Assessment of abnormalities in the cerebral microstructure of schizophrenia patients: a diffusional kurtosis imaging study

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INTRODUCTION: Schizophrenia is a disabling mental disorder, characterized by disordered thinking and hallucinations. In this study, a recently proposed method known as Diffusional Kurtosis Imaging (DKI) (1,2) is applied to subjects with schizophrenia in order to assess microstructural alterations based on the quantitative diffusion metrics of mean kurtosis (MK), fractional anisotropy (FA) and mean diffusivity (MD). A histogram analysis approach is used to compare these diffusion parameters amongst the two groups.

MR IMAGING: MR experiments were conducted on a 3T MR system (Trio, Siemens Medical Solutions, Germany). DKI data were acquired using an echo planar imaging (EPI) diffusion sequence with six *b* values (b=0, 500, 1000, 1500, 2000, 2500 s/mm^2) and 30 diffusion encoding directions. Other imaging parameters were: TR = 2300ms, TE = 109ms, matrix = 128x128, IPAT factor = 2, number of averages = 2, number of axial slices = 16, slice thickness = 4mm, voxel size = 2x2x4mm^3. The scan duration was 11 min and 57 s. For anatomical reference and image segmentation, a 3D T1-weighted image was also acquired using a magnetization prepared rapid acquisition of gradient echoes (MPRAGE) sequence with the following parameters: TR = 2100ms, TE = 3.9ms, TI = 1100ms, matrix = 256x256, IPAT factor = 2, number of slices = 160, slice thickness = 1mm, voxel size = 1x1x1mm^3, scan duration = 3 min and 47 s. An additional non-EPI T2-weighted image at TE = 80ms was acquired with the same imaging parameters as the DKI sequence which served as an "intermediate" to co-register the MPRAGE and EPI diffusion images.

DATA PROCESSING: 3D motion correction was performed on the diffusion images using SPM followed by spatial smoothing. The diffusion tensor and diffusional kurtosis tensor were computed using a previously described method (1,2), and three parametric maps were calculated: MD, FA and MK. To correct for distortion, the EPI b0 images were warped to skull-stripped T2-weighted images using a non-linear 2D warping algorithm. The latter set of images were co-registered with the anatomical MPRAGE image, and the resulting transformation matrix was applied to the parametric maps, thus ensuring that all images were aligned in the same coordinates defined by the MPRAGE image. Image segmentation using FSL was performed on the MRPAGE image, from which the gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) were segmented. The prefrontal cortex (PFC) was defined using standard procedures reported in literature (3). This mask, which included the segmented WM and GM tissues, was transformed back to the original MRPAGE coordinates and applied to the parametric maps. Seven slices encompassing the majority of the PFC were used in the creation of histograms. A data set of 10 subjects with schizophrenia (mean age ± SD: 50.8 ± 11.5 years), and 8 age-matched controls (mean age ± SD: 52.7 ± 10.6 years) were analyzed. Histograms were calculated for each subject using all the voxels within the mask described above. The MD value intervals (bins) ranged from 0 to 3 μm^2/ms with increments (bin sizes) of 0.047 μm^2/ms. The FA bins ranged from 0 to 1 (dimensionless) with bin sizes of 0.016. The MK bins ranged from 0 to 2 (dimensionless) with bin sizes of 0.031.

RESULTS AND DISCUSSION: Fig. 1 shows representative MD, FA and MK maps from a healthy control, while Fig. 2 contains histograms for the three diffusion indices in the PFC. Interestingly, the MD and FA histograms show a single peak, while the MK histogram, appears to have two distinct peaks, corresponding to GM and WM. The histograms in the patient group are characterized by a reduction in MK and FA in the WM. Upon closer inspection, we find that the fraction of voxels with MK > 0.9 is significantly different amongst the two groups ($p<0.005$), as is the fraction of voxels having FA values ranging between 0.34-1.0 ($p=0.02$). In contrast, the fraction of voxels with MD values ranging from 0.7 to 1.0 does not clearly separate the two groups ($p=0.41$). Our results suggest a loss of microstructural integrity in the WM of the PFC in schizophrenia with MK being more sensitive in discriminating between the two groups than FA and MD. These observed alterations may reflect axonal demyelination and loss of oligodendrocytes in the WM of this region.

Figure.1: Parametric maps of MD (a), FA (b) and MK (c)

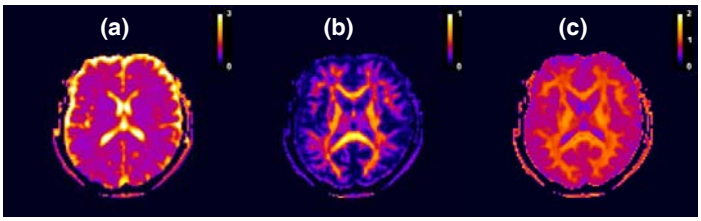
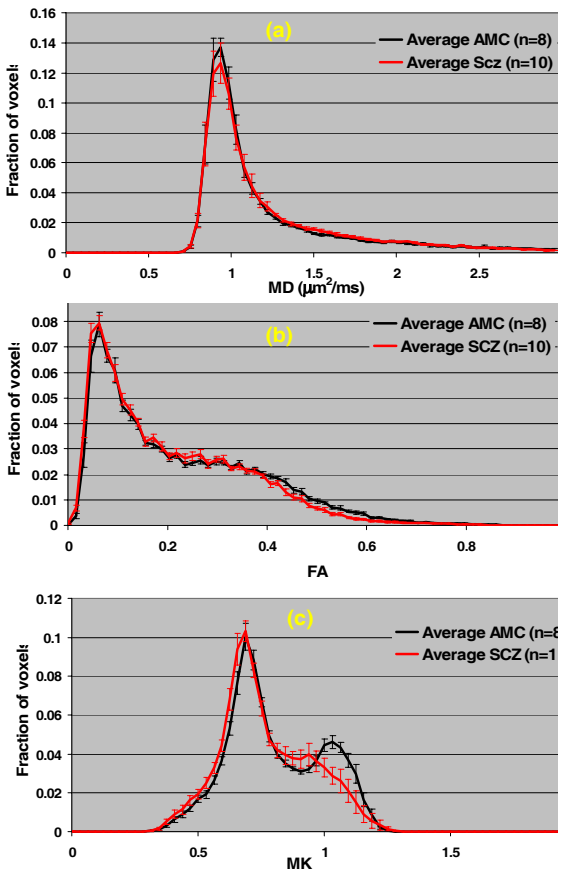


Figure 2: Mean histograms of MD (a), FA (b) and MK (c)



SUMMARY: The presented work demonstrates the successful application of DKI to patients with schizophrenia. This novel technique requires trivial modifications for slightly higher *b* values than conventional diffusion measurements and may provide information that is complementary to that provided by conventional diffusion imaging. A generalization of DTI, DKI directly quantifies the non-Gaussian properties of the water diffusion, and provides a new strategy for characterizing subtle microstructural alterations in the PFC of patients with schizophrenia. Future longitudinal studies might provide clarity on its predictive value. Our findings are consistent with volumetric MR (4) and histological findings (5) and seem to suggest that alterations in both WM orientation and organization might be involved in the pathophysiology of schizophrenia.

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ACKNOWLEDGEMENTS: Supported in part by grants from NARSAD, Werner Dannheisser Trust, and the Litwin Fund for Alzheimer Research.