HCs (N = 51) propensity-matched on age, sex, and verbal IQ were also used to confirm initial findings.

Results: Individuals with SUDs showed poorer task performance than HCs (p = .03, Cohen's d = .33). Compared to HCs, model estimates revealed less precise action selection mechanisms (p = .004, d = .43), a lower learning rate after losses (p = .02, d = .36), and a greater learning rate after wins (p = .04, d = .31). Groups did not differ in goal-directed information seeking.

Conclusions: Findings suggest a pattern of continued uncertainty after positive outcomes in SUDs combined with a tendency to attribute negative outcomes to chance. This could help explain continual maladaptive choices despite negative consequences in substance users, and associated difficulties in adjusting behavior and maintaining adaptive decision-making during and after treatment.

Supported By: William K. Warren Foundation

National Institute of Mental Health (K23MH112949 and K23MH108707)

National Institute of General Medical Sciences (Center Grant, P20GM121312)

Keywords: Substance Use Disorders, Computational Modeling, Active Inference, Reward Learning, information Seeking

SYMPOSIUM
That's a Wrap: Identifying Myelin as a Treatment Target in Psychosis Across Multiple Scales of Resolution

Co-Chair: Carolina Makowski, Lena Palaniyappan

Redox Dysregulation, Myelination Deficit and Dysconnectivity in Schizophrenia: A Translational Study in First Episode Patients and Experimental Models

Kim Q. Do[1], Jan-Harry Cabungcal[1], Martine Cleusix[1], Daniella Dwir[1], Margot Fournier[1], Alessandra Griffa[2], Rolf Gruetter[2], Patric Hagmann[2], Raoul Jenni[1], Paul Klauser[1], Aline Monin[1], Emeline Mullier[3], Pascal Steullet[1], Lijing Xin[4], Michel Cuenod[1], and Philippe Conus[3]

[1]Center for Psychiatric Neuroscience, Lausanne University Hospital, [2]Ecole Polytechnique Fédérale de Lausanne, Lausanne University Hospital, [3]Lausanne University Hospital, [4]Animal Imaging and Technology Core (AIT), Center for Biomedical Imaging (CIBM), Ecole Polytechnique Fédérale de Lausanne

Background: Redox imbalance/oxidative stress affect oligodendrocytes precursor cells (OPC) and myelination, leading to dysconnectivity.

Methods: Gclm-KO mice with impaired GSH synthesis: Immunohistochemistry; 14T MRS/DTI. Early psychosis patients (EPP): white matter (WM) integrity, fractional anisotropy (FA) by DSI; resting state fMRI; glutathione (GSH) by MRS; GSH peroxidase (GPx) activity, sRAGE; neurocognition.

Results: Oxidative stress impaired OPC proliferation and maturation, a dysregulation mediated by Fyn kinase pathway and reversed by antioxidant GSH precursor N-acetylcysteine (NAC) or Fyn kinase inhibitors. In prefrontal cortex of Gclm-KO, oligodendrocyte and myelin markers were decreased concomitantly with increases of oxidative stress and neuroinflammation. Translating to EPP, multimodal brain imaging revealed a positive association between prefrontal GSH levels and both WM integrity and resting-state functional connectivity along cingulum bundle. Fyn was impaired in patients' fibroblasts. The mechanism-based marker of neuroinflammation sRAGE was increased.

In Gclm-KO mice, WM integrity (FA) was reduced in fornix-fimbria. EPP exhibited decreased fornix integrity associated with smaller hippocampus, correlated with higher blood GSH peroxidase (GPx) activity.

In a clinical trial, NAC increased prefrontal GSH levels (target engagement), improved processing speed and positive symptoms in patients with high blood GPx activity. NAC also decreased the neuroinflammation marker sRAGE. NAC improved cingulum connectivity and fornix integrity, in correlation with brain GSH increase and cognition improvement.

Conclusions: Developmental redox dysregulation leads to impairments of myelination, WM maturation, and fiber integrity in both EPP and GSH deficit models. Fyn kinase pathway dysregulation, sRAGE and fornix integrity impairments may constitute markers in EP, paving the way for patient stratification and biomarker-guided treatments.

Supported By: National Center of Competence in Research (NCCR) "SYNAPSY - The Synaptic Bases of Mental Diseases" from the Swiss National Science Foundation (n° 51AU40_125759 to KQD), Alamaya Foundation, Damm-Etienne Foundation

Keywords: Redox Dysregulation - Oxidative Stress, White Matter - Myelin, Schizophrenia, Fornix, Hippocampus

Ultra-High Field Imaging of Intracortical Myelin in Schizophrenia

Sophia Frangou[1]

[1]Icahn School of Medicine at Mount Sinai

Background: The dysmyelination hypothesis of schizophrenia (SCZ) proposes that abnormalities in myelination may underpin or facilitate disease expression. Recent advances in ultra-high-field imaging enable more detailed investigation of intracortical myelin using novel acquisition sequences at submillimeter resolution and improved modelling algorithms. This study tested whether patients with SCZ have abnormal concentration of intracortical myelin, and whether this deficit might be localised within specific regions and distinct depths within the cortical ribbon.

Methods: Fifty healthy individuals and 50 patients with schizophrenia were imaged at 7 Tesla MRI using a T1-weighted sequence optimized for intracortical myelin. T1-values were extracted at 20 cortical depth-levels from 148 cortical regions. In each region, T1 values were used to estimate mean regional and depth-level myelin concentration and to compute a non-linearity index as a measure of the spatial