Article

Thalamocortical Dysconnectivity in Schizophrenia

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Objective: The thalamus and cerebral cortex are connected via topographically organized, reciprocal connections. Previous studies have revealed thalamic abnormalities in schizophrenia; however, it is not known whether thalamocortical networks are differentially affected in the disorder. To explore this possibility, the authors examined functional connectivity in intrinsic low-frequency blood-oxygen-level-dependent (BOLD) signal fluctuations between major divisions of the cortex and thalamus using resting-state functional MRI (fMRI).

Method: Seventy-seven healthy subjects and 62 patients with schizophrenia underwent resting-state fMRI. To identify functional subdivisions of the thalamus, the authors parceled the cortex into six regions of interest: the prefrontal cortex, motor cortex/supplementary motor area, somatosensory cortex, temporal lobe, posterior parietal cortex, and occipital lobe. Mean BOLD time series were extracted for each region of interest and entered into a seed-based functional connectivity analysis.

Results: Consistent with previous reports, activity in distinct cortical areas correlated with specific, largely nonoverlapping regions of the thalamus in both healthy comparison subjects and schizophrenia patients. Direct comparison between groups revealed reduced prefrontal-thalamic connectivity and increased motor/somatosensory-thalamic connectivity in schizophrenia. The changes in connectivity were unrelated to local gray matter content within the thalamus and to antipsychotic medication dosage. No differences were observed in temporal, posterior parietal, or occipital cortex connectivity with the thalamus.

Conclusions: These findings establish differential abnormalities of thalamocortical networks in schizophrenia. The etiology of schizophrenia may disrupt the development of prefrontal-thalamic connectivity and refinement of somatomotor connectivity with the thalamus that occurs during brain maturation.

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Several neurobiological theories of schizophrenia hypothesize that the pathophysiology of the disorder includes abnormal functional interactions between the cortex and thalamus (1–3). Thalamocortical networks are organized topographically into parallel pathways linking distinct cortical areas to specific thalamic nuclei (4, 5). For example, the prefrontal cortex is linked to anterior and dorsomedial areas of the thalamus, whereas motor and somatosensory cortices connect to ventral lateral and ventral posterior-lateral areas of the thalamus, respectively (4). Consequently, dysfunction of thalamocortical networks may account for the wide array of clinical and cognitive symptoms observed in schizophrenia (6). Indeed, functional and structural imaging investigations provide broad support for thalamocortical dysfunction (7–12). However, the topographical arrangement of reciprocal connections between the cortex and thalamus also raises the distinct possibility that thalamocortical networks may be differentially affected in schizophrenia (13). Determining the anatomical specificity of thalamocortical network dysconnectivity using conventional task-based functional imaging is challenging because it requires using multiple cognitive paradigms that reliably activate distinct cortical areas and their corresponding thalamic targets in healthy subjects as well as in patients with schizophrenia. As a result, the anatomical specificity of thalamocortical functional dysconnectivity in schizophrenia remains largely unknown.

Resting-state functional MRI (fMRI), which examines correlations in intrinsic low-frequency fluctuations in the blood-oxygen-level dependent (BOLD) signal across brain regions, sidesteps many of the limitations associated with conventional task-based functional imaging and has proven useful for mapping brain networks. In a series of elegant studies, Zhang et al. (14, 15) systematically mapped functional connectivity between the cortex and thalamus using resting-state fMRI. Specifically, by parceling the cortex into regions of interest that corresponded to prefrontal, motor, somatosensory, temporal, and parietal/occipital cortices and using them as seeds in a functional connectivity analysis, they were able to demonstrate that activity in each cortical area correlated with distinct, largely nonoverlapping regions of the thalamus. For instance, the prefrontal cortex functionally correlated with the anterior and dorsomedial thalamus, whereas the motor cortex correlated with the ventral lateral thalamus (14, 15). Critically, the patterns of intrinsic functional connectivity revealed

using resting-state fMRI correspond closely to anatomical connections based on histology and diffusion tensor imaging of white matter pathways (14–18). Consequently, resting-state fMRI may be an ideal method for examining the integrity of functional connectivity between the cortex and thalamus in individuals with schizophrenia. To this end, we employed an approach similar to that used by Zhang et al. to examine functional connectivity between the cortex and thalamus in schizophrenia and to determine whether specific thalamocortical networks are differentially affected in the disorder.

Method

Participants

The study participants were drawn from a pool of 160 individuals (healthy comparison subjects, N=87; patients with schizophrenia or schizoaffective disorder, N=73) for whom resting-state fMRI data were available. The patient group was recruited through the Vanderbilt Psychotic Disorders Program (Vanderbilt Psychiatric Hospital, Nashville, Tenn.). Healthy comparison subjects were recruited from Nashville and the surrounding area through advertisement and word-of-mouth. The study was approved by the Vanderbilt University Institutional Review Board. All participants provided written informed consent prior to entering the study. The Structured Clinical Interview for DSM-IV Axis I Disorders (19) was administered to confirm diagnoses in patients and rule out current or past psychiatric illness in healthy subjects. Clinical symptoms of psychosis were quantified with the Positive and Negative Syndrome Scale (PANSS [20]). The Wechsler Test of Adult Reading (21) was also administered to provide an estimate of premorbid intellect. Exclusion criteria were <16 years of age or >65 years of age, estimated premorbid IQ <70, presence of a systemic medical illness (e.g., diabetes, cardiovascular disease) or CNS disorder (e.g., multiple sclerosis, epilepsy) that would affect study results, reported pregnancy or lactation, history of significant head trauma, psychotropic drug use (for healthy subjects), substance abuse within the last 3 months (for schizophrenia patients) or lifetime history of substance abuse or dependence (for healthy subjects), and MRI contraindicators (e.g., metal implants, claustrophobia).

Imaging Data Acquisition and Preprocessing

Imaging data were collected on one of two identical 3.0-T Philips Intera Achieva MRI scanners (Philips Healthcare, Andover, Mass.), denoted 3T-A and 3T-B, located at Vanderbilt University Institute of Imaging Science. The 7-minute echo-planar imaging resting-state scan consisted of the following parameters: 28 axial slices, matrix=80×80, in-plane resolution=3.0 mm × 3.0 mm, slice thickness=4.0 mm, 203 volumes, TR=2,000 ms, TE=35 ms. Participants were instructed to rest quietly with their eyes closed and to remain awake during the scan. A high-resolution T_1-weighted fast field-echo structural scan (170 saggital slices, matrix=256×256, isovoxel resolution=1.0 mm, TR=8.0 ms, TE=3.7 ms) was also acquired. The resting-state scan was acquired immediately after the survey and high-resolution structural scans and was not preceded by a cognitive task.

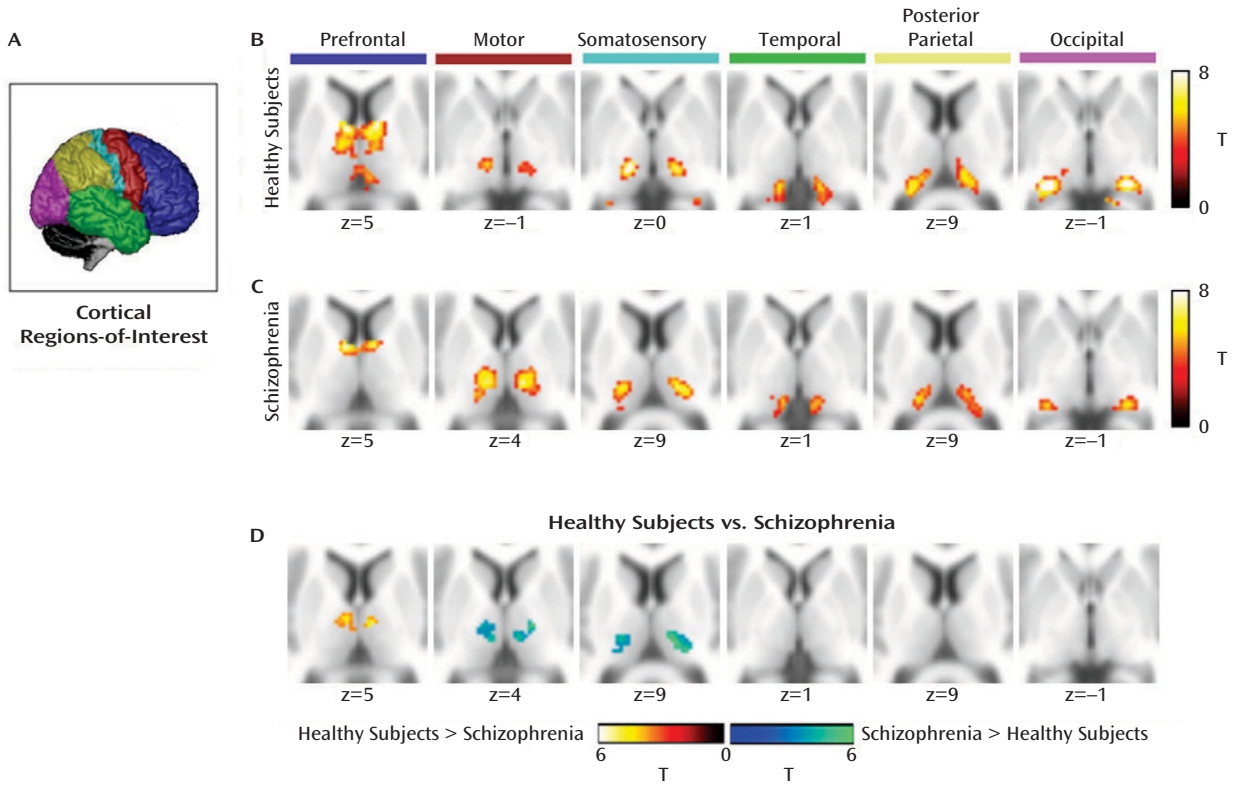
Functional imaging data for each subject were required to pass our in-house quality assurance toolbox based on the Biomedical Informatics Research Network Functional and Structural Neuroimaging Calibration Study quality assurance protocol (22). Five features (signal-to-noise ratio, percent drift, percent fluctuation, radius of decorrelation, and percent standard deviation) were extracted from each scan. Each scan was classified as acceptable if every feature passed the predetermined cutoff points that were derived from a fuzzy clustering algorithm applied to a separate "training" data set of 84 functional runs obtained from a mixed sample of healthy subjects and patients with a psychotic disorder. Subsequent functional imaging preprocessing was carried out using Statistical Parametric Mapping 8.0 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) and included correction for head motion and slice timing offset, band-pass filtering (0.01 Hz–0.1 Hz), and spatial coregistration to the participant's structural image. Consistent with prior thalamocortical resting-state studies that used this method, no spatial smoothing was applied to the functional data (14, 15, 23). Each participant's T_1 structural scan was segmented into gray matter, white matter, and CSF tissue classes using the Voxel-Based Morphometry, 8.0, toolbox (http://dbm.neuro.uni-jena.de/vbm), and the gray matter tissue segment was normalized to the a priori Montreal Neurological Institute (MNI) gray matter template. Normalization parameters derived from this step were then applied to the functional, white matter, and CSF tissue class images in order to bring them into MNI space.

Functional Connectivity Analysis

Consistent with the approach used by Zhang et al. (14, 15), we divided the cortex into nonoverlapping regions of interest (the prefrontal cortex, motor cortex/supplementary motor area, somatosensory cortex, temporal lobe, posterior parietal cortex, and occipital lobe), which were used as seeds in a seed-to-voxel functional connectivity analysis (Figure 1; also see Figure 1 in the data supplemental accompanying the online edition of this article). The only deviations from the Zhang et al. method were that 1) we used the maximum likelihood maps from the Laboratory of Neuroimaging probabilistic atlas of cortical structures (24) and the Harvard-Oxford supplementary motor area probabilistic atlas (http://www.fmrib.ox.ac.uk/fsl/) to construct the regions of interest, rather than tracing them on a single participant's brain, and 2) we divided the parietal/occipital region of interest into posterior parietal and occipital regions of interest. The prefrontal cortex region of interest consisted of the superior, middle, and inferior frontal gyri, the middle and lateral orbitofrontal gyri, the gyrus rectus, and the anterior cingulate gyrus. The motor cortex/supplementary motor area region of interest consisted of the precentral gyrus and the supplementary motor area. The somatosensory region of interest was the postcentral gyrus. The temporal lobe region of interest consisted of the superior, middle, and inferior temporal gyri, the parahippocampal gyrus, and the fusiform gyrus. The posterior parietal region of interest consisted of the superior parietal, supramarginal, and angular gyri, the posterior cingulate, and the precuneus. The occipital region of interest consisted of the superior, middle, and inferior occipital gyri, the lingual gyrus, and the cuneus. The cortical regions of interest were masked using the Laboratory of Neuroimaging probabilistic atlas gray matter tissue map, thresholded at 0.15, to eliminate voxels with low gray matter intensity.

Functional connectivity maps for each cortical region of interest were created for each participant using the CONN-fMRI functional connectivity toolbox (http://www.nitrc.org/projects/conn). Briefly, the mean BOLD time series from each region of interest was entered as a predictor in a multiple regression general linear model at each voxel. Regressors corresponding to six motion correction parameters and their first temporal derivatives, gray matter, white matter, and CSF were also included to remove variance related to head motion, the global signal, white matter, and CSF, respectively. For the white matter and CSF, five regressors each were extracted from the white matter and CSF tissue class images using the anatomical component-based noise correction method. The mean BOLD time course from the gray matter was used to remove the global signal.

FIGURE 1. Altered Resting-State Functional Connectivity Between the Cortex and Thalamus in Schizophrenia Patients[a]



[a] The cortex is partitioned into six nonoverlapping regions of interest that were used as seeds in a functional connectivity analysis (panel A). Activity in each cortical region of interest correlated with distinct areas of the thalamus in both healthy comparison subjects (panel B) and patients with schizophrenia (panel C). Comparison between groups revealed decreased prefrontal connectivity with the thalamus and increased motor and somatosensory thalamic connectivity in schizophrenia (panel D). Images were thresholded at a p value of 0.05 (cluster-wise corrected) for a voxel-wise p value of 0.001. A presentation format similar to that used by Zhang et al. (14, 15) and Fair et al. (23) was employed to facilitate comparison of our results with previous findings in healthy subjects.

Statistical analysis of functional imaging data proceeded by entering the individual participant functional connectivity maps (in beta-weight units) into random-effects analyses to create within-group functional connectivity statistical parametric maps and compare connectivity between groups. Only positive correlations were examined. All statistical maps were thresholded at the cluster-level corrected alpha level (p=0.05) for the voxel-wise p value (0.001), masked to include only voxels within the Harvard-Oxford thalamus atlas.

Results

Ten healthy subjects and 11 patients had either resting-state scans that did not pass our quality assurance protocol or poor-quality structural scans (i.e., significant motion artifact). Thus, the final data set consisted of 77 healthy comparison subjects and 62 schizophrenia patients (schizoaffective disorder, N=24). Demographic characteristics of patients and healthy subjects are summarized in Table 1. With the exception of three individuals who were not receiving antipsychotic medication, patients were receiving treatment with one or two atypical antipsychotics (N=42 and N=9, respectively), one atypical and one conventional antipsychotic (N=6), or one conventional antipsychotic (N=2). The groups did not differ on parental education, gender distribution, or ethnicity. As expected, premorbid intellect was lower for the schizophrenia group (t=4.84, df=137, p<0.001). Group differences on age fell short of statistical significance (t=1.92, df=137, p=0.06), with the patient group slightly older than the healthy comparison group. Rather than selectively remove younger healthy subjects from the analysis to exactly equate the two groups on age, which would have reduced statistical power and possibly introduced bias, age was included as a covariate in the between-group imaging analyses. Chi-square analysis indicated that fewer patients were scanned on the 3T-B scanner (healthy subjects, N=36; patients, N=16; χ^2=4.45, df=1, p=0.01). To ensure that data could be combined across scanners, we compared scanners on the five signal features extracted from the quality assurance protocol. None of the features differed between scanners.

Thalamocortical Connectivity

Healthy comparison subjects. Each cortical region of interest was connected to distinct, largely nonoverlapping regions of the thalamus (Figure 1). The present results are virtually identical to those reported in previous studies using the same method in healthy adults (14, 15, 23). As

TABLE 1. Demographic and Clinical Characteristics of Schizophrenia Patients and Healthy Comparison Subjects[a]

	Healthy Comparison Subjects (N=77)		Schizophrenia Patients (N=62)		Analysis		
Characteristic	Mean	SD	Mean	SD	t	df	p
Age (years)	33.0	11.2	36.8	12.0	1.92	137	0.06
Parental education (years)[b]	13.9	2.0	13.4	2.8	1.24	123	0.22
Premorbid IQ	109.5	11.7	98.2	14.9	4.84	137	<0.001
Age at illness onset (years)			23.0	7.5			
Duration of illness (years)			13.8	10.8			
Positive and Negative Syndrome Scale score							
Positive subscore			19.6	7.3			
Negative subscore			13.8	5.9			
General subscore			33.0	8.3			
Antipsychotic dosage (chlorpromazine equivalents)			468.9	228.7			

[a] The male/female breakdown between healthy comparison subjects and schizophrenia patients was 44/33 and 36/26, respectively (χ^2=0.01, df=1, p=0.09). The racial/ethnic distribution of Caucasian/African American/Other for the healthy comparison subjects and schizophrenia patients was 54/20/3 and 39/20/3, respectively (χ^2=4.85, df=4, t=0.43).
[b] Data on parental education were unavailable for eight healthy comparison subjects and six schizophrenia patients.

expected, the prefrontal cortex was functionally connected to anterior and dorsomedial regions of the thalamus. Motor and somatosensory regions of interest correlated strongly with ventral lateral and ventral posterior-lateral portions of the thalamus, respectively. The temporal lobe and occipital cortex correlated with posterior medial and lateral areas of the thalamus that appeared consistent with the medial geniculate nucleus and the lateral geniculate nucleus, respectively. The posterior parietal cortex was robustly connected with the lateral posterior nucleus and the pulvinar.

Schizophrenia patients. Schizophrenia patients demonstrated a high degree of segregation in the thalamus, and the overall pattern of functional connectivity between the cortex and thalamus corresponded well with previous findings in healthy subjects (Figure 1). However, there were qualitative differences between patients and healthy subjects. In the patient group, prefrontal cortex connectivity with the thalamus appeared markedly less robust and was restricted largely to the anterior thalamus, whereas the spatial extent of motor and somatosensory connectivity was considerably more extensive. Specifically, the thalamic clusters showing connectivity with these regions of interest were expanded in the dorsal and lateral directions in the patient group.

Group Differences in Thalamocortical Connectivity

Group differences in thalamocortical connectivity are summarized in Table 2 and depicted graphically in Figure 1. The patient group demonstrated significantly less connectivity between the prefrontal cortex and left and right dorsomedial thalamus. In contrast, patients exhibited increased thalamic connectivity with the motor and somatosensory cortex. No differences were observed between groups in temporal, posterior parietal, and occipital cortex connectivity with the thalamus.

To ensure that the group differences in connectivity were not a result of antipsychotic medication, structural brain changes in the thalamus, or scanner effects, we extracted the connectivity beta weights from each cluster identified in the between-group analysis and performed several supplementary analyses. To rule out medication effects, we correlated the cluster beta weights with the current antipsychotic dosage in chlorpromazine equivalents. Functional connectivity did not correlate with dosage in any cluster. To rule out the possibility that connectivity differences were a result of structural brain differences in the thalamus, we extracted each participant's mean gray matter content within each cluster (i.e., average fraction of gray matter within the cluster) from the gray matter segmented images and performed an analysis of covariance (ANCOVA) on the connectivity beta weights, with the mean gray matter content included as a covariate. The group effect was highly significant for each cluster (all p values <0.00005), indicating that the functional connectivity changes observed in the schizophrenia group were not due to differences in the content of gray matter within each cluster. Finally, to ensure that the group effects were not a result of differential allocation of patients and healthy subjects to the two scanners, we performed ANCOVAs on the beta weights extracted from the clusters identified in the between-group analysis with scanner included as a covariate. The group effect remained highly significant for all of the clusters (all p values <0.0005). Additionally, the results of the voxel-wise analysis with scanner included as a covariate were virtually indistinguishable from those of the main analysis (see Figure 2 in the online data supplement).

We also examined the relationship between the connectivity changes, clinical symptoms (i.e., PANSS positive, negative, and general psychopathology scores), and illness-relevant demographic characteristics (i.e., duration of

TABLE 2. Thalamocortical Functional Connectivity Changes in Schizophrenia Patients Relative to Healthy Comparison Subjects

Seed Region of Interest, Contrast, and Brain Region[a]	Montreal Neurological Coordinates (x, y, z)	Peak t Value	p[b]	Cluster Size (Voxels)[c]
Prefrontal				
Healthy subjects > schizophrenia				
Right medial dorsal nucleus	8, –10, 6	4.90	0.02	21
Left medial dorsal nucleus	–10, –12, 12	4.85	<0.001	81
Right anterior nucleus	14, 2, 10	3.91	<0.05	15
Schizophrenia > healthy subjects[d]				
Motor/supplementary motor area				
Healthy subjects > schizophrenia[d]				
Schizophrenia > healthy subjects				
Right ventral lateral nucleus	16, –12, 4	5.89	<0.001	102
Right pulvinar	20, –26, 12	5.52	0.03	18
Left ventral lateral nucleus	–10, –16, 10	4.60	<0.001	102
Somatosensory				
Healthy subjects > schizophrenia[d]				
Schizophrenia > healthy subjects				
Right pulvinar	20, –26, 12	6.40	<0.001	150
Left pulvinar	–6, –20, 4	5.17	<0.001	88

[a] No significant differences were observed for either contrast in the temporal, posterior parietal, and occipital seed regions of interest.
[b] Values represent family-wise error corrected rate.
[c] Voxel size was 2×2×2 mm.
[d] No significant differences were observed for this contrast.

illness, premorbid IQ). Given the exploratory nature of this analysis, only correlations with alpha levels <0.005 were considered significant. No correlations between functional connectivity and clinical symptoms or illness-relevant demographic characteristics met this threshold.

Discussion

Dysfunction of thalamocortical networks has been implicated in the pathophysiology of schizophrenia (2, 3). We used resting-state fMRI to determine the anatomical specificity of thalamocortical network dysfunction in schizophrenia (15). We found that functional connectivity between the prefrontal cortex and dorsomedial/anterior thalamus was reduced in schizophrenia. In contrast, thalamic functional connectivity with motor and somatosensory cortical areas was markedly increased. These results indicate that functional networks linking the cortex to the thalamus are abnormal in schizophrenia and that the changes are characterized by both hypo- and hyperconnectivity.

The combination of decreased prefrontal-thalamic and increased thalamic connectivity with motor and somatosensory cortical regions is the most striking aspect of our findings, which, at first glance, appear inconsistent with the general notion that neural connectivity is reduced overall in schizophrenia (e.g., reference 25). However, when interpreted from a developmental perspective, our results provide compelling support for the neurodevelopmental model of schizophrenia. Using the same method, Fair et al. (23) found marked differences in thalamocortical functional connectivity between children, adolescents, and adults. Specifically, prefrontal-thalamic connectivity is largely absent in children and adolescents, suggesting that this network develops abruptly during the transition from adolescence to adulthood. Motor and somatosensory connectivity, on the other hand, appears to follow an inverted U-curve, which is maximal in adolescence compared with childhood and adulthood. The changes observed in schizophrenia may result from abnormal late brain maturation during the transition from adolescence to adulthood, which derails the normal development of prefrontal-thalamic connectivity and refinement of somatomotor-thalamic connectivity. The functional consequences of these changes remain to be characterized; however, reduced structural connectivity between the prefrontal cortex and thalamus has been linked to working memory impairment and prefrontal brain activity in schizophrenia (26). It is possible that a similar relationship may be observed for resting-state functional connectivity.

While the combination of decreased prefrontal and increased somatomotor connectivity with the thalamus is consistent with atypical brain maturation in schizophrenia, the absence of group differences in temporal-thalamic connectivity potentially argues against a neurodevelopmental basis for thalamocortical dysconnectivity. In contrast to prefrontal-thalamic connectivity, temporal cortex connectivity with the thalamus decreases with age in typically developing individuals (23). Therefore, schizophrenia patients might be expected to demonstrate increased temporal-thalamic connectivity if thalamocortical

network dysfunction is indeed associated with atypical brain maturation. However, the precise timing of developmental changes in thalamocortical functional connectivity is poorly understood. The limited available evidence, which comes from a single cross-sectional study, suggests that much of the reduction in temporal-thalamic connectivity occurs between childhood and adolescence (23). Consequently, it is possible that the developmental disruption in schizophrenia occurs after temporal-thalamic connectivity has fully matured but before prefrontal and somatomotor thalamic networks have reached adult levels. A better understanding of the normal developmental trajectories of thalamocortical connectivity and investigation of thalamocortical connectivity in first-episode schizophrenia are required to test this hypothesis. The lack of group differences in temporal-thalamic, as well as occipital-thalamic connectivity, is also interesting given strong evidence of sensory processing deficits in schizophrenia (27). It is possible that connectivity during tasks, rather than in the resting state, may be associated with sensory processing dysfunction. Alternatively, auditory and visual sensory processing deficits in schizophrenia may be related to dysfunction at the level of cortico-cortical interactions, rather than thalamocortical connectivity.

Our findings also raise the possibility that thalamocortical dysconnectivity results from selective pathology of one or more nuclei of the thalamus or their corresponding cortical targets. A reduced number of neurons in the mediodorsal thalamus has been reported by several investigators, although there are also reports of normal numbers of neurons (for a review, see reference 13). Similarly, an array of neuronal and molecular changes have also been observed in dorsolateral prefrontal cortex circuitry (for a review, see reference 28). Thus, thalamocortical dysconnectivity in schizophrenia may result from selective pathology of specific thalamic nuclei or their corresponding cortical targets. Resting-state connectivity networks are conserved across species, suggesting that animal models will be particularly useful in elucidating the effects of focal neuronal, molecular, and genetic manipulations on large-scale brain networks (29–33).

Our results are also informed by considering the physiology of BOLD functional connectivity. There is considerable overlap between functional and structural connectivity in the thalamus, suggesting that thalamocortical functional connectivity reflects direct anatomical connections (14). Results from a recent diffusion tensor imaging investigation demonstrating reduced connectivity between the thalamus and lateral prefrontal cortex and increased connectivity between the somatosensory cortex and thalamus in schizophrenia provide a potential anatomical basis for our findings (26). However, it is clear from the broader functional connectivity literature that brain regions that are not directly anatomically connected can still demonstrate robust functional connectivity, indicating that resting-state connectivity networks reflect extended, polysynaptic networks (e.g., reference 34). This interpretation is supported by findings from a recent combined resting-state fMRI/electrocorticography investigation, which found that functional connectivity, particularly positive correlations, predicted electrically evoked brain responses (35). Combined, these findings confirm a neural basis for low-frequency BOLD functional connectivity but raise the possibility that abnormal thalamocortical connectivity in schizophrenia may reflect alterations in direct or indirect pathways linking the thalamus and cortex. Future work combining functional and structural connectivity will help clarify the nature of thalamocortical dysconnectivity in schizophrenia.

There are several limitations of our investigation that merit consideration. First, schizophrenia patients were receiving antipsychotic medication. Although we did not find any evidence that medication was related to functional connectivity abnormalities observed in patients, it is possible that antipsychotic treatment effects on connectivity may not be dose-dependent. Second, low-frequency BOLD functional connectivity varies to some extent across cognitive states, levels of consciousness (i.e., awake versus light sleep), and even eyes-open versus eyes-closed conditions (36–39). Since we instructed participants to keep their eyes closed during scanning, we cannot rule out the possibility that some may have fallen asleep during scanning and that group differences in arousal may have contributed to our results. Studies examining thalamocortical connectivity across cognitive states and levels of arousal are required to determine whether the alterations observed in schizophrenia patients transcend cognitive states and arousal levels. Moreover, resting-state connectivity is modified by recent experiences, raising the possibility that the abnormalities we observed in thalamocortical connectivity are secondary to negative life experiences associated with illness chronicity, such as long-term reduction in social interaction and cognitive engagement, rather than a result of the pathophysiology of schizophrenia (40). Third, while we argue that the changes are at least partially consistent with neurodevelopmental hypotheses of schizophrenia, it is premature to exclude a neurodegenerative explanation for our findings. A combination of decreased network connectivity with compensatory increases in other networks has been observed in degenerative illnesses, such as Alzheimer's disease (41). Replication of our findings in nonmedicated/minimally treated first-episode or early-phase schizophrenia patients will strengthen the case for a neurodevelopmental basis for thalamocortical dysconnectivity. Finally, although we applied a well-established method to examine thalamocortical functional connectivity, there are nonetheless limitations of the technique. The use of large cortical areas as seeds, while useful for functionally segregating the thalamus, does not allow for a more fine-grained analysis at the cortical level. Interestingly, using a voxel located in the mediodorsal thalamus as the seed for functional

connectivity analysis, Welsh et al. (12) found that mediodorsal thalamic connectivity with the left and right caudate and anterior cingulate gyrus was reduced in schizophrenia. Follow-up investigation using the thalamic clusters identified in our study as seeds in an independent cohort of patients, or an independent-components analysis, may help further refine the anatomical specificity of thalamocortical dysconnectivity.

In conclusion, we observed that altered resting-state functional connectivity between the thalamus and cortex is altered in schizophrenia. The alterations are characterized by decreased prefrontal-thalamic connectivity and increased thalamic connectivity with motor and somatomotor cortex. Combined, our results implicate abnormal late-brain maturation in the neuropathology of schizophrenia. Future studies combining functional connectivity with assessment of phenotypes more closely related to thalamocortical networks than to complex clinical symptoms may help elucidate the functional consequences of thalamocortical dysconnectivity in schizophrenia.

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