CIBM Annual Symposium 2022
Campus Biotech, Geneva | 30th November

WHITE MATTER MICROSTRUCTURE ALTERATIONS IN EARLY PSYCHOSIS AND SCHIZOPHRENIA

Tommaso Pavan[1], Yasser Alemán-Gómez[1], Raoul Jenni[2], Martine Cleusix[2], Luis Alameda[3], Kim Do[2], Philippe Conus[3], Paul Klauser[4], Patric Hagmann[1] and Ileana Jelescu[1]

1. Department of Radiology, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL);
2. Center for Psychiatric Neuroscience, Department of Psychiatry, CHUV/UNIL;
3. General Psychiatry Service, Treatment and Early Intervention in Psychosis Program (TIPP-Lausanne), CHUV/UNIL;
4. Center for Psychiatric Neuroscience and Service of Child and Adolescent Psychiatry, Department of Psychiatry, CHUV/UNIL, Lausanne, Switzerland.

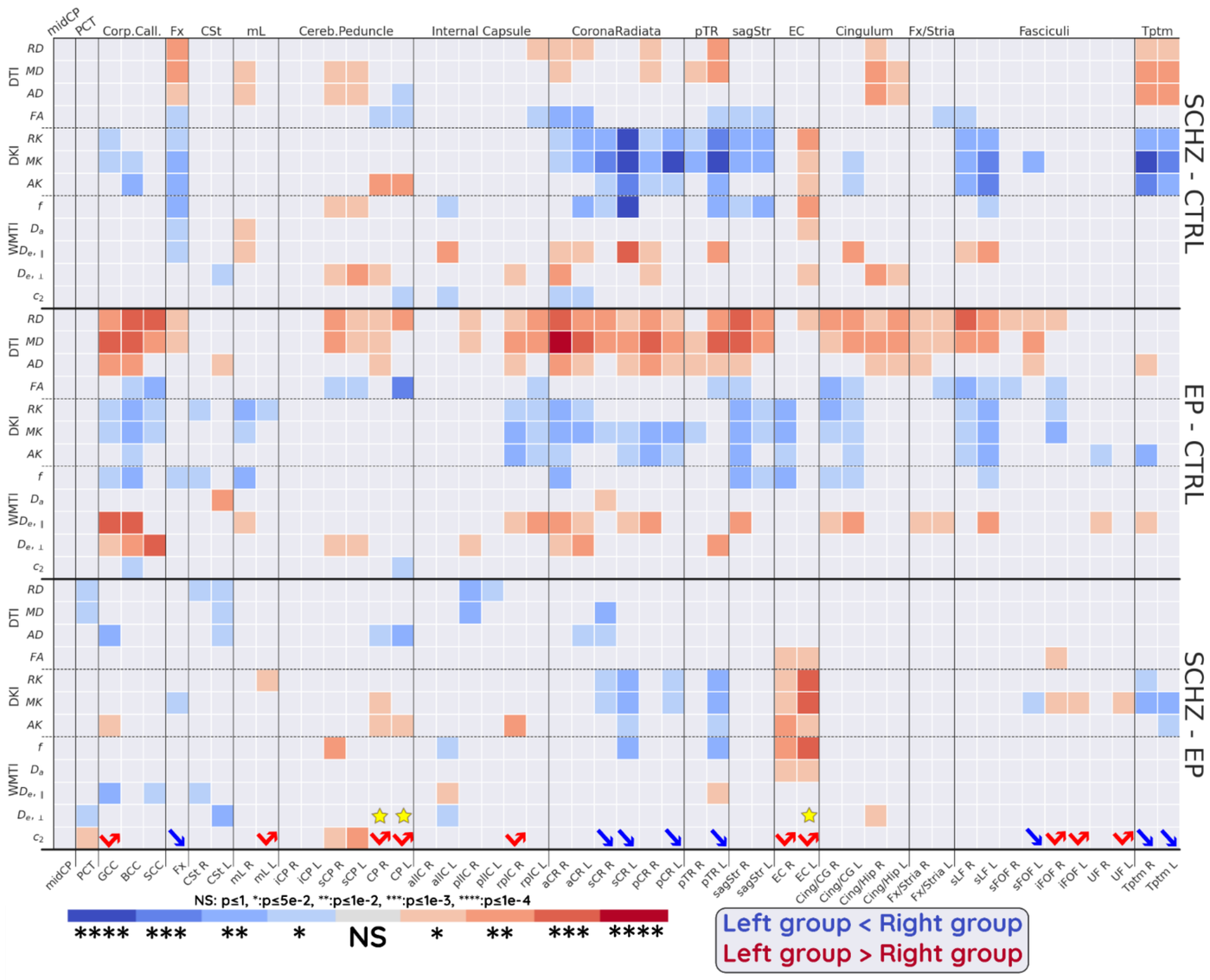
BACKGROUND

In **schizophrenia**, widespread **white matter (WM) abnormalities**[1,2] 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 imaging[3] (DKI) and its derived **White Matter Tract Integrity**[4] - **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/µm2, 2x2x2mm^3.
- Pre-processing: MP-PCA denoising, Gibbs ringing, EPI distortion, eddy currents & motion corrections.
- DTI & DKI and associated scalar metrics estimated from dwi with b≤2.5 ms/µm^2: 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_2: axon alignment, Da: axonal diffusivity, $D_{e,//}$, $D_{e,\perp}$: 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 ComBat[5] 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.



DEMOGRAPHICS

259 individuals were scanned on two scanners (Siemens Prisma and Trio).

- 3 groups:
  - CTRL: healthy individua
  - EP: early psychosis;
  - SCHZ: chronic schizophrenic.
- CTRL matched by age.

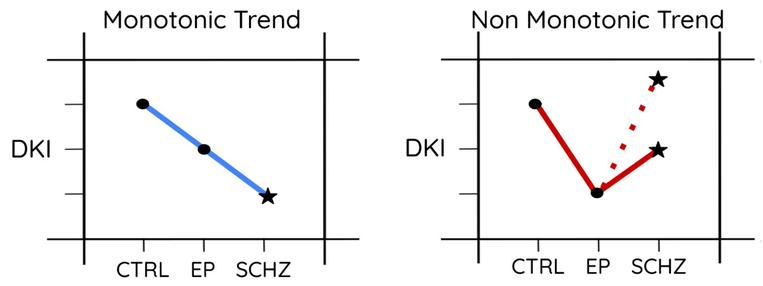
Group	*N*	*Mean Age*	*M/F*	*Prisma/Trio*
CTRL	119	28±8	77/42	55/64
EP	97	24±5	69/28	61/36
SCHZ	43	39±9	32/11	18/25

RESULTS

SCHZ - CTRL general trends:
- higher diffusivity and especially lower kurtosis than CTRL.
  - Interpretation: structure loss and neurodegeneration.
- reduced kurtosis but no changes in DTI maps.
  - Interpretation: reduced tissue complexity.
- WMTI model revealed primarily reduced axonal water fraction and increased extra-axonal diffusivities.
  - Interpretation: reduced cellular density and demyelination.
- increased kurtosis 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).
  - Interpretation: 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).



Trends of degeneration:
- **Monotonic** ↘ : Fx, posterior and superior CR, pTR, tapetum.
- **Non-Monotonic** ↗ : EP kurtosis was the lowest of all groups, found in EC, CP and inferior fronto-occipital fasciculum (iFOF).
-Interpretation: the non-monotonic trend and the overshot, ☆ , 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 cells[6,7,8,9] ending in the WM abnormalities[1,2].

References: References: [1] Kelly et al., Mol Psychiatry 2018. [2] Kubicki et al., Curr Opin Psychiatry 2014. [3] Jensen & Helpern, NMR In Biomedicine 2010. [4] Jespersen, et al., Neuroimage 2018. [5] Fortin et al., Neuroimage 2017. [6] Cuenod et al., Molecular Psychiatry 2018. [7] Juurlink BH et al., Glia 1998. [8] Monin et al., Mol Psychiatry 2015. [9] Smith et al., Proc Natl Acad Sci USA 2000.
Abbreviations: R: right, L: left, midCP: Middle cerebellar peduncle, PCT: Pontine crossing tract, CC: Genu of the corpus callosum, BCC: Body of corpus callosum, SCC: Splenium of the corpus callosum, Fx: Fornix, CSt: Corticospinal tract, mL: Medial lemniscus, iCP: Inferior cerebellar peduncle, sCP: Superior cerebellar peduncle, CP: Cerebral peduncle, alIC : Anterior limb of the internal capsule, plIC: Posterior limb of the internal capsule, rpIC : Retrolenticular part of the internal capsule, aCR : Anterior corona radiata, sCR: Superior corona radiata, pCR: Posterior corona radiata, pTR: Posterior thalamic radiation, sagStr: Sagittal stratum, EC: External capsule, Cing/CG: Cingulum / cingulate gyrus, Cing/Hip: Cingulum / hippocampus, Fx/Stria: Fornix / Stria terminalis, sLF: Superior longitudinal fasciculus, sFOF: Superior fronto-occipital fasciculus, iFOF: Inferior fronto-occipital fasciculus, UF: Uncinate fasciculus, Tptm: Tapetum.