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Dissertation of Doctor of Philosophy in
Brain and Cognitive Sciences

Investigation of Microstructural Changes in Thalamus Nuclei in Schizophrenia using Diffusion Weighted Imaging

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Investigation of Microstructural Changes in Thalamus Nuclei in Schizophrenia using Diffusion Weighted Imaging

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Abstract

Disruption in the thalamus, such as volume and thalamo-cortical connectivity change, is regarded as a core psychopathology in schizophrenia. However, whether the nucleus specific thalamic microstructure changes exist in the early stage of the disorder is still unknown. To determine this gap in knowledge, the microstructural complexity of sub-thalamic ROIs with specific connection to the cortex in patients with first episode psychosis (FEP) was compared to that of healthy controls with diffusion kurtosis imaging (DKI) technique.

A total of 37 FEP and 36 matched healthy controls underwent DKI, diffusion tensor imaging (DTI) and T1-weighted magnetic resonance imaging, to estimate mean kurtosis representing microstructural complexity in each segment of the thalamus from DTI connectivity-based segmentation. We also investigated the relationship with psychopathology.

The mean kurtosis in the thalamic nuclei in high connection with the orbitofrontal cortex ($F = 8.40$, $P < 0.01$) and the lateral temporal cortex ($F = 8.46$, $P < 0.01$) were significantly reduced in FEP compared to healthy controls. However, these mean kurtosis values were not correlated with the clinical scores.

This observed pattern of reduced microstructural complexity in specific regions of the thalamus not only highlights the involvement of the thalamus, but also its network specific microstructural alteration from the early stage of schizophrenia. This finding adds evidence of nucleus specific thalamic defects related to the pathophysiology and it warrants more detailed investigation of the thalamus at the nuclei level in future biomarker studies.

Keyword : Schizophrenia, Thalamus, Mediodorsal nucleus, Pulvinar nucleus, Diffusion Kurtosis, Diffusion Weighted(within 6 words)
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Chapter 1. Introduction

Clinical symptoms and cognitive impairments are heterogeneous in patients with schizophrenia. This has led to the pursuit to discover more specific genetic, chemical, and biological markers that underlie the pathophysiology of schizophrenia. Andreasen's cognitive dysmetria model[1] suggests an abnormality in the thalamo-frontal circuit. It has been supported by many studies that report defects in the thalamus, such as reduced number of neurons,[2, 3] reduced volume,[4-7] altered neurochemistry,[8, 9] and abnormal brain activation.[10-13] However, there are inconsistencies in the postmortem[14, 15] and magnetic resonance imaging (MRI) findings in literature,[11, 16, 17] which suggests a need for further investigation of the thalamus in the nucleus level, rather than approaching the thalamus as a single structure.

The thalamus is composed of nuclei with different characteristics including cytoarchitecture and cortical connections.[18] Byne and his colleagues, using postmortem, reported a reduced volume and number of neurons in the mediodorsal nucleus and pulvinar.[19] As these nuclei make major contributions to the prefrontal cortex that has been highly implicated in schizophrenia, their results suggested the involvement of specific thalamic nuclei in schizophrenia rather than the whole thalamus. Studies with non-invasive methods, such as T1 weighted MRI found anomalies in the shape and volume of the thalamus, that points towards changes specific to the mediodorsal nucleus and the pulvinar.[20, 21] Kim and his colleagues investigated the thalamus in more detail by segmenting the thalamus based on its connectivity to cortex. They reported reductions in the thalamic nuclei volumes that are in connection with the orbitofrontal cortex

and parietal cortex in chronic patients with schizophrenia.[22] They also showed uncoupling of the volumetric correlation between the dorsal prefrontal cortex and its related thalamic nucleus, and between the parietal cortex and its related thalamic nucleus. This pattern of thalamo-cortical uncoupling is consistent with more recent studies of a large scaled NAPLS functional connectivity[23] and our previous report of altered anatomical thalamo-cortical connectivity.[24] It not only highlights the involvement of the thalamo-cortical connection, but also specific thalamic nuclei that has a high connection to the prefrontal cortex in the pathophysiology of schizophrenia.

Conventional MRI investigations of the thalamus could only examine the thalamus as a whole structure due to their limited resolution. This may have resulted in the overlooking of submerged nuclei specific information. The information may be helpful in explaining the role of thalamic nuclei in the pathophysiology of schizophrenia. There are reports of nucleus level investigation of the thalamus, however, the long term effect of the disorder such as medication, limited social activities and nutritional state might have affected the result. Therefore, it is vital to investigate the changes in the early stage of the disorder, using an in-vivo method to confirm the thalamic nuclei changes as an alteration related with the core pathophysiology.

Until recently, rather than using thalamic nuclei templates, which does not represent individual variation in the thalamic anatomical locations, a method called connectivity-based segmentation was invented.[25] This utilizes the anatomical connectivities of each subject's thalamus to cortical regions in segmenting the thalamus. This method successfully segments the thalamus into the structures

that agree with the description from histological reports.[26] However, as the segmentation is based on the altered thalamo-cortical connectivity[24, 27, 28] in patients with schizophrenia, the resulting segmentation is affected by a disorder-related factor.

Rather than comparing the volumes from the thalamic segmentation, the investigation of the microstructural change within core regions of the thalamic segments will have various advantages. It would be less affected by the altered thalamic segmentation in schizophrenia due to their reduced anatomical connectivity, as well as being more sensitive to changes within a voxel. Diffusion kurtosis imaging (DKI) is a relatively recent measure within the diffusion weighted imaging field, which can provide information about the microstructural complexity within a voxel.[29] As shown in animal[30] and human[31] studies of DKI, less well-developed tissue have reduced kurtosis compared to healthy gray and white matter. It is used to quantify 'microstructural complexity' and it could refer to the overall microstructural changes including the changes in somal size, oligodendrocytes, dendritic spine length and density, and neuronal cell density.[32-34] Figure 1 is included to help the understanding of the relationship between diffusion kurtosis and microstructural changes. This approach could add extra information to the state of microstructural anomalies in the thalamic nuclei. Recently, Zhuo and his colleagues reported reduced microstructural complexities, using DKI in the white matter of patients with schizophrenia,[35] suggesting axonal integrity disruption in the white matter. They highlighted the limitations of conventional imaging that could be achieved by DKI. However, the report of microstructural complexity in the thalamus and its nucleus, that can show the state of cellular structural changes in schizophrenia, is still missing.

We hypothesize that the patients with FEP will show an abnormal thalamic microstructure in the nucleus, with high connection to the orbitofrontal cortex. Long term effects of the disorder, such as the effect of medication and defective lifestyle in chronic schizophrenia patients, would be minimized by investigating the subjects who are at the early course of the disorder. We hope to highlight the importance of the thalamus and its early sub-structural changes in the pathophysiology of schizophrenia.

Chapter 2. Methods

Thirty-seven FEP were selected, between April 2010 and June 2014, from a slightly larger pool who visited Seoul National University Hospital for their symptoms and agreed to participate in the research.

Intensive clinical interviews were conducted to all FEP by experienced psychiatrists, using the Structured Clinical Interview for DSM-IV TR Axis I (SCID-I) disorders to identify past and current psychiatric illnesses. The inclusion criteria were being between the ages of 15 and 40, and having a brief psychotic disorder, schizophreniform disorder, schizophrenia or schizoaffective disorder in accordance with the DSM-IV criteria. Furthermore, the duration of symptoms had to be less than a year. Thirty-one FEP patients were receiving antipsychotics at the time of scanning, and of them, four were on antidepressants while twenty were on anxiolytics.

The Positive and Negative Syndrome Scale (PANSS)[36] and the Global Assessment of Functioning (GAF)[37] were administered to FEP groups. To estimate subjects' IQ, an abbreviated form of the Korean version of the Wechsler Adult Intelligence Scale (K-WAIS)[38] was administered to all subjects.

Thirty-six healthy controls (HCs), matched age, gender and education year, were also recruited through Internet advertisements. Exclusion criteria for HCs included past or current SCID-I Non-patient Edition (SCID-NP) axis I diagnoses and any first- to third-degree biological relative with a psychiatric disorder. Informed consent was obtained from all subjects in writing, and the study was conducted in accordance with the Declaration of Helsinki. The study was also approved by the Institutional Review Board of the Seoul National University Hospital.

Image acquisition

T_1-weighted (T1), DTI and DKI data were acquired in the sagittal plane using a 3T scanner (MAGNETOM Trio Tim Syngo MR B17; Siemens, Erlangen, Germany). T1 images utilized 3D magnetization-prepared rapid-acquisition gradient echo (MPRAGE), and the following parameters: TR 1670ms, TE 1.89ms, voxel size of 1 mm^3, 250mm FOV, 9° flip angle and 208 slices. Diffusion weighted images were acquired using echo-planar imaging in the axial plane with TR 11400ms, TE 88ms, matrix 128×128, FOV 240mm and a voxel size of 1.9×1.9×3.5. Diffusion-sensitizing gradient echo encoding was applied in 64 directions using a diffusion-weighting factor b of 1000 s/mm^2. One volume was acquired with b factor of 0 s/mm^2 (without gradient). Diffusion kurtosis images were acquired using echo-planar imaging with TR 5900ms, TE 190ms, matrix 128×128, FOV 240mm and a voxel size of 1.9×1.9×3.5mm^3. Diffusion-sensitizing gradient echo encoding was applied in 30 directions each using six diffusion-weighting factor b values of 0, 500, 1000, 1500, 2000, 2500s/mm^2.

MRI processing

T1

Cortical region of interests (ROI) in each individual's T1 space were automatically selected as binary masks using FreeSurfer.[39] Each side of the cortex was divided into eight ROIs: orbitofrontal (OFC), lateral prefrontal (LPFC), medial prefrontal (MPFC), lateral temporal (LTC), medial temporal (MTC), somatomotor (SMC), and parietal (PC) and occipital cortex (OCC).

DWI

DWI data was preprocessed using eddy current correction, skull

removal and motion correction using FSL.[40] Individual B_0 images were used as a reference in registering their own T1 images to diffusion space, creating transformation matrices that were used to bring the ROIs into the diffusion space. FLIRT[41, 42] was used for this registration with mutual information cost function and trilinear interpolation. Then, for each side of the brain, FSL probabilistic tractography[43] was applied with default options (including 5000 streams per each voxel seed) using thalamus ROI as a seed and eight cortical ROIs as targets.

Connectivity-based segmentation

The output from the probabilistic tractography is a set of values, for every voxel of the thalamus ROI, representing the number of tractography samples that arrive at their target ROIs (out of the 5000 initially seeded). These values represent the probability of connection between the seed and each cortical targets.[28, 43] Each connectivity map was thresholded at 90^{th} percentile in order to obtain the core region with higher connection and to exclude regions with aberrant connections arising from noise. It also minimizes regional overlapping between subthalamic ROIs. These thalamic sub-ROIs are binarized to obtain subthalamic nuclei in individual space.

DKI : Mean kurtosis calculation

DKI data was eddy current corrected and motion corrected using FSL.[40] Diffusion Kurtosis Estimator[44] is used with constrained linear weighting to calculate mean kurtosis image for each subject. Then the thalamic sub-ROIs from the connectivity-based segmentation were used as masks to calculate the mean kurtosis in each sub-ROI.

Statistical analysis

All statistical analyses were performed using R, version 3.0.2 and Scipy, version 0.14.0.[45, 46] The demographics were tested for differences between FEP and HCs using independent t-test and test of equality of proportions. The result is summarized in Table 1.

Mean kurtosis of each thalamic nucleus ROI were tested with analyses of covariance (ANCOVAs), to reveal group effect on mean kurtosis, using age as the covariate. Results from the ANOVAs were corrected for multiple comparisons using the False Discovery Rate (FDR) correction, implemented in statsmodels python module.

Then, the mean kurtosis in the thalamic nucleus ROIs, with significant group differences, were tested for correlations with clinical scales such as PANSS and GAF using Spearman's correlation.

Chapter 3. Results

There was no significant difference in the demographic backgrounds of the subjects between FEP and HCs except their IQ, T (67) = 2.86, $p < 0.05$ (Table 1.)

Results of ANCOVAs on mean kurtosis are summarized in Table 2. There was a significant group effect on the MK, where FEP exhibited reduced mean kurtosis in the thalamic ROIs with the highest connection to OFC, F (1, 70) = 8.40, $p < 0.01$ and LTC, F (1, 70) = 8.46, P < 0.005. The group effect on other thalamic nuclei did not survive multiple comparison correction.

The MK values of the LTC-thalamic ROI and OFC-thalamic ROI were not significantly correlated with PANSS and GAF.

Chapter 4. Discussion

To our knowledge, this is the first study to report microstructural alteration in thalamic nuclei of the FEP. Our results revealed that the thalamic region in high connection to the OFC and the LTC have reduced mean kurtosis that may represent neuronal density reduction. However, the changes in the mean kurtosis showed no significant correlation with clinical scales.

The thalamic region with the highest connection to the OFC follows the ventral medial region of the thalamus, from near the most anterior part of the thalamus to three quarters posteriorly as shown in Figure 2A. Although the region does not perfectly match with the mediodorsal nucleus in the Talairach template, it has the greatest overlap with the mediodorsal nucleus, shown in the Figure 4A.

The thalamic region with the highest connection to LTC follows a more superior medial boundary of the thalamus and follows to the most posterior regions as shown in Figure 2B. This region has the highest overlap with the pulvinar mask in the Talairach mask, shown in the Figure 4B.

The low overlap between the thresholded connectivity-based segmented region and the Talairach thalamus template might have been caused by the Talairach thalamus template being slightly smaller than the thalamus extracted from freesurfer. However, the segmentation pattern is very similar to the pattern published by Behrens and his colleagues (Figure 5.)

The reduction in the mean kurtosis found in these regions are consistent with the previous post-mortem reports of reduced neuronal numbers[47, 48] and volume[19, 49] in mediodorsal and pulvinar nucleus of thalamus of chronic schizophrenia patients. It confirms

that the microstructural anomaly in the thalamus already exists in the early course of the disorder, highlighting its relationship to the pathophysiology rather than the long term effect of the disorder.

The reduction of mean kurtosis in the thalamus region, with the highest connection to OFC, is also consistent with the reduced thalamo-OFC connection.[24, 27] Although it is out of scope for this paper to speculate on the order of development in the thalamo-cortical network defect, the thalamo-OFC network including the OFC itself, the thalamic region and the connection in between them, as a whole, is suggested to be important in schizophrenia pathophysiology.

There are reports of structural abnormalities including volume, cortical thickness and sulcogyral pattern of the OFC.[50-52] OFC is involved in emotion processing and in various higher-order cognitive functions, such as social cognition and decision making.[53] Together with the report of reduced structural thalamo-OFC connection,[24, 27] the defect in the thalamus region is speculated to lead the altered filtering, on top of the problem in the communication between the thalamus and OFC. This may be related with the abnormal emotion processing and reward processing. The mediodorsal nucleus is also known to have connections to the limbic system that has ample backgrounds for the abnormalities in schizophrenia.[54-57] Therefore, the altered microstructure might be pointing to the signal filtering dysfunctions related with the reports of limbic system changes.

On the other hand, the temporal cortex is responsible for sensory processing[58] and it is one of the regions which has been highlighted in schizophrenia for the structural and functional alterations.[59-63] The microstructural changes found in the thalamic region, with high connection to LTC, may have effect on the information flow and filtering. Also, according to the Talairach overlap mapping, the

region is likely be the pulvinar nucleus. The pulvinar nucleus of the thalamus also has extensive projections to the cortex, including the visual, parietal and prefrontal cortex.[64, 65] Therefore, the abnormal microstructure found in this region also points towards a possible link to defects in schizophrenia.

While this is the first study to look at diffusion kurtosis in FEP gray matter, there is one previous study that reported widespread abnormalities in the white matter kurtosis in schizophrenia.[35] Going a step further from the white matter approach, and similar to Palacios and his colleagues' investigations on the hippocampal gray matter with diffusion kurtosis,[32] we measured mean kurtosis in the thalamus.

Our results indicate that this measure of kurtosis may be used to detect changes in the gray matter. Small neurodevelopmental alterations from early life are speculated to cause this, because the development of the thalamus begins early in the embryonic stage.[66] However, there was no correlation between the mean kurtosis and clinical scores. It is speculated that alterations in the thalamic microstructure might be a trait characteristic than a state characteristic of psychosis.

Limitations

Many of the FEP patients were on antipsychotics at the time of the scan. Although the effects are relatively small in FEP subjects compared to that of chronic schizophrenics, anti-psychotics and anti-depressants are reported to have a subtle but measurable impact on generalized and specific brain tissues.[67, 68]

The cortical ROIs used in this study have been chosen based on the previously reported thalamo-cortical connection study,[24, 28] in order to refer to their result of altered connectivity with the findings

in this study. However, using different cortical ROIs in the connectivity-based segmentation would have resulted in the different patterns of segmentation and it remains a limitation of the study.

A single B0 image acquisition and non-isotropic voxel shape are also a possible limitation in the image acquisition. In particular, longer voxel shapes in the z-axis might have affected fiber reconstruction slightly differently depending upon fiber orientation, which might have caused a change in the segmentation pattern. Also, cardiac pulsation, which could result in movement, is not controlled in our study. However, we visually inspected every diffusion weighted image to make sure that none of the subjects evinced highly blurred images due to motion. Acquisition direction related noise could have been improved using techniques such as field map or dual diffusion acquisition direction. The implementation of such techniques is planned for future studies.

Chapter 5. Conclusion

Reduced mean kurtosis in the thalamic regions, in high connection with OFC and LTC, shown in FEP highlights the existence of nuclei specific anomalies in the early course of the disorder. This suggests that the thalamic microstructural change may be an important biomarker for psychosis risk that can be used for early detection and possibly early intervention for schizophrenia.

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Tables

Table 1. Demographic and Clinical Characteristics of the Subjects

Variable		FEP (n = 37)	HCs (n = 36)	χ^2 or T	P
Age (yrs)		22.4 ± 5.5	23.5 ± 6.0	0.82	0.42
Sex (M/F)		16 / 21	17 / 19	0.01	0.92
IQ		97.3 ± 13.8	105.5 ± 10.4	2.86	0.01*
Handedness(L/R)		31 / 6	35 / 1	2.41	0.12
Education (yrs)		13.1 ± 2.1	13.8 ± 1.6	1.54	0.13
PANSS	Total	68.6 ± 13.3			
	Positive	16.3 ± 5.0			
	Negative	17.4 ± 5.3			
	General	34.9 ± 7.0			
GAF		46.2 ± 10.8			

The data are given as mean ± standard deviation. FEP, first episode psychosis; HCs, healthy control subjects; PANSS, Positive and Negative Syndrome Scale; GAF, Global Assessment of Functioning; yrs, in years.

Table 2. Summary of the comparisons of the mean kurtosis in the thalamic sub-regions.

Thalamic region with the highest connection to	Groups		F	P	FDR corrected P
	NOR	FEP			
LPFC	0.96 ± 0.08	0.92 ± 0.10	2.49	0.119	0.190
LTC	0.87 ± 0.10	0.80 ± 0.09	8.46	0.005	0.020 *
MPFC	1.01 ± 0.10	0.99 ± 0.13	0.55	0.460	0.526
MTC	0.85 ± 0.11	0.79 ± 0.10	5.70	0.020	0.053
OCC	0.87 ± 0.07	0.84 ± 0.07	3.92	0.052	0.103
OFC	0.97 ± 0.10	0.88 ± 0.09	8.40	0.005	0.020 *
PC	0.95 ± 0.09	0.95 ± 0.11	0.01	0.940	0.940
SMC	1.04 ± 0.12	1.02 ± 0.16	0.57	0.453	0.530

*, FDR corrected $P < 0.05$

Figures

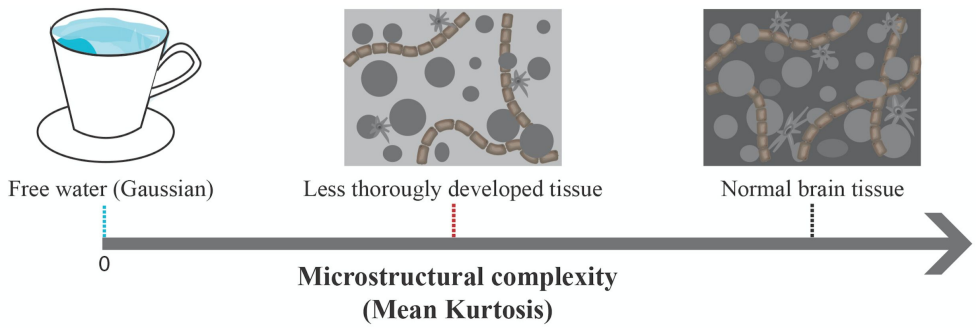

Figure 1. Schematic summary of microstructural complexity investigated with mean kurtosis. Free water has the Gaussian distribution of the displacement profile, which makes its kurtosis zero. However, as brain tissues develop, increasingly occupying space and hindrance on diffusion, the diffusion profile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

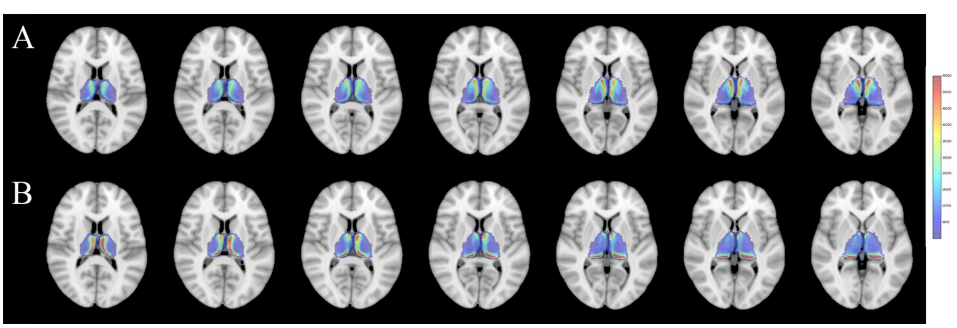

Figure 2. Summation of the thalamo-cortical connectivity maps of every subject in the MNI space. A shows the thalamo-orbitofrontal cortex and B shows the lateral temporal cortex. The warm colors represent higher connection to its target region.

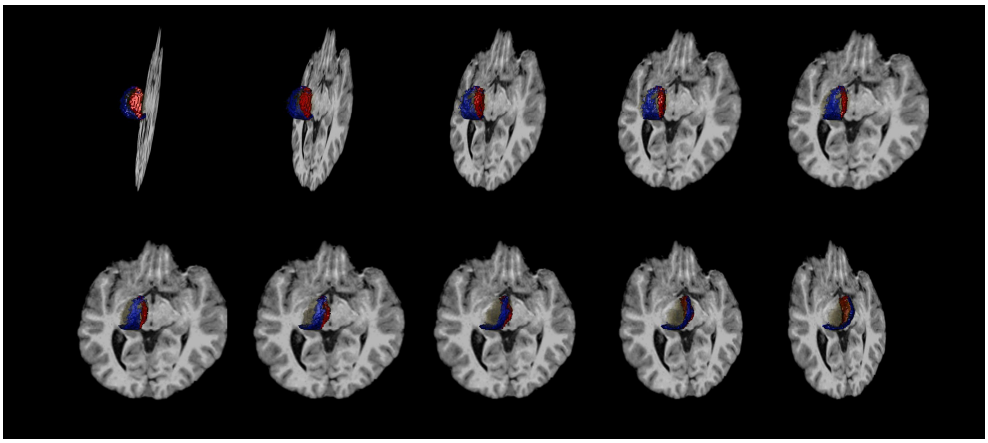

Figure 3. Thalamic regions with high connection to the orbitofrontal cortex (Red) and lateral temporal cortex (Blue) in three dimension.

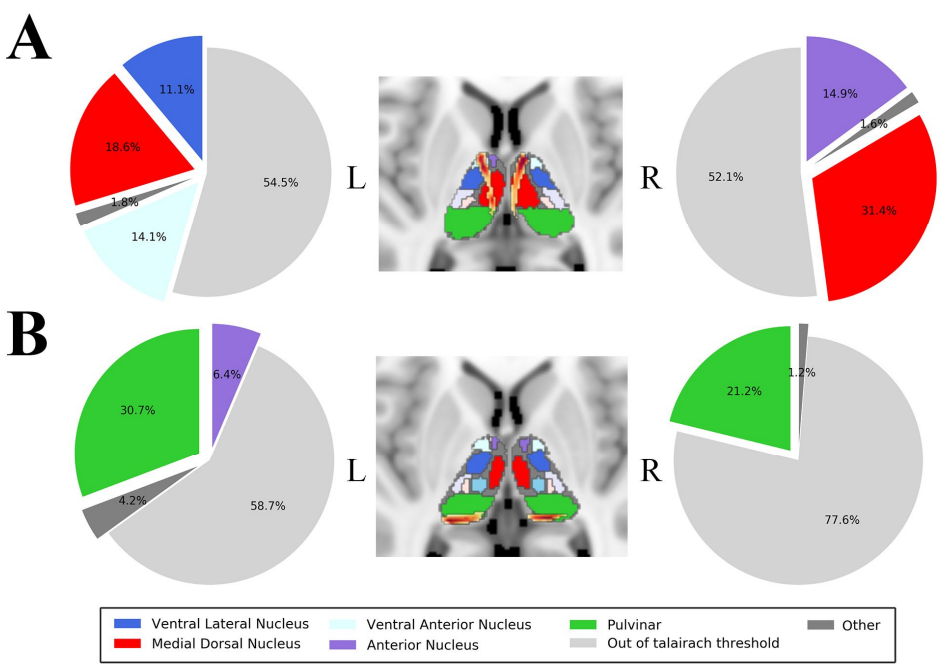

Figure 4. Resulting connectivity map from the thalamo-cortical probabilistic tractography overlaid on the Talairach template.[69] The pie graphs represent the overlap between the region and each template regions. A shows the region with high connection to

orbitofrontal cortex, B shows the region with high connection to lateral temporal cortex.

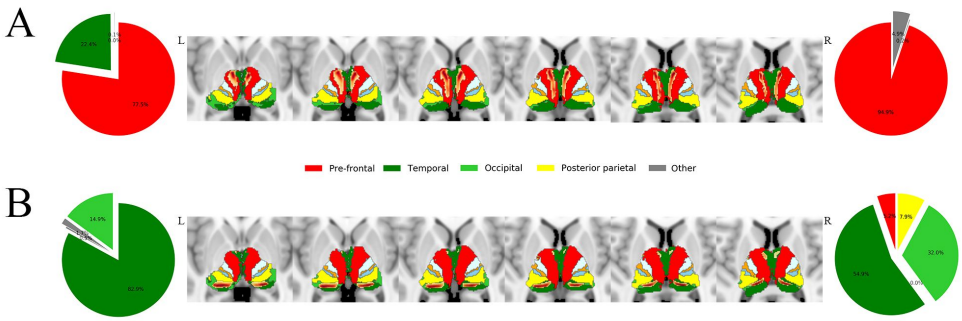

Figure 5. Resulting connectivity map from the thalamo-cortical probabilistic tractography overlaid on the FSL thalamus template.[26] The pie graphs represent the overlap between the region and each template regions. A shows the region with high connection to orbitofrontal cortex, B shows the region with high connection to lateral temporal cortex.

Abstract

시상-대뇌피질의 연결성 변화와 시상의 용적 변화 같은 시상의 이상은 조현병의 정신병리에 중요하다는 것으로 알려져있다. 하지만, 시상 핵들에 특이적인 미세구조 변화가 질병의 초기단계에서도 존재하는지 아직 알려져있지 않다.

이것을 증명하기 위하여, 대뇌피질과의 연결성을 이용해 초발조현병군의 시상을 피질 특이적인 연결을 가진 핵들로 나누고 그들 내부의 미세구조를 확산첨도영상을 사용하여 정상 대조군과 비교해보았다. 총 37명의 초발 조현병 환자와 36명의 정상 대조군에서 미세구조 복잡도를 나타내는 평균 확산첨도를 특이적 대뇌피질과의 연결성을 가진 시상핵에서 구하기 위하여 확산첨도영상, 확산텐서영상 그리고 T1 강조 자기공명영상을 촬영하였다. 평균 확산첨도와 환자의 증상과의 연관성도 살펴보았다.

초발 조현병군의 안와 전두 피질과 연결성을 보이는 시상핵의 평균 확산첨도와 ($F = 8.40, P < 0.01$) 외측두엽 피질과 연결성을 보이는 시상핵의 평균 확산첨도가 ($F = 8.46, P < 0.01$) 정상대조군과 비교하여 유의미하게 감소되어 있었다. 하지만 이는 환자의 증상과 유의미한 연관성을 보이지 않았다.

이러한 미세구조 복잡도 감소를 나타내는 평균 확산첨도 변화들은 조현병의 병리생태에 있어서 시상의 중요성을 재조명하는 것 뿐만 아니라, 특이 시상 네트워크들의 미세구조 변화가 초발 시기부터 중요하다는 것을 보여준다. 이는 특이 시상핵들의 미세구조의 변화가 병리생태와 관련이 있으며 이후 연구들에서 시상핵 단위의 자세한 접근이 필요하다는 증거를 제공한다.