WHITE MATTER MICROSTRUCTURE ALTERATIONS IN EARLY PSYCHOSIS AND SCHIZOPHRENIA

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BACKGROUND

In schizophrenia, widespread white matter (WM) abnormalities1-2 are often reported in the literature but little is known about the specific microstructure alterations. The aim of the study was to uncover changes in WM microstructure during early psychosis and schizophrenia and characterize them using dMRI-derived biomarkers.

Diffusion kurtosis imaging3 (DKI) and its derived White Matter Tract Integrity4 - Watson (WMTI-W) WM model parameters were chosen for their sensitivity and increased specificity to microstructure, respectively.

METHODS

• Acquisition: 129 (Trio, TE=103ms), 257 (Prisma, TE=144) dwi, 15 b-values ranging 0-8 ms/mm2, 2x2x2mm3.

• Pre-processing: MP-PCA denoising, Gibbs ringing, EPI distortion, eddy currents & motion corrections.

• DTI & DKI and associated scalar metrics estimated from dwi with bs2.5 ms/μm2: FA: fractional anisotropy, MD, AD, RD: Mean, Axial, Radial Diffusivity, & MK, AK, RK: Mean, Axial, Radial Kurtosis.

• WMTI-W computed from DKI (f: axonal water fraction, c: axon alignment, Da: axonal diffusivity, Dv, D⊥: extra-axonal parallel/perpendicular diffusivities.

• WM regions of interest (ROI) were projected from the JHU atlas to individual space.

• Averaged dMRI metrics were then harmonized via ComBat6 for scanner effects and controlled for age & sex.

• Groups were compared using the Brunner-Munzel (BM) test and the p-values were corrected via FDR.

RESULTS

SCHZ - CTRL general trends:

• higher diffusivity and especially lower kurtosis than CTRL.

• reduced kurtosis but no changes in DTI maps.

• Inter-period: reduced subjective complexity.

• WMTI model revealed primarily reduced axonal water fraction and increased extra-axonal diffusivities.

• Inter-period: reduced cellular density and demyelination.

• increased kurtosis with respect to CTRL.

• Interpretation: signature of either compensation, renewed inflammation or unknown effect.

EP - CTRL general trends:

• widespread and significant increased diffusivity and reduced kurtosis (also compared to SCHZ-CTRL).

• Inter-period: structure loss and neurodegeneration.

• WMTI-W metrics revealed an increase in compartment diffusivities and reduced axonal water fraction.

• Interpretation: loss of structure in both the extra-axonal and intra-axonal spaces.

SCHZ - EP general trends:

• pronounced differences in the External Capsule (EC): SCHZ’s kurtosis, f and Da >> EP.

• Interpretation: iron release effect and debris due to demyelination reducing the relative contribution of extra-axonal water to the signal via T2 reduction, or resumed inflammation in SCHZ (increased cellularity).

EP abnormalities > SCHZ:

Trends of degeneration:

• Monotonic T

- Fx: posterior and superior CR, pTR, tapetum.

- Non-Monotonic T


- Interpretation: the non-monotonic trend and the overshoot mechanism for kurtosis in SCHZ vs CTRL remain to be established, possibly one of:

A) partial compensation in SCHZ group vs EP

B) renewed inflammation-demyelination in the chronic phase of the disease

C) partial volume effects of the cerebrospinal fluid on the microstructure estimates.

EP abnormalities > SCHZ.

This early effect could be the result of the oxidative stress caused by redox dysregulation, which may alter the proliferation and differentiation of the oligodendrocytes precursor cells2,3,12 ending in the WM abnormalities2,4.

Demographics

<table>
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<tr>
<th>Group</th>
<th>N</th>
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<th>Prisma/Trio</th>
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<td>39/9</td>
<td>32/11</td>
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