White Matter Abnormalities in Schizophrenia Studied by High b Value Diffusion Imaging

T. Hendler[1], M. Blaich[1], A. Mendelsohn[1], P. Pianka[1], Y. Cohen[2], R. Even[3], H. Harari[3], R. D. Strous[4], Y. Assaf[1,2]

[1]Functional Brain Imaging Unit, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [2]School of Chemistry, Tel Aviv University, Tel Aviv, Israel, [3]Shalvata Mental Health Center, Hod Hasharon, Israel, [4]Beer Yaakov Mental Health Center, Tel Aviv, Israel

Introduction

Accumulating evidence is pointing to disturbed neural connectivity as a major source of brain abnormality in schizophrenia (1). One common proposal about this abnormality is the idea of 'disconnection syndrome' that implies disturbed connection between anterior and posterior brain regions. Another possibility is a 'local neuronal disorganization' within functionally critical brain regions. Nowadays Diffusion Tensor Imaging (DTI) provides the only *in-vivo* measure of directionality and organization of white matter including the basis for 3D fiber tractography (2). At the group level in schizophrenia, DTI showed decreased anisotropy in various white matter regions, suggesting reduced coherence (poor organization) along white matter tracts (3). This abnormality was found in prefrontal, temporo-parietal and parieto-occipital regions but also in particular white matter bundles such as cingulum, splenuim and posterior capsule. Based on this type of finding it is not possible to determine what the underling abnormal mechanism for decreased WM organization is in schizophrenia. Is it due to a deviation in fiber's organization (structure) or also functionality (i.e. conduction)?

Recent works using high b value diffusion weighted imaging (DWI) have shown that this method might be more reflective of white matter pathophysiology (4). It was suggested that by using high b values diffusion imaging it is possible to select a portion of water molecules whose diffusion is restricted (4). It is believed that a significant amount of this restricted diffusing water molecules is located at the intra-axonal compartment. Therefore, by using high b value diffusion imaging we increase the sensitivity of DWI towards axon integrity including the myelin. In the present study we applied high-b-value DWI with q-space analysis with the aim to demonstrate regional abnormalities in WM integrity on the single subject's level.

Methods

Nine first episode paranoid schizophrenia patients and eight healthy subjects matched by age and gender were scanned on a 1.5T MRI scanner (GE, Milwaukee, USA). The MRI protocol included the following clinical series: Sagittal and axial T_1-weighed images (TR/TE=600/14ms), axial fast spin echo (FSE) T_2-weighted images (TR/TE=5300/102ms) and axial fluid attenuated inversion recovery (FLAIR) images (TR/TE/TI = 5000/120/2000ms). In all series the field of view (FOV) was 24cm, slice thickness was 4.5mm with 1mm gap between slices. In addition, the MRI protocol included the high b value (q-space) diffusion weighted imaging series. The q-space diffusion data set was acquired using a spin-echo diffusion-weighted echo-planar-imaging (DW-EPI) sequence with the following parameters: TR/TE= 1500/167ms, Δ/δ=71/65ms, matrix dimension of 128x128, FOV of 24cm and number of averages=4. The diffusion gradients were applied in six directions. The magnitude of the gradients was incremented linearly from 0 to 2.2 gauss/cm (in 16 steps) to reach a maximal b-value of 14,000 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 x 6 diffusion gradient directions), the number of slices was 5 (two at the ventricles and 3 below it) with total acquisition time for the q-space data set of 12 minutes. Images analysis of the q-space data was done as described before to produce probability and displacements maps (4).

Results and Discussion

We found two patterns of brain abnormality in the dorso-lateral prefrontal cortex (DLPC) and the temporal cortex. The abnormality in the DLPC included both the gray matter and the adjacent sub-cortical white matter (Figure 1). Q-space probability values in the gray matter approached those of CSF probably indicating atrophy. In addition, probability values in the white matter were significantly smaller than that of the control group suggesting loss of restricted diffusion which might be indicative of demyelination and/or axonal loss. In the temporal lobe the same trend is observed with much severe damage to the gray matter expressed by atrophy (yellow regions, Figure 2). It should be noted that these patients are young below age of 30 years. Using histogram analysis of the q-space images allow to define three value peaks that represent white matter, gray matter and CSF in healthy subjects. This separation between the tissue types in the brain (CSF, gray matter and white matter) provided means for following specific white matter damage. As seen in Figure 3, these histograms revealed significant reduction in the white matter integrity as the number of pixels associated with white matter reduced in the schizophrenia group (red dots) as compared to the control group (black dots). Concomitantly, the number of pixels associated with CSF increased significantly.

Conclusions

These results suggest that white matter damage is a significant and measurable pathological brain marker in schizophrenia that can be detected on the single subject's level. Moreover, abnormal axonal integrity was shown regionally and in direct relation to gray matter abnormality (i.e. atrophy). Therefore it represents a more physiological account for the WM abnormality in schizophrenia.

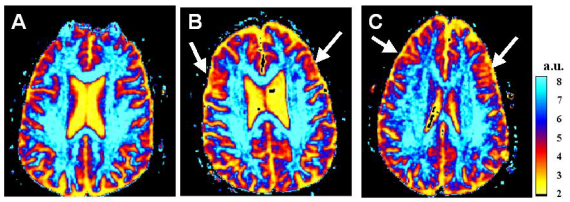

Figure 1: q-space probability map of (A) healthy subject (M/30y), (B&C) First episode paranoid schizophrenia patients (M/21y & M/27y at acute psychotic state). Arrows point to regions of low probability values both in gray and adjacent white matter at bilateral DLPF areas.

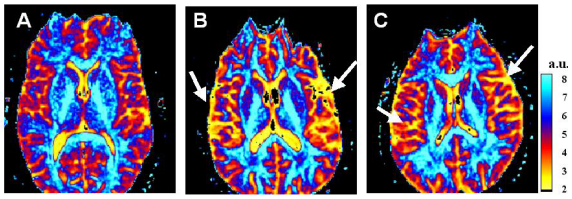

Figure 2: Q-space probability map of (A) Healthy subject (M/37y), (B&C) First episode paranoid schizophrenia patients (M/21 & F/27 at acute psychotic state). Arrows point to regions of low probability values both in gray and adjacent white matter at bilateral temporal lobe areas.

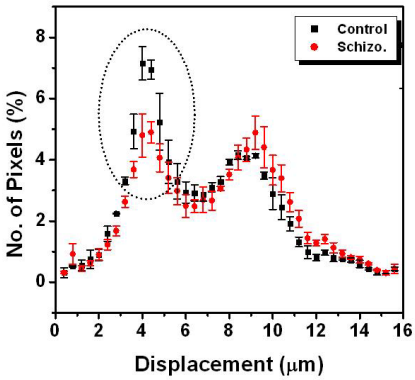

Figure 3: Q-space displacement histogram showing the distribution of displacement values in the acquired slices. Left peak (centered at 3 microns) represent mainly white matter and is markedly decreased in the schizophrenia group (red, n=9) as compared to the control group (black, n=7). This reduction in white matter integrity most probably represents the decreased probability values in Figures 1 and 2. The increased atrophy of the schizophrenia brains is represented by an increase in CSF peak centered around 12 microns.

References

1. Davis KL, Stewart DG, Friedman JI et-al.. *Arch. Gen. Psychiatry*. 60:443-456, 2003.
2. Basser PJ, Pajevic, S, Pierpaoli C et-al.. *Magn. Reson. Med.* 44:625-632, 2000.
3. Ardekani BA, Nierenberg J, Hoptman MJ et-al.. Neuroreport. 14:2025-9, 2003
4. Cohen Y Assaf Y. NMR Biomed. 15:516-42, 2002.