Neurobiology of Disease

www.elsevier.com/locate/ynbdi
Neurobiology of Disease 22 (2006) 702 – 709

Alterations of white matter connectivity in first episode schizophrenia

Andrea Federspiel,[a,1] Stefan Begré,[b,*,1] Claus Kiefer,[a,c] Gerhard Schroth,[c] Werner K. Strik,[a] and Thomas Dierks[a]

[a]*University Hospital of Clinical Psychiatry, Department of Psychiatric Neurophysiology, Berne, Switzerland*
[b]*Department of General Internal Medicine, Division of Psychosomatic Medicine, Inselspital Bern, University of Berne, CH-3010 Berne, Switzerland*
[c]*Inselspital Berne, Department of Neuroradiology, University of Berne, Berne, Switzerland*

Received 22 August 2005; revised 12 December 2005; accepted 22 January 2006
Available online 19 April 2006

Cerebral disconnectivity due to white matter alterations in patients with chronic schizophrenia assessed by diffusion tensor imaging has been reported previously. The aim of this preliminary study is to investigate whether cerebral disconnectivity can be detected as early as the first episode of schizophrenia. Intervoxel coherence values were compared by voxel-based *t* test in 12 patients with first episode schizophrenia and 12 age- and gender-matched control groups. We detected 14 circumscribed significant clusters ($P < 0.02$), 3 of them with higher, and 11 of them with lower IC values for patients with schizophrenia than for healthy control groups. We interpret these white matter alterations in different regions to be disconnected fiber tracts already present early in schizophrenic disease progression.

Keywords: Intervoxel coherence; Fractional anisotropy; Diffusion tensor imaging; Gray matter; White matter; First episode schizophrenia

Introduction

Schizophrenia has been described as a disorder of disrupted connectivity in the fronto-thalamo-striato-cerebellar circuit (Andreasen et al., 1998). The basis of impaired connectivity may be subtle gray and white matter lesions, as described by several investigators (Shenton et al., 2001). Diffusion tensor imaging (DTI) is a relatively new approach to assessing tissue structure and geometry at a microscopic level. It measures diffusion-driven displacements of molecules during their random path along axonal fibers, expressed as fractional anisotropy (FA) or intervoxel coherence (IC) ranging from 0 (isotropic medium) to 1 (fully anisotropic medium). IC guarantees a very robust signal-to-noise ratio and considers the degree of collinearity between the diffusion tensor of the reference voxel and the adjacent voxels (Pierpaoli and Basser, 1996; Pfefferbaum et al., 2000); in literature, IC is also labeled as Coherence Index (Deutsch et al., 2005). IC is a measure similar to FA (Klingberg et al., 1999, 2000). It is related to FA value; high IC value indicates both the local strength of FA and the agreement of fiber direction in neighboring voxels (Deutsch et al., 2005). In both studies, the main orientation of major fiber tracts important for reading and spelling were reported using FA and IC measures. Previous studies have shown a reduced FA in schizophrenia (Agartz et al., 2001; Ardekani et al., 2003; Buchsbaum et al., 1998; Burns et al., 2003; Foong et al., 2000; Hubl et al., 2004; Kubicki et al., 2003, 2005; Kumra et al., 2004; Lim et al., 1999; Minami et al., 2003; Okugawa et al., 2004; Sun et al., 2003; Wang et al., 2004). Only one study reported augmented FA in circumscribed tracts of the brain in hallucinating, chronic schizophrenic patients as compared with FA in healthy control groups (Hubl et al., 2004). Using FA in first episode schizophrenia, two studies found no differences compared to healthy controls in the hippocampus (Begre et al., 2003) or the splenium and genu of corpus callosum (Price et al., 2005). Using IC, two studies of the same group compared amygdale and entorhinal regions in chronic schizophrenia patients to healthy controls (Kalus et al., 2005a,b). To our knowledge, IC has never been used to investigate white matter in first episode schizophrenic patients. Several studies suggest that schizophrenia is a progressive disease accompanied by loss of gray and white matter volume (Cahn et al., 2002; Gogtay et al., 2004; Velakoulis et al., 2002). However, it is not clear whether changes in white matter structure exist from childhood, prior to the first psychotic symptoms, or develop during disease progression. To investigate whether previously described anisotropy changes of white matter in chronic schizophrenia are present at the beginning of the schizophrenic course, we measured IC as an indication of connectivity in 12 first episode psychosis patients. We used 12 age- and gender-matched subjects as the control group. From previous results of studies in chronic schizophrenia using FA, we expected to find clusters of reduced IC in corpus callosum, cingulum, main white matter fascicles, as well as in frontal, temporal, and occipital white matter regions.

* Corresponding author. Fax: +41 31 382 11 84.
E-mail address: stefan.begre@insel.ch (S. Begré).
[1] These authors contributed equally to this work.
Available online on ScienceDirect (www.sciencedirect.com).

0969-9961/$ - see front matter
doi:10.1016/j.nbd.2006.01.015

Materials and methods

Subjects

Twelve patients (8 men and 4 women, mean age 23.4 years ± 3.0 years SD, range 18.1–28.7 years, all right-handed) hospitalized with their first episode of schizophrenia, diagnosed according to ICD-10 diagnosis criteria (Bramer, 1988) were pair matched by gender and age (±6 months) with 12 healthy volunteers (mean age of 23.2 years ± 3.1 years SD, range 17.6–28.5 years, all right-handed). Patients with schizophrenia were recruited from the first episode ward of the University Hospital of Clinical Psychiatry in Berne; the control group consisted of normal volunteers from the region. Patients and their relatives were questioned about the development of psychotic symptoms, substance abuse, and any other psychiatric or medical conditions. All patients had at least first-rank symptoms, but one lacked auditory hallucinations. Three patients, including the one without auditory hallucinations, reported sporadic cannabis use. At the time of the measurements, the average duration of illness was 115.7 days (SD ± 91.0 days, range 14–270 days), and the average duration of medication was 10.5 days (SD ± 11.0 days, range 0–35 days). Three patients were medicated with risperidone, 3 with olanzapine, 2 with quetiapine, 1 with amisulpride, and 2 with both haloperidol and risperidone. One patient was not medicated. None of the control subjects had a history of major medical or neurological disorders, substance abuse, or other psychiatric diseases, or received psychotropic medication before hospitalization. All subjects gave written informed consent, and the study received approval from the local ethical committee. For measurements in the magnetic resonance imaging (MRI) scanner, subjects received no specific instructions other than to relax and keep their head still. The use of restraining foam pads minimized head motion.

MRI recording

MRI imaging was performed on a 1.5-T standard clinical MRI scanner (Siemens Vision, Erlangen, Germany), using the standard radio-frequency head coil. First, a high-resolution three-dimensional data set covering the whole brain was collected for each subject through a 3D magnetization-prepared rapid-acquisition gradient echo (MP-RAGE) sequence. In all, 192 scans were accumulated (TR = 6 s, TE = 95 ms, matrix size = 256 × 256 voxels, field of view [FOV] = 256 mm, voxel dimension = 1.0 mm × 1.0 mm × 1.0 mm).

DTI recording and processing

For diffusion-weighted imaging, a single-shot spin-echo–echo-planar imaging (SE-EPI) sequence was acquired in the same session. Gradient amplitudes and duration were chosen so as to enable detection of tissue-dependent diffusion coefficients by the signal attenuation: G = 22 mT/m, duration TE = 20 ms, intergradient time interval = 40.00 ms, TR = 3000 ms. In total, 12 axial continuous slices (5 mm slice thickness, no gap) were acquired. The matrix size = 64 × 64 voxels, field of view [FOV] = 240 mm, voxel dimension = 3.75 mm × 3.75 mm × 5.0 mm. The diffusion sensitizing gradients were applied simultaneously on two axes around the 180° pulse at b = 1800 s/mm^2/axis along 6 noncollinear directions: $(G_x, G_y, G_z) = [(1, 0, 1), (1, 0, -1), (0, 1, 1), (0, 1, -1), (1, 1, 0), (-1, 1, 0)]/\sqrt{2}$. This gradient scheme was chosen to minimize acquisition time, so as to include as many schizophrenic patients as possible in the study. This, despite suggestions that the optimal gradient scheme may include more than 6 gradient directions (Jones, 2004; Jones et al., 1999). Additionally, one image was acquired with no gradients applied. Eddy-current corrections were included. Images were smoothed using a Gaussian filter with a FWHM of 7.5 mm. To test for nonnormality of the residuals, the Shapiro–Wilk test was computed for each voxel of each cluster. With the Shapiro–Wilk test, the null hypothesis is that residuals follow an normal distribution, i.e., if the P value is greater than alpha value of 0.05, then the null hypothesis will not be rejected (Jones et al., 2005). The calculation and diagonalization of the diffusion tensor were based on the multivariate regression approach (Basser et al., 1994). Six independent elements of the diffusion tensor were extracted (Basser and Pierpaoli, 1996). Eigenvalues (magnitude) and eigenvectors (direction) were determined for each voxel, and the intervoxel coherence maps were constructed using the average of the angle between the eigenvector of the largest eigenvalue of a given voxel and its neighbors, which represents the extent to which the vectors point in the same direction and are, therefore, coherent (Pierpaoli and Basser, 1996). Coregistration of the 2D intervoxel coherence maps to the 3D structural images was manually performed using the scanner's slice position parameters of the SE-EPI measurements and the T1-weighted anatomical measure-

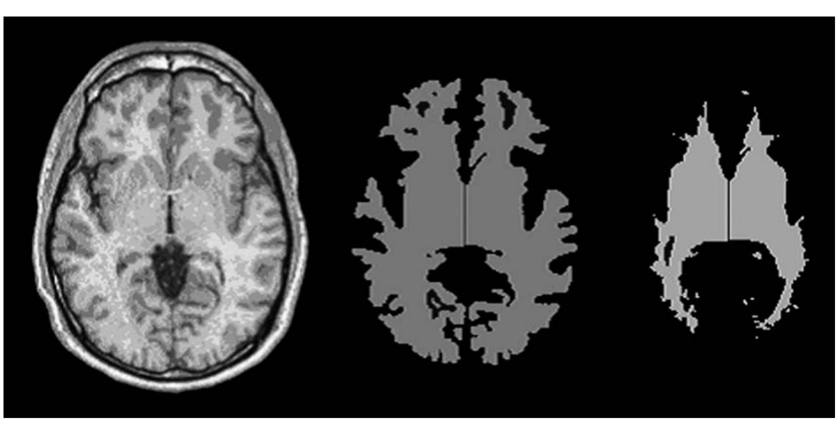

Fig. 1. Representative axial slice in Talairach space of one subject (left), its segmented white matter map (middle), and the largest possible white matter mask including all white matter maps of all subjects (right). To evaluate statistical differences between intervoxel coherence values of patients with schizophrenia and the control group, 3D segmented white matter maps were used to construct the largest possible white matter mask.