167. CHANGES IN FRONTOTHALAMIC CONNECTIVITY ARE ASSOCIATED WITH PRODROMAL PSYCHOSIS IN YOUNG ADULTS WITH 22Q11.2 DELETION SYNDROME

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Background: The 22q11.2 deletion syndrome (22q11DS) represents a genetic high-risk population in which up to 40% of individuals develop psychosis. Studies of brain white matter using Diffusion Tensor Imaging (DTI) have often failed to find differences in white matter between individuals with 22q11DS with and without psychosis. These studies, however, have used the most popular measure, Fractional Anisotropy (FA), which is sensitive to microstructural changes but not specific, as the changes observed could be due to myelin disruption, axonal changes, crossing fibers, extracellular water contamination, as well as other factors. In the current study, we used a measure that separates the diffusion MRI signal into extracellular free water, and water that surrounds or is within tissue, from which tissue FA (FAt) is extracted. To explore biomarkers of psychosis, FA and FAt was studied in the Anterior Limb of Internal Capsule (ALIC), the cingulum bundle and corpus callosum, tracts that were associated with scores on prodromal symptoms in the same cohort of subjects with 22q11DS reported here, but at an earlier time point in the study. FA and FAt in the three white matter tracts were compared between healthy controls, and 22q11DS subjects with and without psychosis.

Methods: We extracted FAt and FA from DTI of 27 controls and 52 individuals with 22q11DS, of whom 5 were diagnosed with psychosis, (mean age 20.8 ± 2.2 years). Tract-Based Spatial Statistics (TBSS) ENIGMA method was applied to analyze the three white matter tracts. Psychosis symptoms in individuals with 22q11DS were assessed using Structured Interview for Prodromal Syndromes (SIPS). Group differences were calculated using ANOVA, followed by posthoc analysis. Zero-Inflated Poisson (ZIP) analysis was performed to explore the associations between FAt and psychotic symptoms in the whole 22q11DS group.

Results: Findings showed significant group differences in FA and FAt in ALIC, and not in the other two tracts, between the control and the 22q11DS group (P = .001). FA and FAt of the ALIC correlated with the SIPS scores (r = -2.10; P = .04) in the whole 22q11DS group. When 22q11DS participants without or with psychosis were compared there was no difference in FA. However, we observed a statistically significant reduction in FAt of the ALIC in participants with psychosis (P = .002).

Conclusion: We conclude that the changes in FAt suggest the presence of microstructural changes in the frontothalamic connectivity that are associated with psychosis.

Concurrent Workshop Presentations

168. NEUROADAPTATIONS TO ANTIPSYCHOTIC DRUGS: OPTIMIZING USE OF CURRENT MEDICATION THROUGH A DEEPER UNDERSTANDING OF ANTIPSYCHOTIC DRUG ACTION IN THE BRAIN AND BODY

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Overall Abstract: Antipsychotic drugs, all of which block the dopamine D2 receptor to a greater or lesser extent, are the mainstay for the pharmacological treatment of schizophrenia. Engaging in a deeper understanding of how antipsychotics act on the brain and body, at the cellular, molecular and physiological level is vital to comprehend both the beneficial and potentially harmful actions of these medications and importantly stimulate development of novel therapeutics. To address this timely and clinically relevant issue, we propose 4 talks covering the most up-to-date clinical and preclinical data focusing on (1) antipsychotic treatment efficacy and failure, (2) brain-mediated cardiometabolic side effects, (3) evidence from human postmortem studies that attempt to dissect neuropathological effects of antipsychotic drugs from organic schizophrenia neurobiology, and (4) the emerging interactions of antipsychotic drugs with the immune system. The 4 proposed speakers are:

(1) Dr Davide Amato: “Effects of antipsychotic treatment on synaptic dopamine levels and its relevance for antipsychotic treatment efficacy and failure: preliminary results from a meta-analysis of microdialysis studies”
(2) Dr Margaret Hahn: “Olanzapine impairs central insulin action leading to dysregulation of hepatic glucose production”
(3) Dr Clare Beasley: “Post-mortem studies of glial pathology: dissecting drug from disease effects”
(4) Dr Anthony Vernon “Do antipsychotics inflame the brain?”

The final part of the workshop will then be given over to an open discussion led by the chair, cochair, and moderator with the workshop audience. Professor Gary Remington will chair the session and Professor Lars Jarkg has agreed to act as moderator / discussant.

Our aim is to stimulate discussion on these highly clinically relevant topics and consider how we might use current and evolving knowledge and new methodologies in the fields of neuropharmacology and neuroscience, to advance our understanding of the long-term impact of antipsychotic treatment. Ultimately, this may inform the clinical use of these drugs and pave the way for development of novel treatment strategies or optimized antipsychotic drugs.

169. COGNITIVE AND NEURAL MECHANISMS UNDERLYING DELUSIONS: NEXT GENERATION PARADIGMS

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Overall Abstract: Delusions are the most prominent symptom of psychotic disorders and are closely tied to patient outcomes. They are also one of the most elusive constructs to study due to a lack of animal models, their heterogeneity among patients, and the paucity of cognitive paradigms used to study delusions in the past. This symposium highlights innovative approaches to the study of delusions, with particular emphasis on the contributions of early-career researchers. Using new computational metrics, the language of people with and without delusions is examined by Philip Corlett (Yale University), suggesting a critical role for semantic coherence in the manifestation of delusions across disorders, including perturbations of NMDA in a case of anti-NMDA receptor encephalitis. Daphne Holt (MGH) reports on a large sample of youth with and without delusional beliefs using functional connectivity MRI. This sample shows higher connectivity of the amygdala with primary visual cortex in those with delusions and particularly in those with persecutory ideation. Krista Wisner (MPRC and the University of Minnesota) used neuroimaging to study a novel variant of the trust paradigm that measured the ecological construct of spite sensitivity. Connectivity analyses in people with schizophrenia and twins discordant for suspiciousness support a 2-factor theory of persecutory ideation, suggesting a failure of top-down modulation of faulty evaluative processes. Raphael Underwood (King's College) reports on a mindreading illusion he refined to image circuitry associated with the threat of mental interference in both clinical and nonclinical psychotic samples. This work lends a convergent perspective on the joint roles of cognitive control and emotional processing systems. This work shows convergent paradigms and an RDoC approach to understanding delusional mechanisms across disorders and levels of analysis.