

Regional axonal abnormalities in first episode schizophrenia: Preliminary evidence based on high *b*-value diffusion-weighted imaging

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Abstract

Connectivity has been implicated as a major source of brain abnormality in schizophrenia. The current study focused on first episode schizophrenia to identify possible early pathology in axonal structure. First episode schizophrenic patients and healthy controls were scanned in a 1.5-Tesla scanner during which high *b*-value diffusion-weighted imaging (DWI) was acquired. Histogram analysis revealed a decrease in overall white matter (WM) tissue, indicating relative axonal abnormality in the schizophrenic group. Subsequent analysis found that this effect was contributed mainly by anterior-prefrontal bundles. Moreover, negative correlations were found between positive and negative symptom severity and whole head WM displacement peak value, implying an overall lesser degree of WM integrity is associated with greater symptom severity. These preliminary results suggest that WM abnormality, as measured by high *b*-value DWI, is already a significant pathological brain marker in early stage of schizophrenia.

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1. Introduction

Converging evidence suggests disturbed neural connectivity as a major source of brain abnormality in

schizophrenia (Davis et al., 2003; Lewis and Lieberman, 2000). This notion has been closely related to the idea of a ‘disconnection syndrome’. It implies that a failure occurs in the functional integration within the brain, affecting connections between anterior and posterior regions (Andreasen et al., 1997; Friston, 2003). Such abnormality can be thought of as a deficit in the organization of large-scale neural networks affecting distributed neural activity (Dolan et al., 1999). Large-scale integration has been implicated in high level

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functional mechanisms such as binding, awareness and goal-directed behavior (Varela et al., 2001).

Schizophrenia has been considered as a neurodevelopmental illness, with pathogenic biological features preceding the symptomatic manifestation of the illness (Lewis and Levitt, 2002; Lieberman et al., 2001). One such feature could be axonal myelination, a process that can affect neuronal connectivity. This process normally occurs from early childhood through adolescence, with frontal and temporal lobe WM being the latest to develop (Davis et al., 2003), occurring around the common early onset of schizophrenia. Moreover, MRI studies have exhibited volumetric increases of WM in the normal population into the mid-forties, while showing less of an increase in schizophrenic brains (Bartzokis et al., 2003b). Thus, differences in WM measures that reflect myelination at the onset of schizophrenia might be indicative of pre-symptomatic developmental impairments.

To test the disconnection hypothesis *in vivo*, it is necessary to apply advanced brain-imaging techniques that differentiate between gray and white matter tissue. So far, such studies have indicated regional abnormalities in both cortical (Lewis and Lieberman, 2000; Goldstein et al., 1999; Kuperberg et al., 2003) and white matter volumes (Spalletta et al., 2003; Job et al., 2002; Kawasaki et al., 2004). Diffusion tensor imaging (DTI) is an MRI-based technique for characterizing white matter tissue that is extracted from diffusion-weighted imaging (DWI). In schizophrenia, DWI methods have either exhibited a local reduction of fractional anisotropy (FA) in various WM tracts, such as prefrontal (Buchsbaum et al., 1998) and splenium (Foong et al., 2002) or have shown a wide spread reduction in WM integrity (Lim et al., 1999). However, the commonly used DWI methods cannot differentiate between specific tissue compartments in white matter such as axons and glia. Thus, the physiological significance of the DTI-based measures of WM abnormalities is not fully clear, due to the averaging of the diffusivity contribution from all cellular compartments. Recent works using high *b*-value DWI have been shown to be more representative of white matter pathophysiology. Using high *b*-value ($b > 3000 \text{ s/mm}^2$) in DWI results in the decay of the free diffusion component, whereas the remaining signal represents restricted diffusion most likely originated from intra-axonal diffusion (Cohen and Assaf, 2002). Therefore, using this method in schizophrenia may reveal certain dysfunctions in WM integrity resulting specifically from the axonal structures.

By examining individuals with first-episode schizophrenia, our aim was to determine whether WM is

compromised even at an early stage of the disorder as detected by DTI and high *b*-value DWI methods. We assumed that measuring WM by high *b*-value DWI could be more specific to axonal pathology than DTI, and therefore may tag early brain pathology in schizophrenia. Given that frontal and temporal cortical regions are the main functional targets in schizophrenia pathology, we focused on regions of interest in WM fibers that are in the vicinity of these cortical areas. In addition, the patients' clinical data were correlated with WM measurements to test for possible association between symptom severity and axonal integrity.

2. Methods

2.1. Subjects

The study population consisted of both individuals with schizophrenia (as defined by DSM-IV criteria) in their first episode of the illness at the Beer Yaakov Mental Health Center (a large state psychiatric referral institution). Two board-certified psychiatrists verified patients' diagnoses by means of a structured interview according to Structured Clinical Interview for DSM-IV Axis I, Patient Edition guidelines (First et al., 1994). MRI scans were acquired from nine such patients (6M, 3F), less than 1 month after hospitalization. All patients were on medication for less than 1 month. Five healthy volunteers (2M, 3F) with no history of neurological or psychiatric illnesses served as a control group. The average age in the schizophrenia and control groups was 26 ± 6 and 29 ± 3 years, respectively (non-significant two-sample *t*-test). The local institutional review board (IRB) committee approved the MRI protocol, and written informed consent was obtained from all participants. The main parameters, including age, sex, handedness, main presenting symptoms and medication given, are presented in Table 1.

2.2. MRI protocol

MRI was performed on a 1.5-Tesla GE Signa horizon echo speed LX MRI scanner (GE, USA). In all MRI scans, the field of view (FOV) was 24cm, slice thickness was 5mm with 1-mm gaps between slices. The MRI protocol included, in addition to some conventional clinical MR images (T_2 -weighted MRI, FLAIR and T_1 -weighted spoiled gradient recalled echo), the high *b*-value series.

The high *b*-value DWI data set was acquired using a spin-echo diffusion-weighted echo-planar-imaging

Table 1
Main characteristics of schizophrenia patients

Subject	Gender	Age	Handedness	Main acute symptoms	Medication
1	M	21	Right	Paranoid delusions	Risperdal
2	M	28	Right	Delusions and hallucinations	Deroquel and lithium
3	M	30	Right	Paranoid delusions	Risperdal
4	M	34	Right	Delusions and hallucinations	Risperdal
5	F	27	Right	Delusions and hallucinations	Clonex and risperdal
6	F	35	Right	Delusions and hallucinations	Perfenan
7	F	21	Left	Paranoid delusions	
8	M	19	Left	Hallucinations	Halidol and tikinet
9	M	19	Left	Delusions and hallucinations	Clopixiol

All patients were given treatment for less than 1 month prior to MRI scan.

(DW-EPI) sequence (without cardiac gating) with the following parameters: TR/TE=2000/167 ms, $\Delta/\delta=71/65$ ms (where Δ is the diffusion time and δ is the diffusion gradient length), matrix dimension of 128×128 (reconstructed to 256×256), and number of averages=4. The diffusion gradients were applied in six directions (xy , xz , yz , $(-x)y$, $(-x)z$ and $y(-z)$). The magnitude of the gradients was incremented linearly from 0 to 2.2 G/cm (in 16 steps) to reach a maximal b -value of $14,000 \text{ s/mm}^2$ and a maximal q -value of 850 cm^{-1} . The q -space data set included 96 images per slice (16 diffusion images \times 6 diffusion gradient directions); the number of slices was 5 (the highest slice was placed above the corpus callosum, as defined in a mid-sagittal view) with total acquisition time of 12 min.

2.3. Image and statistical analysis

The q -space theory was used to analyze the high b -value data. The q -space analysis was performed on a pixel-by-pixel basis as previously described (Assaf et al., 2000). In general, the q -space data set provides a measure of apparent displacement and apparent probability. These measures are extracted from Fourier transformation of the signal decay (after zero filling) to produce the displacement distribution function. The apparent displacement represents the full width at half maximum of the displacement distribution function, and in cases of free diffusion it is proportional to the root-mean-square displacement. The apparent probability

represents the peak intensity of the normalized displacement probability function (i.e. probability for zero displacement). These two measures are referred to as apparent displacement and apparent probability since the experimental parameter forced by the limitation of the human scanner does not meet the requirements of the theory of q -space analysis. Therefore the observed values might deviate from the real displacement distribution function, yet their relative comparison with a control group is meaningful. Fractional anisotropy (FA) images were obtained from the $b=1000 \text{ s/mm}^2$ shell of the q -space data set and analyzed according to Bassler (2002).

2.4. Data analysis

2.4.1. Histogram analysis

Histogram analyses of the displacement maps were performed and averaged for all slices obtained and over subjects. The histogram resulted in three peaks for control data sets, corresponding to WM, grey matter and CSF (see Assaf et al., 2002).

By means of spectral analysis, the peak, area, center and width of the Gaussians comprising each WM histogram graph were obtained and compared between the two groups via two-sample t -tests. In addition, these parameters were used for computing correlations between these parameters and clinical scores.

2.4.2. ROI analysis

ROI analysis was performed blindly on anatomically defined prefrontal and temporal WM regions, as depicted on a DWI slice (see Fig. 2a). The ROIs covered fibers of the superior, middle and inferior frontal gyrus, on axial planes ventral to the corpus callosum midline (portions of the superior longitudinal fasciculus in the PFC), and fibers located in the vicinity of the posterior superior temporal gyrus (STG) and sulcus (STS) (see Fig. 2a). Mean values of the measured parameters (displacement and FA) were calculated for each subject and averaged over the whole patient group. Independent t -tests were used to compare q -space displacement and FA values of healthy controls to the schizophrenic patients per region.

2.4.3. Diagnostic data

Clinical measurements were collected regarding each patient, by rating them on the Positive and Negative Syndrome Scale and the Clinical General Impressions Scale. The total scores of positive and negative symptoms were correlated by using a Pearson

correlation with different WM measurements from whole volume and from each ROI, and the correlations were tested for statistical significance. A one-way analysis of variance (ANOVA) of the WM peak histogram of displacement values for the CGI groups and controls was calculated as well to test for differences between subgroups.

3. Results

3.1. WM measurements

To evaluate the overall reduction in WM tissue, an averaged histogram of the high b -value displacement

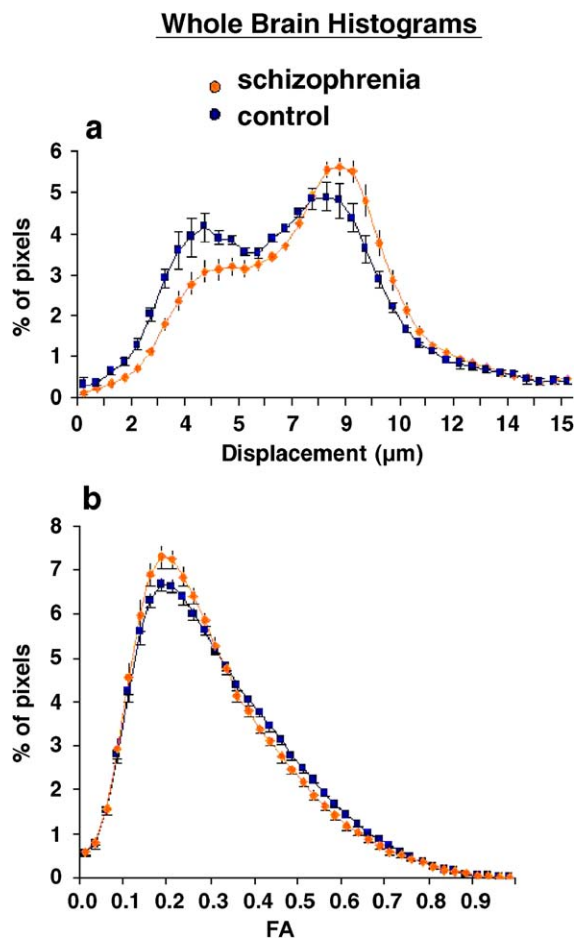


Fig. 1. Whole brain histogram of displacement values per group. Schizophrenia group is denoted in orange, and control group in blue. (a) A histogram depicting percentage of pixels for each displacement value from the QS-DWI displacement image of schizophrenic and control groups with standard errors. The first peak from the left of displacement values corresponds to white matter tissue. A lower percentage of pixels in the peak displacement WM value is apparent in the schizophrenic group compared with controls. (b) A histogram depicting percentage of pixels for FA values of both groups.

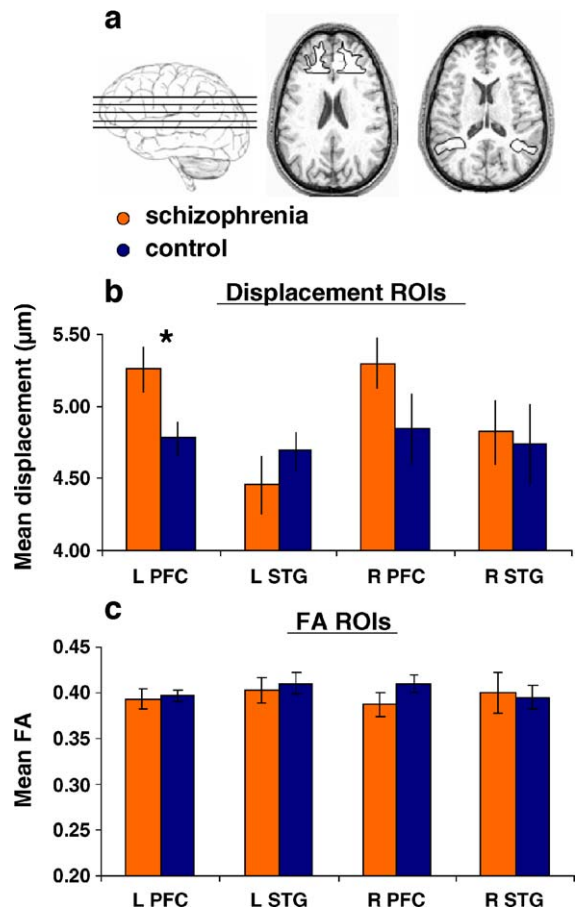


Fig. 2. Region of interest (ROI) analysis of mean displacement and FA values. (a) A brain animation depicting the slices obtained in the q -space analysis (left), and slices depicting the prefrontal (middle picture) and posterior superior temporal gyrus regions (right picture), which were used for ROI analysis. (b) Mean and standard errors of displacement values from right and left prefrontal and temporal lobe for schizophrenic and control groups. (c) Mean and standard errors of FA values from right and left prefrontal and temporal lobes.

values was obtained for whole acquired brain volume. This analysis revealed an overall decrease in the percentage of pixels at peak displacement values that typically correspond to WM (see Assaf and Cohen, 2002) in the schizophrenia compared with the healthy group (see Fig. 1). This difference was based on individual distribution profiles providing mean peaks of white matter, gray matter and CSF. These values exhibited a lower average WM peak in the schizophrenia than in the control group ($t(12) = -2.5$, $P < 0.05$). In an attempt to examine the regional contribution to the abnormality in WM displacement, an ROI analysis was performed. The WM-ROIs are delineated on two slices corresponding to prefrontal cortex and temporal regions (see Fig. 2a). As depicted in Fig. 2b, the ROI analysis of

WM bundles in the prefrontal cortex and temporal cortex revealed a decrease in mean WM displacement in schizophrenic patients compared with controls in anterior brain regions corresponding to left prefrontal cortex ($t(12)=2.2$, $P<0.05$). Right prefrontal cortex displacement values came close to significance in the same direction ($t(12)=2$, $P=0.068$). No such differences were found in the temporal cortex. The same regions did not differ between groups for the FA measurement (see Fig. 2c).

3.2. Clinical data

Symptom severity was evaluated from all schizophrenia subjects based on the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) and the Clinical Global Impressions (CGI) (Guy, 1976) Scale. A negative correlation was found between both positive and negative subtotal PANSS scores and the whole brain pixel percentage of WM displacement peak ($r=-0.69$, $P<0.05$ and $r=-0.68$, $P<0.05$, respectively; see Fig. 3a). This negative correlation indicates that the more severe the symptoms, the lower the WM histogram; peak of displacement values (see group histogram; Fig. 1a). Note that correlations between clinical severity and FA measurements were not found.

The CGI ratings of schizophrenic patients ranged from 4 (mildly ill, $n=4$) to 5 (markedly ill, $n=4$). A one-way ANOVA of the WM peak histogram of displacement values for the two CGI groups and controls revealed a significant effect ($F(2,10)=20.3$, $P<0.001$). Post hoc Scheffé contrasts showed that markedly ill patients had lower WM peaks than both mildly ill

patients and controls ($P<0.01$; see Fig. 3b). No difference was found between mildly ill patients and control subjects.

4. Discussion

The primary findings in this preliminary study indicated that WM integrity, as measured by high b -value DWI, was reduced in the first episode schizophrenia patients (less than 1 month after hospitalization) in comparison to healthy controls. Moreover, this abnormality was more pronounced in anterior-prefrontal than posterior-temporal fibers (Fig. 2b and c) and was correlated with the severity of positive and negative symptoms. Furthermore, it seems that this abnormality was most prominent in patients diagnosed as markedly ill (CGI 5), whereas mildly ill patients did not differ from controls (Fig. 3a and b). These findings suggest that the more severe clinical state is accompanied by overall poorer structural integrity of axons.

In this study, WM damage measured by high b -value DWI was found to be a significant and measurable pathological brain marker in first episode schizophrenia. In contrast, the more typically used DTI-based measurement (i.e. FA) was not sensitive to the early WM changes in schizophrenia. Since a high b -value is a more direct measure of intra-axonal tissue, even minor changes and breakdowns in WM may be detected (Cohen and Assaf, 2002). As such, it may be more suitable for studying the initial stages of brain pathology than FA and more reflective of inter-individual differences. Considering the heterogeneous nature of schizophrenia, such measurement sensitivity might be crucial

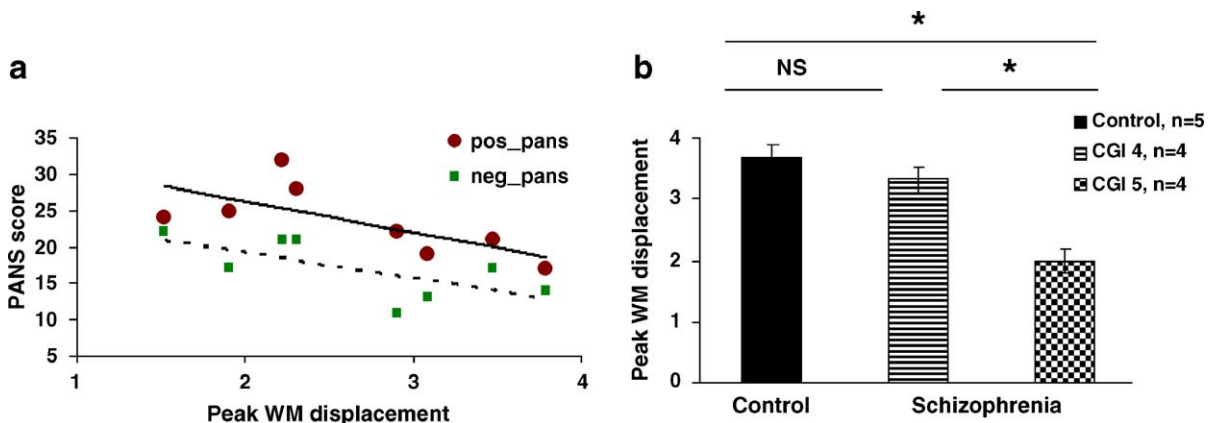


Fig. 3. Correlation between clinical severity and WM displacement peaks in the schizophrenia group. (a) A linear correlation between whole brain peak WM displacement and PANSS scores; red indicates positive scores and green indicates negative scores. (b) Whole brain average peak of WM displacement for schizophrenia patients divided by their clinical general inventory (CGI) that indicates illness severity (horizontal stripes indicate CGI=4: mild illness, checkerboard pattern indicates CGI=5: severe illness). Controls values are shown for comparison on the left (full black bar). Error bars stand for one standard error of the mean. Asterisks indicate significant value of $P<0.05$ in post hoc Scheffé comparisons (see Section 3).

for better and earlier differentiation of the disease subtypes. Indeed, the use of high-*b* value in this study pointed to the relation between WM integrity and individual differences in the severity of symptoms.

The detection of abnormal WM measures as early as at the first episode in young patients may provide a neuro-developmental risk marker, possibly preceding behavioral symptoms. It has been shown that in the normal aging brain, myelin sheaths of bundles in the frontal lobes develop until the mid-forties, and then start to undergo a general breakdown (Bartzokis et al., 2003a). Accordingly, our study shows that the abnormal WM measures at the early stages following the onset of schizophrenia were confined more to frontal than temporal fibers (see Fig. 1). This suggests that local frontal regional WM disorganization may lead to future disconnection between anterior and posterior brain regions, as implied in the ‘disconnection syndrome’ (Friston, 2003).

It remains unknown, however, whether this prefrontal phenomenon occurring close to the onset of illness reflects the arrest of pre-morbid development or the beginning of an ‘aging-like’ deterioration of white matter. It has been noted that the earlier the onset of schizophrenic symptoms, the more severe the prognosis (Eaton et al., 1992). This supports the idea that the early onset of schizophrenia results in the arrest of critical brain organization during development. Further support for this idea comes from genetic studies showing decreased expression in myelin-related and oligodendrocyte-related genes in the dorsolateral prefrontal cortex in schizophrenia (Hakak et al., 2001; Tkachev et al., 2003). This corresponds to previous observations showing that the dysregulation of several of these genes inhibits oligodendrocyte development, maturation and function (Espinosa de los Monteros et al., 1999). Thus, it is possible that the axon-related WM deterioration observed in the present study reflects malfunction in myelin-related gene expression during development.

With regard to the aging notion, neuroimaging studies have pointed to brain profiles in schizophrenia that resemble normal aging or early neurodegenerative processes (Lieberman, 1999). For example, both normal aging and schizophrenia are accompanied by enlarged ventricles, frontal cortical atrophy and dysfunction (Buchsbaum and Hazlett, 1997). Interestingly, this ‘aging hypothesis’ in schizophrenia reflects Kraepelin’s longstanding conception of schizophrenia as ‘dementia praecox’ (Adityanjee et al., 1999). The finding in the current study of greater abnormality in prefrontal cortex than in temporal cortex may support such an idea. This is also in agreement with growing evidence linking

deterioration in prefrontal cognitive functions in old age with disturbed modulation of dopamine (Braver et al., 2001; Braver and Barch, 2002). Moreover, ligand-based neuroimaging studies have found a deficiency in dopamine D1 receptor binding in PFC corresponding to reduced working memory functions in schizophrenia (Abi-Dargham et al., 2002; Goldman-Rakic et al., 2004). Normal aging has also been associated with widespread damage to myelin sheaths, as detected in primates (Peters, 2002), and diffusion-weighted MRI studies in humans (Moseley, 2002). Future studies should examine the possible link between the regulatory deficits of the dopamine system in PFC and the breakdown of myelin tissue observed in schizophrenia.

To further explore the role of WM deficits in either developmental or ‘aging-like’ pathophysiology in schizophrenia, examinations of larger samples of patients in both the pre-morbid and the chronic stages of the disorder are recommended.

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