2001). Importantly, none of these potential confounds are associated with the cortical thickness measure. However, both measures may be susceptible to partial volume effects given that gray matter thickness and concentration are estimated from tissue segmented brain volumes.

Conclusion

Cortical thickness and intensity-based gray matter concentration ratios produce similar results suggesting they index the same pathophysiological processes in schizophrenia. Local reductions in cortical thickness and gray matter concentration appear to be present at disease onset implying the involvement of disturbed neurodevelopmental mechanisms. Cortical thinning and reduced intensity-based gray matter concentration are most notable in frontal, temporal and parietal association cortices that have been linked with functional disturbances in schizophrenia. That is, widespread deficits, affecting the thickness of the cortical mantle over broad areas of heteromodal association cortex, may underlie complex deficits in attentional regulation, executive deficits and deficits in learning/memory functions that appear most prominent in schizophrenia (e.g. Seidman et al., 1994; Baare et al., 1999; Harrison, 1999; Bilder et al., 2000; Pearlson, 2000). Interestingly, motor deficits have also been identified in first episode schizophrenia that appear at least partially independent of medication treatments, perhaps associated with gray matter thinning in primary motor areas particularly in male patients (Bilder et al., 2000). The direct relationships between neuropsychological measures and cortical thickness in schizophrenia, however, remain to be assessed empirically. Earlier post-mortem studies show small reductions in cortical thickness in patients in the presence of increased neuronal packing density and smaller neuronal somal sizes (Selemon et al., 1995, 1998; Rajkowska, 1997). Neuronal reductions and smaller cell sizes, rather than neuronal loss, may thus be the basis for cortical thinning in schizophrenia and account for disturbances in neurotransmission.

Notes

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