Commentary

Indexing the neurobiology of psychotic depression with resting state connectivity: Insights from the STOP-PD study

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Major depressive disorder (MDD) with psychotic features or "psychotic depression" is a pernicious mood disorder with substantial morbidity and mortality. This disorder contrasts with schizophrenia spectrum and other psychotic disorders in that psychotic symptoms attenuate with remission from depressive symptoms. Although there are effective acute interventions for psychotic depression, less is known about longer term continuation and maintenance pharmacologic treatment with agents that can have a profound side effect burden [1]. The neurobiology of psychotic depression is understudied and poorly understood. Notably, there are few prior neuroimaging studies to guide research design and clinical practice [2]. These knowledge deficits highlight common challenges faced in psychiatric clinical practice and interventional study design.

Resting-state functional magnetic resonance imaging provides an efficient and noninvasive methodology for examining brain networks [3–5]. This tool examines the temporal coherence of the blood-oxygen-level-dependent signal among brain regions while a subject is quiescent and not focused on a task [4,5]. Recently, there has been much work and interest focused on resting-state functional magnetic resonance with the hope of developing reliable biomarkers for research and clinical practice [3–7]. Resting-state functional magnetic resonance imaging is an indirect measure of brain function with numerous potential confounds and uncertain neurobiological underpinnings [4,5]. Resting-state functional magnetic resonance imaging studies have great promise despite the realization of limitations and this approach is arguably a leading candidate among biomarkers in the search for tools to optimize clinical practice and interventional studies in psychiatry. One prior resting-state functional connectivity study examined 39 healthy participants, 39 patients with active MDD, and 22 patients with active MDD with psychotic features. Patients with psychotic depression had reduced hypothalamic and subgenual cortex connectivity. Notably this is the only prior resting-state functional magnetic resonance imaging study examining psychotic depression [2].

In *EBioMedicine*, Voineskos, Neufeld and colleagues examined resting-state functional connectivity of patients with psychotic depression and healthy controls within a primary and replication sample. Patients in this study were enrolled in a randomized controlled trial, and all patients reached remission and were taking both sertraline and olanzapine at the time of scanning. Depressed patients in the primary sample had decreased between-network functional connectivity in the default mode network (DMN) and bilateral insular, somatosensory/motor, and auditory cortices with the greatest peak of decreased connectivity within the right planum polare compared to healthy control subjects. Notably, the replication sample of patients with remitted psychotic depression had a similar pattern of functional connectivity. This suggests that the lack of increased DMN associated functional connectivity and attenuated between-network connectivity may be neurobiological correlates of remitted psychotic depression ([8] (In Press)).

The DMN is a collection of widespread brain regions demonstrating functional connectivity while an individual is awake but at rest. This network facilitates unprompted, internal thoughts and emotions [4]. The DMN has been widely studied in unipolar depression and psychiatric disorder in general. Emerging evidence consistently suggests that patients with unipolar, nonpsychotic MDD and psychotic disorders such as schizophrenia have aberrant intra and internetwork patterns of connectivity [5,9]. Abnormalities in subgenual cortex and DMN functional connectivity are a consistent finding in studies of nonpsychotic depression. Further, DMN, hyperactivity and hyperconnectivity may be associated with psychotic symptoms and a reflection of decreased gamma-Aminobutyric acid neurotransmission [9]. Given that the present study by Voineskos and colleagues is the first of its kind and cross-sectional, it is unclear if the demonstrated pattern of a lack of DMN hyperconnectivity to other brain regions is a trait biomarker of psychotic depression or a reflection of dynamic brain changes associated with remission from psychotic depression ([8] (In Press)). Regardless, this important work establishes a benchmark for future longitudinal studies of psychotic depression. This work also underscores the scientific imperative for a broader integration of neuroimaging into interventional studies in psychiatry to advance clinical neuroscience and psychiatric practice.

Further work with resting-state functional magnetic resonance imaging holds the prospect for enhanced classification and diagnostic practices in psychiatric research and practice ([3–5,7]). Clinical diagnoses such as MDD with psychotic features have substantial heterogeneity that contributes to poor outcomes and uncertainty in treatment approaches. Resting state functional connectivity studies such as the effort by Voineskos and colleagues hold promise for understanding the neurobiology of psychiatric disorders and honing treatment approaches ([8] (In Press)). However, one current challenge and unfortunate irony is the widespread heterogeneity of reported findings in neuroimaging

literature. This limitation is not insurmountable however and solutions are exemplified by the efforts of this multicenter team. Large collaborations, data sharing, replication studies, and longitudinal efforts are important considerations [10]. Multimodal work assimilating neuroimaging findings with risk genes, epigenetic markers, refined clinical characterization, and measures of environment will likely be key factors to unlock the mysteries of psychiatric heterogeneity. The study by Voineskos and colleagues is an important step in this process and has provided exciting new insights regarding the neurobiology of psychotic depression([8] (In Press)).

Conflict of interest

The author declares no conflict of interest.

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