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High b-value diffusion-weighted imaging: A sensitive method to reveal white matter differences in schizophrenia

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ABSTRACT

Over the last 10 years, diffusion-weighted imaging (DWI) has become an important tool to investigate white matter (WM) anomalies in schizophrenia. Despite technological improvement and the exponential use of this technique, discrepancies remain and little is known about optimal parameters to apply for diffusion weighting during image acquisition. Specifically, high b-value diffusion-weighted imaging known to be more sensitive to slow diffusion is not widely used, even though subtle myelin alterations as thought to happen in schizophrenia are likely to affect slow-diffusing protons. Schizophrenia patients and healthy controls were scanned with a high b-value (4000 s/mm^2) protocol. Apparent diffusion coefficient (ADC) measures turned out to be very sensitive in detecting differences between schizophrenia patients and healthy volunteers even in a relatively small sample. We speculate that this is related to the sensitivity of high b-value imaging to the slow-diffusing compartment believed to reflect mainly the intra-axonal and myelin bound water pool. We also compared these results to a low b-value imaging experiment performed on the same population in the same scanning session. Even though the acquisition protocols are not strictly comparable, we noticed important differences in sensitivities in the favor of high b-value imaging, warranting further exploration.

1. Introduction

Schizophrenia is a many sided and complex disorder characterized by disturbance in perception, speech, volition, and cognition, as well as more subtle changes such as basic symptoms. Converging evidence points towards an interaction between biological and environmental factors occurring in the developing brain and leading to neural disconnectivity and abnormal functional integration (Stephan et al., 2009). Several lines of evidence such as post-mortem and genetic studies gave rise to the "oligodendroglial dysfunction hypothesis" with subsequent abnormalities in myelin maintenance and repair (Davis et al., 2003; Karoutzou et al., 2008). This led to an increasing number of studies applying diffusion magnetic resonance imaging (MRI) to investigate white matter anomalies in schizophrenia.

Diffusion-related water displacement is a ubiquitous phenomenon in the human body. Since cell and tissue barriers hinder water mobility, water diffusion is neither free nor isotropic. As a matter of fact, the anisotropic tissue organization, as seen in the white matter, is reflected in the behavior of water by exhibiting preferential diffusion in parallel directions to nerve fibers rather than in the perpendicular directions. Diffusion-weighted imaging (DWI) is an MRI-based technique for measuring diffusion of water molecules. Since water diffusion is related to the direction of nerve fibers, DWI allows for characterizing underlying micro-architecture and neuronal direction and integrity. Two main metrics are used to characterize diffusion. The first is the apparent diffusion coefficient (ADC), a measure of the average diffusion distance of water molecules per time unit, measured in mm^2/s (Le Bihan et al., 1986). Fractional anisotropy (FA), another frequently used metric that can be derived from diffusion tensor imaging (Basser et al., 1994; Basser, 1995), is a relative measure of the orientational bias of diffusion.

It became obvious that DWI should be applied to characterize the abnormal white matter wiring in the schizophrenic brain. An extensive literature on the topic has been published over the last 10 years. Many different white matter regions have been implicated with DWI as being abnormal. While for many regions, replication failed, frontal and temporal white matter seem to be consistently more affected (Kyriakopoulos et al., 2008; Kubicki and Shenton, 2009). Several white matter tracts have been implicated in terms of FA,

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which correspond to the cingulum bundle, arcuate fasciculus and corpus callosum. While FA is the most frequently used metric, ADC (or mean diffusivity, which is closely related) has also been used.

Despite the plethora of DWI studies that investigated white matter anomalies in schizophrenia, discrepancies remain which might arise from patient selection (e.g. differences in duration of untreated illness, age, confounders such as medication or substance abuse, small sample size), differences in methodology ranging from data acquisition (type of sequence, number of diffusion directions, voxel size, signal to noise ratio, slice thickness) to data processing and data analysis (regions of interests, voxel-based morphometry (VBM), tractography algorithms) (Kubicki and Shenton, 2009). Further, the exact relationship between the motion of water, the underlying architecture and the MRI signal is not completely elucidated.

The b-value is an important parameter in diffusion imaging. It is a summary measure of different pulse sequence parameters and captures the level to which the signal is made sensitive to the diffusion process. Practically, it is a function of the experimental diffusion time and the strength of the diffusion sensitizing magnetic gradients. Standard b-values used in conventional DWI are in the range of 700 to 1000 s/mm^2. When b-values of more than 1500–2000 s/mm^2 are used, then the term "high b-value diffusion imaging" is more appropriate (Assaf and Cohen, 2009). The DWI signal drops with increasing b-value and this relationship is biexponential rather than monoexponential (Clark and Le Bihan, 2000). Based on these findings as well as on experimental studies in rat (Assaf and Cohen, 2009; Bar-Shir et al., 2009) and human brain, the hypothesis of fast and slow diffusion compartments was elaborated. Although still a matter of debate, it is thought that the main compartment that contributes to the slow-diffusing component is the intra-axonal compartment. Probing slow diffusion can be achieved by using larger b-values making experiments more sensitive to smaller water displacements (Assaf and Cohen, 2009). Recent works suggest that high b-value (b>3000 s/mm^2) DWI is more sensitive to intra-axonal water and the status of myelin sheets, and thus represents higher sensitivity to white matter pathophysiology (Cohen and Assaf, 2002; Bashat et al., 2005; Assaf and Cohen, 2009; Hagmann et al., 2010).

Although the exact attribution of the slow and fast compartments remains conceptual and controversial, the use of different b-values provides important information in characterizing brain tissue. Indeed, high b-value MR imaging has been applied with promising results to the study of normal brain maturation (Jones et al., 2003; Bashat et al., 2005; Hagmann et al., 2010), multiple sclerosis (Assaf et al., 2002a), brain tumors (Maier et al., 2001), autism (Ben Bashat et al., 2007), Alzheimer's disease (Yoshiura et al., 2003), vascular dementia (Assaf et al., 2002b), stroke (Brugieres et al., 2004) and Creutzfeldt-Jakob Disease (Hyare et al., 2010). Using high b-value DWI acquisition may reveal certain anomalies in WM integrity resulting specifically from the axonal structures and status of myelin sheets, and thus not visible with a low b-value. Given these findings, it is surprising that most studies use low b-values in schizophrenia research corresponding to "averaging diffusivity contribution from all cellular compartments" (Mendelsohn et al., 2006).

To our knowledge, only one study (Mendelsohn et al., 2006) used high b-value imaging to investigate schizophrenia. To examine white matter anomalies in first episode schizophrenia with high b-value imaging, Mendelsohn et al. sampled diffusion-weighted images in multiple directions with variable b-values from 0 to 14,000 s/mm^2. This allowed them to estimate using complex Fourier calculations the "mean displacement" (equivalent to ADC) with strong weighting towards slow diffusion. The brain histogram of mean diffusivity ("displacement") demonstrated a shift to the right in schizophrenia patients compared to controls, which is similar to an increase in ADC. Interestingly, subsequent region of interest (ROI) analysis showed prefrontal (predominantly left) but not temporal contribution. In the same study, no differences were found using FA maps with low b-value imaging (b = 1000 s/mm^2).

The aim of this study was to examine white matter differences between schizophrenia patients and healthy controls with high b-value DWI using a simple, clinically feasible two b-value protocol (0 and 4000 s/mm^2). In a second step, we compared the high b-value protocol with a second acquisition protocol differing in parameters including b-value (i.e. low b-value) acquired in the same population during the same scanning session. We focused on large white matter tracts and investigated the anterior and posterior corpus callosum as well as frontal, parietal lobes and centrum semi-ovale bilaterally.

2. Method

2.1. Subjects

All subjects (12 patients and 16 controls) were assessed by using the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994; Preisig et al., 1999). Major mood, psychotic, or substance-use disorder and having a first degree relative with a psychotic disorder were exclusion criteria for controls. Subjects were males, of Caucasian origin with no history of neurological disease and matched for age. Patients were recruited between 2004 and 2007 from an outpatient unit of the Department of Psychiatry, University Hospital Center of Lausanne (CHUV, Switzerland) and met criteria for schizophrenia ($n = 10$) or schizoaffective disorder ($n = 2$) of the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV). All patients were under antipsychotic medication except one. The average ages in the schizophrenia and control groups were 35 ± 3 and 33 ± 2.4 years, respectively. Table 1 summarizes demographic and clinical characteristics of the sample. The study was validated by the local ethics committee and written informed consent was obtained from all subjects.

2.2. MRI acquisition and pre-processing

Imaging was performed on a 3-Tesla MRI scanner (Philips). Parallel imaging with an eight-channel head coil was used (acceleration factor of 2.5 to limit acquisition time and susceptibility distortion). Diffusion-weighted images were acquired using a standard Stejskal–Tanner spin echo sequence with an EPI readout. The field of view was 256×56 mm^2 (matrix was 128×128) and the slice thickness was 3 mm. Patients and controls were scanned with a low b-value and a high b-value protocol as follows (see also Table 2). Because of the low SNR in the high b-value images, correction for head motion and eddy current was not achievable. For fair comparison, this procedure was not applied to both datasets, low and high b-value.

2.2.1. High b-value or slow diffusion protocol

Twenty slices were acquired; the lowest slice was placed above the temporal lobe. The diffusion-sensitizing gradients were applied along 66 non-collinear directions at a gradient strength corresponding b-value of 4000 s/mm^2 (b4000). Each of these directions was averaged 3 times.

Table 1
Demographic and clinical characteristics of the sample.

	Patients	Comparison subjects
Number of subjects	12	16
Age	35	33
Gender (M/F)	12/0	16/0
Handedness (right/left)	10/2	16/0
PANSS Positive symptom score	7	–
PANSS Negative symptom score	8	–
PANSS General symptom score	20	–
Schizophrenia	10	–
Schizoaffective disorder	2	–

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Table 2
Characteristics of the two MRI sequences.

	Protocol A	Protocol B
b-value (s/mm^2)	4000	1000
Number of directions	66	6
Number of average (for b-values >0)	3	12
Number of b0	1	12
TE (ms)	110	72
TR (ms)	3000	5000
Acquisition time (min)	10	7
Slice thickness (mm)	3	3
Signal to noise ratio	23.7	58.5
Correction for eddy current and head motion	No	No

This scan also provided a single b-value = 0 s/mm^2 image. TE was 110 ms and TR lasted 3000 ms. The total acquisition time was 10 min.

2.2.2. Low b-value or fast diffusion protocol

Forty-six slices were acquired through the entire brain. The diffusion-sensitizing gradients were applied along six non-collinear directions at a gradient strength corresponding b-value of 1000 s/mm^2 (b1000). This scan also provided a b-value = 0 s/mm^2 image. TE was 72 ms and TR lasted 5000 ms. The total acquisition time was 7 min and the data were averaged 12 times online.

2.2.3. Pre-processing

The ADC and FA maps were computed from the 6 (low b-value protocol) and 66 (high b-value protocol) directions using an in-house script running on Matlab 6.5 (MathWorks, Natick, Massachusetts, USA). At low b-value the diffusion tensor was calculated by direct inversion of the linear system since only 6 diffusion gradient directions were sampled. At high b-value a tensor was fitted by solving with the least squares method.

2.3. Image analysis

2.3.1. Manual regions of interest (ROIs)

The same analyses were performed for the two data sets acquired with the low b-value and high b-value protocol. Four white matter regions were assessed using an ROI approach. The placement of the ROI and tracing were performed manually by a single operator (PSB) blinded to diagnosis on anatomically defined regions on the low b-value and high b-value ADC maps separately using ITK-SNAP software (Yushkevich et al., 2006). The registered T1 weighted images on the diffusion data of the same slice orientation and thickness were also used to identify the regions accurately. Frontal, parietal and centrum semi-ovale regions were traced bilaterally. The frontal and parietal regions were drawn as spherical coins similar to the procedure of Andreone et al. (2007). Briefly, the frontal region was drawn on the axial plane at the level of the genu of the corpus callosum, posterior and medially to the frontal horns of the lateral ventricles, on four contiguous slices. This resulted in a total volume of 1008 mm^3. The parietal region was also drawn on the axial plane as a coin-shaped region with a total volume of 756 mm^3. The first region was placed where the lateral ventricles first disappeared. Two other regions were placed on the contiguous slices beneath. Centrum semi-ovale regions were drawn as large rectangular shaped regions and traced on three contiguous slices, with a total volume of 2304 mm^3. The first region was placed where the lateral ventricles first disappeared and then on the slice above and beneath. The corpus callosum region was traced manually according to the anatomy in the splenium and genum on three contiguous slices. Group differences (patients versus controls) in corpus callosum volumes were assessed using independent-sample *t*-tests to check for volume differences. There were no significant ($P<0.05$) group differences for anterior (low b-value: 554 mm^3 for patients and 484 mm^3 for controls; high b-value: 582 mm^3 for patients and 497.3 mm^3 for controls) or posterior corpus callosum (low b-value: 582 mm^3 for patients and 458 mm^3 for controls; high b-value: 466 mm^3 for patients and 426 mm^3 for controls). Paired *t*-tests revealed no significant differences when comparing group differences across b-values.

These ROIs were then applied to the FA maps where each slice was controlled for correct anatomic localization. An example of ROI placement is shown in Fig. 1.

2.3.2. Signal to noise ratio (SNR)

SNR was obtained from the formula $SNR = S_p/\sigma_n$ where S_p is the signal intensity value in parenchyma and σ_n the standard deviation of background noise (Cihangiroglu et al., 2009). Mean signal was estimated on diffusion-weighted images (DWI) computed as average of all diffusion directions (6 for b1000 and 66 for b4000). Left centrum semi-ovale ROIs (the same as originally traced and ADC maps) were applied to DWI images in all subjects at low and high b-value. The noise was estimated by placing a square-shaped ROI on three contiguous slices (resulting in a volume of 6912 mm^3) lateral to the head outside any artifacts.

2.4. Statistical analysis

2.4.1. ROI analysis

First, an average white matter ADC (wmADC) was calculated for each subject taking into account all ROIs. The contribution of each ROI to the average was weighted according to its volume.

Differences between patient's and control's ADC values were then analyzed by independent-sample *t*-test for low and high b-value protocols. As a first step, we analyzed differences in wmADC between patients and controls. As a second step, differences of ADC between patients and controls were assessed for each individual ROI. A Bonferroni correction for multiple comparisons was performed according to the number of regions (i.e. 8 ROIs). A corrected *P* value <= 0.006 was considered significant. The same analysis, involving the same steps, was then repeated for FA generating a mean FA (wmFA) as well as the FA for each individual ROI. All statistical analyses were performed using SPSS 18.0.

2.4.2. Clinical assessment and correlation analysis

Clinical measures regarding each patient were collected on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Differences in distribution in age and handedness were assessed using independent *t*-tests and Chi-square tests, respectively. Using low and high b-value protocols and producing ADC and FA maps generated many possible correlations with clinical data. In order to limit the probability of false discovery, only significantly different ROIs in patients compared to controls were used in the correlation analysis. These ROIs were correlated with the positive and negative score from the PANSS using Pearson's correlation analysis from SPSS 18.0. Correction for multiplicity was performed according to the number of comparisons.

These same individual ROIs were correlated with age and mean chlorpromazine-equivalent dose (mean CPZ) using Pearson's correlation.

2.4.3. Signal to noise ratio

First, a mean SNR for all subjects at low and high b-value was computed. A paired *t*-test was used to compare SNR at low and high b-value. Then, a *t*-test was used to assess group differences at low and high b-value.

3. Results

There were no significant group differences between patients and healthy comparison subjects in distribution of age ($P = 0.58$) or handedness (Chi square = 2.87, $P = 0.09$). The results are reported in Table 1.

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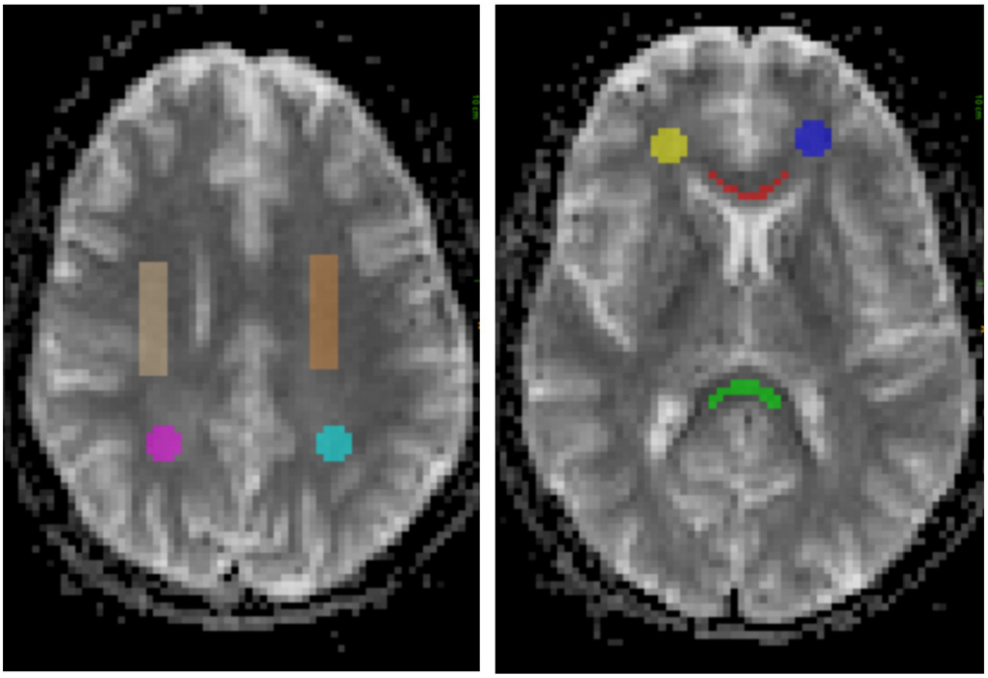

Fig. 1. Geometrical regions of interest were placed in cortical white matter on ADC maps. Centrum semi-ovale and parietal region (on the left) and frontal and corpus callosum (on the right).

3.1. ROIs at high and low b-value

ADC and FA values for all ROIs as well as *P* values are reported in Table 3. ADC's for high and low b-values are also represented in Figs. 2 and 3, respectively. With the high b-value protocol, the segmentation of the centrum semi-ovale was not possible for one patient because the first MRI slice was beneath this structure. This subject was excluded from the wmADC and wmFA calculation.

3.1.1. Apparent diffusion coefficient

All ADCs were numerically higher in patients than in controls, except for the posterior corpus callosum.

With the high b-value protocol, wmADC ($P=0.00034$), right centrum semi-ovale ADC ($P=0.00002$; $Pcorr=0.00016$), left centrum semi-ovale ADC ($P=0.0015$; $Pcorr=0.012$) and right parietal region ADC ($P=0.004$; $Pcorr=0.029$) were significantly higher in patients compared to controls.

With the low b-value protocol, wmADC was higher in schizophrenia patients than in controls ($P=0.035$). Right centrum semi-ovale ADC was significantly higher in patients compared to normal controls at $P=0.001$ ($Pcorr=0.008$). With the low b-value protocol, no other ROI survived correction for multiple comparisons.

3.1.2. Fractional anisotropy

With the low b-value protocol, FA in anterior corpus callosum was reduced in schizophrenia patients compared to controls ($P=0.01$; $Pcorr=0.08$) and considered as a trend. No other region came close to significance.

3.2. Clinical data and correlations

Demographic and clinical data are available in Table 1. Mean chlorpromazine-equivalent dose was 327 mg/day (minimum = 100 and maximum = 750).

Regarding the high b-value protocol, a *P* value = 0.004 was considered as significant (3 regions × 4 dimensions). Regarding the low b-value protocol, a *P* value = 0.01 was considered significant (1 region × 4 dimensions). For either the low or high b-value protocol, there were no significant correlations between the selected ROIs and

Table 3
Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) for cortical white matter.

		FA						ADC (10^{-7} mm^2/s)					
		b = 1000 (s/mm^2)			b = 4000 (s/mm^2)			b = 1000 (s/mm^2)			b = 4000 (s/mm^2)		
		Mean		*t* test	Mean		*t* test	Mean		*t* test	Mean		*t* test
		P	C	*P**	P	C	*P**	P	C	*P**	P	C	*P**
Corpus callosum	Anterior	0.78	0.82	0.011	0.47	0.43	0.690	7229.3	6933.9	0.085	2439.4	2427.9	0.834
	Posterior	0.77	0.80	0.167	0.48	0.42	0.510	6910.9	6796.3	0.414	2369.3	2384.7	0.845
Frontal region	Left	0.33	0.35	0.272	0.25	0.24	0.890	7557.3	7376.9	0.136	2724.8	2626.7	0.032
	Right	0.34	0.34	0.850	0.26	0.26	0.880	7646.3	7527.4	0.216	2781.8	2711.6	0.062
Parietal region	Left	0.38	0.40	0.555	0.30	0.29	0.760	7522.5	7451.0	0.687	2772.3	2725.6	0.400
	Right	0.37	0.39	0.361	0.30	0.29	0.770	7571.9	7412.4	0.403	2825.9	2682.8	0.004
Centrum semiovale	Left	0.42	0.42	0.802	0.33	0.30	0.510	7137.8	6991.5	0.041	2514.5	2438.7	0.002
	Right	0.39	0.41	0.362	0.31	0.29	0.560	7226.2	6912.4	0.001	2516.5	2404.6	<0.001
wm		0.43	0.43	0.250	0.33	0.30	0.538	7285.5	7133.9	0.035	2602.0	2522.6	<0.001

P = patients; C = controls; *P** = uncorrected *P* value; wm = average FA or ADC measures.

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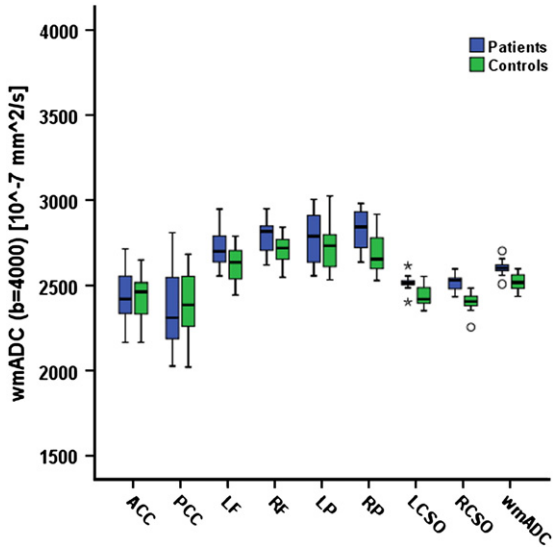

Fig. 2. ADCs for patients and controls at high b-value (4000 s/mm^2). The dark line in the middle of the boxes is the median of the ADC values. The bottom of the box indicates the 25th percentile and the top of the box the 75th percentile. The inner fencers extend to 1.5 times the height of the box. Values that do not fall in the inner fences are outliers (points are outliers and stars extreme outliers). Excluding outliers from the analysis did not change our conclusions. ACC, anterior corpus callosum; PCC, posterior corpus callosum; LF, Left frontal region; RF, right frontal region; LP, left parietal region; RP, right parietal region; LCSO, left centrum semio-vale; RCSO, right centrum semio-vale; wmADC, average white matter ADC.

age, mean CPZ dose or positive and negative symptom scores (4 dimensions in total) after correction for multiple comparisons.

3.3. Signal to noise ratio (SNR)

Mean SNR across all subjects was significantly higher at low b-value (58.5) than at high b-value (23.7) at $P<0.001$. This represented a decrease in SNR by a factor 2.5. There were no significant group differences at high ($P=0.5$; SNR patients = 21.3; SNR control = 25.3) or low b-value ($P=0.27$; SNR patients = 63.7; SNR controls = 54.9).

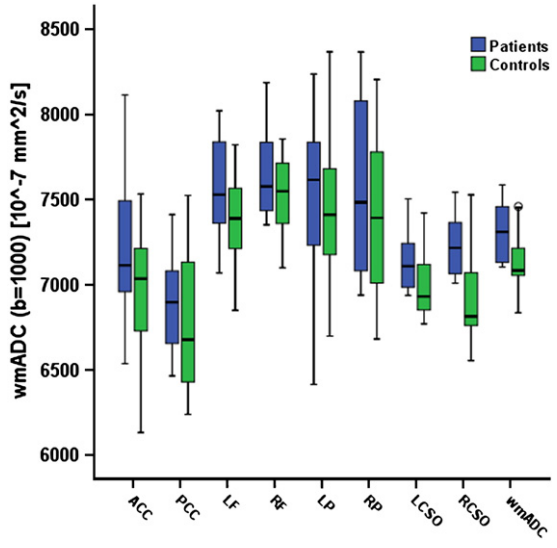

Fig. 3. ADCs for patients and controls at low b-value (1000 s/mm^2). Compare to Fig. 2 and note that at low b-value the data range from ADC = 6133 to 8368 $\times 10^{-7}$ mm^2/s and at high b-value from 2020 to 3024 $\times 10^{-7}$ mm^2/s. The increment on the scale is identical as in Fig. 2. Variance of the data is higher at low b-value than at high b-value and there is more overlap between patients and controls. See Fig. 2 for legend.

4. Discussion

In the present study using high b-value DWI, we found an increase in wmADC in schizophrenia patients compared to controls. The main contribution to the effect came from the right centrum semi-ovale as well as the left centrum semi-ovale and right parietal region. Similar results, but with less power, were found in the same subjects with a second protocol which differed by several parameters including a low b-value. We show that the high b-value imaging protocol is a sensitive method in detecting white matter differences in a small sample of male schizophrenia patients compared to controls.

This study suggests widespread white matter changes in major white matter tracts crossing the centrum semi-ovale as reflected by ADC increase. This finding is in agreement with some studies (Agartz et al., 2001; Jones et al., 2006) but not others (Nenadic et al., 2010). The current study used large ROIs and is thus not anatomically specific, and changes may be present in the cortico-spinal tract, corpus callosum and superior longitudinal tract (or arcuate fasciculus) which have all been implicated in schizophrenia (Kyriakopoulos et al., 2008). An additional finding of this study is altered ADC in right parietal region at high b-value. Parietal lobe dysfunction has been suggested in schizophrenia (Shenton et al., 2001; Zhou et al., 2007), but two recent DWI studies that used ROI approaches do not support this view (Andreone et al., 2007; Nenadic et al., 2010). We also examined ADC in the frontal region, which was higher in patients compared to controls ($P=0.03$ for left frontal region), but did not remain significant after correction for multiple comparisons ($Pcorr=0.24$). The first and only high b-value imaging study in schizophrenia was conducted by Mendelsohn et al. (2006) and found that white matter anomalies predominated in left prefrontal cortex. FA values calculated from the low b-value data were not sensitive enough to detect differences in the same patients (Mendelsohn et al., 2006). They concluded that high b-value imaging was a more sensitive marker in early stages of schizophrenia. A lack of power and/or correction for multiple comparisons in our study might account for this difference. In summary, our findings confirm Mendelsohn et al. (2006) but with a more straightforward image acquisition and processing method (no multiple b-value sampling, no Fourier transformation, etc.), which could if proven useful, easily be implemented in a clinical setting. Computing the ADC at high b-value using the classic monoexponential model may be less optimal than at low b-value. Nevertheless it is a simple approximation of the ADC with an increased sensitivity to slow diffusion and hence has a practical value in a clinical setting where scan sessions must be as short as possible and where online ADC calculation is available on the scanner.

To the best of our knowledge, this is the second study using high b-value imaging in schizophrenia. In a recent study (Hagmann et al., 2010) looking at white matter maturation in the late developing brain, ADC at high b-value better captured changes in relation to age. This kind of evidence suggests that high b-value ADC is a better marker of white matter maturation (or alteration). Several lines of evidence including post-mortem studies, phospho-spectroscopy and electron microscopy demonstrated myelin and oligodendrocyte anomalies in schizophrenia (Davis et al., 2003). At the microscopic level, they include inclusions between lamella of myelin sheaths, a loss of myelin sheath compactness, and the formation of concentric lamellar bodies (Davis et al., 2003). The above-mentioned changes at the microstructural level, which can be summarized as a loosening of the myelin sheets, could account for the increased diffusivity in the slow diffusion regime, which is indeed best captured by high b-value imaging. We thus propose, based on imaging studies applied to investigate brain development but also on the knowledge of microscopic changes in schizophrenia, that high b-value imaging is a sensitive method to capture in vivo the white matter pathology of schizophrenia or at least to contribute to its understanding.

Intuitively, using higher b-values would not bring any advantage regarding ADC since there is a steady decrease in SNR with increasing

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b-values (Yoshiura et al., 2003). In the current study, ADC values calculated from high b-value imaging were lower than those calculated from low b-value imaging, which is in agreement with previous studies (Burdette et al., 2001; Cihangiroglu et al., 2009). In our study, even though we did more diffusion-weighted measurements at high b-value, the high b-value averaged diffusion-weighted image (average over all 66 directions) had a 2.5 less SNR than our low b-value measurement. Our results suggest that there is an important gain in sensitivity with the high b-value maps despite the decrease in SNR. We can hypothesize that this high sensitivity may be in relation to increased specificity to the underlying pathological process engaged in schizophrenia that over-compensates the loss in signal and creates a good contrast between normal and diseased white matter. Our study also suggests that high b-value imaging is more sensitive than standard b1000 DWI in the present clinical setting. However, our study design does not allow proving it formally as our two MRI sequences are not well matched and differ not only in b-values but also in other parameters (see Table 2). The reason for this is that the present study used a dataset available in our institution and was not initially designed for a formal comparison between low and high b-value imaging which resulted in good matching for some parameters (voxel size and slice positioning) but not for others (brain coverage, TR, acquisition time, number of b0 images and number of directions).

Some of these parameters could have been better matched; however, given the inherent signal loss at high b-value, beyond the change in b-value, some adaptation of the acquisition parameters would have been in any case necessary to keep up with SNR. For the low b-value scans we used one b0 image for six diffusion-weighted images, each of a different direction. These seven images have each been averaged 12 times online. This 1:6 ratio is a good balance to maximize SNR in the ADC map (Jones et al., 1999). For most accurate ADC and FA mapping and highest sensitivity, it would have been optimal to spread the 12×6 diffusion-weighted images over non-collinear directions. Unfortunately, this was difficult to implement on our clinical scanner. For the high b-value data, the evaluation of the ideal ratio of b0:b4000 diffusion directions has, to our knowledge, not been formally evaluated. Given the drop in SNR, the number of b4000 samples needs to be increased to keep a balanced ratio between b0 and b4000 acquisitions. We used 1 b0 image for 66 acquisitions at b4000. This ratio is probably excessive and therefore expected to penalize the high b-value experiment compared to the classic DTI experiment by adding noise in the ADC due to poor SNR in the b0 image, given the absence of averaging. Motion correction was performed for neither b1000 nor b4000 experiments and scanning time was shorter for the b1000 than the b4000 experiment. Therefore, potential subject motion would more negatively affect the latter one.

Regarding FA values based on the low b-value data, FA in anterior corpus callosum was smaller in patients compared to controls but did not survive correction for multiple comparison ($P=0.01$; $Pcorr=0.08$). There were no other differences between patients and controls that came close to significance at low or high b-value. There are several positive reports of reduced FA in corpus callosum (Ardekani et al., 2003; Kubicki et al., 2005a; Buchsbaum et al., 2006; Caan et al., 2006) but not in all studies (Kanaan et al., 2005). Reduced FA in frontal region is one of the most replicated findings in the field (Lim et al., 1999; Minami et al., 2003; Kumra et al., 2004; Kitamura et al., 2005; Mitelman et al., 2006) although negative results have also been reported (Steel et al., 2001; Sun et al., 2003; Mendelsohn et al., 2006).

As it appears from the above-mentioned literature, heterogeneity of findings still prevails in this domain (Kubicki and Shenton, 2009; Melonakos et al., 2011). Nevertheless, we failed to replicate the fairly consistent finding of reduced FA in the frontal region. This is most likely related to the small sample size of our study. It is, however, possible that too little date entering into averaging might have translated into a lower SNR than in the studies reporting positive findings. The determination of FA with six directions is not optimal (Jones, 2004) and may lead to a slight decrease in sensitivity. It is also noteworthy that ROI studies are more prone to give negative findings compared to VBA studies (Kyriakopoulos et al., 2008). Similarly, we found no difference in FA for the high-b value data. Although the results are in line with our expectations, the explanation for the failure of FA measured at high b-value to differentiate patients from controls is not straightforward. Our hypothesis is that two mechanisms are involved. First, when looking at high b-value FA maps, it is striking that only the deep white matter exhibits high anisotropy (i.e. the regions that are almost exclusively represented by coherent and compact major fiber tracts, e.g. corpus callosum, cortico-spinal tract). The global white matter FA signal is therefore even more heterogeneous at high than at low b-value, which is a confounding factor when taking measures of large ROIs. Secondly, FA is intrinsically not robust to noise since it is a measure of orientational variance and becomes unreliable with increasing isotropy. Isotropic regions are larger at high b-value. Finally, FA is a ratio which can be problematic when dealing with regions such as the centrum semi-ovale where multiple fibers cross, especially at high b-value (Hagmann et al., 2010).

A further limitation of our study is the small sample size which could also explain our negative finding for FA measures. FA differences in small samples are found in some studies [10 patients/10 controls] (Lim et al., 1999), [12 patients/11 controls] (Minami et al., 2003) but not in others [7 patients/7 controls] (Begre et al., 2003), [14 patients/19 controls] (Foong et al., 2002), [10 patients/10 controls] (Steel et al., 2001), [9 patients/5 controls] (Mendelsohn et al., 2006); also, some studies with small samples do not include comparison to a control group (Hoptman et al., 2002; Wolkin et al., 2003). We believe that future studies should systematically report FA as well as ADC and not just the positive results for either of these scalars.

The differential results between the ADC and FA metrics in our study deserve some further comment. Although differences in FA and ADC have both been reported in schizophrenia, the latter is far less often used, which is surprising given that ADC was the first metric which proved to be useful in a clinical setting, i.e., early diagnosis of acute stroke (Moseley et al., 1990). As mentioned above, it is possible that our sequence resulted in an FA not sensitive enough to detect differences between patients and controls. It is, however, noteworthy that our study was able to show differences in ADC at low and high b-values in the same population. This is in line with the evidence suggesting that ADC is a sensitive marker to detect white matter difference in patients at high risk for schizophrenia (DeLisi et al., 2006) and is even more sensitive than FA to detect differences in first episode psychosis (Moriya et al., 2010) or distinguish schizophrenia patients from controls (Ardekani et al., 2011).

The question arises whether our positive results reflect a specific underlying pathological process or whether they are in relation to the limitations of this study. First, limitations of this study, as already mentioned, include small sample size, and replication in a larger sample is necessary. We used an ROI method that results in further limitations. Large ROIs were used which do not allow teasing out which specific tracts are implicated and contributed most to the described effect. Nevertheless, our finding is in keeping with the reported involvement of a large number of regions in the schizophrenia literature (Davis et al., 2003) and diffuse white matter anomalies. Corpus callosum ROIs were manually traced, and as they have higher FA (compared to the other ROIs), it could be that larger corpus callosum ROIs tend to correlate with higher wmFA values and bias these results. This is unlikely as there were no significant group differences in corpus callosum volumes. Further, computing wmFA without corpus callosum values did not change the results. However, computing wmADC excluding corpus callosum resulted in a gain in power for wmADC at high b-value ($P=0.00014$) but not at low b-value ($P=0.036$).

Finally, we also examined possible correlation between FA, ADC values and antipsychotic medication as well as symptom scores but found no

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association. Findings regarding association with symptomatology have been mixed (Kyriakopoulos et al., 2008). Age is another potential confounding factor in DTI studies in schizophrenia patients (Jones et al., 2006). Diffusion properties of the normal brain change with age according to an anterior to posterior gradient (Salat et al., 2009). We found, however, no significant correlations between wmADC and age in normal controls or schizophrenia patients. Age and medication are thus unlikely to be confounding factors in the current report.

Further exploration is needed to determine specificity and sensitivity of high b-value imaging. Magnetization transfer imaging (MTI) (Schmierer et al., 2004; Price et al., 2010) is another MRI modality with the potential of investigating myelin integrity. T2 relaxation analysis is a modality which is sensitive to the amount of water tied to myelin (Kubicki et al., 2005b). The combination and correlation of data acquired from different MRI modalities could be a way to increase our understanding of the signal acquired with high b-value imaging. Further, animal models of white matter changes in schizophrenia may be a way of relating the MRI signal to microstructural and histological correlates.

The dogma that diffusion imaging should be performed at a b-value of 1000 s/mm^2 is strongly related to the diffusion tensor formalism and technical equipment available 10–15 years ago. Since then, gradient technology, acquisition speed and SNR as well as our understanding of the physics of diffusion imaging have made dramatic progress. High b-value imaging is no more problematic and it may be very valuable in a variety of medical conditions (Cohen and Assaf, 2002; Bashat et al., 2005; Assaf and Cohen, 2009; Hagmann et al., 2010). Multi-shell and multi-b-value imaging has the additional advantage of necessitating much more limited assumptions on the shape of the underlying diffusion probability density function (Wedeen et al., 2005) and offers the possibility to explore all diffusion regimes simultaneously. We can foresee a number of groundbreaking applications of these techniques in the search for sensitive early biomarkers in several brain disorders.

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