Archival Report

Biological Psychiatry

Mapping Thalamocortical Functional Connectivity in Chronic and Early Stages of Psychotic Disorders

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BACKGROUND: There is considerable evidence that the thalamus is abnormal in psychotic disorders. Resting-state functional magnetic resonance imaging has revealed an intriguing pattern of thalamic dysconnectivity in psychosis characterized by reduced prefrontal cortex (PFC) connectivity and increased somatomotor-thalamic connectivity. However, critical knowledge gaps remain with respect to the onset, anatomical specificity, and clinical correlates of thalamic dysconnectivity in psychosis.

METHODS: Resting-state functional magnetic resonance imaging was collected on 105 healthy subjects and 148 individuals with psychosis, including 53 early-stage psychosis patients. Using all 253 subjects, the thalamus was parceled into functional regions of interest (ROIs) on the basis of connectivity with six a priori defined cortical ROIs covering most of the cortical mantle. Functional connectivity between each cortical ROI and its corresponding thalamic ROI was quantified and compared across groups. Significant differences in the ROI-to-ROI analysis were followed up with voxel-wise seed-based analyses to further localize thalamic dysconnectivity.

RESULTS: ROI analysis revealed reduced PFC-thalamic connectivity and increased somatomotor-thalamic connectivity in both chronic and early-stage psychosis patients. PFC hypoconnectivity and motor cortex hyperconnectivity correlated in patients suggesting they result from a common pathophysiological mechanism. Seed-based analyses revealed thalamic hypoconnectivity in psychosis localized to dorsolateral PFC, medial PFC, and cerebellar areas of the well-described executive control network. Across all subjects, thalamic connectivity with areas of the fronto-parietal network correlated with cognitive functioning, including verbal learning and memory.

CONCLUSIONS: Thalamocortical dysconnectivity is present in both chronic and early stages of psychosis, includes reduced thalamic connectivity with the executive control network, and is related to cognitive impairment.

Keywords: Chronic, Cortex, Early stage, Psychosis, Resting-state fMRI, Thalamus

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There is considerable evidence that the thalamus and associated cortical connections are abnormal in psychotic disorders (1–4). However, it has been difficult to localize thalamic pathology and identify dysfunction in specific thalamocortical circuits due to the complex architecture of the thalamus and limitations of traditional neuroimaging methods (5). Furthermore, postmortem investigations have produced conflicting findings or, in the case of bipolar disorder, are few in number (6,7).

Resting-state functional magnetic resonance imaging is a useful method for mapping functional brain networks and identifying circuit abnormalities in neurological and psychiatric disorders (8,9). Recently, we used resting-state functional magnetic resonance imaging to investigate thalamocortical functional connectivity in a sample of 62 individuals with schizophrenia and 77 healthy subjects (10). Consistent with an earlier small investigation of 10 patients (11), we found that prefrontal cortex (PFC) connectivity with the thalamus was reduced in schizophrenia. Surprisingly, patients also demonstrated increased thalamic connectivity with motor and somatosensory cortex. The combination of reduced prefrontal and increased sensorimotor connectivity was subsequently replicated by several groups and extended to bipolar disorder (12–14).

Despite the consistency of the findings across studies, key questions remain about the onset, anatomical specificity, and clinical correlates of thalamic dysconnectivity. It is unclear if the abnormalities are present early in the illness or emerge as the illness progresses. Based on what is known about the development of thalamocortical functional connectivity, we hypothesized that the combination of reduced PFC connectivity and increased somatomotor connectivity results from a disturbance in brain development during the transition from adolescence to adulthood that prevents PFC-thalamic circuitry from fully developing and derails the normal refinement of somatomotor-thalamic connectivity (10,15). Evidence of similar connectivity disturbances in the early stage of psychosis would support this hypothesis. Alternatively, if the abnormalities are not present in early-stage patients, it would suggest that thalamocortical dysconnectivity may be progressive and a possible target for treatment intervention.

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The anatomical details of thalamocortical functional dysconnectivity in psychotic disorders are not well known. Our prior study used a method initially developed to map anatomical connectivity in which the cortex is divided into large regions of interest (ROIs) corresponding to the main targets of specific thalamic nuclei (e.g., PFC, occipital lobe), which are then used as seeds to delineate connectivity within the thalamus (16–18). While this method is excellent for localizing connectivity abnormalities within the thalamus, the use of large cortical ROIs limits anatomical specificity in the cortex and the rest of the brain. Alternatively, other groups have used the whole thalamus as a seed to identify thalamic connectivity abnormalities throughout the brain (12,14). However, by averaging blood oxygen level-dependent (BOLD) signals across the entire thalamus, this approach treats the thalamus as a homogenous structure with a unitary connectivity profile, thereby obscuring network specific disturbances.

With these knowledge gaps in mind, the current investigation was undertaken to determine if similar patterns of thalamocortical dysconnectivity are observed in the early and chronic stages of psychotic disorders. Specifically, using a novel approach to better localize thalamocortical network abnormalities, we hypothesized that both chronic and early-stage patients with psychosis would exhibit reduced PFC-thalamic connectivity and increased somatomotor-thalamic connectivity. Additionally, we performed exploratory analyses comparing thalamocortical dysconnectivity between schizophrenia and psychotic bipolar disorder and examined the cognitive correlates of thalamocortical connectivity.

METHODS AND MATERIALS

Study Participants

One hundred five healthy subjects and 148 individuals with a psychotic disorder were included in this investigation (Table 1). The psychosis group included individuals with schizophrenia/schizoaffective disorder (i.e., nonaffective psychosis) and bipolar I disorder with psychotic features (i.e., affective psychosis). Fifty-three patients were within 2 years of illness onset and considered early stage (19). Most early-stage psychosis patients were studied at the time of their first hospitalization for a psychotic disorder or very shortly thereafter and had been ill for less than 4 months on average. At the time of study participation, 25 early-stage patients were diagnosed with schizophreniform disorder. Follow-up diagnostic data were available on 22 of these patients: 20 converted to a nonaffective psychotic disorder, 1 remained diagnosed with schizophreniform disorder, and 1 was subsequently reclassified as affective psychosis. All subjects underwent a structured clinical interview and completed a brief cognitive assessment that included the Wechsler Test of Adult Reading to estimate premorbid IQ (20) and the Screen for Cognitive Impairment in Psychiatry (21), which includes tests of verbal learning, working memory, verbal fluency, and processing speed. In addition, patients were also assessed with the Positive and Negative Syndrome Scale (PANSS) (22) to quantify severity of clinical symptoms (23). Study procedures and exclusion criteria are described in detail in Supplement 1. This study was approved by the Vanderbilt University Institutional Review Board.

Table 1. Sample Demographics

			Psychosis						
	Healthy Subjects		Chronic		Early Stage		Statistics		
	n = 105		n = 95		n = 53		$F/t/\chi^2$	p	Post Hoc
Gender (Male:Female)	61:44		50:45		39:14		6.29	.043	CP > ESP (males)
Ethnicity (White:AA:Other)	69:29:7		57:31:7		36:14:3		1.17	.882	–
Affective:Nonaffective Psychosis	–		17:78		21:32		8.42	.004	–
Antipsychotic Medicated (yes:no)	–		86.9		45:8		1.06	.304	–
	Mean	SD	Mean	SD	Mean	SD			
Age	32.5	11.3	38.1	11.8	22.0	3.7	40.28	<.001	CP > HS > ESP
Premorbid IQ	109.9	12.0	96.8	16.2	101.3	13.3	21.19	<.001	HS > CP, ESP
SCIP Global Cognition Z-Score	.0	.68	−1.53	.94	−.68	.87	77.06	<.001	HS > ESP > CP
% of fMRI Volumes Excluded	6.1	11.4	12.9	16.4	7.6	12.5	6.41	.002	CP > ESP, HS
Pre-motion Scrubbing rmsFD	.22	.13	.31	.22	.30	.42	3.52	<.031	CP > HS
Post-motion Scrubbing rmsFD	.18	.06	.20	.07	.16	.05	6.60	.002	CP > HS, ESP
Duration of Illness (Years)	–	–	15.7	11.1	.36	.5	10.01	<.001	–
PANSS Positive	–	–	19.4	7.0	19.3	8.1	.09	.925	–
PANSS Negative	–	–	14.6	6.7	15.3	8.3	.53	.597	–
PANSS General	–	–	31.7	8.0	31.5	8.6	.14	.886	–
CPZ Equivalents	–	–	478.0	247.8	308.4	174.3	4.08	<.001	–

AA, African American; CP, chronic psychosis; CPZ, chlorpromazine; ESP, early-stage psychosis; fMRI, functional magnetic resonance imaging; HS, healthy subjects; PANSS, Positive and Negative Syndrome Scale; SCIP, Screen for Cognitive Impairment in Psychiatry.

Neuroimaging Data Acquisition and Functional Connectivity Analysis

Imaging data acquisition and preprocessing are described in detail in Supplement 1. Briefly, a 7-minute echo-planar imaging resting-state scan and a high-resolution T1-weighted structural scan were collected on each subject. Functional images were slice-time corrected, motion corrected, co-registered to native space structural data, and normalized to Montreal Neurological Institute space. As described earlier, prior investigations of thalamocortical functional dysconnectivity in psychosis have either: 1) parceled the cortex into large, anatomically defined ROIs corresponding to the primary cortical targets of specific thalamic subregions (e.g., PFC) and used these as seeds to identify functional connectivity within the thalamus; or 2) used the whole thalamus as a seed to map thalamic connectivity with the rest of the brain (10,12,14). The primary advantage of the first method is that it can map multiple thalamic networks and segment the thalamus according to its functional connectivity (16). However, the use of large cortical ROIs limits spatial specificity within the cortex. Using the whole thalamus as a seed overcomes this limitation but, by averaging BOLD signals from the entire thalamus, precludes an analysis of specific thalamocortical networks.

To overcome these limitations, we combined elements of both methods. First, we performed a cortical ROI-to-thalamus ROI analysis in which connectivity between anatomically defined cortical ROIs and functionally defined thalamic ROIs was calculated and compared across groups (Figure 1A). This primary analysis was followed up with seed-based analyses examining connectivity of functionally defined thalamic subregions with the rest of the brain. The analysis steps were as follows. First, as described previously, the cortex was divided into six, a priori defined nonoverlapping ROIs shown in Figure 1A (10). Functional connectivity maps, restricted to

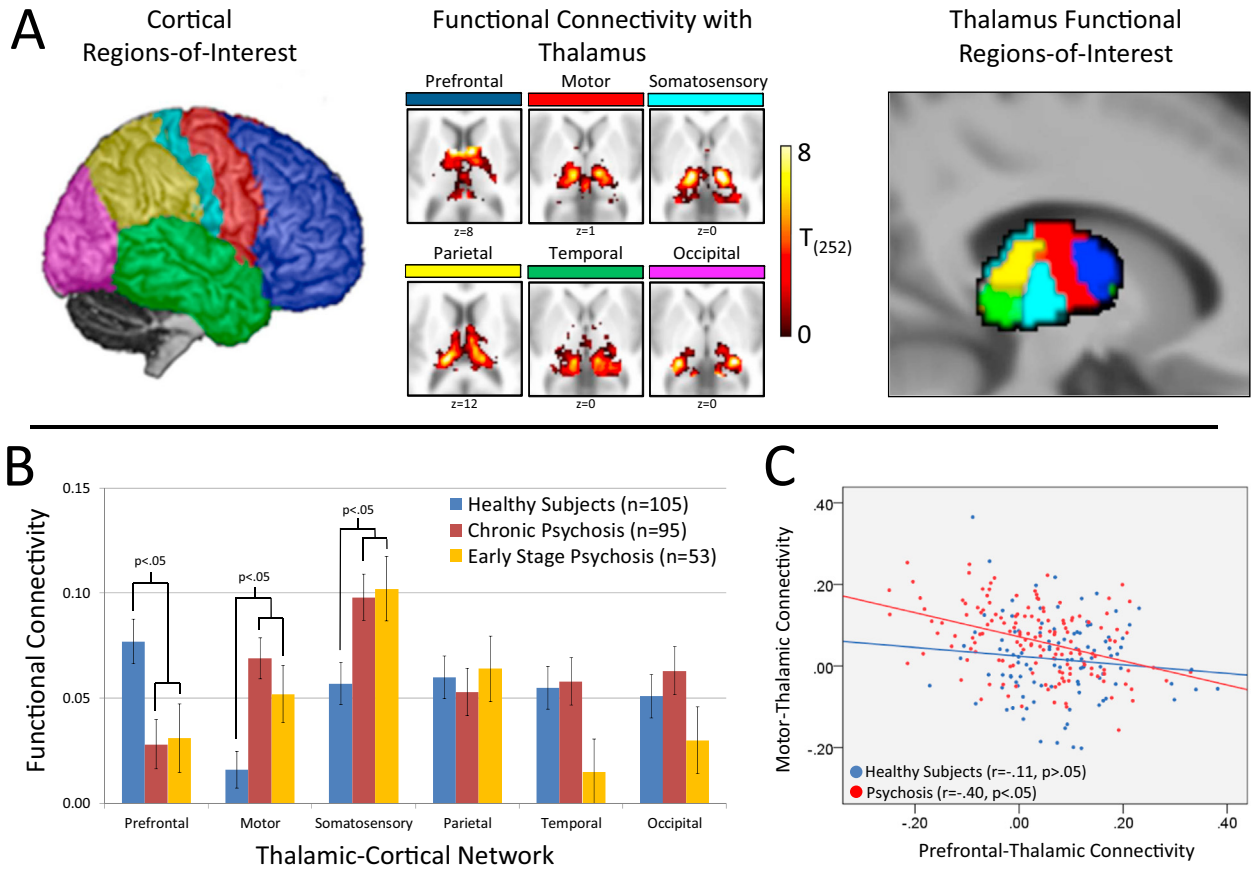

Figure 1. Thalamo-cortical functional connectivity in chronic and early-stage psychosis. **(A)** Within the entire sample of 253 subjects, connectivity of 6 a priori defined cortical areas (left) correlated with distinct, largely nonoverlapping regions of the thalamus (middle). The thalamus was parceled into functional regions of interest (ROIs) using the winner-take-all approach in which each voxel in the thalamus is classified according to which cortical ROI it is most strongly connected to (right). Connectivity between each cortical ROI and its corresponding thalamic functional ROI was then calculated for each subject. **(B)** Thalamic-cortical network functional connectivity varied between groups (repeated measures analysis of variance network × group interaction: $F_{10,490} = 3.20$, $p = .001$). Follow-up univariate analyses of variance indicated that, compared with healthy subjects, prefrontal cortex-thalamic network connectivity was reduced in both chronic ($p = .002$) and early-stage ($p = .020$) psychosis, whereas connectivity in the motor-thalamic and somatosensory-thalamic networks was increased in chronic ($p = .00006$ and $p = .006$, respectively) and early-stage psychosis ($p = .027$ and $p = .014$, respectively). **(C)** Prefrontal cortex-thalamic network connectivity inversely correlated with motor-thalamic network connectivity in patients with psychosis ($r = -.40$, $p = .0000006$) but not healthy subjects ($r = -.11$, $p = .264$). Direct comparison between groups indicated that the correlation was significantly greater in the psychosis group compared with healthy subjects (Fisher $Z = 2.42$, $p = .016$).

the Harvard-Oxford thalamus probabilistic atlas (thresholded at 10%; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases), were then created for each cortical ROI. Using the entire dataset of 253 individuals, the thalamus was parceled into functional ROIs using the winner take all strategy (15); each voxel in the thalamus was assigned to the cortical ROI it was most strongly connected to. Average connectivity of the voxels within each thalamic ROI with its respective cortical ROI was then calculated resulting in six thalamocortical network values for each subject, one for each cortical anatomical ROI and its corresponding thalamic functional ROI, which served as the dependent variables in the statistical analysis. Thalamocortical network values were analyzed using multivariate repeated measures analysis of variance (ANOVA) with network entered as the within the subjects variable, group as between-subjects variable, and age and sex entered as covariates.

The cortical ROI-to-thalamic ROI analysis described above was followed up with seed-based connectivity analyses using the thalamic functional ROIs as seeds to examine connectivity of specific thalamic subregions with the rest of the brain. Briefly, the mean BOLD times series derived from the thalamic ROIs was extracted from each subject's unsmoothed functional data and entered into a general linear model to create functional connectivity maps of specific thalamic ROIs. The functional connectivity maps, in beta units, were then smoothed (6 mm) and entered into a one-way ANOVA with group entered as the between-subjects variable and age and sex as covariates. A priori contrasts comparing healthy subjects with psychosis patients and each patient group (i.e., chronic, early stage) with healthy subjects were performed. Results were thresholded at the cluster-level $p_{\text{family-wise error (FWE)-corrected}} = .05$ for voxel-wise $p = .005$, masked to include only voxels that demonstrated significant positive functional connectivity in healthy subjects and/or psychosis patients at the cluster-level $p_{\text{FWE-corrected}} = .05$ for voxel-wise $p = .005$.

Functional connectivity maps for the thalamic ROIs were created using the CONN-fMRI Functional Connectivity toolbox (24). Briefly, the mean BOLD time series was extracted from an ROI and entered as a predictor in a multiple regression general linear model. Regressors corresponding to the six motion correction parameters and their first temporal derivatives, along with gray matter, white matter, and cerebrospinal fluid (CSF), were included to remove variance related to head motion, the global gray matter signal, white matter, and CSF, respectively. Functional data were band-pass filtered (.01–.10 Hz). We took several steps to limit the effects of head motion. First, resting-state scans underwent motion scrubbing as described by Power *et al.* (25). Volumes with frame-wise displacement greater than .5 and BOLD intensity changes between frames greater than .5% were identified and excluded from the functional connectivity analysis by including the tagged scans as nuisance regressors in the connectivity general linear model. Second, nuisance regressors for white matter and CSF were derived from each subject's white matter and CSF segmentations using the anatomical component-based noise reduction method, as implemented in the Conn-fMRI toolbox. The anatomical component-based noise reduction method has been shown to be effective at reducing the effects of head movement on functional connectivity estimates (26). Finally, motion correction parameters were regressed out before temporal band-pass filtering was applied, as performing these steps in reverse order (i.e., band-pass filtering before nuisance regression) overestimates connectivity and exacerbates the effects of head motion due to re-introduction of nuisance-related variation (27).

RESULTS

Demographic, cognitive, and clinical data are presented in Table 1. The overall patient cohort was well matched to healthy subjects on sex (healthy subjects: 58.1% male subjects; psychosis: 60.1% male subjects; $\chi^2_1 = .11$, $p = .745$) and age (healthy subjects: 32.5; patients: 32.3; $t_{251} = .07$, $p = .941$). Importantly, the distribution of ages was virtually identical in healthy subjects and patients (Figure S1 in Supplement 1). As expected, early-stage patients were younger than healthy subjects ($p < .001$), who, in turn, were younger than chronic patients ($p < .001$). Average daily dose of antipsychotic, in chlorpromazine equivalents based on Gardner *et al.* (28), was higher in chronic patients (478.0 ± 247.8 mg vs. 308.4 ± 174.3 mg; $t_{128} = 4.08$, $p < .001$).

Thalamocortical Functional Connectivity: Cortical ROI-to-Thalamic ROI Analysis

As shown in Figure 1A and Figure S2 in Supplement 1, functional subdivisions of the thalamus were very consistent with prior studies that have parceled the thalamus based on its functional and structural connectivity [e.g., (15,17,18)].

Results of the cortical ROI-to-thalamic ROI analysis are presented in Figure 1B. Multivariate repeated measures ANOVA revealed a significant network × group interaction ($F_{10,490} = 3.20$, $p = .001$) but no main effects of network ($F_{5,244} = 1.56$, $p = .165$) and group ($F_{2,248} = 1.22$, $p = .298$). Follow-up univariate ANOVAs indicated that the interaction was due to significant group differences in PFC-thalamic ($F_{2,248} = 5.97$, $p = .003$), motor-thalamic ($F_{2,248} = 8.96$, $p = .0002$), and somatosensory-thalamic ($F_{2,248} = 5.37$, $p = .005$) networks. Compared with healthy subjects, PFC-thalamic network connectivity was reduced in both chronic ($p = .002$) and early-stage ($p = .020$) psychosis, whereas motor-thalamic and somatosensory-thalamic network connectivity was increased in chronic ($p = .00006$ and $p = .006$, respectively) and early-stage psychosis ($p = .027$ and $p = .014$, respectively). In terms of effect sizes (ES), the reduction in PFC-thalamic hypoconnectivity was comparable in chronic (ES = −.45) and early-stage (ES = −.43) patient groups. Motor-thalamic hyperconnectivity was somewhat larger in chronic compared with early stage patients (ES = .59 and ES = .41, respectively), although somatosensory-thalamic hyperconnectivity was virtually identical in chronic and early-stage groups (ES = .40 and ES = .43, respectively).

To confirm the results were not affected by head motion, scanner assignment, age, and sex, we performed a series of analyses controlling for these effects as best as possible (Supplement 1). In brief, adding scanner or percentage of functional volumes excluded due to head motion as covariates did not affect the results (Figure S3 in Supplement 1). We also obtained very similar results when we compared subgroups of patients and healthy subjects matched on age and sex and age, sex, and head motion.

In light of a previous report linking PFC-hypoconnectivity and somatomotor-thalamic hyperconnectivity in psychosis (12),

we examined correlations between PFC-thalamic, motor-thalamic, and somatosensory-thalamic networks. Replicating the results of Anticevic *et al.* (12), we found a significant inverse correlation between PFC-thalamic network underconnectivity and motor-thalamic network hyperconnectivity in patients with psychosis ($r = -.40$, $p < .001$). However, in contrast to Anticevic *et al.* (12), this relationship was not present in healthy subjects ($r = -.11$, $p = .264$). As shown in Figure 1C, the correlation was significantly greater in the psychosis group compared with healthy subjects (Fisher $Z = 2.42$, $p = .016$). Somatosensory-thalamic connectivity was unrelated to PFC-thalamic connectivity in both psychosis ($r = -.02$, $p = .816$) and healthy subjects ($r = .01$, $p = .906$).

Additional analyses examining the relationship between thalamocortical functional connectivity and diagnosis, antipsychotic medication, clinical symptoms, and cognitive functioning were also performed. As shown in Figure S4 in Supplement 1, after adjusting for age, sex, and illness stage, PFC-thalamic network connectivity was lower in nonaffective psychosis patients compared with affective psychosis at the trend significance level ($F_{1,143} = 3.11$, $p = .080$). In contrast, there were no differences between affective and nonaffective psychosis in motor ($F_{1,143} = .03$, $p = .869$) and somatosensory ($F_{1,143} = .34$, $p = .562$) network connectivity. Among patients, antipsychotic dose; PANSS positive, negative, and general scores; and overall cognitive function (i.e., Screen for Cognitive Impairment in Psychiatry global *Z*-score) did not correlate with functional connectivity of any thalamocortical network (all r values $< |.11|$, $p > .217$).

Thalamocortical Functional Connectivity: Thalamus ROI Seed-Based Analysis

The cortical ROI-to-thalamus ROI analysis was followed up with seed-based analyses using the thalamic PFC, motor, and somatosensory subregions as seeds to better localize thalamic dysconnectivity with the rest of the brain. Functional connectivity of the thalamus PFC, motor, and somatosensory seeds in healthy subjects and individuals with psychosis are shown rendered on the cortical surface and cerebellum in Figure 2 and on serial axial slices covering the entire brain in

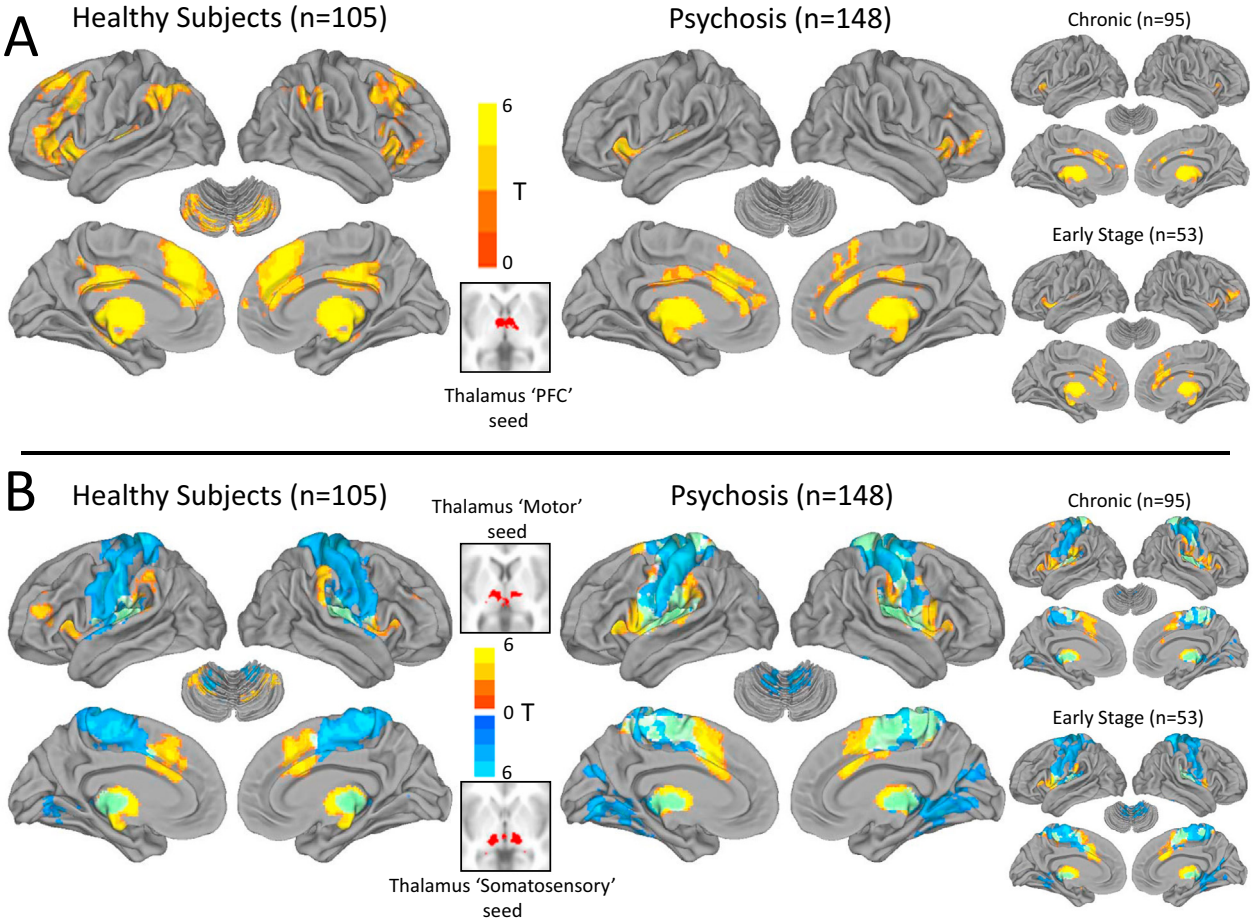

Figure 2. Functional connectivity of prefrontal cortex (PFC), motor, and somatosensory thalamus seeds in psychosis. **(A)** Functional connectivity of the PFC thalamus seed in healthy subjects resembled the well-described executive control network [i.e., Niendam *et al.* (29)] and included the dorsolateral PFC, medial PFC/anterior cingulate, mid-cingulate, inferior parietal lobule, and cerebellum. This pattern was markedly attenuated in psychosis, including both chronic and early-stage patients. **(B)** Functional connectivity of the thalamus motor seed (warm colors) and somatosensory seed (cool colors) included mainly motor and somatosensory areas and cerebellum. Qualitatively, functional connectivity of the thalamus motor and somatosensory seeds appeared more widespread and less segregated in psychosis patients (overlap in motor and somatosensory thalamus seed connectivity is shown in green).

Figure S5 in Supplement 1 (cortical and cerebellum renderings were created using Caret v5.65; http://brainmap.wustl.edu/caret.html).

In healthy subjects, the thalamic PFC seed was functionally connected to dorsolateral PFC, inferior frontal gyrus/anterior insula, anterior cingulate cortex, inferior parietal lobule (supramarginal and angular gyri), mid cingulate, left transverse temporal gyrus, and posterior quadrangle of the cerebellum. Subcortically, significant connectivity was detected with the caudate, especially the head of the caudate, and putamen (Figure S5 in Supplement 1). This pattern of connectivity bears a striking resemblance to the fronto-parietal executive control network [e.g., (29)]. Functional connectivity of the motor and somatosensory thalamus seeds was restricted almost exclusively to primary and secondary motor and somatosensory cortex, striatum, and cerebellum. In psychotic disorders, functional connectivity of the thalamus PFC seed was restricted to the medial PFC and anterior cingulate cortex; inferior frontal gyrus/anterior insula; mid cingulate; and left transverse temporal gyrus (Figure 2; Figure S5 in Supplement 1). Connectivity with the cerebellum was notably absent. In contrast, connectivity of the motor thalamus seed was more extensive and there was greater overlap between motor and somatosensory seeds in midline cortical areas. Functional connectivity patterns were very similar in chronic and early-stage psychosis patients.

Direct comparison between healthy subjects and psychosis patients confirmed that some of the qualitative differences observed between groups were statistically significant (Figure 3; Table 2). As shown in Figure 3, thalamus PFC seed connectivity with medial superior frontal gyrus extending laterally to middle frontal gyrus was reduced in psychosis. Thalamic PFC seed connectivity with cerebellum was reduced bilaterally. Chronic patients demonstrated less connectivity with medial and lateral aspects of the superior frontal gyrus, left cerebellum, and left inferior parietal lobule. No differences between healthy subjects and early-stage psychosis patients were observed at the a priori defined statistical threshold. However, relaxing the voxel-wise threshold to $p = .05$, while still maintaining a cluster-level corrected threshold of $p_{FWE\text{-}corrected} = .05$, revealed a very similar pattern of thalamic dysconnectivity in early-stage psychosis. In contrast to the thalamus PFC seed, psychosis patients exhibited greater motor thalamus seed connectivity with a cluster that included midline Brodmann areas 6 and 4 and left precentral gyrus corresponding to Brodmann area 44. In chronic patients, hyperconnectivity of the thalamus motor seed localized to the right lateral precentral gyrus corresponding to Brodmann area 6, midline cortical areas corresponding to medial aspects of Brodmann areas 4 and 6, and left postcentral gyrus corresponding to Brodmann area 5. No significant differences between healthy subjects and early-stage psychosis patients were observed at the corrected significance level. However, relaxing the voxel-wise threshold to $p = .05$, while still maintaining a whole-brain cluster-level corrected threshold of $p_{FWE\text{-}corrected} = .05$, revealed a similar pattern of thalamus motor seed hyperconnectivity in early-stage psychosis: elevated connectivity with medial aspects of precentral and postcentral gyrus and lateral precentral gyrus. With respect to the thalamus somatosensory seed, no differences in functional connectivity were detected between healthy subjects and psychosis patients. To better appreciate the similar patterns of thalamic dysconnectivity in chronic and early-stage psychosis, the results of the voxel-wise contrasts comparing each illness stage group with healthy subjects are also presented in Figure S6 in Supplement 1 without statistical thresholding.

Exploratory analyses were performed examining the relationship between thalamic functional connectivity and cognition, clinical symptoms, and psychotic disorder diagnosis.

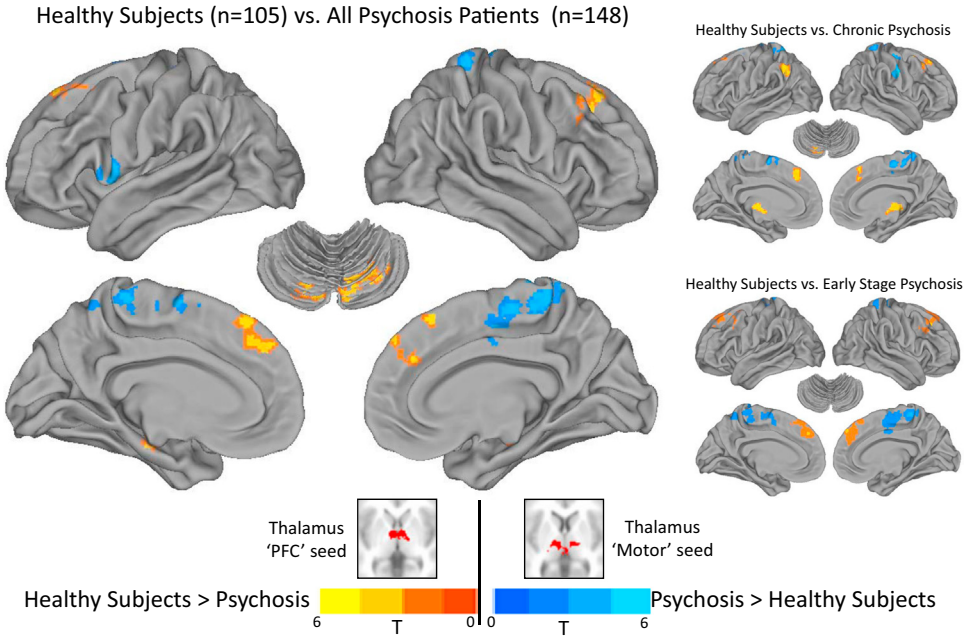

Figure 3. Functional dysconnectivity of the thalamus prefrontal cortex (PFC) and motor seeds in psychosis. Compared with healthy subjects, functional connectivity of the PFC thalamus seed with lateral PFC (i.e., superior frontal gyrus), anterior medial PFC, and cerebellum was reduced in individuals with a psychotic disorder (warm colors). In contrast, functional connectivity of the thalamus motor seed was increased in patients with a psychotic disorder in medial and ventral-lateral primary motor cortex (cool colors). Chronic and early-stage psychosis patients exhibited very similar patterns of functional connectivity abnormalities. All results thresholded at cluster-level corrected $p_{FWE\text{-}corrected} = .05$ for voxel-wise $p = .005$ ($p = .05$ for the healthy subjects versus early-stage psychosis patients contrast). FWE, family-wise error.

Table 2. Group Differences in Functional Connectivity of Thalamus Seed Regions at a Cluster-Level Corrected $p_{(FWE)} = .05$

	All Psychosis Patients					Chronic Psychosis					Early-Stage Psychosis				
		MNI					MNI					MNI			
Brain Area	Voxels	x	y	z	Peak *t*	Voxels	x	y	z	Peak *t*	Voxels	x	y	z	Peak *t*
Thalamus PFC Seed															
Healthy Subjects > Psychosis															
R Cerebellum, posterior lobe	669	10	−78	−28	5.02										
		30	−70	−28	4.25										
		40	−66	−40	3.76										
L Cerebellum, posterior lobe	351	−10	−76	−30	4.77	352	−8	−78	−28	4.66					
L/R Superior/medial frontal gyrus (BA 8/9)	1507	−30	24	54	3.95	1267	−30	22	54	3.90	2780	−22	34	46	2.51
		18	34	50	3.49		18	32	50	3.79		24	28	40	3.61
		−6	46	36	3.55		−2	34	40	3.72		−6	46	38	3.18
		4	52	42	3.53							5	52	42	3.52
Thalamus						471	6	−22	2	4.76					
							−2	−8	−4	3.64					
							18	−28	4	3.50					
L Inferior parietal lobule (BA 39/40)						508	−46	−50	42	4.25					
							−62	−60	38	4.05					
							−32	−62	42	3.26					
Psychosis > Healthy Subjects	No Significant Clusters														
Thalamus Motor Seed															
Healthy Subjects > Psychosis	No Significant Clusters														
Psychosis > Healthy Subjects															
L Precentral/inferior frontal gyrus (BA 44)	335	−60	10	6	4.9										
R/L Paracentral lobule (BA 4)	1320	4	−32	62	4.12						2068	4	−32	62	3.41
												−14	−30	60	3.14
R Medial frontal/postcentral gyrus (BA 6)		8	−26	80	3.88	567	8	−26	80	4.47		8	-6	50	2.93
							8	−18	58	3.72					
							8	−42	72	3.86					
L Superior/medial frontal gyrus (BA 6)		−12	6	72	3.93	753	−12	6	72	4.43					
							−14	4	64	4.32					
							−2	−4	68	3.75					
R Pre/postcentral gyrus (BA 3/4)						431	44	−16	56	3.83					
							62	-10	36	5.19					
							46	-14	42	2.83					
L Postcentral gyrus (BA 5/7)						424	-14	50	68	3.7					
							-30	-40	64	3.63					
							-24	-46	64	3.47					

BA, Brodmann area; FWE, family-wise error; L, left; MNI, Montreal Neurological Institute; PFC, prefrontal cortex; R, right.

Functional connectivity, in beta units, was extracted from the clusters identified in the healthy subjects versus psychosis contrasts and averaged to create two values per subject, one indicating average PFC thalamic underconnectivity and the other indicating average motor thalamus hyperconnectivity. In ES terms, thalamus PFC seed hypoconnectivity was similar in chronic and early-stage patients (ES = −.94 and ES = −.87, respectively), as was thalamus motor seed hyperconnectivity (ES = .78 and ES = .85, respectively). After controlling for group, average connectivity in the PFC thalamus seed regions demonstrating reduced connectivity in psychosis correlated with Screen for Cognitive Impairment in Psychiatry global *Z*-score of cognitive functioning across all subjects (partial $r = .14$, $p = .029$). This relationship was strongest for the verbal learning subtest (partial $r = .18$, $p = .006$). Scatter plots depicting these correlations are presented in Figure S7 in Supplement 1. Motor thalamus hyperconnectivity was unrelated to cognitive functioning (partial $r = -.06$, $p = .319$). Neither PFC hypoconnectivity nor motor thalamus seed hyperconnectivity was related to positive, negative, and general symptoms from the PANSS (all r values $< .14$, $p > .101$). Consistent with the cortical ROI-to-ROI analysis presented earlier, PFC-thalamic seed connectivity was lower in nonaffective psychosis compared with affective psychosis at the trend significance level after controlling for age, sex, and illness stage ($F_{1,143} = 2.86$, $p = .093$) (Figure S8 in Supplement 1). Motor functional connectivity did not differ between psychotic disorders ($F_{1,143} = .12$, $p = .730$).

DISCUSSION

We confirmed that the combination of reduced PFC-thalamic connectivity and somatomotor-thalamic hyperconnectivity observed in prior investigations of chronic patients is present in the early stage of psychosis. Models of the etiology of psychotic disorders have oscillated over time between neurodegenerative and neurodevelopmental models (30). Mounting evidence indicates that both processes are likely involved; some abnormalities are detected early in the course of psychotic illnesses and remain relatively static, whereas other abnormalities emerge over time and progressively worsen (31,32). Based on earlier findings in chronic patients, we hypothesized that reduced PFC-thalamic connectivity and increased somatomotor-thalamic connectivity in psychosis may result from abnormal late brain maturation that derails the normal development of PFC-thalamic circuitry and refinement of somatomotor-thalamic connectivity (10). The current results obtained from a sample of early-stage patients are consistent with a neurodevelopmental explanation for thalamocortical dysconnectivity. Nonetheless, our results, while consistent with neurodevelopmental models, cannot definitively confirm that thalamocortical network abnormalities result from atypical neurodevelopment. It remains possible that thalamocortical dysconnectivity emerges before or at the onset of psychosis. Recent findings from a cross-sectional investigation showing reduced dorsal caudate connectivity with PFC and thalamus in individuals at high risk for psychosis further support a developmental basis for thalamic dysconnectivity (33). Longitudinal investigations of high-risk/prodromal patients will be useful in further pinpointing the timing and clarifying the functional relevance of cortico-striatal-thalamic dysconnectivity.

The present investigation also clarifies the anatomical specificity of thalamic circuitry abnormalities. Prior studies investigated either connectivity of large swaths of cortex with the thalamus or connectivity of the whole thalamus with the rest of the brain. The former approach provides excellent anatomical specificity within the thalamus but at the cost of cortical specificity [e.g., (10)], while the second approach provides better specificity within the cortex and rest of the brain but by treating the thalamus as a homogeneous structure it obscures network specific abnormalities [e.g., (12)]. Using a combination of ROI-to-ROI and seed-to-voxel approaches, we found that the anterior/medial-dorsal region of the thalamus is functionally connected to medial and dorsolateral PFC, mid cingulate, inferior parietal lobule, striatum, primarily the caudate, and cerebellum. The connectivity profile of the anterior/medial-dorsal thalamus bears a striking resemblance to the fronto-parietal or executive control network that has been linked to a range of higher cognitive functions often impaired in psychotic disorders, including working memory, cognitive flexibility, initiation, and inhibition (29). Consistent with our findings, human lesion and animal electrophysiology studies support a role for the mediodorsal thalamus in executive cognitive functions and memory (34–39). Both task-based and resting-state imaging studies have repeatedly found abnormal executive control network function in psychotic disorders; however, most investigations focused on cortical components and cortico-cortical connectivity of this network (40–42). Recently, reduced PFC-caudate was identified in first-episode psychosis (43). The current results deepen our understanding of executive control network dysfunction in psychosis by showing that dysconnectivity within this network extends to the thalamus, is present in the early stage of the illness, and is related, albeit modestly, to cognition. Additionally, reduced thalamic connectivity with the cerebellum is particularly noteworthy as it further supports cortico-thalamo-cerebellum circuitry models of psychosis and is consistent with the growing appreciation of the cerebellum's role in cognition (1,44).

Consistent with a prior investigation (12), we found that PFC-thalamic hypoconnectivity and motor-thalamic hyperconnectivity were inversely correlated in psychosis, suggesting that they are related. Anatomical investigations of nonhuman primates have found that there is greater connectivity between mediodorsal thalamus and motor cortical areas than is often appreciated (45–47). Direct microinjection of gamma-aminobutyric acid agonists into the mediodorsal nucleus leads to increased motor activity and reduced dopamine metabolism in the PFC (48). Interestingly, a recent rodent electrophysiology investigation found that modest inhibition of mediodorsal nucleus activity disrupts PFC-thalamic functional connectivity and impairs cognition (34). Combined, these findings suggest that disruption of mediodorsal thalamus function may lead to reduced PFC-thalamic functional connectivity and a corresponding increase in motor-thalamic connectivity. Human neuroimaging and animal electrophysiology investigations examining the interrelationships between thalamic networks and the impact of selective cortical and thalamic lesions on multiple thalamic networks will help clarify the mechanisms underlying thalamocortical deficits in psychosis.

Our investigation has several limitations. First, it is unclear if functional dysconnectivity is a consequence of compromised anatomical connectivity. Altered thalamocortical structural connectivity has been reported in schizophrenia (49). However, brain regions exhibiting strong functional coupling do not always share a direct anatomical pathway, suggesting functional connectivity likely represents polysynaptic connectivity (50). Multi-modal investigations will be helpful in clarifying the nature of thalamocortical dysconnectivity. Anatomical connectivity methods may also improve localization of thalamic subregions, which are difficult to delineate using conventional anatomical imaging (51). The relatively small number of psychotic bipolar patients included in our sample is another limitation. The finding that reduced thalamic-PFC connectivity was more prominent in nonaffective psychosis should be considered preliminary, especially given evidence that other brain areas, such as the ventral anterior cingulate, exhibit similar patterns of dysconnectivity in psychotic bipolar disorder and schizophrenia (52). Similarly, our sample sizes were too small to examine diagnosis by illness stage effects. This may prove important, given evidence that cognitive impairment is more severe in nonaffective psychosis at the early stage of the illness, in contrast to the chronic stage when affective and nonaffective psychosis patients exhibit a similar degree of impairment (32).

In conclusion, we confirmed that the combination of PFC-thalamic hypoconnectivity and somatomotor-thalamic hyperconnectivity is present at both the chronic and early stages of psychotic disorders. These two features are related; lower

PFC-thalamic connectivity correlates with motor-thalamic hyperconnectivity, suggesting they result from a common pathophysiological mechanism. Moreover, thalamic hypoconnectivity is characterized by reduced connectivity between the anterior/medial-dorsal thalamus and the executive control network and correlated with cognitive functioning. Future studies are required to: 1) clarify the relationship between thalamocortical functional dysconnectivity and anatomical connectivity; 2) confirm that thalamic dysconnectivity, especially reduced connectivity with the PFC and executive control network, is more severe in nonaffective psychosis; and 3) determine if there is diagnosis by illness stage interactions.

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