Prefrontal Gray Matter Volume Reduction in First Episode Schizophrenia

Functional measures have consistently shown prefrontal abnormalities in schizophrenia. However, structural magnetic resonance imaging (MRI) findings of prefrontal volume reduction have been less consistent. In this study, we evaluated prefrontal gray matter volume in first episode (first hospitalized) patients diagnosed with schizophrenia, compared with first episode patients diagnosed with affective psychosis and normal comparison subjects, to determine the presence in and specificity of prefrontal abnormalities to schizophrenia. Prefrontal gray and white matter volumes were measured from first episode patients with schizophrenia (n = 17), and from gender- and parental socio-economic status-matched subjects with affective (mainly manic) psychosis (n = 17) and normal comparison subjects (n = 17). Age-matched within a narrow age range (18–29 years). Total (left and right) prefrontal gray matter volume was significantly reduced in first episode schizophrenia compared with first episode affective psychosis and comparison subjects. Follow-up analyses indicated significant left prefrontal gray matter volume reduction and trend level reduction on the right. Schizophrenia patients showed 9.2% reduction on the left and 7.7% reduction on the right compared with comparison subjects. White matter volumes did not differ among groups. These data suggest that prefrontal cortical gray matter volume reduction is selectively present at first hospitalization in schizophrenia but not affective psychosis.

Introduction

Patients with schizophrenia show cognitive and behavioral problems such as deficits in performance on the Wisconsin Card Sorting Test (Weinberger et al., 1986), smooth pursuit eye movement (Holzman et al., 1977) and performance on spatial working memory tasks (Park and Holzman, 1992) that are frequently associated with frontal lobe lesions in humans–see recent review of effects of prefrontal lesions (Knight et al., 1995) and from gender- and parental socio-economic status-matched subjects with affective (mainly manic) psychosis (n = 17) and normal comparison subjects (n = 17). Age-matched within a narrow age range (18–29 years). Total (left and right) prefrontal gray matter volume was significantly reduced in first episode schizophrenia compared with first episode affective psychosis and comparison subjects. White matter volumes did not differ among groups. These data suggest that prefrontal cortical gray matter volume reduction is selectively present at first hospitalization in schizophrenia but not affective psychosis.

Inconsistent findings for prefrontal volume change would also suggest the importance of adequate control of potential confounds such as age or factors associated with chronic illness, including chronic medication. MRI prefrontal gray matter volume is known to decline with age, and data suggests it does so in an accelerated manner compared with other regions (Pfefferbaum et al., 1998). Chronic medication is another potential confound. Selemon and co-workers have recently reported glial proliferation and hypertrophy of the prefrontal cortex (area 46) in rhesus monkeys given typical or atypical antipsychotic drugs for 6 months (Selemon et al., 1999). If this hypertrophy were present in humans on neuroleptics, then chronic neuroleptic dosage might reduce the opportunity to measure a schizophrenia-related decline in gray matter.

Use of a first psychotic episode population of schizophrenic subjects may thus be useful in controlling for both potential confounds. First, age distribution in first episode subjects can be more easily chosen to span a more limited and younger range than in chronic patients and, second, chronic neuroleptic exposure in this population is rare.

MRI frontal lobe abnormalities have been reported in first episode schizophrenia, but frontal gray and white matter have not generally been separately evaluated. Zipursky et al. (Zipursky et al., 1998) found whole brain gray matter reduction in first episode schizophrenia. Gur et al. (Gur et al., 1998) found whole frontal lobe volume significantly decreased in both first episode and chronic schizophrenics compared with controls. Nopoulos et al. (Nopoulos et al., 1995) showed a significant decrement in whole frontal lobe tissue in first episode patients compared with controls. However, to our knowledge, no MRI studies have separately evaluated whole prefrontal gray and white matter volumes in first episode schizophrenia – although Gur et al. (Gur et al., 2000) looked at dorsal and orbital prefrontal subdivisions.

A further advantage of a first episode sample is the ease with which comparisons to first episode psychotic affective disorder can be made. This appears important because it remains uncertain, and even controversial, whether the psychosis associated with affective disorder and that associated with schizophrenia represent manifestations of different disorders or are variants of a single underlying disorder with somewhat different clinical manifestations. MRI studies evaluating both...
first episode affective and schizophrenic patients may assist in answering this question. We note that MRI studies of affective disorder have reported volume reductions in several regions, including frontal lobe, temporal lobe and putamen, although these findings have been described as somewhat inconsistent (Dougherty and Rauch, 1997; Benton et al., 1997, 2001; McCarley et al., 1999; Pearson and Marsh, 1999). We have previously reported (Hirayasu et al., 1998) that first episode schizophrenic patients were different from first episode affective patients and normal comparison subjects in having a smaller gray matter volume in a posterior superior temporal gyrus (STG), and a significant left smaller than right asymmetry. We also reported that first episode affective patients, but not first episode schizophrenic patients, showed a reduction in the subgenual cingulate cortex (Hirayasu et al., 1999). Schlaepfer and co-workers reported gray matter volume reduction in heteromodal association cortex including prefrontal cortex in schizophrenia but not in bipolar disorder (Schlaepfer et al., 1994). However, to our knowledge, no studies have evaluated similarities or differences of prefrontal gray matter and white matter in first episode schizophrenia and affective psychosis.

The present study used high spatial resolution MRI to evaluate prefrontal gray and white matter in young (<30 years old) first episode schizophrenia patients, first episode affective psychosis patients (mainly manic) and normal comparison subjects. We predicted that first episode patients with schizophrenia, but not first episode patients with affective psychosis, would show reduced prefrontal volumes. Consistent with the hypothesis of reduced neuropil but not cell count (Seolom and Goldman-Rakic, 1999), we predicted reductions in gray but not white matter.

Materials and Methods

Subjects

Patients were recruited from the inpatient population at McLean Hospital, a private psychiatric hospital in Belmont, Massachusetts. The total subject population from which the study sample was drawn consisted of 23 first episode schizophrenia, 24 first episode affective (manic) and 13 normal comparison subjects. Twenty-four patients (11 affective and 13 schizophrenic subjects) were tested within 4 weeks of their first hospitalization, nine (six affective and three schizophrenic subjects) within 2 years of first hospitalization, and one schizophrenic subject within 11 months. Each subject group included two female subjects. Twenty-four patients (11 affective and 13 schizophrenic subjects) were tested within 4 weeks of their first hospitalization, nine (six affective and three schizophrenic subjects) within 2 years of first hospitalization, and one schizophrenic subject within 11 months. Demographic data for subjects are summarized in Table 1.

The affective psychosis patient group included 13 bipolar (manic) disorder and four major depressive disorder patients. The statistically significant results reported below represent the same with the exclusion of the four major depressive patients. Diagnoses were confirmed via a 1-year follow-up interview. Table 1 shows the short median duration of any psychotropic medication prior to MRI acquisition (seven schizophrenics and 10 affective psychotic patients were unmedicated prior to admission). In terms of onset of psychosis, we selected the date of first psychiatric hospitalization as a reliable marker. Although the time of onset of prodromal symptoms may be a better indicator of the actual onset of the disease, in practice this retrospective measure is difficult to verify and may be unreliable. Thus, for comparative purposes, we have provided age at time of first medication, which we believe to be a more objective measure (most medication onset dates were taken from hospital records), less equivocal than time of prodrome onset, and thus to be a better index of the severity and timing of symptom onset. The present study included 11 individuals in each subject group who were also included in our previous temporal lobe MRI study (Hirayasu et al., 1998).

The Mini-Mental State Examination was used to rule out any dementia or delirium. Additionally, the Information subscale of the WAIS-R (Wechsler Adult Intelligence Scale – Revised) (Wechsler, 1981) was used as a gross estimate of general fund of information, and the digits-forward and digits-backward subscales of the WAIS-R were used to evaluate immediate/short-term memory, attention and concentration. SES and parental SES (Hollingshead, 1965) were also assessed. Evaluation of psychotic features was made using the Brief Psychiatric Rating Scales (BPRS) (Overall and Gorham, 1962) for most patients. For six of the first episode schizophrenia patients and four of the affective psychosis patients, BPRS scores were calculated from the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1986), which includes all of the BPRS items. Overall functioning was evaluated using the Global Assessment Scale (GAS) (Endicott et al., 1976). After complete description of the study, written informed consent was obtained from all subjects. Subjects were paid for participating.

MRI Methodology

Magnetic resonance images were acquired with a 1.5 T General Electric scanner (GE Medical Systems, Milwaukee, WI). The acquisition protocol had two MRI sequences. The first was a coronal series of contiguous spoiled gradient (SPGR) images (124 slices of 1.5 mm thickness, voxel dimensions, 0.9375 x 0.9375 x 1.5 mm). The second acquisition resulted in...
in an axial series of contiguous double-echo images (proton density and $T_2$-weighted, with 3.0 mm slice thickness, voxel dimensions, $0.9375 \times 0.9375 \times 3.0$ mm). This latter protocol was also used to assess whole-brain volume. Details are described elsewhere (Dickey et al., 2000). $T_2$ information from the double-echo spin echo axial slices was registered with data from SPGR images by reformatting the axial voxels to the voxel dimensions corresponding to those in the coronal SPGR images. The intensity information from both the SPGR and $T_2$ images was then used in a fully automated segmentation program to classify tissue into gray matter, white matter and CSF. An iterative expectation-maximization (EM) algorithm initially estimated image intensity inhomogeneities, applied intensity corrections based these estimates, and then classified tissue based on the same set of signal intensity parameters for all subjects (Wells et al., 1996). An anisotropic diffusion filter ($k = 14$ for SPGR and 90 for proton/$T_2$ images, iteration $\times 3$) was applied to reduce noise prior to processing each set of scans (Kikinis et al., 1990). The results of the segmentation were then superimposed on the coronal SPGR image and edited on the computer workstation to assign the left and right prefrontal gray/white matter to separate tissue classes.

**Prefrontal Definition**

Definition of the prefrontal cortex has been described in detail elsewhere (Wible et al., 1995). Briefly, the gray matter of the prefrontal cortex was measured starting anteriorly from the first slice that contained brain tissue. The posterior landmark was determined by first locating the most anterior slice that contained the temporal stem (the white matter tract connecting the temporal and frontal lobes), then moving anteriorly three slices. Anteriorly, the white matter was measured beginning with the first slice that contained white matter and extended posteriorly to the slice immediately anterior to the slice that contained the lateral ventricles. Prefrontal segmented images on a coronal slice are shown in Fig. 1A, and Fig. 1B–D illustrate the anterior–posterior boundaries of the gray and white matter regions of interest (ROI). Inter-rater reliability was computed for the ROIs by three independent raters (S.T., J.J.L. and M.D.) who were blind to group membership. Ten cases were randomly selected for inter-rater reliability. Intraclass correlation coefficients for inter-rater reliability for the three raters were: 0.996 for left prefrontal gray, 0.999 for right prefrontal gray, 0.999 for left prefrontal white, and 0.999 for right prefrontal white.
Table 2

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Three-factor ANOVA was performed with GROUP (schizophrenia, affective psychosis, control) as a between-factor, and TISSUE (gray, white) and SIDE (left, right) as within-factors. Statistics were performed based on relative volumes (ROI volume/volume of intra-cranial contents (ICC) × 100).

Statistical Analyses

Three-factor ANOVA was performed with GROUP (schizophrenia, affective psychosis, control) as a between-subjects factor, and TISSUE (gray, white) and SIDE (left, right) as within-subjects factors. Statistics were performed based on relative volumes [ROI volume/volume of intra-cranial contents (ICC)] × 100. Testing absolute volumes with ICC as a covariate did not change the results reported below. Follow-up analyses included a two-factor (GROUP and SIDE) ANOVA for each tissue (gray and white), one-way ANOVA, and post hoc Tukey's Honestly Significant Difference (HSD) tests for individual regions with left and right compared separately. Results were considered significant at P<0.05. In addition, an asymmetry coefficient (AC) was calculated by using the formula (R−L)/[(R+L)/2] where R and L were the prefrontal volumes on the right and left sides in subjects, respectively.

Correlations of prefrontal structures using absolute and relative volumes were performed with the demographic data of Table 1. Correlations were also performed for schizophrenic and affective patients between the syndrome factors of the BPRS and prefrontal left and right gray and white matter to assess the degree of association between symptomatology and prefrontal volume measurements with absolute volumes and relative volumes.

Results

There were no significant group differences in age or parental SES. First episode schizophrenia patients showed significantly lower socio-economic status than comparison subjects, consistent with reduced premorbid functioning. There were no significant differences between schizophrenia and affective patients on any of the clinical scale measures, age of first medication, medication dosage, or duration of illness. The age, SES, parental SES, age of first medication, duration of medication, and dose (chlorpromazine equivalent) of medication did not correlate with the volume of any prefrontal lobe ROI in the patients. The WAIS-R Information score was correlated with right white matter volume in first episode schizophrenia (rho = 0.755, d.f. = 16, P = 0.001 for absolute volume; rho = 0.723, d.f. = 16, P = 0.002 for relative volume).

Although there were no significant differences on BPRS scores between schizophrenia and affective psychosis, the schizophrenic patients showed significantly higher scores for items of hallucination and suspiciousness compared with affective patients. Total BPRS score significantly correlated with left white matter volume in first episode schizophrenia (rho = 0.542, d.f. = 16, P = 0.030 for absolute; rho = 0.620, d.f. = 16, P = 0.010 for relative volume). We emphasize that correlations are reported only if values were significant using both absolute and relative volume measures.

There was no significant difference in ICC volume among the three groups. The results of the main three factor ANOVA are presented in Table 2, and all absolute and relative gray and white matter volumes for each group and follow-up analyses are presented in Table 3. The main ANOVA showed a significant difference in total cortical gray and white matter among the three groups [F(2,48) = 3.60, P = 0.035]. Post hoc tests revealed that the schizophrenia patients showed smaller total relative volume (13.8%) compared with affective patients (14.9%) and control subjects (14.9). There was more gray matter than white matter volume for all three groups [R^2 = 0.22, P<0.001]. However, groups differed in the relative amounts of gray to white matter at the trend level, evinced by a GROUP by TISSUE interaction [F(2,48) = 4.42, P = 0.017]. The ratio of gray to white matter differed in the hemispheres, with relatively more gray on the left and more white on the right.

The main ANOVA revealed significantly more tissue in the right hemisphere for all three groups [F(1,48) = 10.26, P = 0.001]. There was no significant difference in ICC volume among the three groups [F(2,48) = 0.014], but not in left white matter (see Table 3). In the right hemisphere, there was a trend for differences in total gray plus white matter volume.
All three groups showed more gray matter than white matter volume in the right hemisphere ($F(1,48) = 1819.11, P < 0.001$). There was no GROUP by TISSUE interaction on the right. Despite the lack of statistical significance on the right, follow-up analyses are presented in Table 3 for comparative purposes. There was no significant difference of AC among three groups for gray or white matter volumes.

**Discussion**

In this study, first episode patients with schizophrenia showed a significant volume reduction in total (left + right) prefrontal gray matter volume compared with first episode patients with affective psychosis and normal comparison subjects. Compared with comparison subjects, the percent reduction for total gray matter was 8.4% with an effect size of 0.69 [(schizophrenic – control subjects’ volume)/SD of controls]. The percent reduction on the left (9.2% with an effect size of 0.81) was slightly greater than on the right (7.7% with an effect size of 0.59). The left difference showed statistical significance while the right difference showed only trend level statistical significance. We regard these data as providing suggestive evidence of a slight difference between left and right volume reductions, although the absence of a GROUP × SIDE interaction for gray matter indicates this must be a tentative conclusion.

It is also of interest to compare first episode schizophrenia with first episode affective psychosis (mainly manic) on gray matter volumes. Compared with this group, schizophrenic subjects on the left showed a 8.7% decrease and an effect size of 0.77 (the SD of control subjects was used in this computation). On the right there was a 8.2% decrease with an effect size of 0.63. No difference was found in prefrontal white matter volume between first episode schizophrenic patients, first episode affective patients or normal comparison subjects.

The subjects in this study were selected from larger samples in order to provide closeness of age matching and a narrow age range in a relatively young (< age 30) sample. These findings suggest that prefrontal cortical gray matter abnormalities may be present at first hospitalization in schizophrenic but not in affective psychosis patients.

Overall, in reviewing the MRI literature, MRI abnormalities in the frontal lobe in schizophrenia have been somewhat inconsistent (Shenton et al., 1997, 2001; McCarley et al., 1999). In fact, our own previous study of chronic schizophrenia (Wible et al., 1995) found no difference. Several factors may be involved in this inconsistency of findings.

First, reductions in frontal volume in schizophrenia may be just at the threshold for detection. For example, the quantitative post-mortem study of Selem et al. (Selemon et al., 1998) found but a small reduction in prefrontal cortical thickness in schizophrenia, a reduction that was not statistically significant (and thus comparable to the MRI negative results), although significant abnormalities in density of various cell types were present. Thus, these post-mortem data would be consistent with...
the observed findings in MRI studies, since random variation in subjects and their prior history, as well as variation in imaging technology could easily account for the split in findings for the prefrontal structures. Our previous reviews have extensively discussed MRI technical factors that may be responsible for such variation (Shenton et al., 1997, 2001; McCarley et al., 1999).

Second, it is likely that control of age factors may be useful, since prefrontal gray matter decreases with age (Pfefferbaum et al., 1994) and there is the possibility that this decrease may vary in a non-linear manner, with an increased rate of decline with increasing age. Our choice of a young subject group with a narrow age range (18–29) and with a 1:1 age-matching strategy from a larger sample may have decreased the variance associated with age variations. It can be seen that our coefficient of variation (SD/mean) for relative gray matter is small for schizophrenic subjects, 0.90 for whole, 0.92 for left and 0.87 for right gray matter. While statistical correction methods can be applied for age differences, it is a statistical truism that such correction methods necessitate a model for age correction, and both the parameters of the model and/or the nature of the model itself (usually linear) may not be precise and thus contribute additional variance. Thus, we think that the advantage of age matching and the consequent increase in effect size more than outweighs the reduction in subject number it entailed.

Third, there is the possibility that prefrontal structural MRI volumes may be influenced by chronic medication. The most direct animal evidence comes from Selemion et al. (Selemion et al., 1999) who gave typical or atypical antipsychotic drugs orally to monkeys for 6 months, and then used a stereologic method to assess neuronal and glial density and cortical thickness in prefrontal area 46. While neuronal density in drug-treated monkeys and their controls did not differ, glial density was elevated in monkeys that received antipsychotic medications. This was as much as 35% in layers that receive dense excitatory afferents (layers I in typical- and IV in atypical-treated monkeys). This was as much as 33% in layers that receive dense excitatory afferents (layers I in typical- and IV in atypical-treated monkeys).

In addition, layer V was wider in all drug-treated monkeys. There are no comparable prefrontal cortex studies in humans, but data from basal ganglia have indicated typical neuroleptics are associated with a reversible increase in MRI volume (Chakos et al., 1995). Thus, a possible confound in chronic studies is drug-associated structural changes. While some subjects in the present study had a brief exposure to neuroleptics, neither duration nor dosage was correlated with ROI volumes. Moreover, while schizophrenics had somewhat more exposure to neuroleptics than the other groups, the volume reduction in schizophrenia vs affective disorder and controls was in the opposite direction from that expected as a drug effect, based on the animal studies.

The present study is one of a few MRI structural studies of the prefrontal region in first episode schizophrenia. A recent study by Szczeklo et al. (Szczeklo et al., 1999) reported that male patients with first episode schizophrenia (sample had 10 male and 9 female subjects) had significantly larger whole (gray + white) right orbital frontal volume compared with left orbital frontal volume and compared with healthy men (Szczeklo et al., 1999). In a study of chronic schizophrenia, Buchanan et al. (Buchanan et al., 1998) showed selective gray matter volume reductions in the right and left inferior prefrontal cortex (12 male and 6 female subjects). Additionally, these patients showed decreased prefrontal total white matter and total volumes although there was no significant difference in prefrontal total gray matter volumes (reduction was 5% for left and 6.7% for right). Gur et al. studied 20 first episode and 20 chronic patients and found whole (gray + white) frontal lobe volume significantly decreased in both first episode and chronic schizophrenics compared with controls (Gur et al., 1998). Nopoulos et al. studied 12 male and 12 female first episode patients with schizophrenia and controls; their automated analysis revealed that the patient group had a significant regionally specific decrement in whole (gray + white) frontal lobe tissue compared with controls (Nopoulos et al., 1995).

Functionally, the frontal lobe has been intensely studied and associations with functions disturbed in schizophrenia have been reported, as described in the Introduction. In contrast, structural MRI–clinical correlations have been relatively sparse, perhaps due to the small extent of the frontal volume change and the failure to segment into gyri, which might have stronger clinical correlates. Several reports have suggested associations between frontal abnormalities and negative symptoms. Supporting this is our laboratory’s finding (Wible et al., 1995) of Scale for the Assessment of Negative Symptoms scores having a negative correlation with left prefrontal cortical white matter volume in chronic schizophrenia. However, findings have been inconsistent, since many studies have failed to find a correlation between negative symptoms and frontal volumes, and some results have suggested the opposite, e.g. Buchanan et al.’s finding that non-deficit chronic patients had significantly smaller right and left total prefrontal volumes than did deficit patients (Buchanan et al., 1993).

The present first episode study did not find a significant correlation between prefrontal volumes and clinical symptoms except between total BPRS and left white matter volume. However, this was one of multiple correlations, and should be replicated before considering it a firm finding. In addition to the factors just discussed, we hypothesize that an important additional factor might be the unstable nature of symptoms and signs in the early stages of schizophrenia, compared with a more stable clinical picture in chronic patients. Obviously, a test of this hypothesis would require a longer duration follow-up of the present sample.

Parcellation of the prefrontal region is potentially important because this area is both functionally and structurally heterogeneous. It is also worth noting that few studies have been reported for evaluation of individual frontal gyral gray matter in schizophrenia, and it may be that this approach, for which the technical methodology has been developed (Wible et al., 1997), may show changes in volumes in some gyri but not in others. Gur et al. have recently investigated 70 patients with schizophrenia including 29 neuroleptic-naive cases (Gur et al., 2000). They found reduced prefrontal gray matter volume for the dorsolateral area in men (9%) and women (11%), for the dorsomedial area only in men (9%), and for orbital regions only in women (25% and 10% for lateral and medial, respectively). Medication also did not affect the reduction since the differences were evident in neuroleptic-naive patients. The specificity of MR abnormalities to schizophrenic vs affective psychosis is a long-standing conundrum, as is the more general question of whether these psychoses are manifestations of a single basic disorder or are distinct. Few first episode studies have compared prefrontal gray matter volumes between schizophrenia and affective psychosis although several studies suggested global and/or regional cortical volume reduction may be specific to schizophrenia relative to affective disorder. Schlaepfer et al. reported that chronic bipolar patients did not show heteromodal cerebral cortex volume reduction while gray matter volume was reduced in chronic schizophrenic patients (Schlaepfer et al., 1994). Zipursky et al.
similarly found regional volume reduction in gray matter in schizophrenic patients but not in non-first episode bipolar patients, as well as a decrease in global gray matter volume in schizophrenia (Zipursky et al., 1997). Harvey et al. also reported a decrease in cortical volume in chronic schizophrenic patients, but not in bipolar patients (Harvey et al., 1994).

In conclusion, our findings of volume reduction in prefrontal gray matter in first episode schizophrenia suggest the presence of structural abnormalities in regions associated with cognitive and behavioral impairment in this disorder. Our sample gender distribution did not allow us to contrast findings based on this important variable. Finally, we suggest that first episode studies provide a major advantage in having fewer confounds from chronicity variables and, additionally, offer a baseline for longitudinal studies evaluating the presence or absence of progression of MRI changes over time.

**Notes**

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