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Follow-up MRI study of prefrontal volumes in first-episode psychotic patients

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Structural MRI findings of abnormalities in the prefrontal cortex in schizophrenia and affective disorder have been inconsistent likely due to small, heterogeneous samples, the evaluation of prefrontal gray and white matter combined, and the fact that prefrontal cortex is typically not delineated into separate gyri (e.g., Shenton et al., 2001; Strakowski et al., 2002). We previously reported smaller prefrontal gray matter in first-episode schizophrenia relative to first-episode affective psychosis and controls (Hirayasu et al., 2001). One unresolved question in the literature is whether or not further volume reduction will be observed over time, the focus of this report.

Prefrontal gray and white matter volumes were measured (see Fig. 1) in patients at the time of first hospitalization for schizophrenia ($n=12$, 3 females) or affective psychosis ($n=10$, 1 female, 9 bipolar, 1 unipolar), and psychiatrically well subjects ($n=15$, 1 female). Subjects were rescanned approximately 1.5 years later. Seven schizophrenia, six affective, and four comparison subjects were previously described solely at first scan (Hirayasu et al., 2001). Samples did not differ in age (28.1 ± 8.4 ; 22.9 ± 2.8 ; 25.4 ± 4.5 ; $F(2,34)=2.2$, $p=0.12$) or WAIS Information scores (11.8 ± 3.4 ; 12.2 ± 3.1 , 11.8 ± 2.0 ; $F(2,32)=0.6$, $p=0.9$), nor in parental socioeconomic status ($F(2,34)=2.32$, $p=0.11$) or handedness ($F(2,33)=1.6$, $p=0.22$). BPRS scores were higher in schizophrenics (41.2 ± 13.2) than affectives (33.8 ± 8.0) ($F(1,20)=5.71$, $p=0.027$). Similar neuroleptics were prescribed for the patient groups (schizophrenics: 7 typical, 4 atypical, 1 none; affectives: 6 typical, 3 atypical, 1 none).

Relative volumes [i.e., absolute volumes divided by intracranial contents (ICC)] were used in the analyses. Repeated-measures ANOVA was performed with diagnosis as the between-

subjects factor and time and side as the within-subjects factors for gray and white matter separately.

Prefrontal gray matter at time 1 was significantly different among groups ($F_{2,30}=5.56$, $p=0.009$), with schizophrenics smaller than controls and affectives, who did not differ from each other. There was no interaction for group by time by side for prefrontal gray matter ($F_{2,34}=0.65$, $p=0.53$). All groups showed larger gray matter on the left ($F_{2,30}=8.72$, $p=0.006$).

White matter volumes did not differ among groups ($p>0.87$), and all groups showed more white matter on the right ($F_{1,30}=39.20$, $p<0.001$) and a reduction over time ($F_{1,30}=10.902$, $p=0.002$), there was a trend for this effect to be larger on the right ($F_{1,30}=3.14$, $p=0.086$) (% change over time for right white matter: schizophrenics 2.8%; affectives 6.5%; controls 2.1%). Neither removing the unipolar depression subject nor removing the females altered the results. There was no significant correlation between ROI volume change and medication dosage at time 1 for either patient group (Time 2 data came from out patients based on self-report and was for this reason not used).

These data suggest that prefrontal cortical gray matter is selectively smaller at first hospitalization for schizophrenia relative to affective psychosis and controls, but this volume difference did not change over the relatively short post-first hospitalization time examined. Small gray matter volumes may be due to reduced dendritic arborization or increased neural density in prefrontal cortex in schizophrenia (Benes et al., 1992; Selemon et al., 1998). White matter, which was not different among groups, showed a decline with time in all groups, possibly consistent with normal aging (Good et al., 2001, although Bartzokis et al., 2001).

Potential reasons for our not observing selective gray matter reductions point to several limitations of this study including the gender distribution, as females may have greater dorsolateral and orbitofrontal lobe involvement and males greater dorsomedial changes in schizophrenia (Gur et al., 2000); the use of large ROI, as sub-regions within the prefrontal cortex may change in volume at different rates (Gur et al., 1998; DeLisi et al., 1997); and lack of exact medication dosages and compliance histories during the intrascan interval cannot be ruled out as possible confounds. Although the sample size was small, the effect size was also small (Fig. 1) suggesting that even enlarging the sample would not result in a significant change in volume over time for either gray or white matter.

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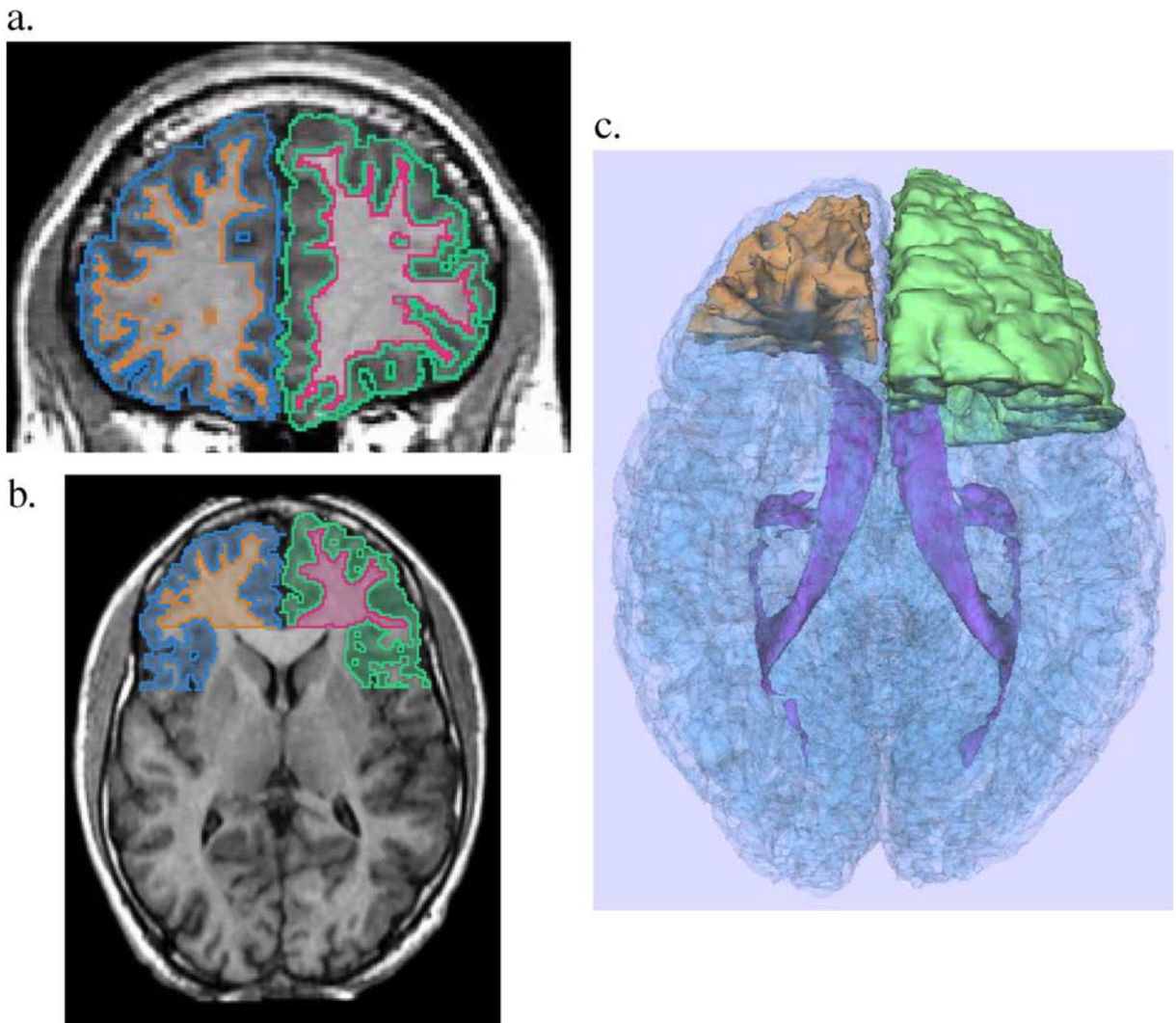


Fig. 1.

Prefrontal ROI definitions and volumes. (a) Coronal slice, (b) axial slice showing prefrontal gray and white matter, and (c) three-dimensional reconstruction of the extent of gray and white matter boundaries. MR images were acquired with a 1.5-T scanner (GE Medical Systems, Milwaukee). Coronal SPGR images 1.5 mm thick were segmented into tissue class and subsequently realigned, reformatted, and resampled (isotropic voxels 0.9375 mm^3) to ensure similar head alignment between time 1 and time 2. Minimal manual editing was performed by a single rater. Axial double-echo images 3 mm thick were used to determine the ICC. Measurement of gray matter began on the most anterior slice containing brain tissue. The five most anterior slices were considered to be solely gray matter, with the anterior boundary of the white matter commencing on the sixth slice. The posterior landmark for gray matter was the slice five slices anterior to the appearance of the temporal stem (the white matter tract connecting the temporal and frontal lobes) and for the white matter, the tip of the frontal horns. Right side of image is left side of brain. ANOVA revealed no significant differences in ICC volume among the three groups. Follow-up ICC volumes were smaller ($F_{1,30}=10.66$, $p=0.003$), however, the average difference was 0.58%. ROI absolute volumes in ml given for time 1 for schizophrenic, affective, and comparison subjects respectively with standard deviations in parentheses, effect sizes given as partial eta squared are listed: left gray: 80.0

(9.3), 86.0 (9.7), 88.7 (11.2); right gray: 79.3 (9.5), 84.6 (10.7), 87.1 (11.6) [for left and right gray matter over time=0.037, small effect]; left white: 28.3 (3.0), 28.8 (4.1), 30.0 (5.0); and right white 31.3 (3.5); 32.2 (6.2), 31.8 (5.0) [for left and right white matter over time=0.048, small effect]; and time 2 left white 27.6 (2.8), 27.5 (3.8), 29.4 (4.9); and time 2 right white 30.2 (3.2), 29.8 (4.2), 31.1 (4.9).