Inferior Frontal White Matter Anisotropy and Negative Symptoms of Schizophrenia: A Diffusion Tensor Imaging Study

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Objective: The purpose of this study was to test the hypothesis that abnormalities of inferior frontal white matter are related to the negative symptoms of schizophrenia.

Method: Fractional anisotropy of white matter tracts in the prefrontal area of 10 schizophrenic patients was determined by diffusion tensor imaging. Patients were also assessed for severity of negative symptoms by using the Schedule for the Assessment of Negative Symptoms (SANS).

Results: Inferior frontal white matter fractional anisotropy was significantly inversely correlated with the SANS global ratings of negative symptoms.

Conclusions: These data, while preliminary, suggest that impaired white matter integrity in the inferior frontal region may be associated with the severity of negative symptoms in schizophrenia.

(Brief Report)

Brain imaging studies (1–6) have demonstrated volumetric white matter deficits (primarily in the frontal lobe and in the corpus callosum) among patients with schizophrenia. In addition, several studies have used diffusion tensor imaging to specifically characterize potential CNS white matter abnormalities in schizophrenia. Although not absolutely correlated with morphological structure, the displacement distribution of water as measured by diffusion tensor imaging can provide information regarding microstructure, organization, and integrity of tissue. Four of six studies using diffusion tensor imaging (8–13) have indicated differences in diffusion measures suggestive of abnormalities in white matter structure in schizophrenia.

Data from structural magnetic resonance imaging (MRI) studies in schizophrenia have further indicated that white matter abnormalities may be specifically associated with negative symptoms (2–4); these data include our prior finding (3) that patients with high levels of negative symptoms have the lowest white matter volume in inferior regions. Diffusion tensor imaging is a useful modality for probing white matter structures, and we know of no studies that have used this method to examine the potential relationship of frontal white matter microstructure and negative symptoms. Therefore, we conducted diffusion tensor imaging studies of 10 patients with schizophrenia who had varying degrees of negative symptoms. These studies were performed in order to test the hypothesis that negative symptoms are associated with abnormalities in inferior frontal white matter.

Method

After complete description of the study to the subjects, written informed consent was obtained from 10 male schizophrenic in- and outpatients. The patients were all under 50 years of age and met the DSM-IV criteria for schizophrenia. Patients with depression meeting diagnostic criteria, drug abuse/dependence within the last year, or history of neurological disease were excluded. The subjects were selected on the basis of a priori clinical familiarity in order to obtain a range of negative symptom severity. All subjects were receiving antipsychotic medication. The clinical rating measures included the Brief Psychiatric Rating Scale (BPRS) (14) and the Schedule for Assessment of Negative Symptoms (SANS) (15). Ratings were obtained when the patients were considered to be at maximal clinical stability (“baseline”), up to 40 days after the MRI scan. For the statistical analyses, negative symptom ratings were reduced to the SANS subscale global scores, a single total of the SANS global subscores, and the score on the withdrawal-rewarding factor from the BPRS.

To minimize artifacts induced by eddy currents, the diffusion tensor imaging data were acquired by using a double-echo pulsed-gradient echo planar imaging method without cardiac gating, with TR=6 sec, TE=100 msec, field of view=24 cm, 128×128 matrix reconstructed to 256×256, b=1000 sec/mm², four averages, six noncollinear directions aligned to the anterior-posterior commissure (AC-PC) plane, and acquisition time=2 minutes, 36 seconds. Fractional anisotropy and mean diffusivity were computed as described in a previous report (16). All raw and processed images were examined for artifacts by a reviewer who was blind to subject identity (K.O.L. or S.J.C.).

Standardized circular regions of interest were positioned, by an investigator blind to subject identity (S.J.C.), on the T2-weighted image (b=0) of the diffusion tensor imaging data set; thus, coregistration of images across different MRI acquisition methods was not needed. A single region of interest was placed bilaterally in the frontal white matter of five consecutive 5-mm-thick slices. These slices included three that were above the index slice, the index slice itself (defined as the most inferior slice containing the genu of the corpus callosum—approximately 10 mm above the AC-PC plane), and one slice below. For the three most superior frontal slices, large regions of interest (area=84.4 mm²) were centered in white matter with the posterior boundary of each region of interest on the imaginary line formed across the anterior most tips of the two frontal horns of the lateral ventricles. For the two most inferior frontal slices, medium-sized regions of interest...
lated with the severity of affective blunting (r=–0.02) and anhedonia (r=–0.84, p=0.002) (Figure 1). Similarly, greater withdrawal-retardation, indicated by the BPRS, was inversely correlated with white matter fractional anisotropy in the same inferior frontal region (r=–0.76, p=0.02).

Results

The mean age of the 10 patients was 41 years (SD=9); their mean duration of illness was 17 years (SD=9), and their mean sum of SANS global subscores was 12.8 (range=9–18).

Across subjects, frontal white matter fractional anisotropy at 5 mm below the AC-PC plane was inversely correlated with the severity of affective blunting (r=–0.72, p=0.02) and anhedonia (r=–0.69, p=0.03), according to the SANS subscales, and with a higher overall sum of SANS global subscores (r=–0.84, p=0.002) (Figure 1). Similarly, greater withdrawal-retardation, indicated by the BPRS, was inversely correlated with white matter fractional anisotropy in the same inferior frontal region (r=–0.76, p=0.02).

Discussion

The main finding of this study is that fractional anisotropy in the inferior frontal white matter is lower among patients with more severe negative symptoms than among other patients with schizophrenia. This finding is consistent with those of our previous structural MRI study (3), in which significant inverse correlations were found between the severity of negative symptoms and prefrontal white matter volumes. These findings suggest that orbitofrontal white matter microstructure may play an important role in the pathophysiology of negative symptoms in schizophrenia by disruption of cortical-cortical or cortical-subcortical connectivity within neuronal networks. Further elucidation of such abnormalities may shed light on the “anatomy” of negative symptoms. Given the limitations of this preliminary study, these results also need to be replicated with a larger number of subjects.

References

1. Woodruff PW, McManus IC, David AS: Meta-analysis of corpus callosum size in schizophrenia. J Neurol Neurosurg Psychiatry 1995; 58:457–461
Brief Report

Psychotic Depression and Mortality

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Objective: Major depressive disorder is associated with elevated mortality rates that increase with the severity of depression. The authors hypothesized that patients with psychotic depression would have higher mortality rates than patients with nonpsychotic depression.

Method: Survival analytic techniques were used to compare the vital status of 61 patients with psychotic major depression with that of 59 patients with nonpsychotic major depression up to 15 years after hospital admission. Medical status was assessed with the Cumulative Illness Rating Scale. Dexamethasone suppression test (DST) data were available for 101 patients.

Results: The mortality rate for subjects with psychotic depression was significantly greater than that for those with nonpsychotic depression, with 41% versus 20%, respectively, dying within 15 years after hospital admission. A proportional hazards model with age and medical status entered as covariates confirmed a significantly higher mortality rate in patients with psychotic depression (hazards ratio=2.31). A positive DST result was associated with psychotic depression but was not related to vital status.

Conclusions: Patients with psychotic depression have a two-fold greater risk of death than do patients with severe, nonpsychotic major depression.

Major depressive disorder is associated with greater mortality (1–4) even after the effects of age, sex, and coexisting medical illness are controlled (5, 6). Mortality rates increase with an increasing number of depressive symptoms (7).

Unipolar psychotic depression is distinct from nonpsychotic depression (8, 9) and is associated with severe symptoms, prolonged course, poor response rates, more residual symptoms, frequent relapses (8–11), and higher rates of hypercortisolism or dexamethasone nonsuppression (12). Given the severity of this disorder, we hypothesized that the mortality rates would be higher in subjects with psychotic depression than in those with nonpsychotic depression. We also hypothesized that hypercortisolism might be associated with greater mortality.

Method

The Yale University Human Investigation Committee approved the research protocol. Inpatients who had participated in prior studies of psychotic depression or cortisol hypersecretion at Yale New Haven Hospital from 1977 to 1990 (8, 12–14) were selected and reviewed. All patients met RDC (15), DSM-III, or DSM-III-R (16) criteria for major depressive disorder. The distinction between psychotic and nonpsychotic depression was based on the presence of clear delusions or hallucinations. Patients with bipolar disorder, schizophrenia, schizoaffective disorder, substance abuse, or acute medical illness were excluded. The attending psychiatrist (J.C.N.) established the psychiatric diagnosis at the time of admission. All of the patients with psychotic depression from this group were included. A comparable number of patients with nonpsychotic depression who were given a standard dexamethasone suppression test (DST) during their hospitalization were selected. For patients with multiple hospitalizations, the first admission was chosen as the index admission.

To assess medical comorbidity, medical records of the index hospitalization were reviewed using the Cumulative Illness Rating Scale (17). A single rater blind to diagnosis (M.V.) performed the Cumulative Illness Rating Scale assessment.

All of the nonpsychotic and 42 of the 61 patients with psychotic depression had a standard DST during their hospital stay. Administration of the DST has been described previously (13, 14). Briefly, 1 mg of dexamethasone was given at 11:00 p.m., and two cortisol samples (8:00 a.m. and 4:00 p.m. or 8:00 p.m.) were drawn the next day.