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RESEARCH HIGHLIGHT

Further evidence that MRI based measurement of midbrain neuromelanin may serve as a proxy measure of brain dopamine activity in psychiatric disorders

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During the past two decades, substantial progress has been made in developing and applying neuroimaging tools to investigate the pathophysiology of psychiatric disorders. Advances in neuroimaging acquisition and analysis methods have also led to progress toward the development of imaging biomarkers, linked to pathophysiological mechanisms, that can provide important insights into the heterogeneity of psychiatric disorders and individual differences in treatment response. One important example of this is the association between treatment response of psychotic symptoms in schizophrenia and pre-synaptic dopamine (DA) activity in the basal ganglia. Building on over 2 decades of radionuclide imaging studies showing increased striatal DA [1] in schizophrenia that is associated with positive symptoms and response to DA blocking therapies, recent studies have shown that individuals in the early phases of the illness who fail to respond to antipsychotics do not show this pattern of increased DA [2].

In the current issue, Wengler et al. [3] present data using another potential biomarker related to the measurement of DA activity in the brain, neuromelanin (NM) imaging of the substantia nigra (SN) and ventral tegmantal area (VTA) in the midbrain. While PET can be considered a gold standard molecular imaging tool that is well validated to measure DA synthesis, release, and density of multiple DA receptors, NM imaging is an emerging MRI based measure of brain DA activity that has the potential for broad clinical application. Early studies using this method showed decreases in SN/NM in Parkinson's disease [4] and increases in schizophrenia. The Horga lab has extensively validated midbrain NM measures against striatal DA release and symptoms in the psychosis spectrum [5]. This group has also optimized the acquisition and post-processing methods for NM measurement in the human brain. In the present study the authors present data from individuals with late life depression (LLD), which is associated with reduced DA neurotransmission.

In two modest sized samples of individuals receiving treatment for LLD the authors tested predictions related to psychomotor slowing and the relationship between baseline NM levels and treatment response to L-DOPA therapy in LLD. They also measure change in NM signal in a very small sample of individuals scanned before and after 3 weeks of L-DOPA treatment. The primary finding of the study is in the full sample of 33 individuals, where a significant cluster of voxels in the SN/VTA showed the predicted positive correlation between higher gait speed and higher NM levels. A second measure related to the psychomotor slowing construct, the digit symbol substitution test (DSST), was not related to NM levels, and there were no significant relationships between baseline NM levels and changes in psychomotor slowing or mood associated with 3 weeks of L-DOPA therapy. The sample size for this analysis was just 15 subjects. A final intriguing result was that in the six subjects scanned before and after L-DOPA, SN/VTA NM increased following 3 weeks of therapy, providing very preliminary evidence for NM sensitivity to changes in DA synthesis in midbrain neurons.

These findings add to those using NM imaging in PD, schizophrenia, and the psychosis spectrum, as well as in post mortem human brains, in support of the utility of NM imaging as a biomarker reflecting the state of the DA system and its relationship to neuropsychiatric symptomatology. If the treatment related results are replicated in an appropriately powered study they would also support the sensitivity of SN/VTA to relatively short-term changes in DA activity associated with L-DOPA therapy. Given the central role of dopamine in healthy brain function in a range of psychiatric and neurological disorders the importance of a developing a valid, non-invasive, and scalable biomarker of DA activity in the brain cannot be overstated.

The authors highlight a number of important caveats and limitations of the present work that will need to be addressed in future studies of LLD. While their primary finding in an N of 33 appears robust, the sample size is still modest and the lack of results with the DSST and the negative findings related to baseline NM levels and symptom changes with treatment must be considered in the context of the very small sample size. And while the exploratory analysis of treatment effects has yielded intriguing preliminary results, a robust replication of this finding is needed before the sensitivity of the NM method to L-DOPA treatment is established.

Recently investigators have raised concerns regarding methodological limitations and the risk for spurious or artefactual findings in studies involving MRI imaging in psychiatric populations [6]. These concerns, which encompass factors such as head movement, the effects of medications, comorbidities, and effects of pathophysiological processes on tissue relaxation times that can distort MRI measures of brain structure, function, or chemistry must be taken seriously. Each needs to be rigorously explored in human and animal model systems and subject to experimental control in neuroimaging research studies. Notwithstanding these concerns, it is also important to note that the field of DA imaging

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has progressed dramatically over the past 25 years, with early SPECT and PET studies leading the way in establishing increased pre-synaptic DA in psychosis as the best validated molecular biomarker in psychiatric illness. Despite this progress however, the technical complexity, limited availability, risks associated with radiation exposure, and the cost of radionuclide-based methods have limited their clinical application. The present paper adds to a growing body of evidence that MRI based measurement of SN/VTA NM may serve as a proxy measure of altered DA activity in an as yet limited but important set of brain disorders. Given the present study's limitations, it is important that additional work be pursued in LLD, and that the NM method continues to be refined and applied more broadly to determine the extent to which it can serve as a useful biomarker related to DA function and sensitivity to the effects of DA-related therapies in human psychiatric disorders.

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ADDITIONAL INFORMATION

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