## Symposium

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### 540. INFLAMMATION AND AGING IN PSYCHOSIS – A TRANSDIAGNOSTIC PROTEOMICS STUDY USING THE HUMAN CONNECTOME PROJECT FOR EARLY PSYCHOSIS (HCP-EP)

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**Background**: Since protein expression plays a key role in mediating genetic risk, the field of proteomics—the in-depth analysis of proteins—has gained renewed importance in neuropsychiatric research. Recent technical advancements now allow for the simultaneous examination of multiple proteins, revealing complex pathological processes in mental illnesses. Various studies have demonstrated that proteomics can elucidate underlying molecular mechanisms, identify clinically relevant biomarkers, and suggest novel treatment strategies, particularly in neurodegenerative disorders. Although its application in psychiatry remains less explored, proteins have proven to be promising transdiagnostic markers for understanding disease heterogeneity. In psychosis, proteomic studies support the "inflamm-aging" hypothesis, wherein chronic low-grade inflammation accelerates biological aging and contributes to disease onset and progression. These insights underscore the importance of integrating protein-based approaches to detect inflammatory subtypes.

**Aims & Objectives**: This study examines whether psychosis exhibits a unique proteomic profile derived from 374 peripheral proteins and seeks to clarify the affected pathways. Additionally, it evaluates cellular aging indices based on senescence-associated secretory phenotype (SASP) proteins.

**Method**: Data was obtained from the Human Connectome Project for Early Psychosis (HCP-EP), which recruited participants aged 16 to 35 years across four institutions. Out of 303 participants of the original cohort, 120 individuals were included in the analyses. This sample consists of 35 healthy controls and 85 individuals with transdiagnostic psychosis (schizophrenia, schizophreniform disorder, schizoaffective disorder, psychosis not otherwise specified, delusional disorder, brief psychotic disorder, major depression with psychosis, or bipolar disorder with psychosis). Proteomic plasma analyses were performed using the Olink platform across four panels relevant to "inflamm-aging." We conducted analyses comparing individual protein expression levels between groups using ANCOVAs (controlling for age, sex, and storage time). Subsequent Gene Set Enrichment Analysis (GSEA) identified enriched pathways between the groups, and principal component analyses (PCA) were used to derive composite measures for the significant protein sets and the SASP indices.

**Results**: Our analysis revealed significant differences in the expression of proteins associated with inflammation, cell communication, and cardiometabolic regulation between individuals with psychosis and healthy controls (pFDR-corrected $< 0.1$). GSEA demonstrated significant enrichment in pathways related to the cellular response to tumor necrosis factor and monocyte chemotaxis in the psychosis group (qFDR $< 0.05$). PCA of the SASP indices indicated that individuals with psychosis exhibited a significantly higher SASP index compared to controls ($p < 0.05$). Moreover, these indices were associated with age, sex, body mass index, alcohol consumption and psychological well-being ($p < 0.05$).

**Discussion & Conclusions**: Our findings provide preliminary evidence that psychosis is characterized by a transdiagnostic proteomic profile marked by increased levels of inflammatory and aging-related proteins. The enrichment of specific inflammatory pathways and the elevation of the SASP index support the concept of premature biological aging in psychosis. These results underscore the potential of protein-based biomarkers to enhance our understanding of psychosis as a whole-body disorder and may inform future efforts in developing targeted therapeutic interventions. However, larger and longitudinal studies are needed to confirm these associations and to further delineate the clinical utility of these proteomic signatures.