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6. FACT OR ARTIFACT? BENEFITS AND LIMITATIONS OF ADVANCED NEUROIMAGING METHODS FOR PSYCHOSIS

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Overall Abstract: Neuroimaging tools introduced the ability to non-invasively search for pathological signatures in the brains of subjects suffering from psychosis. In fact, with almost any neuroimaging modality there are studies that report the identification of abnormalities in the brains of schizophrenia subjects. The abundance of findings made it much clearer that brain abnormalities are common and expected in mental disorders. However, the quantity of findings, and especially their inconsistence across studies also raise questions as to the source of these abnormalities. Are they signifying a complicated range of pathologies and interactions? Or do they reflect auxiliary changes that are not directly related to the root, or the etiology of the disorder?

In addition, these inconsistencies raise technical questions such as are our tools sufficiently sensitive to reliably identify brain abnormalities in psychosis? And, to what extent are our tools sensitive to misinterpretation and to artifacts, which may explain some of the group differences found when comparing psychotic populations with controls? Emerging imaging modalities attempt to address these concerns by improving the specificity, i.e., the ability to relate identified abnormalities with underlying pathologies. At the same time analysis must carefully pay attention to common physiological sources of artifacts, such as subject motion, blood flow, brain metabolism, partial volume, etc.

This symposium will bring together five leading neuroimagers from 4 continents, who will present paradigm-shifting state of the art in their field, while providing critical cautionary remarks regarding the shortcomings of these methods, as well as recommendations for proper use in the context of psychosis studies. Speakers are:

1) Prof. Jennifer Caughlin, M.D. Department of Psychiatry and Behavioral Sciences, Johns Hopkins University. She will present state of the art in TSPO-PET acquisition and analysis, and its potential for the evaluation of neuroinflammation in schizophrenia.

2) Prof. Ofer Pasternak, Ph.D. Departments of Psychiatry and Radiology, Harvard Medical School. He will present recent advances in diffusion MRI, and how microstructural imaging may inform the study of psychosis.

3) Prof. Christoph Mulert, M.D. Department of Psychiatry and Psychotherapy, University medical center Hamburg, Germany. He will present new approaches for EEG acquisitions combined with fMRI that may shed light on neuronal activity.

4) Prof. Helen Juan Zhou, Ph.D. Neuroscience & Behavioural Disorders Programme, Duke-Nus Medical School, Singapore. She will present the emerging field of connectomics and its potential application to study functional and structural brain networks in schizophrenia.

The discussant will be Prof. Christos Pantelis, M.D. Department of Psychiatry, University of Melbourne, Australia. Dr. Pantelis will complement the panel by bringing in a more clinical point of view, informed of the needs in psychiatric neuroimaging. The panel will also benefit from his vast experience across all imaging modalities.

This symposium is designed to provide information and considerations that can be essential for psychosis researchers before considering the application of advanced imaging tools. We will describe the main and unique findings that were provided by each modality, towards a discussion of how far are imaging studies from leading to a breakthrough in the understanding of the pathophysiology of psychosis or its treatment.

6.1 STUDY OF ALTERED NEUROIMMUNITY IN PSYCHOSIS USING PET-BASED IMAGING OF THE TRANSLATOR PROTEIN 18 KD: PROMISES, PITFALLS, AND FUTURE DIRECTIONS

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Background: Successful development of high affinity radioligands for the translocator protein 18 KDa (TSPO) has contributed to a rapid rise in their use with positron emission tomography (PET) imaging to quantitatively detect the higher density of TSPO in neuropsychiatric conditions with putative microglial activation or reactive gliosis in vivo. [11C]PK11195 has been widely used to study TSPO in many neurological and psychiatric diseases, but the quality of quantified binding estimates using this first-generation radioligand is hampered by low signal to noise ratio, which also limits the sensitivity to detect group differences in binding. Second-generation radiotracers for TSPO such as [11C]DPA-713, [11C]PBR28, or [18F]FPDPB have superior specificity for the target and improved brain penetration. However, in spite of these promising newer generation radioligands, their use with PET neuroimaging to study the immune response in psychotic diseases like schizophrenia has yielded inconsistent results of low, unchanged, or even tendency toward decreased binding to TSPO compared to data from controls.

Methods: In this presentation, we will provide necessary biological and methodological perspective to help interpret better the recent results from imaging TSPO in psychosis. We will first review its expression by many cell types including activated microglia, the resident immune cells in the brain, and its diverse functional roles including TSPO as a biomarker of classic neuroinflammatory processes. We will then present optimized methods for estimating useful binding outcomes that go beyond correction for TSPO genotype to minimize effects of factors, including those related to the diverse roles of TSPO, which otherwise introduce limiting, inter-individual variability in binding.

Results: These methods include the reporting of relative binding in one tissue to another, where such global factors are cancelled out by their appearance in the numerator and denominator of the outcome ratio. Use of this ratio approach may decrease inter-individual variability in binding measures and improve the sensitivity and statistical power to detect differences between cohorts. In contrast, use of a relative outcome measure may limit the utility of TSPO imaging since a difference between cohorts or within a subject over time may reflect either abnormal TSPO density or a mere shift in possibly normal, relative distribution between the two tissue regions. The most useful pseudoreference region is therefore one in which the true regional density of TSPO is unchanged in the study population, and is yet unidentified in schizophrenia. Building on this biology and methodology, we discuss misconceptions about imaging TSPO in psychosis and cautiously remind the field that this technique should not be equated with ‘imaging microglial activation’ or ‘imaging neuroinflammation.’ Indeed, PET-based TSPO estimates have not correlated with increased peripheral or central pro-inflammatory cytokine levels in schizophrenia or other psychiatric diseases like major depressive disorder.

Discussion: Together, a less simplified approach to imaging TSPO may inform its utility in studying other biological processes captured by its use in psychosis, and may guide future, complimentary research in vitro and in vivo to enhance our understanding of altered neuroimmune processes in psychosis.