Differentiation of white-matter differences across sub-clinical psychotic experiences using diffusion tensor and quantitative relaxometry imaging

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Target audience: Researchers and clinicians working with psychosis, particularly those investigating white-matter microstructure.

Introduction: A wide range of white matter areas have been implicated in psychosis. It is likely that structural brain abnormalities vary greatly depending on stage of illness, environmental influences and specific psychotic experiences[1]. Few studies have differentiated effects in white-matter across psychotic traits[2,3] and non have done so in a birth cohort. Here we use DTI and mcDESPOT[4], a quantitative relaxometry technique sensitive to myelination, to identify microstructural abnormalities associated with specific psychotic experiences in a large homogeneous birth cohort.

Method: 248 subjects were selected from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort[5], based on the psychotic-like signs (PLIKS) interview[6] at age 17. (124 cases, 126 controls). At the time of scanning all subjects were 18 years old. All data were acquired on a 3T GE HDx MRI system. HARDI acquisition: cardiac-gated EPI sequence, TE=87ms, 60 gradient orientations, b-value=1200 smm^{-2}, FOV=96×96mm, 60 slices, voxel-size=1.6×1.6×2.4mm. mcDESPOT acquisition: SPGR: TE=2.112ms, TR=4.7ms, flip angles = 3°, 4°, 5°, 6°, 7°, 9°, 13° and 18°. IR-SPGR: TE=2.112ms, TR=4.7ms, IR=450ms, flip angle = 5°. SSFP: TE=1.6ms TR=3.2ms, flip angles of 10.59°, 14.12°, 18.53°, 23.82° 29.12° 35.29°, 45°, 60° and phase-cycling angles of 0° and 180°. HARDI data was analysed in ExploreDTI and corrected for motion, eddy current distortions and field inhomogeneities. Fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD) were derived using the RESTORE algorithm[7] and corrected for partial volume effects[8]. mcDESPOT data were analyses using in-house software to derive quantitative T1 relaxation times. FA, AD, RD and T1 were analysed using TBSS [9]. Independent sample *t*-tests between PLIKS and control groups and correlations with individual items on the PLIKS inventory were carried out. Correlations were conducted across 5 domains in the PLIKS inventory: Auditory hallucinations (AH), visual hallucinations (VH), delusions (DL), unusual sensations (US), and thought insertion (TI). All tests were corrected for multiple comparisons with permutation tests (500 permutations / test).

Table 1: PLIKS variables showing significant negative FA correlation

Category	PLIKS variable	min p_{corr}	# sig. vox.
AH	Subject's voices commanded them to do things	0.004	64106
	Subject's voices talked directly to them, or told them things	0.006	57457
	Length of time in a day that voice was present, when at it's worst	0.016	49976
	External rating of subject's auditory hallucinations	0.026	2769
	Frequency subject has heard the voice, in last 6 months	0.038	2327
	Subject has ever heard voices that other people could not hear	0.040	2138
	Subject ever hears 2 or more voices talking to each other, or about subject	0.044	158
VH	Subject has ever seen something or someone that other people could not see	0.032	1019
	External rating of subject's visual hallucinations	0.032	4946
TI	Subject has ever felt that thoughts were put in their mind which were not their own	0.018	24034

Table 2: PLIKS variables showing significant negative T1 correlation

Category	PLIKS variable	min p_{corr}	# sig. vox.
DL	Length of time in a day that subject thought they were being sent special messages	0.008	32939
US	Length of time in a day that subject's unusual experience lasted when at it's worst	0.046	1012
TI	Frequency subject has felt that thoughts were put in their mind, in last 6 months	0.038	7418

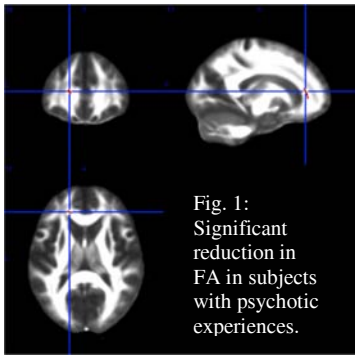


Fig. 1: Significant reduction in FA in subjects with psychotic experiences.

Fig. 2: Significant (p_{corr}<0.05) negative correlations with FA.

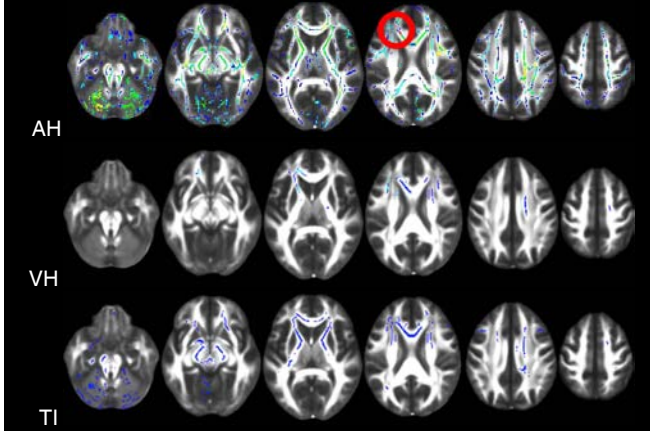
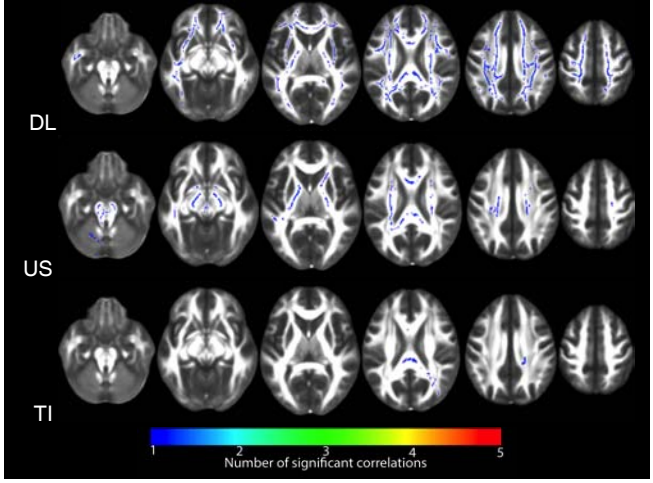


Fig. 3: Significant (p_{corr}<0.05) negative correlations with T1.



Results: In the PLIKS group, a significant reduction was found in FA and AD in the left medial frontal white-matter, whereas RD values were increased (fig. 1), suggesting tissue microstructure is affected in the genu, cingulum and anterior thalamic radiation fiber populations. Correlations with individual psychotic experiences show large widespread effects for many AH variables, with a large overlap in the same left anterior medial frontal region implicated in the t-test (fig 2). Widespread effects were also seen for some VH and TI variables (table 1). In all significant cases positive correlation in RD was found in similar areas but no significant correlations with AD. t-tests on T1 showed no significant differences between groups but some variables (US, TI and DL) were negatively correlated with T1 (table 2), also over widespread regions of white-matter (fig 3).

Discussion: We show a reduction in white-matter anisotropy in executive and motivational pathways in individuals with sub-clinical psychotic experiences. Similar changes in DTI indices have been shown in schizophrenia patients [1]. Correlates of specific variables show many psychotic experiences, in particular AH, have a prominent white-matter signature. Previous studies have found positive correlations between auditory hallucinations and FA in schizophrenia patients, whereas we show a negative correlation in a sub-clinical population. For some psychotic experiences, there are decreases in T1, suggesting increased myelination is associated with these experiences. The lack of overlap with the DTI indices suggests a different microstructural signature for these experiences. Given that only a small proportion of individuals with PLIKS transition to full psychosis [10], it is likely that our results include a significant proportion that will not develop psychosis. Future identification of subjects who transition to full psychosis will better differentiate which experiences, and which corresponding microstructural markers predict the development of psychosis.

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