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Altered Thalamo-Cortical White Matter Connectivity: Probabilistic Tractography Study in Clinical-High Risk for Psychosis and First-Episode Psychosis

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Disrupted thalamo-cortical connectivity is regarded as a core psychopathology in patients diagnosed with schizophrenia. However, whether the thalamo-cortical white matter connectivity is disrupted before the onset of psychosis is still unknown. To determine this gap in knowledge, the strength of thalamo-cortical white matter anatomical connectivity in subjects at clinical-high risk for psychosis (CHR) was compared to that of first-episode psychosis (FEP) and healthy controls. A total of 37 CHR, 21 FEP, and 37 matched healthy controls underwent diffusion-weighted magnetic resonance imaging to examine the number of probabilistic tractography "counts" representing thalamo-cortical white matter connectivity. We also investigated the relationship with psychopathology. For FEP, the connectivity between the thalamus and parietal cortex was significantly increased ($F = 5.65$, $P < .05$) compared to that of healthy controls. However, the connectivity between thalamus and orbitofrontal cortex was significantly reduced compared to both healthy controls ($F = 11.86$, $P < .005$) and CHR ($F = 6.63$, $P < .05$). Interestingly, CHR exhibited a similar pattern as FEP, albeit with slightly reduced magnitude. Compared to healthy controls, there was a significant decrease ($F = 4.16$, $P < .05$) in CHR thalamo-orbitofrontal connectivity. Also, the strength of the thalamo-orbitofrontal connectivity was correlated with the Global Assessment of Functioning score in CHR ($r = .35$, $P < .05$). This observed pattern of white matter connectivity disruptions in FEP and in CHR suggests that this pattern of disconnectivity not only highlights the involvement of thalamus but also might be useful as an early biomarker for psychosis.

Key words: schizophrenia/clinical high risk/first-episode psychosis/thalamus/tractographythalamocortical

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, and 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 postmortem[14,15] and magnetic resonance imaging (MRI) findings in the literature,[11,16,17] which suggests a need for further investigation of the thalamus.

The thalamus relays and modulates communication between subcortical regions and the cortex, as well as plays a major role in cortico-cortical information transfer,[18] which depends upon signal propagation through white matter connections. Of note here, a number of recent studies in schizophrenia have focused on connectivity between the thalamus and the prefrontal cortex rather than on the thalamus alone. Using diffusion weighted imaging (DWI), these studies report reduced white matter connectivity between the thalamus and the prefrontal cortex,[19,20] which are consistent with the disconnection theory of schizophrenia.[21,22] These findings are further supported by the fact that some of the symptoms in schizophrenia, such as dysfunction in execution, attention and sensory gating, are related to the thalamo-prefrontal circuit.[1]

The connection-mediated interaction between the thalamus and early cortical subplate, and thalamofugal axons and subcortical plate, are critical for establishing layer-specific thalamo-cortical connections[23,24] during development. Inevitably, developmental changes either in the thalamus or cortex are reflected in their white matter connections.

We believe that changes in thalamo-prefrontal anatomical connections will be apparent not only in patients with a first-episode of psychosis (FEP), but also in subjects with subthreshold symptoms, albeit more attenuated—such as subjects at clinical-high risk for psychosis (CHR) (defined using Structured Interview of Prodromal Symptoms,[25] see Methods). This assumption is based also on studies of subjects at CHR that report similar but more attenuated findings compared to those reported for schizophrenia, including cognitive impairments,[26–28] structural,[29–32] and functional alterations.[33,34] Moreover, characterizing those at the prepsychotic phase of illness, who evince potential prodromal symptoms, is critical for establishing biomarkers that can be used to follow the effects of treatment or to identify subjects who are at higher risk for developing the illness.[26]

Despite the surge of interest in CHR subjects, based on the possibility of early intervention and conducting research with less confounding factors such as chronic medication and chronic illness, the investigation of white matter pathology in CHR is not common. Changes in frontal, temporal, parietal and occipital white matter have, nonetheless, been reported.[35–37] However, negative findings have also been reported.[38,39] Additionally, there are no direct studies that examine changes in thalamo-cortical white matter structural connections in CHR.

Although we have found reduced volume in the anterior limb of the internal capsule in individuals at CHR using structural MRI,[30] important properties of white matter, such as coherence of axonal bundles, could not be appreciated using these techniques. Volume is only a gross indicator of the width of the white matter path, and as such it may be greatly affected by volumetric changes in surrounding structures.

Recently, von Hohenberg and his colleagues revealed early white matter changes in CHR in the superior longitudinal fasciculus, in the corona radiate, and in the corpus callosum.[40] However, their method involved hypothesis-free whole brain white matter group comparisons, and, therefore, might not have been sufficiently sensitive to detect subtle changes in the thalamo-cortical white matter connections.

DWI is used to measure the degree of white matter connectivity by quantifying the amount of diffusion along the axonal fibers. However, when white matter bundles propagate into gray matter, the diffusion becomes isotropic, and reconstructing white matter bundles using tractography becomes very difficult under the near isotropic environment. In this study, probabilistic tractography was used, which follows white matter tracts based on the probability density function.[41] This approach enhances the robustness and sensitivity of the tractography, and, in our case, it makes possible the investigation of thalamo-cortical connections, where white matter fibers propagate into the thalamus and the cortex. Of note, measures calculated from the diffusion tensor, such as fractional anisotropy (FA), are limited to estimating fiber integrity in manually selected regions of interests (ROIs), or in coherent fiber tracts obtained through the streamline tractography process. They are less useful, however, when axons are fanning out of the small structure, and propagate by taking various paths to the cortex, as in the case of thalamo-cortical connections. Accordingly, it is more appropriate to use probabilistic tractography, and probabilistic tractography derived measures of fiber count and "relative connectivity,"[19] to quantify thalamo-cortical connectivity.

In this study, in order to demonstrate early white matter changes in the thalamo-prefrontal connections in CHR, probabilistic tractography was performed between the thalamus and cortex in FEP and CHR groups, which were then compared to that of healthy controls (HCs). The FEP group was included in this study to confirm previously reported findings of thalamo-prefrontal white matter alterations, and also to document that schizophrenia onset has a progressive aspect.

Methods

Thirty-seven CHR and 21 FEP were selected between April 2010 and August 2013 from a slightly larger pool that was part of a prospective high risk cohort study in the Seoul Youth Clinic. All participants made initial contact with the Seoul Youth Clinic by telephone, by website (http://www.youthclinic.org) or by a referral from a local clinic.

Intensive clinical interviews were administered to all FEP and CHR individuals by experienced psychiatrists using the Structured Clinical Interview for DSM-IV Axis I (SCID-I) disorders to identify past and current psychiatric illnesses. For FEP, inclusion criteria were being between the ages of 15 and 40, as well as 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 1 year. Seventeen FEP patients were receiving antipsychotics at the time of scanning, and of those, 2 were on antidepressants while 8 were on anxiolytics. In the CHR group, 4 patients were receiving antipsychotics, 7 were receiving antidepressants, and 6 were receiving anxiolytics.

The validated Korean version of Structured Interview of Prodromal Symptoms[25,42] was also administered to CHR participants. To be included, they had to fulfill at least 1 of the 3 established criteria for prodromal

psychosis state: present attenuated positive symptoms state, have brief intermittent psychotic symptoms below the threshold required for a DSM-IV Axis I psychotic disorder diagnosis (BIPS), or show a 30% decline in global functioning over the past year as well as have a diagnosis of schizotypal personality disorder or a first-degree relative with psychosis (genetic risk with deterioration state; GRD). The Positive and Negative Syndrome Scale (PANSS) and the Global Assessment of Functioning (GAF) were administered to both CHR and FEP groups. To estimate subjects' IQ, the Korean version of the Wechsler Adult Intelligence Scale (K-WAIS) was administered to all subjects. Exclusion criteria for CHR subjects included the following: lifetime diagnosis of a psychotic disorder, substance use disorder, neurological disease or significant head injury, evidence of a medical illness that could manifest as psychiatric symptoms, and/or intellectual disability (IQ < 70). Thirty-seven age and gender-matched HCs were also recruited through Internet advertisement. 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) and DWI data were acquired in the sagittal plane using a 3T scanner (MAGNETOM Trio Tim Syngo MR B17, 12 channel head coil). T1 images utilized 3D magnetization-prepared rapid-acquisition gradient echo (MPRAGE), and the following parameters: TR 1670 ms, TE 1.89 ms, voxel size of 1 × 0.98 × 0.98 mm,[3] 250 mm FOV, 9° flip angle and 208 slices. Diffusion weighted images were acquired using echo-planar imaging in axial plane with TR 11400 ms, TE 88ms, matrix 128 × 128, FOV 240 mm 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).

MRI Processing

T1. Cortical ROIs and thalamus ROIs in each individual's T1 space were automatically extracted as binary masks using FreeSurfer.[43] Based on the previous probabilistic tractography study by Marenco and his colleagues,[19] bilateral cortex was divided into 8 cortical ROIs as shown in figure 1A: orbitofrontal (OFC), lateral prefrontal (LPFC), medial prefrontal (MPFC), lateral temporal (LTC), medial temporal (MTC), somatomotor (SMC), and parietal (PC), and occipital cortex (OCC). Bilateral thalamus was also extracted in individual T1 space, using FreeSurfer.[43] All ROIs were visually inspected to determine whether or not there were any erroneous automatic extractions.

DWI. DWI data were preprocessed using eddy current correction, and skull removal and motion correction using FMRIB Software Library (FSL).[44] 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. FMRIB's Linear Image Registration Tool[45,46] was used for this registration with mutual information cost function and trilinear interpolation. Then for each side of the brain, FSL probabilistic tractography[41] was applied with default options (including 5000 streams per each voxel seed) using thalamus ROI as a seed and 8 cortical ROIs as targets.

Connectivity Calculation

The output from the probabilistic tractography is a set of values, one for every voxel of the seed ROI, representing the number of tractography samples that arrive at their target ROIs (out of the 5000 initially seeded). This value represents the probability of connection between the seed and the target. In order to remove the aberrant connections arising from noise and errors, the connectivity values were further routinely thresholded at 10%.[19,41] Also, in order to take into account individual variances in total connectivity between the thalamus and the whole cortex, each thalamic connectivity value to different cortices was divided by the sum of connectivity values from all 8 cortical ROIs as Marenco and his colleagues did in their study.[19] We named this "relative connectivity." In supplementary material, FA group analysis was conducted on the thalamo-OFC tract as additional information that revealed a significant group effect for FA, although the FA index was not significantly correlated to the relative connectivity.

Statistical Analysis

All statistical analyses were performed using R.[47] The demographics were tested for differences among FEP, CHR, and healthy controls using ANOVA and a test of equality of proportions. Then, the group differences in thalamo-cortical connections to 8 cortical ROIs were tested with 8 separate analyses of covariance, with age and sex as covariates, to reveal group effects. Results from the ANCOVAs were corrected for multiple comparisons using Bonferroni correction. Any significant difference in connectivity was then followed by post hoc ANCOVAs to reveal differences between each group. Correlational analyses were also performed for FEP and

CHR connectivity measures and PANSS and GAF score, using Pearson correlation.

Results

There was no significant difference in demographic background between groups. PANSS positive symptom scores were significantly different between FEP and CHR, t (27.8) = −2.41, P < .05, with FEP having higher scores than CHR (table 1). Clozapine dose equivalents were significantly higher in FEP compared to CHR, t (20.6) = −4.99, P < .001.

Results of ANCOVAs for investigating group effect on thalamo-cortcial connectivity are summarized in table 2. There was a significant group effect in the thalamo-OFC relative connectivity, F (2, 90) = 7.55, P < .001. This difference remained significant (P < .05) after correcting for multiple comparisons of the 8 connectivities using the Bonferroni correction. Post hoc comparison of the thalamo-OFC relative connectivity revealed that it was

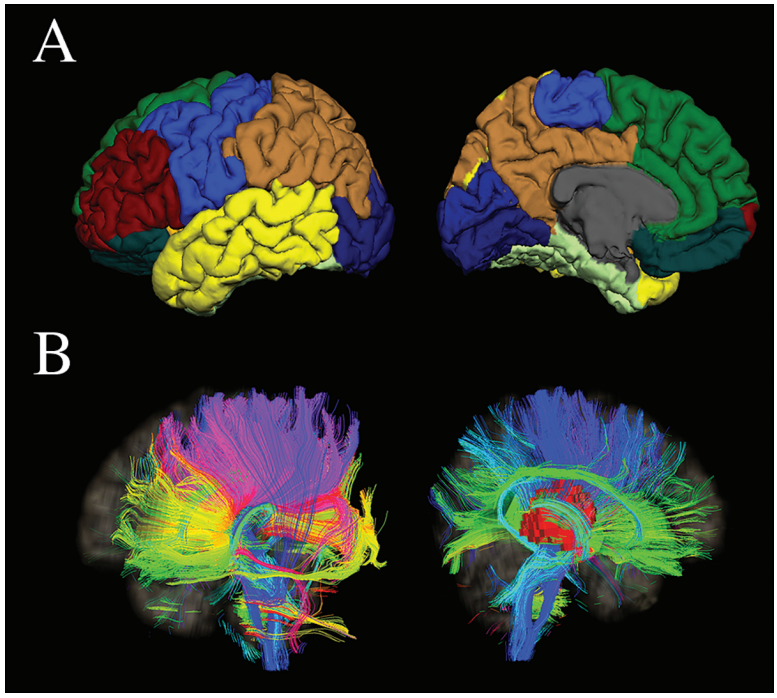

Fig. 1. Graphical presentation of cortical regions of interests, white matter tracts. (A) is color distinguished regions of interests of orbitofrontal, Dark-green; lateral prefrontal, red; medial prefrontal, green; lateral temporal, yellow; medial temporal, neon lime; somatomotor, blue; parietal, brown; occipital cortex, dark blue. (B) shows whole brain white matter tracts and the location of the thalamus (red) at the center.

Table 1. Demographic and Clinical Characteristics of the Subjects

Variable		FEP (n = 21)	CHR (n = 37)	HCs (n = 37)	χ^2, F, or T	P
Age (y)		21.8 ± 4.0	20.8 ± 2.6	21.4 ± 2.1	1.05	.36
Sex (M/F)		8/13	26/11	23/14	5.90	.05
IQ		103.3 ± 11.0	111.5 ± 12.1	111.1 ± 13.3	2.37	.10
Handedness (L/R)		20/1	33/4	34/3	0.64	.73
Education (y)		13.2 ± 2.1	13.2 ± 1.3	13.5 ± 0.9	0.64	.53
Parental SES		2.8 ± 0.8	2.9 ± 1.1	2.6 ± 0.8	0.80	.45
PANSS	Total	67.0 ± 12.8	63.9 ± 12.7		−0.90	.37
	Positive	15.8 ± 4.9	13.3 ± 2.8		−2.41	.02*
	Negative	16.4 ± 5.6	17.0 ± 5.4		0.38	.71
	General	34.8 ± 6.4	33.5 ± 7.8		−0.63	.53
Clozapine dose equivalents		344.8 ± 304.1	11.1 ± 47.6		−4.99	<.001*
Duration of treatment (d)		89 ± 116.9	21.3 ± 14.1			
GAF		49.3 ± 12.0	48.9 ± 6.5		−0.14	.89

Note: FEP, First-Episode Psychosis; CHR, Clinical high risk; HCs, Healthy Controls.
Data are given as mean ± standard deviation. *P < .05.

significantly different between groups; FEP and HCs, F (1, 54) = 11.86, P < .005, being higher in HCs and the lowest in FEP; FEP and CHR, F (1, 54) = 6.63, P < .05, being higher in CHR; HCs and CHR, F (1, 70) = 4.16, P < .05, being higher in HCs. Thalamo-OFC relative connectivity of each group is shown in figure 2A.

There was a significant group effect in the thalamo-PC relative connectivity, F (2, 90) = 3.19, P < .05, although it did not remain significant after the Bonferroni correction. This is shown in figure 2B. Post hoc comparison of the thalamo-PC relative connectivity revealed that it was significantly different between HCs and FEP, F (1, 54) = 5.65, P < .05, being higher in FEP.

The thalamo-OFC relative connectivity was statistically significantly correlated with the GAF score in CHR subjects, r = .35, P < .05, but this correlation was not statistically significant in FEP patients.

Table 2. Mean Connectivity Between Thalamus and Each Cortex and the Result of ANCOVAs Investigating Group Effect on the Connectivity With Age and Sex as the Covariates

Cortex	FEP	CHR	HCs	F	P
LPFC	0.14 ± 0.04	0.14 ± 0.04	0.14 ± 0.03	0.31	.733
LTC	0.11 ± 0.06	0.11 ± 0.04	0.11 ± 0.04	0.13	.878
MPFC	0.15 ± 0.07	0.18 ± 0.07	0.18 ± 0.07	1.13	.327
MTC	0.09 ± 0.11	0.06 ± 0.07	0.06 ± 0.07	0.95	.392
OCC	0.03 ± 0.02	0.04 ± 0.02	0.03 ± 0.01	2.86	.063
OFC	0.06 ± 0.02	0.07 ± 0.02	0.09 ± 0.03	7.66	.001*
PC	0.19 ± 0.09	0.17 ± 0.05	0.15 ± 0.03	3.19	.046*
SMC	0.23 ± 0.09	0.23 ± 0.05	0.24 ± 0.04	0.44	.646

Note: LPFC, lateral prefrontal; LTC, lateral temporal; MPFC, medial prefrontal; MTC, medial temporal; OCC, occipital cortex; OFC, orbitofrontal; PC, parietal; SMC, somatomotor.
Data are given as mean ± standard deviation. *P < .05.

Discussion

To our knowledge, this is the first study to report thalamo-cortical connectivity disruptions in CHR subjects. Our results revealed that the thalamo-OFC white matter connection was reduced not only in FEP but also in CHR compared to that of HCs. Thalamo-OFC connectivity was also highly correlated with the GAF score in CHR patients. Interestingly, the thalamo-PC connectivity presented the opposite trend of change, with the connection

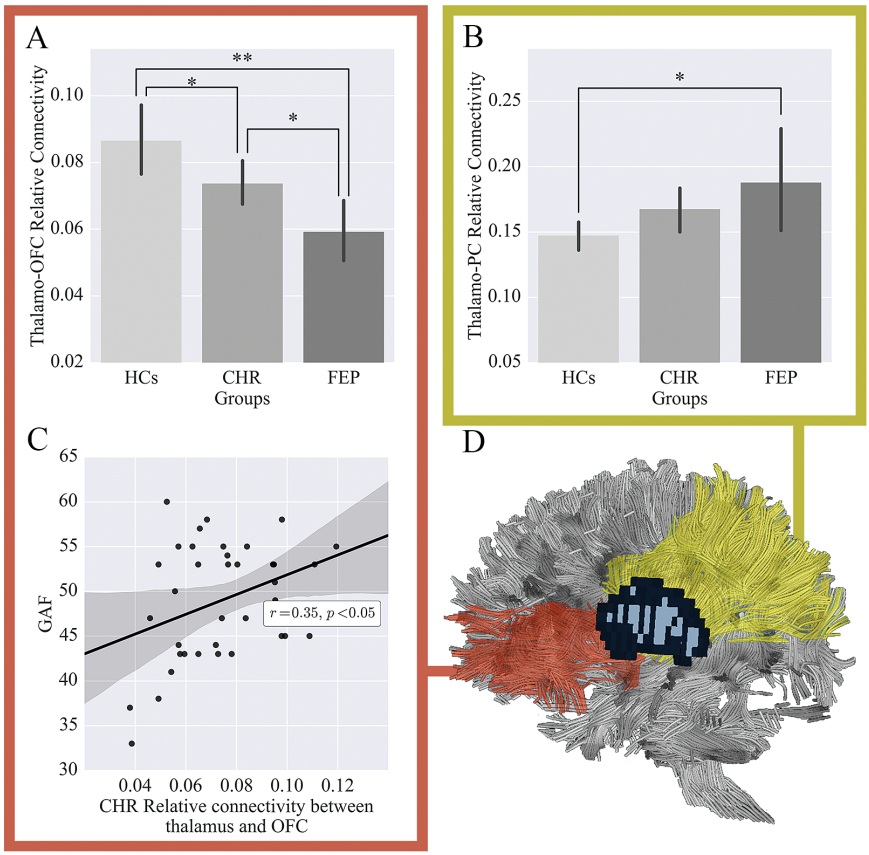

Fig. 2. The graphs show the relative connectivity (A,B) between thalamus and orbitofrontal (A), between thalamus and parietal (B) in each group. Results from post hoc analysis using ANCOVA between each group have been represented as "*", P < .05; "**", P < .005 on the graph. (C) shows significant correlation between Global Assessment of Functioning score and the relative connectivity of thalamo-orbitofrontal tracks in Clinical-high risk, r = .35, P < .05. (D) shows the tractography paths from thalamus to orbitofrontal (red) and parietal (yellow).

strongest in FEP, weakest in HCs, and intermediate in CHR.

Along with the previously reported structural abnormalities including volume, cortical thickness and sulcogyral pattern of the OFC,[48–50] the anomaly in the white matter connection between thalamus and OFC might have a significant impact on schizophrenia pathophysiology. OFC is involved in emotion processing and in various higher-order cognitive functions such as social cognition and decision making.[51] Reduced structural connection in OFC was revealed not only in FEP but also in CHR. This suggests that dysfunctions associated with OFC, such as social dysfunction, emotion dysregulation, anhedonia and etc., found not only in FEP but also in CHR, may result from a common anomaly in the thalamo-OFC connection.

While this is the first study to look at thalamo-cortical connectivity in CHR, 2 previous studies reported abnormalities in thalamo-prefrontal connections in schizophrenia.[19,20] Our results indicate that this anomaly may be detected early, even in those with subthreshold clinical symptoms for the diagnosis of schizophrenia. Small neurodevelopmental alterations from early life are speculated to cause this, because the development of the thalamo-cortical connection begins early in the embryonic stage.[52] The significant correlation between the thalamo-OFC connection and the GAF score in CHR subjects suggests that the functional decline is linked with changes in anatomical connectivity. However, there was no correlation between anatomical connectivity and GAF score in FEP. It is speculated that alterations in brain structure, including thalamo-cortical connectivity, might have occurred around the onset of illness in FEP, complicating the relationship between brain structure and functional outcome.

If CHR were assumed to convert to psychosis, the intermediate level of CHR thalamo-OFC connectivity found in our study would support the progressive nature of the thalamo-cortical white matter defect. Among the progressive structural changes found in schizophrenia,[53,54] OFC volume reduction has been associated with duration of untreated psychosis.[55,56] In a similar fashion to retrograde degeneration, abnormal progressive changes in the gray matter might result in progressive changes in white matter connections. This suggestive idea is in line with our result of intermediate reduction in thalamo-OFC connectivity in CHR. Thus early detection of change in CHR could constitute a biomarker for the early detection of psychosis. However, follow up studies of CHR individuals that convert to psychosis would provide valuable information regarding the progressive nature of the thalamo-cortical white matter connectivity.

The trend level group effect of connectivity between thalamus and PC is also worth mentioning. The thalamo-PC connection showed the opposite pattern of thalamic connectivity to that of OFC, where HCs had the lowest and patients with FEP had the highest connectivity, while the CHR connectivity was intermediate. It is possible that the connection between thalamus and PC changes to compensate for decreased connectivity between thalamus and OFC. There is a report of increased functional connectivity between thalamus and the PC region in schizophrenia,[57] which is consistent with our trend finding, and an interesting venue to explore in further studies.

It is also of note that Kim and his colleagues' reported reduction in volumes of thalamic subregions connected to orbitofrontal cortex and parietal cortices in chronic schizophrenia.[58] Our result is consistent with findings from this study in that it demonstrates anomalies in OFC and PC, adding further evidence to the body of literature, with our current study reporting alterations in thalamo-cortical connections that are present in early psychosis, even in prodromes. Increased connectivity between thalamus and PC found in our study might seem contrary to the Kim et al finding. We speculate, however, that although we cannot rule out chronicity in their subject group as a reason, we view this difference to be a result of using volumes of connectivity defined regions, rather than tractography, to indirectly represent structural connectivity. Further study in chronic schizophrenia using our method would provide the full trajectory of the thalamo-cortical connection changes in each stage of the disorder. The significant reduction in thalamo-lateral prefrontal connectivity found in Marenco's study[19] was not found in our study. In Marenco's study, the OFC and MTC were excluded from their analysis due to a low reproducibility in tractography. This problem with reproducibility may be related to using a 1.5T scanner that has higher noise than the 3T scanner that we used. More importantly, however, the difference in findings might be due to differences in the patient populations. Their patient population consisted of patients with chronic schizophrenia who were in their early 30's, whereas our patient population consisted of patients with FEP as well as patients with CHR, both groups in their early 20's. They also had a higher ratio of male subjects compared to our FEP population. These factors, taken together, likely contribute to differences reported between Marenco's and our study.

There is a report of thalamic glutamate in CHR subjects that was negatively correlated with orbitofrontal activation during verbal fluency task.[59] This aberrant activation and abnormal glutamate concentration might be the result of inefficient communication and feedback between frontal cortex and thalamus, which is consistent with our results. Further studies that investigate the relationship between functional and anatomical thalamo-cortical connection and their feedback vis a vis neurotransmitters, are needed to understand the underlying mechanisms.

Limitations

Many of the FEP patients and a few of the CHR subjects were on antipsychotics at the time of the scan. Although

the effects are relatively small in FEP subjects compared to that of chronic schizophrenics, antipsychotics and antidepressants are reported to have a subtle but measurable impact on generalized and specific brain tissues.[60,61] However, there was no significant correlation between the thalamo-cortical connectivity and clozapine equivalent of subjects with antipsychotics.

A single B_0 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. 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. Although the variability in probabilistic tractography is not particularly high in OFC, as shown in table 2, relatively higher signal distortion in DWI near the OFC region 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. Nonetheless, since the variability was similar to other thalamus-cortical connections, we think that such consistency in standard deviations could imply that thalamo-OFC connections were consistent across the 8 thalamus-cortical connections, although a reproducibility measure is required in future studies. Another possible limitation is that we did not apply any exclusion masks in the connectivity estimation, as we were interested in the white matter fiber bundles from thalamus radiating into cortex. However, we note that probabilistic tractography thresholds takes into account erroneous fibers in a manner similar to that of exclusion criteria when using a streamline tractography approach. Thus we, as well as others using probabilistic tractography for thalamo-cortical connection investigation,[19,58,62,63] find the use of exclusion ROI unnecessary.

Conclusion

Reduced thalamo-OFC white matter connections were evident not only in FEP but also in CHR, suggesting that there are early white matter changes even prior to the onset of psychosis. Further, GAF score in CHR subjects was shown to correlate with thalamo-OFC connectivity. This suggests that the thalamo-cortical connectivity, especially thalamo-OFC white matter connectivity, may be an important biomarker for psychosis risk that can be used for early detection and possibly early intervention.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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