O5.6. ADVANCED DIFFUSION IMAGING IN PSYCHOSIS RISK: A CROSS-SECTIONAL AND LONGITUDINAL STUDY OF WHITE MATTER DEVELOPMENT

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Background: Studies in individuals at clinical high risk (CHR) for psychosis provide a powerful means to predict outcomes and inform putative mechanisms underlying conversion to psychosis. In previous work, we applied advanced diffusion imaging methods to reveal that white matter pathology in a CHR population is characterized by cellular-specific changes in white matter, suggesting a preexisting neurodevelopmental anomaly. However, it remains unknown whether these deficits relate to clinical symptoms and/or conversion to frank psychosis. To address this gap, we examined cross-sectional and longitudinal white matter maturation in the largest imaging population of CHR individuals to date, obtained from the North American Prodrome Longitudinal Study (NAPLS-3).

Methods: Multi-shell diffusion magnetic resonance imaging (MRI) data were collected across multiple timepoints (1–6 at ~2 month intervals) in 286 subjects (age range=12–32 years). These were 230 unmedicated CHR subjects, including 11% (n=25) who transitioned to psychosis (CHR-converters), as well as 56 age and sex-matched healthy controls. Raw diffusion signals were harmonized to remove scanner/site-induced effects, yielding a unified imaging dataset. Fractional anisotropy of cellular tissue (FAt) and the volume fraction of extracellular free-water (FW) were assessed in 12 major tracts from the IIT Human Brain Atlas (v.5.0). Linear mixed effects (LME) models were fitted to infer developmental trajectories of FAt and FW across age for CHR-converters, CHR-nonconverters and control groups, while accounting for the repeated measurements on each individual.

Results: The rate at which FAt changed with age significantly differed between the three groups across commissural and association tracts (5 in total; $p<0.05$). In these tracts, FAt increased with age in controls (0.002% change per year) and in CHR-nonconverters, albeit at a slower rate (0.00074% per year). In contrast, FAt declined with age in CHR-converters at a rate that was significantly faster (-3.944% per year) than the rate of increase in the other two groups. By 25 years of age, FAt was significantly lower in both CHR groups compared to controls ($p<0.05$). With regard to FW, the rate of change significantly differed between CHR-converters and controls across the forceps major and the left inferior longitudinal and fronto-occipital fasciculi (IFOF; 3 tracts in total; $p<0.05$). This was due to increased FW with age in the CHR-converters (0.0024% change per year) relative to controls (-0.0002% per year). Consequently, FW was significantly higher in CHR-converters compared to controls by 20 years of age ($p<.05$). With regard to symptoms, there was a significant impact of IFOF FW on positive symptom severity across CHR subjects, regardless of conversion status ($t=2.37$, $p<0.05$).

Discussion: Our results revealed that clinical high-risk for psychosis is associated with cellular-specific alterations in white matter, regardless of conversion status. Only converters showed excess extracellular free-water, which involved tracts connecting occipital, posterior temporal, and orbito-frontal areas. We also demonstrate a direct impact of free-water on positive symptomatology, collectively, suggesting that excess free-water may signal acute psychosis and its onset. This marker may be useful for patient selection for clinical trials and assessment of individuals with prodromal psychosis.

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