Thalamocortical Disconnection in the Orbitofrontal Region Associated With Cortical Thinning in Schizophrenia

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Context: Dysfunction of the thalamocortical pathway has been proposed as a putative underlying pathology of schizophrenia. Although the mechanisms involved remain unclear, postmortem studies suggest the involvement of altered neural projections from the thalamus to layers within the prefrontal cortex.

Objectives: To investigate thalamocortical connectivity in schizophrenia and to examine its possible association with cortical thinning in vivo.

Design: Case-control cross-sectional study.

Setting: Department of Psychiatry at Kyoto University Hospital, Japan.

Patients and Other Participants: A total of 37 patients with schizophrenia and 36 age-, sex-, and education-matched healthy controls recruited from the local community underwent diffusion-weighted imaging and T1-weighted 3-dimensional magnetic resonance imaging.

Main Outcome Measures: Probabilistic tractography was performed to investigate thalamocortical pathways. Group differences in mean fractional anisotropy (FA) values were examined in the entire thalamocortical pathway, the thalamolateral prefrontal pathway, the thalamomedial prefrontal pathway, and the thalamorbitofrontal pathway. Surface-based analysis was performed to investigate cortical thickness, and the correlation between FA values and cortical thickness was examined.

Results: The patient group exhibited reduced FA values within the right thalamo-orbitofrontal pathway (P < .05 for the 8 group comparisons of FA, Bonferroni correction). In the patient group only, the mean FA value for this pathway was positively correlated with thickness of the right frontal polar and lateral orbitofrontal cortices (P < .05, clusterwise correction).

Conclusions: These results suggest that, in schizophrenia, regional thalamocortical white matter pathology is specifically associated with cortical pathology in regions where fibers connect.


Magnetic resonance imaging (MRI) studies have revealed anatomical alterations in multiple brain regions associated with schizophrenia. Gray matter (GM) reductions in cortical and subcortical areas (such as the orbitofrontal and other prefrontal cortices, the superior temporal gyrus, medial temporal lobe structures, thalamus, and basal ganglia) have been reported. Moreover, recent studies on schizophrenia using a surface-based approach have reported reduced cortical thickness within widespread regions, including the prefrontal and temporal cortices. Alterations of cortical thickness might reflect underlying pathological abnormalities such as reduced neuronal density, as revealed in postmortem studies of schizophrenia.
Diffusion tensor imaging techniques have recently been developed to provide information about white matter (WM) tracts and their organization based on water diffusion. Fractional anisotropy (FA) is the most commonly used index, and FA reduction implies decreased WM tract integrity. Diffusion tensor imaging studies on schizophrenia have reported FA reductions in several areas, including the frontotemporal connections, prefrontal WM, and the internal capsule. These findings suggest that WM abnormalities may provide an anatomical substrate for the “disconnection hypothesis” of schizophrenia. Moreover, diffusion tractography techniques enabled us to examine specific fiber connections, and several tractography studies have provided evidence for disrupted connectivity of thalamocortical pathways, especially within the prefrontal regions in schizophrenia. The prefrontal cortex can be divided according to its various functions, and previous studies have suggested that thalamocortical integrity of the lateral, medial, and orbitofrontal regions may be disrupted in schizophrenia.

Furthermore, recent studies have provided evidence that GM reduction and WM disruption in schizophrenia are connected, suggesting that WM pathology is related to GM pathology. To our knowledge, however, no study has investigated the relationship between impaired thalamocortical pathway integrity and cortical thickness reduction in schizophrenia. Investigating the interrelationship between WM and GM pathology in neuroimaging studies may be particularly valuable because some of the most rigorous postmortem studies have suggested that the thalamo-prefrontal projection to a specific cortical layer constitutes a possible neuropathological mechanism underlying schizophrenia.

The present study sought to examine the association between thalamocortical connectivity and cortical thickness in schizophrenia by combining probabilistic tractography and a surface-based approach. We hypothesized that the prefrontal thalamocortical pathways would exhibit reduced FA in schizophrenia and that this reduction would be positively correlated with cortical thinning within the regions where the thalamic fibers connect.

**METHODS**

**PARTICIPANTS**

The schizophrenia group consisted of 37 patients who were referred to the Department of Psychiatry at the Kyoto University Hospital in Japan. Each patient fulfilled the criteria for schizophrenia based on the Structural Clinical Interview for DSM-IV. All patients were receiving antipsychotic medication. The Positive and Negative Syndrome Scale (PANSS) was used to assess the severity of clinical symptoms. The 5-factor model was used to calculate the PANSS subscales (negative, positive, activation, depressive, and cognitive factors). Smoking history was also examined and was used to test the effects of smoking on thalamocortical pathway alterations, as detailed in the eAppendix.

The comparison group consisted of 36 healthy individuals recruited from the local community, via referrals and advertisements, who were matched to the schizophrenia group by age, sex, educational level, and predicted IQ level. Predicted IQ was measured by the Japanese Version of the National Adult Reading Test short form, which is considered to reflect the premorbid IQ of patients with schizophrenia. They were also evaluated with the Structural Clinical Interview for DSM-IV. None of the control participants had a history of psychiatric disease or had any first-degree relatives with a history of psychotic episodes. The patients and controls were all physically healthy at the time of scanning. None had a history of neurological injury or disease, severe medical diseases, or substance abuse that could affect brain function.

Our study was approved by the Committee on Medical Ethics of Kyoto University and was conducted in accordance with the Code of Ethics of the World Medical Association. After being given a complete description of the study, each participant provided written informed consent.

**MRI ACQUISITION**

Diffusion-weighted data were acquired using single-shot spin-echo echo-planar sequences and structural MRI data using 3-dimensional magnetization-prepared rapid gradient echo (3D-MPRAGE) sequences, on a 3.0-T MRI unit (Trios; Siemens) with a 40-mT/m gradient and a receiver-only 8-channel phased-array head coil. Parameters for the diffusion-weighted data were as follows: echo time, 96 milliseconds; repetition time, 10 500 milliseconds; 96 × 96 matrix; field of view, 192 × 192 mm; 70 contiguous axial slices of 2.0 mm thickness; 81 noncollinear motion-probing gradients; and b = 1500 s/mm². The b=0 images were scanned before every 9 diffusion-weighted images, thus consisting of 90 volumes in total. Parameters for the 3D-MPRAGE imaging were as follows: echo time, 4.38 milliseconds; repetition time, 2000 milliseconds; inversion time, 990 milliseconds; field of view, 225 × 240 mm; 240 × 256 matrix; resolution, 0.9375 × 0.9375 × 1.0 mm³; and 208 total axial sections without intersection gaps. The MRI images were assessed for quality, as detailed in the eAppendix.

**DATA PROCESSING**

**Diffusion-Weighted Data Preprocessing**

All data processing was performed using programs in the FMRIB Software Library (FSL) version 4.1.6 (http://www.fmrib.ox.ac.uk/fsl). Source data were corrected for eddy currents and head motion by registering all data to the first b=0 image, with affine transformation. The FA maps were calculated using the DTIFIT program implemented in FSL. For probabilistic tractography, probability distributions on 2 fiber directions were modeled at each voxel using FSL’s BedpostX program, based on a multifiber diffusion model. For voxelwise statistical analysis, tract-based spatial statistics version 1.2 was used (eAppendix).

**Structural MRI Data Preprocessing**

The 3D-MPRAGE images were preprocessed using the FreeSurfer software package version 5.0.0 (http://surfer.nmr.mgh.harvard.edu). In brief, the processing stream included a Talairach transformation of each subject’s native brain, removal of nonbrain tissue, volumetric subcortical labeling, and surface-based segmentation of GM/WM tissue (for details of labeling and segmentation processes, see the eAppendix). Cortical thickness was computed as the shortest distance between the pial surface and the GM/WM boundary at each point across the cortical mantle. This method has been previously validated via histological and manual measurements in schizophrenia. The global mean cortical thickness for each subject was computed...
by averaging the cortical thickness at each vertex—right and left hemispheres separately. The regional thickness value at each vertex for each subject was mapped to the surface of an average brain template (http://surfer.nmr.mgh.harvard.edu/fswiki/FsAverage). The cortical map of each subject was smoothed with a Gaussian kernel of 10-mm full-width at half-maximum.

FIBER TRACKING

Probabilistic tractography from the seed region (thalamus) to the target cortical regions (the entire cortical region, the lateral prefrontal cortex, the medial prefrontal cortex, and the orbitofrontal cortex) was performed using FSL’s ProtrackX program, separately for each hemisphere. The thalamus was extracted from the automated segmentation in FreeSurfer. Targeted cortical regions were extracted from the surface-based procedure in FreeSurfer, based on cortical parcellation details of this procedure are described in the eAppendix).

To investigate only direct pathways from the thalamus to the targeted cortices, an exclusion mask was also created using an automated procedure in FreeSurfer. The exclusion mask consisted of all other subcortical regions, nonbrain regions, the brainstem, cortical regions except the targeted cortex, and all brain regions in the other hemisphere. In the initial fiber-tracking trials, extraneous fibers were detected through the WM region encompassing the subcallosal area. In addition, the initial trial from the thalamus to the lateral prefrontal, the medial prefrontal, and the orbitofrontal cortices detected extraneous fibers that went through the WM region encompassing the inferior segment of the circular sulcus of the insula (ie, uncinate bundles). Such extraneous fibers, which do not go through the internal capsule, were eliminated by adding these regions into the exclusion mask.

These masks were transformed from each subject’s 3D-MPRAGE space to the diffusion space by applying the rigid-body transformation matrix, which was calculated by use of FSL’s FLIRT program. To check the quality of the transformation, we visually inspected each mask in the diffusion space for each subject and confirmed that there were no gross transformation errors (eFigures 1, 2, 3, 4, and 5). Probabilistic tractography was performed in the diffusion space, and streamlined samples were traced through the probabilistic distributions of fiber direction, with 5000 iterations per thalamic seed voxel (curvature thresholds, 0.73). Each tract was created in the 3D-MPRAGE space and “thresholded” to exclude voxels in which the streamlined sample count corresponded to the lower 5% of the outer tail of the histogram, to eliminate extraneous tracking results (Figure 1). The thresholded tracts were transformed back into diffusion space, and the mean FA value of each tract was calculated.

STATISTICAL ANALYSES

Whole-Brain Analyses

First, the general linear model was implemented at each vertex in the whole brain, separately for each hemisphere, to identify the regions in which patients showed significant differences in cortical thickness relative to controls, using FreeSurfer’s mri_glmfit (http://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/GroupAnalysis). The effects of age and sex were regressed out. To correct for multiple comparisons, a Monte Carlo simulation procedure was used (2-tailed): Clusters were formed by thresholding at $P < .05$; then each cluster was tested for significance at $P < .05$ (ie, $P < .05$; corrected cluster threshold, $P < .05$).

Second, voxelwise permutation-based nonparametric inference was performed on skeletonized FA data using the FSL Randomise version 2.5. Group comparisons were performed by means of an analysis of covariance design, with age and sex as nuisance covariates. Both covariates were centered (de-meaned) before being fed into the design matrix, and they were pre-removed from the data before implementing the permutation tests. Both control-patient and patient-control contrasts were tested using 10 000 permutations. The statistical threshold was set at $P < .05$, correcting for multiple comparisons by means of threshold-free cluster enhancement.

FA Values for Each Thalamocortical Pathway

Two independent-sample $t$ tests were used to examine group differences of FA values for each thalamocortical pathway. To reduce the risk of type I error, a Bonferroni correction was applied to the 8 group comparisons of FA (the entire thalamocortical, thalamolateral prefrontal, thalamomedial prefrontal, and thalamo-orbitofrontal pathways of each hemisphere). The statistical threshold was set at $P < .05$ for the 8 group comparisons of FA. In the patient group, correlations between each FA value and duration of illness (in years), dose of medication (haloperidol-equivalent daily doses), and PANSS subscales were also examined using Pearson correlation coefficients. Data were analyzed using SPSS version 19.0 (SPSS Inc), and statistical significance was defined as $P < .05$ (2-tailed).

Correlational Analyses Between Global WM and Global GM

Two independent-sample $t$ tests were conducted to examine the group differences in global mean cortical thickness for each hemisphere. To reduce the risk of type I error, a Bonferroni correction was applied to the 2 group comparisons (for each hemi-
sphere), and the statistical threshold was set at $P < .05$ for the 2 group comparisons of global mean cortical thickness. In both groups, correlations between the FA of the entire thalamocortical pathway and global cortical thickness were examined, separately for each hemisphere. Data were analyzed using SPSS version 19.0, and statistical significance level was set at $P < .05$ (2-tailed).

Correlational Analyses Between Regional WM and Regional GM

In cases in which a significant group difference in FA was found for a certain pathway, a vertexwise general linear model analysis was performed independently in both groups to examine brain regions that showed significant correlations between the FA of this pathway and cortical thickness at each vertex in the same hemisphere, using FreeSurfer's mri_glmfit. The effects of age and sex were regressed out in these analyses. To correct for multiple comparisons, a Monte Carlo simulation procedure was used ($P < .05$; corrected cluster threshold, $P < .05$; 2-tailed).

Further Analyses of Regional Specificity of WM and GM

In the patient group, a group-based thalamocortical map was created to visually examine whether the mentioned cortical regions were connected with the WM fiber regions. The pathways of all patients were transformed to the Montreal Neurological Institute template, merged, and examined using FSL's FLIRT program. Next, the significant cortical regions were automatically mapped onto each subject's brain, the mean thickness of each region was calculated for each subject in both groups, and correlational analyses were performed to further elucidate the relation between FA and cortical thickness. In the patient group, we further investigated correlations between thickness in these regions and global thickness for the same hemisphere, to examine whether the effect of FA on cortical thickness was regionspecific. Partial correlational analyses were also performed, controlling for global cortical thickness and for demographic and clinical variables. In addition, group comparison of mean thickness of each region was performed using 2-sample t tests. SPSS version 19.0 was used for these analyses, and statistical significance was defined as $P < .05$ (2-tailed).

RESULTS

DEMOGRAPHIC DATA

The demographic and clinical data are shown in Table 1. Many patients were in the chronic stages, with mild symptom severity.

WHOLE-BRAIN ANALYSES

In multiple regions (including the bilateral superior frontal cortex, the left middle and inferior frontal cortices, the bilateral medial orbitofrontal cortex, the right lateral orbitofrontal cortex, the left frontal pole, and the bilateral insula), the patient group exhibited reduced cortical thickness compared with the control group (Figure 2A). There was no significant region of thicker cortex in the patients. Patients exhibited a widespread cluster of significant reductions in FA, including in the corpus callosum, the bilateral superior and inferior longitudinal fasciculi, the

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient Group (n = 37)</th>
<th>Control Group (n = 36)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>35.0 (9.9)</td>
<td>33.3 (12.2)</td>
<td>-0.66</td>
</tr>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Handedness, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>36</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Education, mean (SD), y</td>
<td>13.4 (2.1)</td>
<td>14.0 (2.4)</td>
<td>1.19</td>
</tr>
<tr>
<td>Predicted IQ, mean (SD)</td>
<td>102.4 (9.4)</td>
<td>106.1 (8.7)</td>
<td>1.76</td>
</tr>
<tr>
<td>Smoking history, No.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>20</td>
<td>19</td>
<td>d</td>
</tr>
<tr>
<td>Smoker</td>
<td>17</td>
<td>6</td>
<td>d</td>
</tr>
<tr>
<td>Duration of illness, mean (SD), y</td>
<td>11.8 (10.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug (haloperidol equivalent), mean (SD), mg/d</td>
<td>10.4 (7.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PANSS factor, mean (SD), subscale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>16.3 (6.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>11.4 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activation</td>
<td>7.9 (2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive</td>
<td>8.5 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive</td>
<td>5.8 (1.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PANSS, Positive and Negative Syndrome Scale.

a Two-tailed t test ($\alpha = .05$).
b Two-tailed $\chi^2$ test ($\alpha = .05$).
c Measured by the Japanese Version of the National Adult Reading Test short form.29,30

d Control data available for 25 participants, including the subjects who never smoked and the smokers.

All patients were receiving antipsychotic medication (typical [n = 2], atypical [n = 29], and typical and atypical [n = 6]). Haloperidol equivalents were calculated according to the practice guidelines for the treatment of patients with schizophrenia.38,39
bilateral inferior fronto-occipital fasciculus, the right cingulum, the right anterior limb, the posterior limb, and the bilateral retrolenticular part of the internal capsule, the right external capsule, the right cerebral peduncle, the bilateral corona radiata, and the bilateral corticospinal tracts (Figure 2B). No region in patients exhibited a significant increase in FA compared with controls.

**FA OF EACH THALAMOCORTICAL PATHWAY**

There was no group difference in FA in the right or left entire thalamocortical pathway. Among the regional thalamocortical pathways, the patient group demonstrated significantly decreased FA of the right thalamo-orbitofrontal pathway. No other group difference in FA values was found (Table 2). In the patient group, no significant correlation was found between the FA value of each pathway and the duration of illness, dose of medication, or PANSS subscales.

**CORRELATIONAL ANALYSES BETWEEN THALAMOCORTICAL INTEGRITY AND CORTICAL THICKNESS**

The global mean cortical thickness was significantly reduced in the patient group for both hemispheres (Table 3). There was no significant correlation between the FA of the entire thalamocortical pathway and the global cortical thickness for each hemisphere in the 2 groups. In the regional correlational analyses, the vertexwise correlational analysis revealed that the FA of the right thalamo-orbitofrontal pathway in the patients was positively correlated with the cortical thickness in the right frontal polar and right lateral orbitofrontal regions (Figure 3A; Table 4). No significant correlation was found in the controls between FA in this pathway and cortical thickness.

**FURTHER ANALYSES OF REGIONAL SPECIFICITY OF WM AND GM**

The right thalamo-orbitofrontal pathway of each patient was transformed into the Montreal Neurological Institute template and merged. The result appears in Figure 3B together with the right thalamus and the 2 cortical regions already mentioned.

Next, the mean thickness within these 2 cortical regions was calculated. Scatterplots of mean cortical thickness against FA for these regions are shown in Figure 3C. The patient group showed a significant correlation between the FA of the right thalamo-orbitofrontal pathway and the thickness in both the right frontal pole ($r_{35} = 0.493, P = .002$) and the right lateral orbitofrontal cortex ($r_{35} = 0.531, P = .001$), but not in other regions within the right hemisphere. However, in the controls, no significant correlations were found between FA and thickness within either the right frontal pole ($r_{34} = 0.129$, $P = .55$).

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**Table 2. Group Comparison of FA for Each Thalamocortical Pathway**

<table>
<thead>
<tr>
<th>Pathway</th>
<th>FA Value, Mean (SD)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient Group (n = 37)</td>
<td>Control Group (n = 36)</td>
</tr>
<tr>
<td>Entire R thalamocortical region</td>
<td>0.440 (0.023)</td>
<td>0.441 (0.022)</td>
</tr>
<tr>
<td>Entire L thalamocortical region</td>
<td>0.433 (0.025)</td>
<td>0.436 (0.024)</td>
</tr>
<tr>
<td>R thalamolateral prefrontal region</td>
<td>0.368 (0.034)</td>
<td>0.365 (0.023)</td>
</tr>
<tr>
<td>L thalamolateral prefrontal region</td>
<td>0.348 (0.030)</td>
<td>0.348 (0.037)</td>
</tr>
<tr>
<td>R thalamomedial prefrontal region</td>
<td>0.435 (0.024)</td>
<td>0.436 (0.023)</td>
</tr>
<tr>
<td>L thalamomedial prefrontal region</td>
<td>0.432 (0.027)</td>
<td>0.435 (0.021)</td>
</tr>
<tr>
<td>R thalamo-orbitofrontal region</td>
<td>0.320 (0.033)</td>
<td>0.340 (0.025)</td>
</tr>
<tr>
<td>L thalamo-orbitofrontal region</td>
<td>0.321 (0.039)</td>
<td>0.334 (0.030)</td>
</tr>
</tbody>
</table>

Abbreviations: FA, fractional anisotropy; L, left; R, right.

a $P < .05$ for the 8 group comparisons of FA (Bonferroni correction).
or the right lateral orbitofrontal cortex ($r_{34} = 0.200, P = .24$) (Figure 3C).

In the patient group, the global cortical thickness for the right hemisphere was significantly correlated with thickness for both the right frontal pole ($r_{35} = 0.462, P = .004$) and the right lateral orbitofrontal cortex ($r_{35} = 0.700, P < .001$). However, the FA-thickness correlations for the 2 regions were significant after controlling for the global thickness and for demographic and clinical variables (Table 5). In addition, the patient group exhibited significant cortical thinning within these regions compared with the controls (Table 6).

To test for FA-thickness correlations in the other thalamo-prefrontal pathways (ie, the left orbitofrontal pathway, the right and left thalamolateral prefrontal pathways, and the right and left thalamomedial prefrontal pathways), post hoc analyses were performed for the patients, by applying the same methods. These analyses revealed no significant correlation between FA and cortical thinning.

**COMMENT**

To our knowledge, this is the first study to demonstrate an association between disrupted thalamocortical connectivity and reduced cortical thickness in schizophre-
fibers, in accordance with previous findings.15,16 The tract-based spatial statistics analysis revealed reduced WM integrity in widespread regions containing thalamo-orbitofrontal fibers. This discrepancy may be due to the relatively small sample size of the present study compared with previous results. Among the thalamo-prefrontal pathways, alterations to a pathway in the orbitofrontal circuitry20,41 were found between the FA of other thalamo-prefrontal pathways and the cortical thinning in the patients. The group comparison of FA for each thalamocortical region and the insula in schizophrenia, consistent with previous studies.11,13 In contrast to previous reports, we did not find significant cortical thinning in other regions, such as the temporal cortex. This discrepancy may be due to the relatively small sample size of the present study compared with previous reports or differences in the characteristics of subjects. The group-based map indicates that the right thalamo-orbitofrontal pathway is closely connected to these cortical regions, and no significant correlation was found between the FA of other thalamo-prefrontal pathways and the cortical thinning in the patients.

The present study characterized the thalamo-prefrontal pathology in vivo in schizophrenia. The present results are in line with postmortem studies suggesting alterations in thalamo-prefrontal circuitry in schizophrenia.4,5 In addition, our findings are in accordance with an influential hypothesis1,40 suggesting that pathology for circuitry, including the thalamo-prefrontal pathway, may mediate certain aspects of symptomatology and cognitive dysfunction in schizophrenia.

The group comparison of FA for each thalamocortical pathway revealed significantly reduced connectivity in the right thalamo-orbitofrontal pathway in patients with schizophrenia. This result is consistent with past studies demonstrating a disrupted thalamo-orbitofrontal pathway in schizophrenia.10,15 Our additional analysis of smoking effects suggests that this structural change is not attributable to smoking. Although there was a trend toward decreased FA in the left thalamo-orbitofrontal pathway in patients, the difference did not reach statistical significance. This may have been due to the moderate sample size in the present study.

The results of the vertexwise correlational analyses constitute the major novel findings of the present study. For the patients, reduced right thalamo-orbitofrontal WM integrity was correlated with cortical thinning in the right lateral orbitofrontal region and the right frontal pole. Both of these WM-thickness correlations are likely to reflect regional-specific associations rather than global alterations because (1) the global thalamocortical integrity was not significantly correlated with global cortical thickness, (2) both of these WM-thickness correlations remained significant after controlling for global thickness, (3) the group-based map indicates that the right thalamo-orbitofrontal fibers are closely connected to these cortical regions, and (4) no significant correlation was found between the FA of other thalamo-prefrontal pathways and the cortical thinning in the patients.

### Table 5. Results of Partial Correlational Analyses Between FA for the Right Thalamo-Orbitofrontal Pathway and Thickness of the Right Frontal Polar and Orbitofrontal Cortices in the Patient Group

<table>
<thead>
<tr>
<th>Control Variables</th>
<th>FA (R Orbitofrontal Pathway)–Thickness (R Frontal Pole) Correlation</th>
<th>FA (R Orbitofrontal Pathway)–Thickness (R Orbitofrontal Cortex) Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pearson r</td>
<td>df</td>
</tr>
<tr>
<td>RH cortical thickness</td>
<td>0.430</td>
<td>31</td>
</tr>
<tr>
<td>RH cortical thickness, age, sex, education, JART</td>
<td>0.464</td>
<td>30</td>
</tr>
<tr>
<td>RH cortical thickness, age, sex, education, JART, duration of illness</td>
<td>0.492</td>
<td>29</td>
</tr>
<tr>
<td>RH cortical thickness, age, sex, education, JART, duration of illness, medication</td>
<td>0.514</td>
<td>28</td>
</tr>
<tr>
<td>RH cortical thickness, age, sex, education, JART, duration of illness, medication, PANSS subscales, negative, positive, activation, depressive, and cognitive factors</td>
<td>0.493</td>
<td>23</td>
</tr>
</tbody>
</table>

Abbreviations: FA, fractional anisotropy; JART, Japanese Version of the National Adult Reading Test; PANSS, Positive and Negative Syndrome Scale; R, right; RH, right hemisphere.

### Table 6. Group Comparison of Cortical Thickness of Regions That Showed Significant Positive Correlations With FA for the Right Orbitofrontal Pathway in Patient Group

<table>
<thead>
<tr>
<th>Region</th>
<th>Cortical Thickness, Mean (SD), mm</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Group (n = 37)</td>
<td>Control Group (n = 36)</td>
<td>t, Value</td>
</tr>
<tr>
<td>R frontal pole</td>
<td>2.271 (0.196)</td>
<td>2.371 (0.132)</td>
</tr>
<tr>
<td>R lateral orbitofrontal</td>
<td>2.843 (0.232)</td>
<td>2.946 (0.154)</td>
</tr>
</tbody>
</table>

Abbreviation: FA, fractional anisotropy; R, right.

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and Gold\textsuperscript{49} demonstrated that patients with schizophrenia exhibit deficits in reinforcement learning compared with healthy controls. Nakamura et al\textsuperscript{44} established the association between orbitofrontal volume deficit and formal thought disorder in schizophrenia. Takayanagi et al\textsuperscript{45} reported volume reduction and abnormal sulcogyral patterns of the orbitofrontal cortex in first-episode schizophrenia, suggesting a neurodevelopmental or neurodegenerative process in this region at a very early stage of the illness. Our findings suggest that these pathological alterations in schizophrenia are related not only to the orbitofrontal cortex, per se, but also to circuitry involving the thalamus and prefrontal cortex. Further work is needed to determine the extent to which the circuitry contributes to these processes.

Our results also revealed a WM-thickness correlation in the frontal pole adjacent to the orbitofrontal cortex. The orbital and medial prefrontal cortices are grouped into the orbital network and the medial network, and a number of pathways are thought to provide communication between them.\textsuperscript{60,61} Because the frontal pole is considered to be involved in the medial network, the WM-thickness correlation in the frontal pole might indicate abnormalities in these communicative pathways, as well as alterations in direct pathways from the thalamus.

To date, a number of studies have reported neuropathological abnormalities in schizophrenia that are thought to explain macroscopic findings of GM alterations, particularly a reduction in neuronal size in regional cortical GM, lamina-specific deficits in parvalbumin-immunoreactive varicosities, a decrease of presynaptic markers, and decreased dendritic spine density in layer 3 pyramidal neurons.\textsuperscript{14} On the other hand, recent neuropathological and neurogenetic studies have indicated WM-related alterations such as myelin-related changes and disrupted myelination gene expression in schizophrenia.\textsuperscript{16}

Previous studies have suggested putative pathological mechanisms linking these GM and WM changes in schizophrenia. Oligodendrocyte loss and dysmyelination have been suggested to lead to neuronal deficits such as alterations in synaptic function, which is maintained by glial cells.\textsuperscript{68,69} In addition, disruption of myelination of axons may be associated with regression of synapses that are normally formed by these axons.\textsuperscript{50} The present finding of correlations between GM and WM alterations may reflect the involvement of such pathological processes in this disorder.

One explanation for such a coupled mechanism in the thalamo-prefrontal circuit is the existence of altered projections from the thalamus to the middle layers of the prefrontal cortex in schizophrenia.\textsuperscript{50,51} This change might reflect a pathological process that includes regional myelin-related alterations and synaptic changes in the prefrontal cortex.

Other possible explanations should be taken into account. First, such a coupled mechanism may be caused by thalamic neuronal loss, which leads to a reduced number of thalamic-prefrontal fibers and targeted prefrontal neurons. As for the thalamic pathology, previous neuroimaging and postmortem studies have yielded mixed results regarding volume and neuronal changes in the thalamic nuclei, including the mediodorsal nucleus.\textsuperscript{32-35} Second, the correlation might reflect other MRI-sensitive microstructural changes such as the packing of fibers or neurite ramification. The present study alone cannot distinguish among these possibilities because of the differences in sensitivity between imaging and histopathology. Third, the apparent correlation might reflect the heterogeneity of patients (comprising several subgroups of patients or patients at different stages with different pathological alterations).

We did not detect a significant association between the FA value for each pathway and duration of illness, dose of medication, or clinical symptoms. In line with our results, Kito et al\textsuperscript{21} found no significant correlation between the FA for the thalamocortical pathway and antipsychotic dosage, and Marenco et al\textsuperscript{22} reported no significant correlation between connectivity for the thalamo-lateral prefrontal pathway and medication dosage or duration of illness. One possible explanation is that the alteration in the thalamocortical pathway is not a “state” marker of schizophrenia but rather a “trait” marker. These alterations may partly reflect neuropathological GM and WM alterations prior to or around the onset of illness.\textsuperscript{56-59} Unfortunately, our cross-sectional study does not allow a clear conclusion to be drawn as to how these GM and WM changes emerged in the course of development or whether the changes are progressive.\textsuperscript{55}

In contrast to our results, Kim et al\textsuperscript{10} demonstrated a significant negative correlation between thalamo-prefrontal WM connectivity and severity of positive symptoms. An explanation for this inconsistency may be the mild symptom severity of the patients in our study.

Several limitations involved in the present study should be considered. First, to image thalamocortical fibers, tractography was performed from the thalamus to the cerebral cortex. However, this tractography technique is not sensitive to the directionality of the neuronal fibers, and our fibers are considered to contain both thalamocortical and corticothalamic fibers. Although earlier neuropathological studies indicated a disruption in the thalamocortical fibers rather than in the corticothalamic fibers, our results should be interpreted with caution. Moreover, we should be careful when interpreting the results of correlational analyses of the entire thalamocortical pathway because even though our multifiber model for probabilistic tractography is robust to fiber crossing,\textsuperscript{23} the paths from the thalamus to other regions (such as the inferior and medial temporal lobes and the lateral motor cortex) are relatively difficult to depict compared with other pathways. This is due to the existence of large tracts that intersect the thalamocortical pathways in these regions. Second, because all the patients were receiving medication, we were unable to eliminate the effects of medication. Third, although a correlation between regional FA and cortical thickness was found only in the patients, this may have been due to the greater variability in the patient group, as shown in Figure 3C. Fourth, we did not perform B0 unwarping because we did not obtain field-map images for all the subjects. Although we carefully checked every cortical and subcortical mask and tract, the orbitofrontal region is subject to susceptibility artifacts, and this has to be carefully considered with regard to its impact.
on the study results. Fifth, we did not include any functional measures corresponding to the prefrontal cortical regions. Finally, the patients included in our study had relatively mild and stable symptoms; therefore, they may not be representative of the general population of patients with schizophrenia. Future research with a more widely distributed sample population will be required to test the generalizability of these results.

In conclusion, the present results revealed that schizophrenia was associated with reduced thalamocortical connectivity in the right orbitofrontal region. Fractional anisotropy in this pathway was correlated with thinning of the right frontal polar cortex and the right lateral orbitofrontal cortex. These findings suggest that, in schizophrenia, regional thalamocortical WM pathology is specifically associated with cortical pathology in regions where the fibers connect.

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