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Perspective

Thalamo-cortical system involving higher-order nuclei in patients with first-episode psychosis

Kang Ik K. Cho[1,2], Yoo Bin Kwak[2], Wu Jeong Hwang[2], Junhee Lee[3], Minah Kim[3], Tae Young Lee[1,3] & Jun Soo Kwon[1,2,3,]*

[1]Institute of Human Behavioral Medicine, SNU-MRC, Seoul 03080, [2]Department of Brain and Cognitive Sciences, College of Natural Sciences, Seoul National University, Seoul 08826, [3]Department of Psychiatry, Seoul National University College of Medicine, Seoul 03080, Korea

Based on the piling reports of disruptions in the thalamus of patients with schizophrenia, the alteration in the thalamo-cortical system has been regarded as the core pathophysiology. As the thalamus is composed of distinctive nuclei with different cytoarchitecture and cortical connections, nuclei specific investigations have been actively conducted in post-mortem studies. In addition, the importance of early changes has been highlighted, which in turn has led to investigations of the thalamo-cortical system using non-invasive neuroimaging methods. From this perspective, the early structural changes in the thalamo-cortical system, such as the thalamo-cortical connection and nuclei specific microstructural changes (which are coherent with findings from post-mortem methods) will be briefly discussed. The main findings, which are the reduced thalamo-prefrontal connection and reduced microstructural complexity in the higher-order nuclei detected in first-episode psychosis patients, suggest the occurrence of early alterations within and between the communication hub of the brain and cortex. These findings suggest not only directions for further studies for unveiling the thalamo-cortical system related pathophysiology, but also the possibility of using the reduced microstructural complexity in the higher order nucleus as a biomarker for schizophrenia. [BMB Reports: Perspective 2018; 51(9): 427-428]

As a hub of the brain system, the thalamus is involved in various functions including attention and sensory information processing. Logically, such roles could be closely linked to the symptoms of patients with schizophrenia, where the external information is incorrectly processed or attributed. Consistent with this view, many post-mortem studies have been conducted that investigated the thalamus in schizophrenia. One of the most consistent findings is the reduced volume of the thalamus in patients with schizophrenia compared to healthy controls. The same findings have been confirmed in the structural magnetic resonance imaging (MRI) studies of living patients, which highlight that the thalamic change is closely linked to the pathophysiology.

However, the thalamus is composed of nuclei that have a distinctive cytoarchitecture, cortical connections, and functions. The higher-order nuclei show prominent connections to the cortex, and this property demonstrates they are good candidates to investigate for any changes related to the schizophrenia pathophysiology. In addition, we previously found a reduced thalamo-orbitofrontal connection not only in the first-episode psychosis patients but also in subjects with clinical-high risk for psychosis (Cho KI *et al* (2016) Schizophr Bull 42, 723-731). In addition to the previous findings of thalamo-cortical connection alterations in chronic schizophrenia patients, our study revealed that this change occurs early, even before the onset of the disorder. Also, as the thalamic region with strong connection to the orbitofrontal cortex mostly overlaps the mediodorsal nucleus, it indirectly highlights the possible involvement of the higher-order nucleus in the pathophysiology.

However, the thalamo-cortical connection studies could only indirectly suggest the involvement of the higher-order nuclei, as the information is derived from the connection rather than from the thalamic nuclei themselves.

Therefore, most of the nuclei-specific findings have been derived from post-mortem studies, in which a large number of reports indicate a reduced number of neurons and volume of the higher-order nuclei. However, the findings remain inconsistent overall. Several factors need to be accounted for in post-mortem approaches. Apart from the changes in the brain that can occur around the time of death, it is very difficult to collect an adequate number of samples around the time of onset. Therefore, it is very challenging to distinguish

*Corresponding author. E-mail: kwonjs@snu.ac.kr

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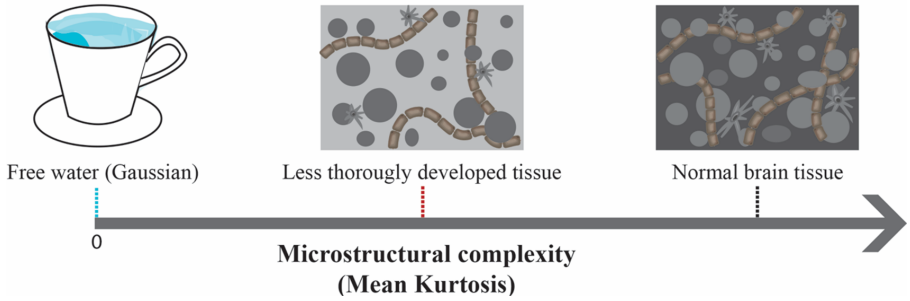

Diagram 1. Schematic summary of microstructural complexity investigated with mean kurtosis. Free water has the Gaussian distribution of the displacement profile, leading to zero kurtosis. However, as brain tissues develop, increasingly occupying space and hindering diffusion, the diffusion profile becomes more complicated and deviates from the Gaussian distribution. This results in increased kurtosis.

the core pathophysiologic changes from the secondary impacts. This not only hinders the detection of onset related changes, but also reduces the power of studies due to the small number of samples.

Non-invasive methods, such as MRI, are needed to reveal the nuclei specific changes occurring around the onset of the disorder. Although it has been difficult to classify each nucleus using a conventional structural image, new techniques such as connectivity-based segmentation using diffusion tensor imaging (DTI) have enabled a more precise classification of the nuclei within the thalamus. Furthermore, a new technique that utilizes diffusion kurtosis imaging could represent the microstructural complexity within the voxel, which may represent cell or organelle packing densities, as shown in Diagram 1.

In our recent study, we aimed to find early nuclei specific changes, the information of which is derived more directly from the thalamic nuclei, by using a combination of neuroimaging techniques in patients with schizophrenia within their first year of the diagnosis.

We investigated the nuclei specific microstructural complexity in the thalamus of 37 first-episode psychosis patients and 36 demographically matched healthy controls using the measure of mean kurtosis from diffusion kurtosis imaging. We found significantly reduced microstructural complexity in the higher-order nuclei, namely the mediodorsal and pulvinar nucleus. Also, we found a significant relationship between the microstructural complexity in the mediodorsal area and spatial working memory accuracy in the patient group.

This finding of higher-order nuclei specific microstructural abnormality not only strengthens the previous reports that suggested the involvement of the higher-order nuclei in the pathophysiology, but also highlight that this change is already present, even from an early stage of the disorder, facilitating the possibility of an early biomarker.

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