

White matter abnormalities before the onset of psychosis: a prospective study of an ultra-high-risk cohort

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Background. Structural neuroimaging studies have shown that psychotic disorders such as schizophrenia are associated with white matter (WM) abnormalities in the left frontal deep white matter and the left temporal deep white matter (1). Recent evidence indicates that some of these WM changes are evident before the onset of psychosis (2, 3) pointing to a neurodevelopmental origin (4, 5). A recent group-wise analysis of a cohort at 'ultra high risk' (UHR) for developing psychosis reported fractional anisotropy (FA) changes in individuals who later developed psychosis (UHR-P) compared to those who did not (UHR-NP)(2). However it remains unclear whether prior to disease transition there are FA changes at the individual level.

Aims. To determine whether z-score mapping of DTI data (i.e. comparison of individual subjects' data to a population based mean and standard deviation) can detect at the individual level (i) FA changes in UHR subjects and (ii) identify patterns of FA change in UHR-P subjects prior to psychosis onset.

Methods. *Participants:* A total of 62 subjects, comprising 32 UHR and 30 matched healthy controls (HC) were recruited for the study. After a mean period of 24 months, 8 (25%) of the UHR subjects had developed psychosis (UHR-P) while 24 (75%) had not (UHR-NP). All the participants were scanned (at recruitment) on a 1.5T MRI scanner using a cardiac-gated single-shot echo-planar sequence (TE=107 ms; TR=15 R-R; 60 contiguous 2.5 mm thick slices; 7 images without diffusion gradients along with diffusion encoding in 64 directions; b=1300 s.mm⁻²; voxel size = 1.875 x 1.875 x 2.5 mm³). *Image analysis:* Images were corrected for head movement and eddy currents, skull-stripped using FSL (6) and non-linearly aligned to the bi-commissural line of a target image (chosen from the study participants) using Camino (7, 8). A population-specific tensor template was constructed from all 62 subjects using an iterative diffeomorphic registration methodology (9, 10). DTI data were normalised to the template using dti-tk (9, 10) and FA images were created and thresholded at a value of 0.3 to exclude gray matter/CSF voxels. *Statistical analysis:* A normative reference database of FA values in HC was obtained from the normalised FA images by calculating mean and standard deviation across subjects at each voxel. Normalised FA images of each UHR-P and UHR-NP individual were compared with the normative reference using a voxelwise z-test and displayed for visual inspection. *Outcome measurements and result localisation:* The number of voxels where subject FA was significantly different from the population ($Z \geq |4|$) was calculated on an individual basis. As the population-specific tensor template was not in the MNI space, white matter labels of the ICBM template (11) were warped to the population-specific template using a nonlinear registration strategy (6) and the most likely anatomic localisation of the results is reported with reference to the white matter labels in the native space.

Results. Analysis (i): at the individual level, UHR is associated with higher absolute z-values than matched HC in 31% of voxels, that corresponded in 98% of cases to a reduced FA in UHR. Analysis (ii): the number of voxels highlighted was not significantly different in UHR-P and UHR-NP. Visual inspection showed a different spatial distribution of significant voxels in UHR-P and UHR-NP (see Fig 1 for example).

Conclusions. Comparing each individual at UHR for psychosis with a population norm using a voxelwise z-score analysis, we found that subtle white matter abnormalities were evident before the transition to psychosis, as reported by some (2, 3), but not all previous studies of UHR populations (12). This is in line with an anomalous trajectory of white matter development (4, 5), possibly due to mechanisms including synaptic pruning, dendritic remodelling, axonal myelination and neuronal apoptosis (13). Our study revealed a different spatial distribution of changes in UHR individuals who may or may not develop psychosis. This result suggests that it is possible to use this technique to explore UHR changes in relation to psychosis development at the individual level, although it currently does not allow for a diagnosis of psychosis development based on the localisation of FA changes. Future study will investigate the performance of regional voxelwise z-tests, along with summary statistics capturing the spatial distribution of changes, in predicting the onset of psychosis. The spatial variations seen suggest that application of machine learning techniques such as Support Vector Machines (SVM) (either to Z-score maps such as those above, or to raw DTI data) may be useful, again with the aim of predicting the transition to psychosis.

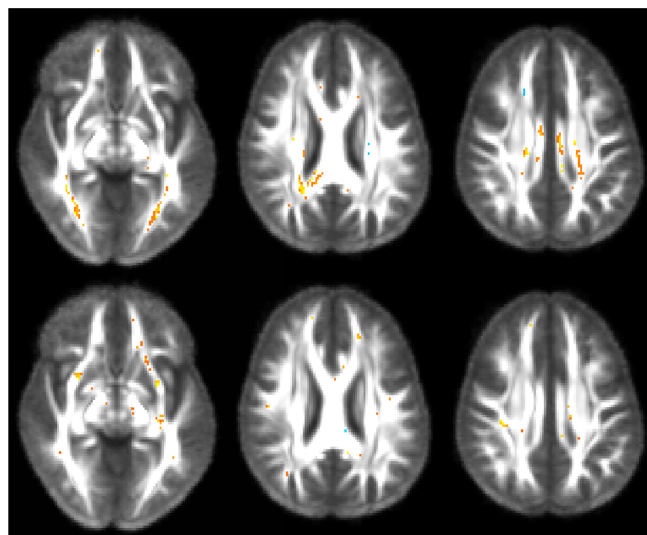


Figure 1 – Selected slices showing significant z-score areas in UHR-P (top row; subject 07) and in UHR-NP (bottom row; subject 02). Colours correspond to lower (red-yellow) and higher (blue) FA than in controls. Images are radiologically oriented (participant's left is to the right)

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