Title of Session: Doing More with Less

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Highlights:

- Extensive research in the past decade has advanced MR to its status as an important tool for investigating mental disorders, which are the leading cause of disability worldwide.
- Multi-modal MR techniques, including structural, functional, and molecular imaging, may provide "radiological signs" for currently symptom-based psychiatric diagnoses.
- Several technical and methodological developments of psychiatric MR have already proven useful in several clinical applications (e.g., predicting the treatment response in depression patients and detecting early brain abnormalities in individuals at high risk for PTSD) and are under active investigation for a wide spectrum of mental disorders.

TALK TITLE: Emerging MRI to uncover the "disordered mind": are we in an era of "psycho-radiology"?

TARGET AUDIENCE – Neuroradiologists, neurologists, psychiatrists, clinical psychologists, neuroscientists, MR technologists and other researchers with an interest in the technical and clinical aspects of psychological and neuropsychiatric imaging.

OUTCOME/OBJECTIVES – To discuss methodological challenges and opportunities provided by psychiatric MR and to present relevant clinical applications.

SYNOPSIS – Mental disorders are the leading cause of disability worldwide, and their human and economic costs, as measured by the WHO in Disability Adjusted Life Years (DALYs), exceed those of infectious, cardiovascular, or neoplastic diseases[1, 2]. One person in four becomes mentally ill at some point in their life, yet most patients do not receive the help that they need, i.e., early detection and early intervention. For example, China has an estimated 173 million people with mental disorders, of whom 158 million have never received treatment, and it took 27 years for adoption of China's mental health law initially drafted in 1985 by the West China Hospital of Sichuan University in Chengdu[3]. The major obstacle to the effective diagnosis and treatment of mental disorders has been our poor understanding of the underlying neuropsychopathology and, particularly for radiologists and psychiatrists, the lack of biomarkers for diagnosis and prognosis[1-4].

Magnetic resonance (MR) imaging allows noninvasive investigation of brain structure and function in vivo and is well suited for the study of psychiatric patients. The past ten years have witnessed a remarkable increase in the number of neuropsychiatric MR studies, resulting in significant advances in the context of technical and methodological improvements, as well as clinical applications.

Technically, the development of the multi-modal MRI has allowed quantification of brain tissue at the structural, functional and molecular levels[5-11]. Using high-field MR imaging (i.e., 3.0 Tesla MR), the structural and functional correlates of a number of mental disorders

have been identified. Taking advantage of novel approaches and techniques for the acquisition and analysis of MR imaging data, several clinical studies have revealed imaging biomarkers in populations that are at high risk for developing mental disorders[12-17] and diagnostic biomarkers of mental disorders and underlying pathological mechanisms[18-48]. The results not only support the current focuses on biological investigation of mental disorders advocated by the U.S. National Institute of Mental Health's Research Domain Criteria (RDoC)[4] but also provide the first step toward the translational use of high-field MR imaging for diagnosis, prediction of treatment response, and monitoring of therapeutic effects.

For example, multi-modal MR imaging studies of treatment-naive first-episode schizophrenia patients gave us the opportunity to examine the fundamental psychopathologies caused by the disease, irrespective of the medications[18-21]. Both short-term and long-term effects of antipsychotic treatment on a patient's brain can be observed based on the connectivity analysis of the resting state fMRI data[22, 23]. However, the elevated prefrontal brain connectivity in schizophrenia patients appears to be a robust biomarker associated with the clinical severity of the disorder[23], in contrast to the results from other studies[24-27].

A similar approach has been adopted for imaging the depressed brain[28-34]. Depression is the third leading contributor to the global disease burden; it has high rate of suicide and is often difficult to treat. By 2020, an estimated 1.5 million people will die each year by suicide, and between 15 and 30 million will make an attempt[1]. Thus, MR imaging research into depression has generally focused on two major clinical issues: suicidality[35, 36] and refractoriness[37-40]. Studies have revealed microstructural abnormalities associated with suicidality among patients with major depression[35, 36]; more specifically, they have provided evidence for altered frontal-striatal circuits passing through the anterior limb of the internal capsule[35]. These potentially disrupted connections are in areas that regulate affect and behavior and might trigger the onset of depression and confer a biological vulnerability, which in combination with environmental stressors, could result in suicidal behaviors.

Additionally, the above studies have revealed differences in psychopathophysiology in patients who either do or do not respond to antidepressant treatment. Approximately 30% of patients do not respond to standard antidepressant treatment and are classified as having refractory depression; those who do respond are considered to have non refractory depression. Studies have revealed differences in functional connectivity related to treatment responsiveness, with the non refractory group showing a decrease mainly in the limbic-striatal-pallidal-thalamic circuits, and the refractory group showing a decrease mainly in thalamo-cortical circuits[37]. Taken together, these findings suggest that refractory depression may be associated predominantly with disrupted connectivity in the thalamo-cortical-circuits. This may explain in part why patients with refractory depression are resistant to standard antidepressants but respond well to treatments targeting the frontal areas[37-40]. Based on graph theory analysis, one study showed disrupted topological organization of intrinsic functional brain networks during rest in patients with depression[30]. In light of the sensitivity of resting-state functional MR imaging to neuronal alterations

associated with medication[37, 38], further work needs to be done to investigate the therapeutic effect on the brains of patients with other mental disorders. In addition, the use of novel analytical methods that allow inferences to be made at an individual rather than a group level may facilitate the translational impact of the results[40].

In summary, reflecting the greater awareness of mental illness worldwide, there has been a significant increase in efforts to better understand and treat psychiatric disorders. This is best exemplified by the "psycho-radiological" (i.e., psychiatric imaging) research that allows us to obtain various objective “radiological signs” (i.e., imaging biomarkers) of mental disorders, which could be used in a clinical context similar to the current methods that neuroradiologists use to manage neurological diseases. For example, the application of anatomical "signs" allows prediction of patient responses to medication in depression with an accuracy as high as 84.65% ($p<0.001$)[40]. In addition to the aforementioned major mental illnesses, abundant psychiatric MR imaging findings and relevant methodological developments have been reported for other disorders, e.g., posttraumatic stress disorder, obsessive-compulsive disorder, and attention deficit hyperactivity disorder[41-48]. These results may represent an initial step toward the use of "psycho-radiological" findings to inform early clinical diagnosis as well as effective treatment for patients with mental disorders. In particular, the development of novel quantitative MRI (*qMRI*) methods such as macromolecular tissue volume estimation[5] and Magnetic Resonance Fingerprinting[6], if validated clinically, will expedite the translation of "psycho-radiological" discoveries into patient care.

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