

## Thalamocortical Anatomical Connectivity in Schizophrenia and Psychotic Bipolar Disorder

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**Background:** Anatomical connectivity between the thalamus and cortex, including the prefrontal cortex (PFC), is abnormal in schizophrenia. Overlapping phenotypes, including deficits in executive cognitive abilities dependent on PFC-thalamic circuitry, suggest disrupted thalamocortical anatomical connectivity may extend to psychotic bipolar disorder. We tested this hypothesis and examined the impact of illness stage to inform when in the illness course thalamocortical dysconnectivity emerges. **Methods:** Diffusion-weighted imaging data were collected on 70 healthy individuals and 124 people with a psychotic disorder (schizophrenia spectrum = 75; psychotic bipolar disorder = 49), including 62 individuals in the early stage of psychosis. Anatomical connectivity between major divisions of the cortex and thalamus was quantified using probabilistic tractography and compared between groups. Associations between PFC-thalamic anatomical connectivity and executive cognitive abilities were examined using regression analysis. **Results:** Psychosis was associated with lower PFC-thalamic and elevated somatosensory-thalamic anatomical connectivity. Follow-up analyses established that lower PFC-thalamic and elevated somatosensory-thalamic anatomical connectivity were present in both schizophrenia and psychotic bipolar disorder. Lower PFC-thalamic anatomical connectivity was also present in early-stage and chronic psychosis. Contrary to expectations, lower PFC-thalamic anatomical connectivity was not associated with impaired executive cognitive abilities. **Conclusions:** Altered thalamocortical anatomical connectivity, especially reduced PFC-thalamic connectivity, is a transdiagnostic feature of psychosis detectable in the early stage of illness. Further work is required to elucidate the functional consequences of the full spectrum of thalamocortical connectivity abnormalities in psychosis.

**Key words:** psychosis/thalamus/cortex/anatomical/connectivity/diffusion

### Introduction

Characterizing brain abnormalities, establishing phenotypic boundaries between disorders, and uncovering the neural substrates of symptom dimensions are critical challenges in psychiatry. In the case of psychotic disorders, there is considerable evidence that the thalamus is abnormal. Consistent findings include reduced volume, altered activity during cognition, and decreased expression of neurochemical markers of neuronal integrity.<sup>1–7</sup> These findings prompted the development of several models of thalamic dysfunction, many of which emphasize disruption of thalamic interactions with the prefrontal cortex (PFC) in the etiology of psychosis and mechanisms of cognitive impairment.<sup>8–14</sup>

Thalamocortical models of psychosis are further supported by neuroimaging studies showing that thalamocortical functional connectivity, including functional coupling between the PFC and thalamus, is altered during resting-state and task performance.<sup>15–17</sup> Findings from diffusion-weighted imaging (DWI) indicate that functional dysconnectivity is accompanied by disrupted white matter connectivity between cortex and thalamus.<sup>18,19</sup> For instance, we found that anatomical connectivity in schizophrenia is characterized by reduced PFC-thalamic and elevated somatomotor-thalamic connectivity,<sup>20</sup> replicating a prior small study by Marengo et al.<sup>21</sup> Moreover, reduced PFC-thalamic anatomical connectivity has been linked to cognitive impairment and abnormal PFC activation during working memory, which is consistent with thalamic models of psychosis, and animal

and human studies implicating PFC-thalamic connectivity in cognition.<sup>20–22</sup>

While compelling, critical questions remain unaddressed. First, it is unknown whether thalamic dysfunction extends to other psychotic disorders, primarily bipolar disorder with psychotic features (ie, psychotic bipolar disorder). Shared phenotypes, including overlapping deficits in executive cognitive functions supported by PFC-thalamic circuitry, suggests this may be the case.<sup>23,24</sup> Indeed, findings from resting-state functional magnetic resonance imaging (fMRI) studies indicate that disrupted thalamocortical functional connectivity is also present in bipolar disorder,<sup>25,26</sup> including psychotic bipolar disorder.<sup>27</sup> However, the thalamus is understudied in psychotic bipolar disorder and anatomical connectivity between cortex and thalamus has not been comprehensively assessed.

It is also unclear when thalamocortical dysconnectivity emerges and how it evolves over the course of illness. Most studies included individuals that had been ill for several years and/or did not explicitly examine the effect of illness stage. Resting-state fMRI studies suggest thalamocortical dysconnectivity is present early in the course of illness, possibly even before the onset of frank psychosis.<sup>27–29</sup> However, this has only been demonstrated in schizophrenia spectrum disorders. Studying both early and chronic stages will further inform our understanding of the etiology and course of thalamocortical anatomical dysconnectivity.

Building on prior work by our group and others, the present study sought to (1) confirm thalamocortical anatomical connectivity abnormalities observed in prior studies are present in a relatively large ( $n > 120$ ) cohort of individuals with a psychotic illness; (2) test the hypothesis that schizophrenia and psychotic bipolar disorder demonstrate similar thalamocortical abnormalities; (3) determine whether abnormalities in thalamocortical anatomical connectivity are present in both the early and chronic stages of psychosis; and (4) verify that associations between PFC-thalamic connectivity and impaired executive cognitive abilities observed in prior smaller studies hold up in a larger cohort of individuals with psychosis.

## Methods and Materials

### *Study Participants*

Two hundred and thirty-five individuals that completed a neuroimaging session that included a T1- and diffusion-weighted scan as part of their participation in a now completed study of thalamocortical networks in psychosis (1R01 MH102266) were initially included in this investigation. Data were collected between August 2014 and April 2019. Neuroimaging data from 41 individuals did not pass our quality assurance (QA) procedures described later. Therefore, the final study cohort comprised

194 participants: 70 healthy individuals and 124 individuals with a psychotic illness (schizophrenia spectrum:  $n = 75$ ; psychotic bipolar disorder:  $n = 49$ ). A subset of the healthy participants ( $n = 41$ ) and individuals with schizophrenia ( $n = 53$ ) were included in an earlier study by our group.<sup>20</sup> Consistent with prior studies from our group<sup>23</sup> and the critical period of psychosis hypothesis,<sup>30</sup> 62 individuals within the psychosis group were classified as early stage, defined as duration of psychotic illness  $\leq 2$  years (schizophrenia spectrum:  $n = 37$ ; psychotic bipolar disorder:  $n = 25$ ). The remaining 62 were considered chronic (schizophrenia spectrum:  $n = 38$ ; psychotic bipolar disorder:  $n = 24$ ). Demographic data are presented in [table 1](#) and [supplementary material](#), which also contains additional details of the study procedures. This study was approved by the Vanderbilt University Institutional Review Board. All subjects provided written informed consent prior to participating.

### *Neuropsychological Testing*

Study participants completed a brief neuropsychological assessment. Given our a priori interest in PFC-thalamic circuitry, testing concentrated on assessing the 3 domains of executive function identified by Miyake et al<sup>31</sup>: working memory, set-shifting/cognitive flexibility, and inhibition. The Wechsler Memory Scale-III (WMS-III)<sup>32</sup> Working Memory Index, Wisconsin Card Sorting Test-64 Card Version (WCST-64),<sup>33</sup> and AX-Continuous Performance Test (AX-CPT)<sup>34</sup> were administered to quantify working memory, set-shifting, and inhibition, respectively. The WMS-III Working Memory Index, WCST-64 total errors standard score, and d-prime from the AX-CPT served as the dependent variables. The Screen for Cognitive Impairment in Psychiatry (SCIP)<sup>35</sup> was also administered to quantify overall neuropsychological functioning.

### *Neuroimaging Data*

Neuroimaging data acquisition, preprocessing, and quantification of thalamocortical anatomical connectivity using probabilistic tractography are described in detail in [supplementary material](#). Briefly, a T1-weighted structural scan (1-mm isotropic resolution) and high-angular resolution diffusion-weighted imaging (HARDI) scan (60 directions, 2.5-mm isotropic resolution) were collected on each subject during a single imaging session on a 3T Philips Intera Achieva scanner. Image processing was performed on the Vanderbilt University Institute of Imaging Science XNAT platform.<sup>36</sup> Each subject's structural T1-weighted MRI was segmented into 133 cortical and subcortical brain structures.<sup>37</sup> Six bilateral cortical regions-of-interest (ROIs), created by combining selected cortical structures, and the thalamus were used as targets and the seed, respectively, in the probabilistic tractography analysis described later. The 6 cortical ROIs

**Table 1.** Sample Characteristics

					Statistics		
	Healthy Individuals		Psychosis		<i>t</i> / $\chi^2$	df	<i>P</i>
Sample size	70		124				
Gender (M/F)	44/26		85/39		0.65	1	.420
Race (W/AA/O)	51/14/5		91/28/5		0.98	2	.613
Age, mean (SD)	28.2	9.0	27.3	8.6	0.66	192	.508
Education, mean (SD)	16.0	1.9	13.9	2.1	7.06	192	<.001
Parental education, mean (SD)	14.9	2.3	15.0	2.6	0.21	191	.837
Premorbid IQ, mean (SD)	108.0	14.6	104.0	9.8	2.29	192	.023
Neuropsychological functioning, mean (SD)							
AX-CPT d-prime	3.5	0.7	2.7	1.1	5.61	192	<.001
WCST total errors standard score	107.4	12.5	95.8	13.9	5.43	165	<.001
WMS-III Working Memory Index	106.6	12.6	97.5	13.2	4.69	191	<.001
SCIP Composite Z-score	0.28	0.59	-0.69	0.84	8.46	192	<.001
Clinical characteristics							
Psychotic disorder (BP/SCZ)			49/75		—	—	—
Early stage/chronic			62/62		—	—	—
APD (yes/no)			95/29		—	—	—
Mood stabilizer (yes/no)			51/73		—	—	—
Age at illness onset, mean (SD)			22.0		5.9	—	—
Duration of illness (years), mean (SD)			5.8		7.4	—	—
PANSS positive, mean (SD)			15.3		9.0	—	—
PANSS negative, mean (SD)			12.5		5.0	—	—
PANSS general, mean (SD)			27.9		7.9	—	—
Depression (HAMD), mean (SD)			10.0		9.2	—	—
Mania (YMRS), mean (SD)			6.8		12.2	—	—
APD dose (CPZ equiv), mean (SD)			336.2		217.7	—	—

Abbreviations: AA = African American; APD = Antipsychotic Drug; BP = Psychotic Bipolar Disorder; C = Caucasian; CPT = Continuous Performance Test; CPZ = Chlorpromazine; F = female; HAMD = Hamilton Depression Scale; HI = Healthy Individuals; M = male; O = Other; PANSS = Positive and Negative Syndrome Scale; SCIP = Screen for Cognitive Impairment in Psychiatry; SCZ = Schizophrenia; WCST = Wisconsin Card Sorting Test; WMS = Wechsler Memory Scale; YMRS = Young Mania Rating Scale.

included the PFC, motor cortex/supplementary motor area, somatosensory cortex, posterior parietal cortex, temporal cortex, and occipital cortex (see [supplementary material](#) for an example segmentation).

All HARDI data underwent QA using an automated pipeline that includes visualization of HARDI data, and extraction of mean head translation and rotation in the X, Y, and Z directions and average number of voxels (in percent) rejected per gradient due to poor diffusion tensor imaging (DTI) model fitting.<sup>38</sup> QA included visual inspection of HARDI scans for artifacts and plotting the distributions for the 7 QA metrics (6 head motion parameters, DTI model fitting outliers) using stem and leaf plots to identify outliers (defined as greater than or equal to 3 times the interquartile range). T1-weighted anatomical scans and segmentation results were also visually inspected for imaging artifacts and segmentations failures. As noted above, 41 participants (8 healthy individuals; 33 individuals with psychosis) did not meet our QA standards: 10 scans were excluded due to imaging artifacts/segmentation failures based on visual inspection, and 31 were excluded for having an outlier value on one or more of the 7 HARDI scan QA metrics. Within the psychosis cohort, individuals excluded from the study due to

not meeting QA standards were significantly older, had a higher percentage of females, and later age of onset of psychosis compared with individuals with psychosis that were included in the study (see [supplementary material](#)).

Following QA, HARDI data preprocessing and probabilistic tractography were performed within FMRIB's Diffusion Toolbox (FDT) for FSL software package (<http://www.fmrib.ox.ac.uk/fsl/>). Briefly, seed-to-target tractography analyses were run using probtrackx2,<sup>39</sup> separately in each hemisphere, to quantify anatomical connectivity between the thalamus (ie, seed) and each of the 6 cortical ROIs (ie, targets). A distance-adjusted measure of overall connectivity with the thalamus was calculated for each cortical area from the seed-to-target voxel-wise images generated from probtrackx2. These values, expressed as “total connectivity” (in percent), served as the dependent variables for the primary analysis described later. In addition, voxel-wise probability maps were generated and used in the voxel-wise analysis described later.

### Statistical Analysis

For the analysis of total thalamic connectivity, left and right hemisphere connectivity values were averaged as

we did not have any a priori hypotheses regarding laterality, and to minimize the number of dependent variables. This resulted in six dependent variables per subject, one for each cortical target ROI. We first compared total thalamocortical anatomical values between healthy individuals and our complete psychosis cohort using independent groups *t*-tests with the critical alpha adjusted using the Bonferroni–Holm method for correcting for multiple comparisons. Subsequent analyses of diagnosis and illness stage/age effects focused on results surviving correction for multiple comparisons. Specifically, one-way analysis of variance (ANOVA) including healthy individuals, schizophrenia, and psychotic bipolar disorder groups was performed to determine whether schizophrenia and psychotic bipolar disorder demonstrate the same abnormalities in thalamocortical anatomical connectivity. Similarly, one-way analysis of variance (ANCOVA) with healthy individuals and illness stage (early stage, chronic) as the independent group variable and age included as a covariate were performed to determine whether early-stage and chronic psychosis demonstrate similar patterns of thalamocortical anatomical dysconnectivity. Associations between neuropsychological functioning and PFC-thalamic anatomical connectivity were examined using regression analyses with age, sex, and diagnostic group (model 1) as well as group  $\times$  connectivity interaction terms (model 2) entered as predictors of WMS Working Memory Index, WCST total errors standard score, and AX-CPT d-prime scores. The distributions of the cognitive variables were inspected prior to regression analysis using stem–leaf plots and outliers excluded from the regression analyses.

## Results

### *Thalamocortical Anatomical Connectivity in Psychotic Disorders*

Total connectivity of each cortical ROI with the thalamus in healthy individuals and the combined psychosis cohort are presented in [table 2](#). Psychosis was associated with

lower PFC-thalamic connectivity ( $t(192) = 2.72, P = .007$ ; effect size [Cohen's  $d$ ] =  $-0.41$ ) and higher somatosensory-thalamic connectivity ( $t(192) = 2.69, P = .008; d = 0.40$ ). As shown in [figure 1A](#), schizophrenia and psychotic bipolar disorder demonstrated similar patterns of thalamocortical dysconnectivity. Follow-up one-way ANOVAs were significant for both PFC ( $F(2,191) = 3.69, P = .027$ ) and somatosensory ( $F(2,191) = 3.66, P = .027$ ) anatomical connectivity with the thalamus. Post hoc contrasts indicated that PFC-thalamic connectivity was reduced in both schizophrenia ( $P = .015; d = -0.40$ ) and psychotic bipolar disorder ( $P = .032; d = -0.41$ ). Similarly, elevated somatosensory-thalamic anatomical connectivity was present in both schizophrenia ( $P = .025; d = 0.41$ ) and psychotic bipolar disorder ( $P = .019; d = 0.43$ ). Although it did not survive correction for multiple comparisons in the initial analysis comparing healthy individuals to the combined psychosis cohort, one-way ANOVA for occipital-thalamic connectivity ( $F(1,191) = 3.63, P = .028$ ) was significant due to the fact that occipital-thalamic connectivity was higher in schizophrenia compared to both healthy individuals ( $P = .018, d = 0.40$ ) and psychotic bipolar disorder ( $P = .031, d = 0.40$ ). Complete statistical results as well as supplemental voxel-wise analyses confirming lower PFC-thalamic and elevated somatosensory-thalamic anatomical connectivity in psychosis are presented in [supplementary material](#).

### *Thalamocortical Anatomical Connectivity in Early Stage and Chronic Psychosis*

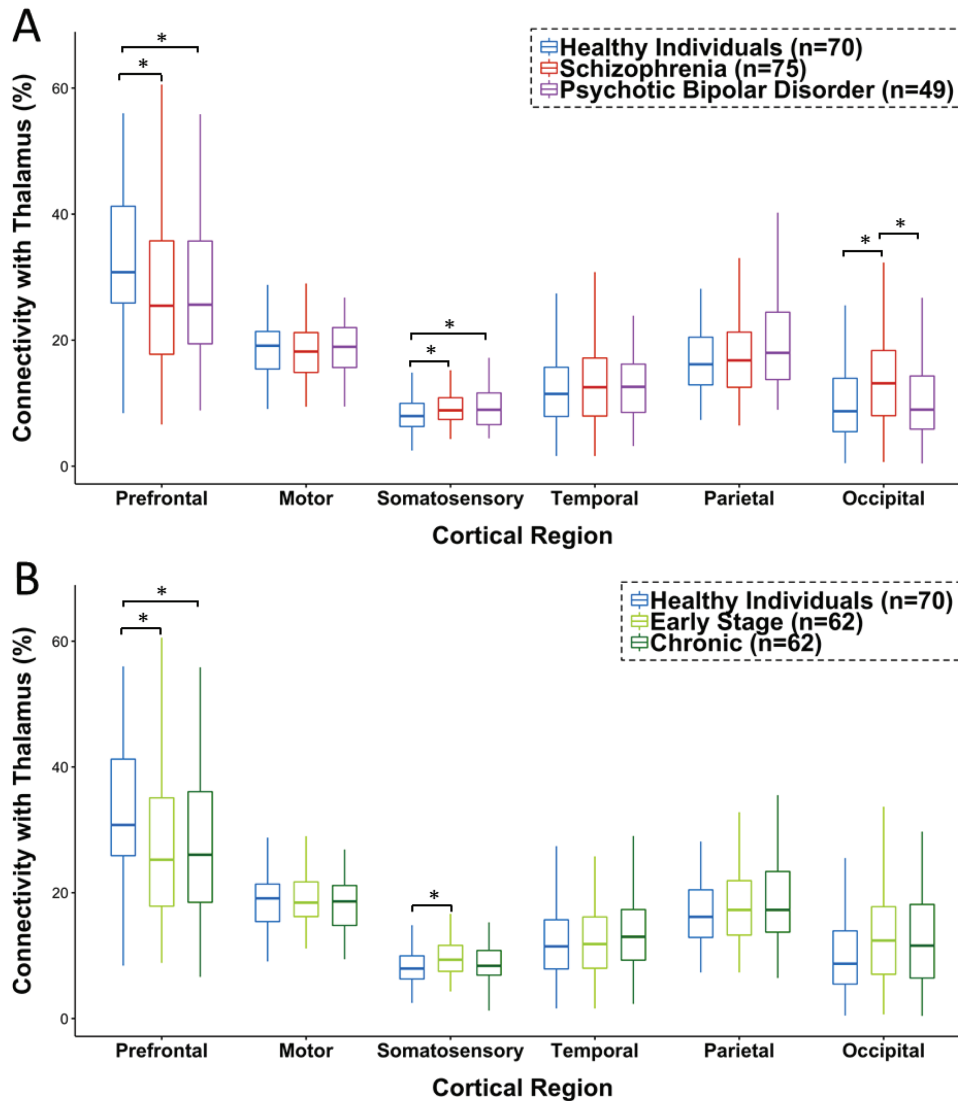
One-way ANCOVAs with healthy individuals and psychosis illness stage (early, chronic) entered as group variables and age as a covariate were significant for both PFC ( $F(2,190) = 3.71, P = .026$ ) and somatosensory ( $F(2,190) = 4.48, P = .013$ ) connectivity with the thalamus. As shown in [figure 1B](#), post hoc contrasts indicated that PFC-thalamic connectivity was lower in both chronic ( $P = .014, d = -0.40$ ) and early-stage psychosis at the trend level ( $P = .054, d = -0.42$ ). In contrast,

**Table 2.** Thalamocortical Anatomical Connectivity in Psychosis

	Healthy Individuals		Psychosis		Statistics		
	<i>n</i> = 70		<i>n</i> = 124		<i>t</i> *	<i>P</i>	Effect Size
	Mean	SD	Mean	SD			
Prefrontal cortex	32.39	12.46	27.43	12.00	2.72	.007	-0.41
Motor cortex	18.87	4.97	18.91	5.06	0.06	.953	0.01
Somatosensory cortex	8.13	2.78	9.40	3.36	2.69	.008	0.40
Temporal cortex	12.33	7.12	12.98	6.15	0.67	.505	0.10
Posterior parietal cortex	17.59	7.52	18.83	7.76	1.09	.279	0.16
Occipital cortex	10.70	7.30	12.44	7.42	1.58	.114	0.24

Note: Values for mean and SD indicate percent connectivity with thalamus; effect size = Cohen's *d*.

\*Degrees of freedom (df) = 192 for all *t*-statistics.



**Figure 1.** Anatomical connectivity between cortex and thalamus in psychosis. (A) Thalamic anatomical connectivity with the prefrontal cortex (PFC) is reduced in both schizophrenia and psychotic bipolar disorder. In contrast, anatomical connectivity between thalamus and somatosensory cortex is increased in schizophrenia and psychotic bipolar disorder. Occipital cortex connectivity with the thalamus is elevated in schizophrenia compared with both healthy individuals and psychotic bipolar disorder. (B) Within the combined psychotic disorders group (ie, schizophrenia plus psychotic bipolar disorder), PFC anatomical connectivity with the thalamus is reduced in both chronic and early-stage psychosis. Elevated somatosensory anatomical connectivity is present only in early-stage psychosis. See text and [supplementary material](#) for complete statistical results. \* $P < .05$ .

compared with healthy individuals, somatosensory-thalamic connectivity was elevated in early stage ( $P = .003$ ,  $d = 0.63$ ), but not chronic psychosis ( $P = .152$ ,  $d = 0.24$ ). Additionally, a 2-factor ANCOVA with illness stage (early, chronic) and diagnosis (schizophrenia, psychotic bipolar disorder) and age and sex as covariates was performed within the psychosis cohort to determine whether the trajectories of thalamocortical anatomical connectivity differ between schizophrenia and psychotic bipolar disorder. There was no evidence of diagnosis by illness stage interactions for either PFC- and somatosensory-thalamic connectivity indicating that illness stage effects did not differ as a function of psychotic

disorder diagnosis (see [supplementary material](#) for complete statistical results).

Emerging evidence indicates that both functional and anatomical connectivity of cortical networks demonstrate differential aging effects in psychotic disorder. For example, functional connectivity within frontoparietal and cingulo-opercular networks, and the integrity of cortical association white matter tracts show accelerated aging effects in psychosis compared to healthy individuals.<sup>40,41</sup> As such, we complemented the primary analysis of illness stage effects presented above with exploratory regression analyses examining the effects of age, group (healthy individuals, psychosis), and age  $\times$  group

interaction on thalamocortical connectivity. Results of these supplementary analysis are summarized in [supplementary material](#). Briefly, the age  $\times$  group interaction term did not reach significance for any thalamocortical network indicating that age effects were similar in healthy individuals and psychosis.

#### *Thalamic Anatomical Connectivity, Cognition, and Clinical Symptoms*

Compared with healthy individuals, WMS-III Working Memory Index, WCST-64 total errors standard score, and AX-CPT d-prime were impaired in psychosis (see [table 1](#)). Inspection of the distributions of the neuropsychological test variables identified outlier scores for the WMS Working Memory Index ( $n = 7$ ), WCST total errors standard score ( $n = 4$ ), and AX-CPT d-prime ( $n = 1$ ), which were excluded from the analyses reported below. Preplanned analysis focused on PFC-thalamic connectivity did not find any associations between total PFC-thalamic anatomical connectivity and WMS Working Memory Index, WCST total errors standard score, and AX-CPT d-prime (all  $t$  values  $< 1.72$ ,  $P > .088$ ). Adding diagnosis by connectivity interaction terms did not significantly improve model fit for any neuropsychological variable and none of the interaction terms reached significance (all  $t$  values  $< 1.41$ ,  $P > .161$ ).

We also performed exploratory partial correlation analyses examining associations between thalamocortical anatomical connectivity values and symptoms of psychosis (ie, Positive and Negative Syndrome Scale [PANSS] positive, negative, and general scores) controlling for age, sex, and psychotic disorder diagnosis. Total percent connectivity for all thalamocortical networks did not correlate with PANSS positive, negative, and general symptoms (all partial correlations  $< |.10|$ ,  $P > .278$ ).

#### *Thalamocortical Anatomical Connectivity, Antipsychotic Medication, and Substance Use*

We leveraged our relatively large psychosis cohort to explore the effects of antipsychotic medication and past substance disorder (SUD) on thalamocortical anatomical connectivity. As detailed in [supplementary material](#), thalamocortical anatomical connectivity did not differ between medicated ( $n = 95$ ) and unmedicated patients ( $n = 29$ ). Additionally, among patients taking antipsychotic medication, average daily dose of antipsychotic medication (in chlorpromazine equivalents) was unrelated to thalamocortical connectivity (all partial correlations controlling for age and sex  $< |.07|$ ,  $P > .507$ ).

Seventy-two of the 124 individuals in our psychosis cohort met DSM-IV criteria for past SUD. To explore the impact of past SUD on thalamocortical anatomical connectivity, we repeated the analyses comparing healthy individuals to psychosis after splitting our psychosis cohort

based on past SUD. Age was included as a covariate in this analysis. Briefly, effect of group remained significant for both PFC-thalamic ( $F(2,190) = 5.10$ ,  $P = .007$ ) and somatosensory-thalamic ( $F(1,190) = 4.26$ ,  $P = .015$ ) anatomical connectivity. Within the psychosis cohort, PFC and somatosensory cortex connectivity with the thalamus did not differ between patients with and without past SUD. However, lower PFC-thalamic anatomical connectivity was more pronounced in psychotic disorder with past SUD ( $P = .002$ ;  $d = -0.55$ ) than the subgroup with no history of SUD ( $P = .235$ ;  $d = -0.23$ ). In contrast, elevated somatosensory-thalamic anatomical connectivity was present in psychosis individuals without history of SUD ( $P = .005$ ;  $d = 0.53$ ) and those with history of SUD, at the trend significance level ( $P = .076$ ;  $d = 0.34$ ). Complete results are presented in [supplementary material](#).

#### **Discussion**

The present study quantified anatomical connectivity between the cortex and thalamus in psychotic disorders using DWI. We confirmed prior reports of reduced PFC-thalamic and elevated somatosensory-thalamic connectivity in a relatively large cohort of individuals with a psychotic disorder. Our hypothesis that abnormal thalamocortical connectivity, particularly anatomical connectivity between the PFC and thalamus, extends to psychotic bipolar disorder was confirmed. Moreover, reduced PFC-thalamic anatomical connectivity was present in both chronic and early stages of psychosis. In contrast, anticipated associations between PFC-thalamic anatomical connectivity and executive cognitive functioning were not detected.

Our investigation was motivated, in part, by the relative paucity of studies examining thalamocortical circuits in bipolar disorder and ongoing debate about whether schizophrenia and psychotic bipolar disorder are distinct disorders with unique neural substrates. The present study makes 2 important contributions to these issues. First, our findings inform the pathophysiology of psychotic bipolar disorder. Although disrupted thalamocortical anatomical connectivity has been identified previously, existing studies either focused on specific tracts or used methods that are ill-suited for identifying selective dysfunction among thalamocortical networks.<sup>42-48</sup> Moreover, no study has examined psychotic bipolar disorder specifically. The current results build on prior studies by localizing dysfunction to specific thalamocortical networks, further supporting models emphasizing PFC and thalamus involvement in bipolar disorder.<sup>7</sup>

Second, our results add to growing evidence that some brain abnormalities are shared across psychotic disorders. For instance, meta-analyses of structural MRI studies concluded that many abnormalities in brain structure observed in schizophrenia are also present in

bipolar disorder, including volume reductions in the PFC and thalamus.<sup>49–51</sup> As briefly reviewed earlier, resting-state fMRI studies indicate that psychosis is characterized by reduced PFC-thalamic functional connectivity; although few studies included psychotic bipolar disorder.<sup>25,27</sup> The present study extends these findings by demonstrating that reduced PFC-thalamic anatomical connectivity is present in both schizophrenia and psychotic bipolar disorder, thereby further questioning the strict dichotomization of psychotic disorders.

Confirmation that reduced PFC-thalamic anatomical connectivity is present in early-stage psychosis further strengthens the argument that thalamocortical dysconnectivity is involved in the pathophysiology of psychosis. Our results are consistent with prior reports of altered mediodorsal nucleus microstructure and anatomical connectivity in first episode and clinical high-risk individuals,<sup>18,22</sup> and dovetail nicely with evidence that thalamic functional dysconnectivity is detectable during the first 2 years of illness and may even precede the onset of a full-blown psychotic disorder.<sup>27,28</sup> Our findings may also inform ongoing debates about the trajectory of illness in bipolar disorder. In contrast to schizophrenia, which is typically considered a neurodevelopmental disorder, there is speculation that bipolar disorder is a neuroprogressive illness characterized by relatively normal premorbid brain development and progressive decline following illness onset.<sup>52,53</sup> The combination of reduced PFC-thalamic connectivity in early-stage psychosis and the absence of interactions between psychotic disorder diagnosis and illness stage implicate atypical neurodevelopment. Indeed, our group and others have hypothesized that disrupted thalamocortical connectivity in psychosis is a consequence of atypical brain maturation.<sup>20,27,54,55</sup> However, our findings do not rule out the possibility of neuroprogression in nonpsychotic bipolar disorder. Studies in psychotic and nonpsychotic bipolar disorder, ideally longitudinally, as well as mapping the normal developmental trajectories of thalamocortical circuits will further inform the etiology of thalamocortical dysconnectivity in schizophrenia and bipolar disorder.

Contrary to expectations based on a prior report<sup>21</sup> and our earlier analyses of a subset of these data,<sup>20</sup> PFC-thalamic anatomical connectivity was unrelated to impaired executive cognitive abilities in psychosis. Unfortunately, identifying reliably brain–behavior relationships remains elusive, even in well-characterized circuits, and many associations often fail to replicate.<sup>56</sup> Obstacles to identifying brain–behavior associations include small sample sizes, multifactorial nature of many cognitive constructs, and imperfect mapping of functions onto specific brain circuits.<sup>57</sup> It is possible that our approach, which quantifies connectivity of the whole PFC, rather than subregions, is too coarse to reliably identify cognition–connectivity associations. It is also possible that reduced PFC-thalamic anatomical connectivity may

be associated with more proximal measures of brain function, including PFC activation and functional connectivity during task performance,<sup>21</sup> than behavioral performance.

Although we were especially interested in PFC-thalamic connectivity given theoretical models of psychosis and the importance of PFC-thalamic circuitry to cognitive abilities often impaired in psychosis, our analyses also revealed increased anatomical connectivity between somatosensory cortex and thalamus in psychosis. The combination of reduced PFC and enhanced sensory connectivity is consistent with functional connectivity studies.<sup>15,17</sup> The relevance of elevated somatosensory anatomical connectivity to psychosis-related phenotypes is unclear as somatosensory-thalamic circuitry has received considerably less attention than other thalamic networks. Interestingly, abnormal motor behavior, including volitional motor activity, dyskinesia, and catatonia, has been linked to elevated motor-thalamic anatomical and functional connectivity in schizophrenia.<sup>58,59</sup> Moreover, increased thalamic functional connectivity with primary motor cortex is associated with psychomotor slowing in clinical high-risk individuals.<sup>60</sup> Similar associations may extend to somatic perceptual abnormalities and somatosensory-thalamic dysconnectivity.

Our study has several limitations that should be considered when interpreted the results. Exploratory analyses revealed that, although there were no differences between psychosis patients with and without past SUD, only the subgroup of psychosis participants with past SUD exhibited reduced PFC-thalamic anatomical connectivity compared with healthy individuals. Although the findings suggest that substance use might exacerbate PFC-thalamic dysconnectivity, the results should be interpreted very cautiously as there are numerous caveats to the analysis. Patients with past SUD were combined into a single group regardless of the type(s) of drug abused. Moreover, the groups differed on several demographic and clinical variables. Thalamocortical circuitry has been implicated in both the etiology<sup>61</sup> and consequences<sup>62</sup> of substance abuse. Therefore, it is unclear if thalamocortical dysconnectivity is a cause or consequence of substance abuse. Regardless, our findings underscore the need for additional research on the effects of SUD on thalamocortical connectivity.

Additionally, approximately 20% ( $n = 33/157$ ) of our original psychosis cohort did not meet our QA criteria and were excluded from the analysis. Demographic differences between included and excluded participants may affect generalization of our findings to the broader population of individuals with a psychotic disorder. Relatedly, the relatively low level of psychosis symptoms may have limited our ability to detect associations between thalamocortical anatomical connectivity and psychotic symptoms. Variability in the size of the cortical seeds may also affect sensitivity of probabilistic tractography

to detecting group differences. Finally, our study may have been underpowered to detect subtle differences between schizophrenia and psychotic bipolar disorder. For instance, post hoc analyses revealed increased occipital-thalamic connectivity in schizophrenia compared with healthy individuals and psychotic bipolar disorder. This finding warrants further investigation given evidence that visual hallucinations are more common in schizophrenia than affective psychoses.<sup>63</sup>

In sum, the current findings identify common thalamocortical anatomical dysconnectivity in schizophrenia and psychotic bipolar disorder that emerges early in the illness course. These results converge with established functional connectivity abnormalities in psychotic disorders. Further work is required to elucidate the functional consequences of thalamocortical anatomical dysconnectivity, including both compromised PFC-thalamic connectivity and exaggerated somatosensory-thalamic connectivity, and clarify the potential effects of substance abuse on thalamic circuitry.

### Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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