Biological Psychiatry: Celebrating 50 Years

# Commentary

# Diffusion Magnetic Resonance Imaging Advances the Study of Nuclei-Specific Thalamocortical Connectivity in Early Stage Psychosis

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In the human brain, the thalamus serves a critical role as the anatomical nexus for multiple brain circuits. Its healthy functioning is paramount to the processing of information and to the modulation of connectivity between different regions of the brain. The thalamus also plays a key role in regulating attention, motor coordination, sensory gating, emotional processing, and higher-order cognitive functioning (1). Anatomically, the thalamus is composed of several nuclei, many of which have multiple cytoarchitectural subdivisions that are organized according to the cortical and subcortical areas to which and from which they project. The majority of thalamic nuclei are not interconnected either within or across hemispheres, which means that most of the thalamocortical pathways are generally segregated from one another. Therefore, any pathology that affects individual thalamic nuclei, including the cortical region(s) to which they project or the white matter fiber tracts that connect them, will have a significant impact on the function of that particular loop (1).

In the field of schizophrenia, the thalamus has been a structure of great interest since it was first hypothesized as serving a central role in the "cognitive dysmetria" model, proposed by Andreasen *et al.* (2) in 1998. This model posits that aberrant function and structure of a critical network of brain regions, specifically involving the thalamus, prefrontal cortex, and cerebellum, can lead to the manifestation of cognitive and clinical symptoms. Indeed, there is a large body of evidence that demonstrates structural and functional abnormalities in the thalamus in schizophrenia [for reviews, see Pergola *et al.* (1) and Byne *et al.* (3)]. Postmortem studies also report reductions in neuronal number and size in the thalamus overall, as well as specific histological deficits in anterior, mediodorsal, and pulvinar nuclei (3). More recently, several neuroimaging studies have focused on understanding the contributions of thalamic structure and function in the development of psychosis [for review, see Pergola *et al.* (1)]. Current evidence, however, is inconclusive, primarily owing to the relative heterogeneity of findings across imaging studies, but also owing to the lack of precise tools for investigating thalamic connectivity in vivo.

In the current issue of *Biological Psychiatry*, Cho *et al.* (4) present an innovative approach to investigate microstructural alterations in cortical connectivity–based subregions of the thalamus in patients with first-episode schizophrenia. In this study, Cho *et al.* (4) leverage a novel application of two advanced diffusion methodologies. First, the authors generate a connectivity-based parcellation of the thalamus using eight bilateral cortical regions of interest as seed points for probabilistic tractography (i.e., the orbitofrontal, lateral prefrontal, medial prefrontal, lateral temporal, medial temporal, somatosensory, parietal, and occipital cortices). They then pair this information with the advanced diffusion measure kurtosis to assess the degree of "microstructural complexity" within each parcellated area. This is the first study to combine these two approaches in first-episode patients.

The primary findings of this study are a reduction in mean kurtosis in first-episode schizophrenia patients compared with control subjects in subdivisions of the thalamus that have high connectivity to the orbitofrontal cortex and to the lateral temporal cortex. Upon further investigation, Cho *et al.* (4) demonstrate that these subdivisions of the thalamus strongly correspond with the mediodorsal and pulvinar nucleus, respectively. The authors also demonstrate a relationship between spatial working memory accuracy and mean kurtosis of the thalamic region with high connectivity to the orbitofrontal cortex (i.e., mediodorsal nucleus) in patients but not in control subjects. The authors note, however, that this association did not withstand corrections for multiple comparisons and suggest further studies for confirmation. In addition, Cho *et al.* (4) observe that these findings suggest that thalamic connections to the orbitofrontal cortex (mediodorsal nucleus) were weaker in patients than in control subjects. There were no additional significant relationships between mean kurtosis and clinical or cognitive measures. Taken together, this study is the first to show evidence of microstructural alterations in higher-order thalamic nuclei in first-episode schizophrenia, which the authors propose may be useful as an imaging biomarker, although they rightly caution that such work needs further replication.

The use of a connectivity-based parcellation approach is an important component of the Cho *et al.* study (4), because, as the authors note, the use of traditional anatomical parcellations for subcortical structures can potentially be misleading or ambiguous. Moreover, because specific nuclei are not visible on conventional magnetic resonance imaging scans, the accurate segmentation of individual nuclei is a nontrivial problem in the field. Thus, the approach by Cho *et al.* (4) represents a powerful approach to probe nuclei-specific abnormalities in early-stage psychosis. Owing to the discrete functional roles for each nuclei and its associated thalamocortical loop, the ability to differentiate abnormalities at the

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level of individual nuclei is a tremendous step forward in the field. In addition, because the connectivity-based parcellation was completed in subject space, Cho *et al.* (4) were able to generate individualized segmentations of the thalamus, thereby increasing the sensitivity to detect interindividual differences. The results of the study by Cho *et al.* (4) align quite well with previous studies that reported specific histological alterations in discrete nuclei as well as abnormal structural connectivity between the thalamus and cortical regions, particularly the frontal lobe (1). In the future, the application of connectivity-based parcellations, like those used in this study, will allow for the investigation of other complex neural circuitry, such as corticostriatal and corticocerebellar pathways, and their contribution to psychiatric illness.

A further contribution by Cho *et al.* (4) is the use of diffusion kurtosis imaging to investigate properties of gray matter in higher-order thalamic nuclei. In fact, this is the first study to apply these methods in early-stage psychosis. Earlier diffusion imaging methodologies have focused primarily on the assessment of microstructural properties of white matter owing to their ease of interpretation and higher signal-to-noise ratio. However, it is now possible to use diffusion imaging to investigate microstructural gray matter, which can be complementary to macrostructural features of gray matter, such as volume or cortical thickness. T1-based methods that focus on macrostructural features are limited, however, in their ability to describe differences in microstructural features like cytoarchitectural complexity and cellular composition. This is why measures like the kurtosis imaging, as used in the current study, have the potential to increase sensitivity to microstructural pathologies beyond what can be achieved using traditional neuroimaging methods and measures. As demonstrated in this study, the greater sensitivity inherent in diffusion kurtosis imaging provides a way to detect subtle changes in microstructural environments earlier in the course of illness. Future work focusing on prodromal populations, a period when reports of macrostructural and microstructural pathologies are mixed, could help establish a clearer timeline for the involvement of thalamocortical connectivity alterations in the development of psychosis.

The present study, which uses diffusion metrics to understand gray matter microstructure in both healthy controls and first-episode patients, has some precedence in the literature [e.g., (5–7)]. In fact, several groups previously used diffusion metrics to specifically investigate the thalamus in schizophrenia populations, although with quite inconsistent results. More specifically, in a study investigating a chronic population, diffusion measures (e.g., fractional anisotropy) detected the presence of microstructural alterations in the patient group despite a lack of volumetric changes (8), while a separate study in first-episode patients found the opposite (i.e., volume differences but no diffusion differences) (9). The Cho *et al.* (4) study, in using more advanced diffusion methods than these earlier studies, provides evidence for reduced microstructural complexity in specific subdivisions of the thalamus in the early stages of illness. The authors speculate that these reductions in mean kurtosis may reflect changes in macromolecule concentration and cell-packing density. These findings are encouraging as they overlap with previous postmortem data that report reductions in the neuronal number in specific thalamic nuclei in schizophrenia (3). Importantly, the use of advanced diffusion-based methods to investigate subcortical gray matter is an exciting and potentially promising way to increase the sensitivity of neuroimaging tools to detect changes in vivo. Nonetheless, it is equally important to note that for all diffusion-based measures, increases in sensitivity do not necessarily come with increases in biological specificity. Thus, attempts to understand further the biological bases of changes in diffusion signals are needed.

In conclusion, the work of Cho *et al.* (4) represents a step forward in the use of advanced diffusion methods to investigate microstructural complexity in higher-order thalamic nuclei. Important next steps are to understand whether these nuclei-specific alterations in microstructural properties are present prior to the onset of psychosis and if they are predictive of transition to illness, of treatment response, or of functional outcomes in patients across the psychosis spectrum. Advances in neuroimaging techniques provide an extremely powerful approach toward a greater understanding of the role of the thalamus in the pathophysiology of burgeoning psychosis, yet the consistency and interpretability of neuroimaging findings are ultimately limited by the scope and biological relevance of the tools used to ask these critical questions. Therefore, it is critically important that the field continue to develop, apply, and properly interpret these new approaches, but also to make concerted efforts toward biological validation of imaging measures to elucidate further the pathophysiological mechanisms underlying psychosis.

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