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An Activation Likelihood Estimate Meta-analysis of Thalamocortical Dysconnectivity in Psychosis

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ABSTRACT

BACKGROUND: Thalamocortical dysconnectivity is hypothesized to underlie the pathophysiology of psychotic disorders, including schizophrenia and bipolar disorder, and individuals at clinical high risk. Numerous studies have examined connectivity networks seeding from the thalamus during rest, revealing a pattern of thalamo-fronto-cerebellar hypoconnectivity and thalamosensory hyperconnectivity. However, given variability in these networks, as well as their relationships with clinical and cognitive symptoms, thalamocortical connectivity's status as a biomarker and treatment target for psychotic disorders remains unclear.

METHODS: A literature search was performed to identify thalamic seed-based connectivity studies conducted in patients with psychotic disorders. Activation likelihood estimate analysis examined the reported coordinates for hypoconnectivity (healthy control participants > patients with psychosis) and hyperconnectivity (patients with psychosis > healthy control participants). The relationship between hypoconnectivity and hyperconnectivity, as well as their relationships with clinical and cognitive measures, was meta-analyzed.

RESULTS: Each activation likelihood estimate included 20 experiments (from 17 publications). Thalamocortical hypoconnectivity was observed in middle frontal, cingulate, and thalamic regions, while hyperconnectivity was observed in motor, somatosensory, temporal, occipital, and insular cortical regions. Meta-analysis of the studies reporting correlations between hypo- and hyperconnectivity showed a strong negative relationship. Meta-analysis of studies reporting correlations between hyperconnectivity and symptoms showed small but significant positive relationships.

CONCLUSIONS: Activation likelihood estimates of thalamocortical hypoconnectivity revealed a network of prefrontal and thalamic regions, while hyperconnections identified sensory areas. The strong negative relationship between these thalamocortical deflections suggests that they arrive from a common mechanism and may account for aspects of psychosis. These findings identify reliable thalamocortical networks that may guide future studies and serve as crucial treatment targets for psychotic disorders.

Keywords: Activation likelihood estimate, Connectivity, Psychosis, Schizophrenia, Thalamocortical, Thalamus

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The thalamus holds a critically important role in the functional connectedness of the mammalian brain, with well-known relays to cortical, subcortical, and cerebellar regions (1). Given the role of the thalamus in aspects of sensory and cognitive processing (2,3), it is perhaps not surprising that pathology of the thalamus has been implicated in numerous psychiatric and neurologic disorders (4–7). Notably, thalamic disruptions have been hypothesized to play a crucial role in the development, presentation, and course of psychotic disorders such as schizophrenia and bipolar disorder (8–10). Psychotic disorders have been characterized by metabolic abnormalities in the thalamus, which have important implications for thalamic structure, function, and subsequent neural circuitry (11). As such, meta-analyses of individuals with schizophrenia and those at high genetic risk have previously shown both structural and functional abnormalities localized to the thalamus (12,13) and may subsequently characterize a psychosis endophenotype (14,15).

However, identifying the precise thalamic circuitry that characterizes psychotic disorders has remained a challenge. Over 2 decades ago, the cognitive dysmetria hypothesis of schizophrenia proposed an aberrant functional network, consisting of the thalamus, prefrontal cortex, and cerebellum, as a plausible marker of illness-related pathophysiology (16). Seminal studies relied on positron emission tomography to demonstrate disruptions in both task-based and resting-state functional activation of a prefrontal-thalamic-cerebellar circuit in patients with schizophrenia compared with healthy control (HC) subjects (17,18). Overall, this work suggested that network alterations accounted not only for aspects of perceptual and cognitive abnormalities observed in psychotic disorders, but also for disruptions in social functioning and outcome (16,19). Since that time, advances in neuroimaging and computational methodologies have continued to validate aspects of this hypothesis (20), with many honing in on

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dysfunctional connectivity of the thalamus as a crucial aspect of aberrant neural functioning in psychotic disorders (21,22).

The observation of both structural and functional thalamocortical dysconnectivity in schizophrenia and related psychotic disorders has been previously reviewed (23,24), and numerous individual studies have examined seed-based resting-state functional connectivity to examine its clinical significance. This type of analysis identifies the functional time course of the thalamus at rest and correlates that signal with all other voxels in the brain. The resulting brain map identifies brain regions whose time courses significantly correspond to that of the thalamus, suggesting that they are intrinsically connected. This approach has been carried out in numerous samples, including patients with schizophrenia or bipolar disorder and individuals at clinical high risk for developing psychosis (i.e., individuals experiencing attenuated or prodromal psychosis) and depression (25–29). In a large multisite sample, a thalamic seed-based analysis revealed a swath of regions across the cortex, subcortex, and cerebellum connected to the thalamus in both HC subjects and patients with schizophrenia (27). However, the contrast between control and psychiatric populations has illuminated hypo- and hyperconnected thalamocortical networks that may relate to illness course or severity and could highlight potential neural treatment targets.

Across numerous studies, consistent observations feature a pattern of thalamic functional hyperconnectivity (in patients with psychosis greater than in HC subjects) with sensory regions including the motor cortex, temporal cortex, and occipital regions. Limited observations have also shown that this pattern of hyperconnectivity may relate to aspects of psychosis (27,28) and even disease duration (30), leading to speculation that this functional circuitry may account for the pathophysiology of schizophrenia and related disorders. Conversely, thalamic hypoconnectivity (in HC subjects greater than in patients with psychosis) has been observed in relation to prefrontal, cerebellar, and thalamic regions (27,28) and has been shown to correspond to disruptions in cognition (31). These observations align with animal studies that have demonstrated a relationship between thalamoprefrontal projections and aspects of working memory and attention (32–34), offering insights on the clinical relevance of thalamocortical functional connectivity in psychotic disorders and how targeted interventions might modulate these networks.

However, while patterns of thalamocortical hyper- and hypoconnectivity have been observed across multiple studies of individuals with schizophrenia, bipolar disorder, and related psychotic disorders, other studies have failed to demonstrate this effect (35). And in studies that do identify hypo- and hyperconnectivity networks, the distinct spatial nature of these patterns remains unclear. For example, while some studies have observed thalamoprefrontal hypoconnectivity (25), other studies have not shown this relationship and instead observe hypoconnections localized to cerebellar regions (27). Similarly, while many studies have identified thalamocortical hyperconnectivity broadly throughout the sensory cortex, other studies have observed hyperconnectivity more localized to visual cortex (36,37). Clarifying such inconsistencies will be critical to more clearly understand this pathophysiology and to specify precise neural treatment targets. Activation likelihood estimate (ALE) is a spatial meta-analytic approach that models statistically significant coordinates from individual neuroimaging studies, offering probabilistic estimates of consistent brain activation across studies (38). Such an approach allows for an examination of the emerging corpus of studies investigating seed-based resting-state thalamocortical connectivity in psychotic disorders, thereby clarifying which brain areas consistently exhibit hyperconnectivity or hypoconnectivity. By establishing these patterns, this study hopes to clarify the specificity of a potential biomarker underlying psychotic disorders, as well as to characterize the relationship between this hypothesized biomarker to aspects of the symptoms and course of the illness.

To identify reliable thalamocortical networks in psychotic disorders, a systematic literature search was conducted to identify publications reporting the spatial coordinates of functional hypoconnectivity and hyperconnectivity networks. ALEs were carried out on the resulting hypoconnectivity and hyperconnectivity coordinates to reveal the spatial convergence of these networks. When available, meta-analyses were also performed on the correlations between hypoconnectivity and hyperconnectivity networks, as well as the correlation between hypoconnectivity or hyperconnectivity and psychiatric symptoms or cognition.

METHODS AND MATERIALS

Literature Search

The current study sought to identify studies that reported the results of experiments (in this case, an "experiment" was defined as a single mapwise contrast between a psychiatric population and HC subjects) examining differences between individuals on the psychosis spectrum and healthy subjects on measures of seed-based thalamic connectivity. A literature search was conducted in PubMed on January 1, 2019, using the search terms "((thalamocortical) OR (thalamo-cortical) OR (thalamus connectivity)) AND ((schizophrenia) OR (bipolar) OR (psychosis))." Inclusion criteria required experiments to 1) examine resting-state functional blood oxygen level–dependent (BOLD) activity in a whole-brain seed-based connectivity analysis; 2) seed from a thalamic or thalamic subregion of interest; 3) examine psychosis spectrum subjects including individuals with schizophrenia, bipolar I disorder, bipolar II disorder, or individuals at clinical high risk for psychosis; 4) compare subjects with psychotic disorder (PSY) to an HC sample; and 5) report findings in either Montreal Neurological Institute or Talairach space.

ALE Analysis

ALE analysis was conducted in GingerALE version 2.3.6 in the BrainMap environment (BrainMap Project, San Antonio, TX) (38–40). All experiment coordinates were entered into the database in Montreal Neurological Institute space. To calculate the ALE, GingerALE carries out multiple steps: First, modeled activation maps are built by forming Gaussians based on the experimental sample size around each data point or foci for each experiment. Second, the ALE image is then created by building an additive image of all of the modeled activation maps. Third, the probabilities of finding activation in each modeled activation map are combined to create a table of

p value scores that can then be used to make a three-dimensional p value image. Finally, significance thresholding can be performed on the resulting p value image. Consistent with recommendations from Eickhoff *et al.* (40,41), the current analysis used a cluster-level familywise error thresholding inference ($p < .05$) with 5000 permutations and an uncorrected cluster forming threshold ($p < .001$) to derive the ALE maps. Because each experimental entry reflected a contrast between two groups, the analysis relied on the n of the smaller of the two groups to more conservatively estimate the activation likelihood.

Correlation Meta-analysis

Among the studies identified in the literature search, Pearson correlation values examining the relationship between hypoconnectivity (HC > PSY) and hyperconnectivity (PSY > HC), as well as the relationship between cognition or symptoms and both hypoconnectivity and hyperconnectivity separately were assessed. For studies that examined the relationship with connectivity and symptoms in brain regions individually, individual region correlation values were converted from r to z using Fisher's transformation before taking the average across all reported regions. Meta-analyses were performed using the metafor package in R (version 3.5.1; R Foundation, Vienna, Austria) (42). All correlation values were converted to effect sizes using Fisher's r-to-z transformation before statistical modeling using the random-effects Hedges' estimator method. Likelihood of heterogeneity and subsequent publication bias was assessed using Cochrane's Q test for heterogeneity, though this test is known to have low inferential power in the case of small sample sizes such as in this study (43).

RESULTS

Literature Search Results

The literature search yielded 520 articles. After reviewing all titles and abstracts, 37 articles were identified for further methodological review. Of these, 17 articles met all methodological criteria for inclusion in the ALE analysis (see Supplemental Figure S1). Among the discarded articles, six did not use a seed-based method, six did not seed from a thalamus region of interest (ROI), five did not report whole-brain findings, one did not compare psychotic disorder subjects to HC subjects, one featured a subsample of subjects included in another experiment, and one study performed a thalamic seed-based analysis but reported null findings (i.e., no significant thalamocortical connectivity). The 17 retained articles included 20 experiments comparing HC subjects to subjects with psychotic disorder (HC > PSY) (Table 1) and 20 experiments comparing subjects with psychotic disorder to HC subjects (PSY > HC) (Table 1). These studies focused primarily on measurement of the BOLD signal from functional magnetic resonance imaging, with 38 of the experiments examining seed-based functional activation, one examining functional connectivity using a seed-based Granger causality analysis, and one using a seed-based measure of regional cerebral blood flow.

In the HC > PSY sample, the 20 experiments comprised 1272 unique HC subjects (321 HC subjects were used in contrasts for multiple experiments) and 1582 subjects with psychotic disorders, which resulted in 178 foci and an experimental n = 1426 (the lower n of the two contrast groups was used for each individual experiment). In the PSY > HC sample, the 20 experiments comprised 1590 psychotic disorder subjects and 1237 unique HC subjects, with 184 foci and an experimental n = 1440. The experiments varied in precise thalamus ROI placement (described in Table 1), with 21 studies focusing on functionally defined ROIs, 15 using established structurally defined atlas-based ROIs (e.g., Automated Anatomical Labeling Atlas, Harvard-Oxford Atlas), and four generating subject-specific individual ROIs based on subcortical segmentation procedures.

ALE Results

Significant ALEs characterizing thalamocortical hypoconnectivity (HC > PSY) were observed in five clusters highlighting thalamic and prefrontal areas including the right thalamus extending into the ventral lateral nucleus and substantia nigra, the left anterior cingulate gyrus, bilateral middle frontal gyrus, and left posterior cingulate gyrus (Figure 1, Table 2). ALEs characterizing thalamocortical hypoconnectivity (PSY > HC) were observed primarily in sensory regions including bilateral postcentral gyrus, bilateral middle temporal gyrus, left inferior temporal gyrus, right superior temporal gyrus, left transverse temporal gyrus, right insula extending into the claustrum, right paracentral lobule, and right precentral gyrus (Figure 1, Table 2).

Correlation Meta-analysis

From the 17 articles identified, only six experiments reported on the statistical relationship between thalamocortical hyperconnectivity and hypoconnectivity in the patients with psychotic disorders. The meta-analysis suggested a significant negative relationship between hyperconnectivity and hypoconnectivity (estimate = −0.78; confidence interval: −0.98 to −0.58; $p < .0001$) (Figure 2A), though this analysis was shown to have significant heterogeneity ($Q = 32.32$; $p < .0001$), and visual inspection of the funnel plot indicated a possible publication bias (Figure 2B). Next, among the included studies, seven experiments reported a relationship between hyperconnectivity and positive symptoms. The meta-analysis showed a small but significant effect, where positive symptoms positively correlated with hyperconnectivity (estimate = 0.10; confidence interval: 0.001 to 0.20; $p < .05$) (see Supplemental Figure S2). Only five experiments could be included in the meta-analysis examining correlated hyperconnectivity and negative symptoms (measured by the Positive and Negative Syndrome Scale), again showing a small but significant relationship (estimate = 0.14; confidence interval: 0.01 to .29; $p < .05$) (see Supplemental Figure S2). Similarly, five experiments characterized the correlation between "general" psychiatric symptoms (measured by the Positive and Negative Syndrome Scale) and hyperconnectivity, showing a small, significant effect (estimate = 0.17; confidence interval: 0.02 to 0.32; $p < .05$) (see Supplemental Figure S2). Only one study reported on the relationship between cognition and either hypoconnectivity or hyperconnectivity, so no meaningful meta-analyses could be performed.

Table 1. Studies Included in the ALE Analysis

Study	Connectivity Type	Experiment	*n*	Seed (Coordinates/Atlas)	Correlations
Hypoconnectivity (HC > PSY)					
Welsh *et al.*, 2010 (73)	Seed-based functional activation	HC > SZ	HC = 12; SZ = 11	Left and right MD nucleus (±7.5, −13.5, 7.5)	No reported significant correlations with clinical and/or cognitive variables
Anticevic *et al.*, 2014 (28)	Seed-based functional activation	HC > SZ	HC = 90; SZ = 90	Individual anatomically defined bilateral thalamus (FreeSurfer Segmentation)	No reported significant correlations with clinical and/or cognitive variables
Anticevic *et al.*, 2014 (72)	Seed-based functional activation	HC > BPP	HC = 56; BPP = 33	Anatomically defined MD and LGN (Oxford Thalamic Connectivity Atlas)	No reported significant correlations with clinical and/or cognitive variables
Anticevic *et al.*, 2014 (72)	Seed-based functional activation	HC > BPW	HC = 56; BPW = 40	Anatomically defined MD and LGN (Oxford Thalamic Connectivity Atlas)	No reported significant correlations with clinical and/or cognitive variables
Anticevic *et al.*, 2015 (26)	Seed-based functional activation	HC > CHR	HC = 154; CHR = 243	Individual anatomically defined bilateral thalamus (FreeSurfer Segmentation)	Connectivity with hypoconnected regions negatively correlated with SOPS Positive symptoms
Lui *et al.*, 2015 (68)	Seed-based functional activation	HC > SZ	HC = 59; SZ = 37	Right thalamus ROI (18, −12, 9)	Reduced connectivity with right MFG positively correlated with reduced GAF scores
Wang *et al.*, 2015 (74)	Seed-based functional activation	HC > SZ	HC = 72; SZ = 60	Anatomically defined bilateral thalamus (AAL)	No reported significant correlations with clinical and/or cognitive variables
Zhu *et al.*, 2015 (75)	Seed-based cerebral blood flow	HC > SZ	HC = 94; SZ = 100	Functionally defined left thalamus (−20, −28, 2)	No reported significant correlations with clinical and/or cognitive variables
Woodward and Heckers, 2016 (31)	Seed-based functional activation	HC > EP	HC = 105; EP = 53	Functionally defined PFC thalamus (not reported)	Reduced connectivity with PFC correlated with cognitive impairment
Woodward and Heckers, 2016 (31)	Seed-based functional activation	HC > CP	HC = 105; CP = 95	Functionally defined PFC thalamus (not reported)	Reduced connectivity with PFC correlated with cognitive impairment
Bernard *et al.*, 2017 (67)	Seed-based functional activation	HC > SZ	HC = 88; SZ = 82	Functionally defined sphere in left posterior thalamus (−18, −18, 16)	No reported significant correlations with clinical and/or cognitive variables
Martino *et al.*, 2018 (71)	Seed-based functional activation	HC > SZ	HC = 82; SZ = 112	Left and right thalamus ROIs (Harvard-Oxford Atlas)	No reported significant correlations with clinical and/or cognitive variables
Ferri *et al.*, 2018 (27)	Seed-based functional activation	HC > SZ	HC = 178; SZ = 183	Anatomically defined bilateral thalamus (TD Atlas)	Reduced connectivity with the right posterior cerebellum negatively correlated with SAPS Total Positive symptoms
Hua *et al.*, 2018 (30)	Seed-based functional activation	HC > SZ	HC = 14; SZ = 14	7 anatomically defined thalamic subregions (Oxford Thalamic Connectivity Atlas)	No reported significant correlations with clinical and/or cognitive variables
Lencer *et al.*, 2019 (69)	Seed-based functional activation	HC > PSY	HC = 50; PSY = 88	Left and right thalamus ROIs (−12, −12, 3, and 15, −12, 9)	No reported significant correlations with clinical and/or cognitive variables
Penner *et al.*, 2018 (70)	Seed-based functional activation	HC > SZ	HC = 24; SZ = 24	Left and right pulvinar nucleus (±12, −27, 5)	Reported nonsignificant mapwise correlations with SANS and SAPS
Tu *et al.*, 2018 (25)	Seed-based functional activation	HC > SZ	HC = 160; SZ = 100	Anatomically defined bilateral thalamus (not reported)	Reported weak nonsignificant correlations with PANSS Total
Tu *et al.*, 2018 (25)	Seed-based functional activation	HC > BP1	HC = 160; BP1 = 100	Anatomically defined bilateral thalamus (not reported)	No significant correlations with clinical and/or cognitive variables
Tu *et al.*, 2018 (25)	Seed-based functional activation	HC > BP2	HC = 160; BP2 = 88	Anatomically defined bilateral thalamus (not reported)	No reported significant correlations with clinical and/or cognitive variables

Table 1. Continued

Study	Connectivity Type	Experiment	*n*	Seed (Coordinates/Atlas)	Correlations
Yamamoto *et al.*, 2018 (37)	Seed-based functional activation	HC > SZ	HC = 34; SZ = 29	Functionally defined left thalamus (−6, −10, 0)	No reported significant correlations with clinical and/or cognitive variables
Hyperconnectivity (PSY > HC)					
Anticevic *et al.*, 2014 (28)	Seed-based functional activation	SZ > HC	SZ = 90; HC = 90	Individual anatomically defined bilateral thalamus (FreeSurfer Segmentation)	Connectivity with all hyperconnected regions positively correlated with PANSS Total
Anticevic et al., 2014 (72)	Seed-based functional activation	BPP > HC	BPP = 33; HC = 56	Anatomically defined MD & LGN (Oxford Thalamic Connectivity Atlas)	No reported significant correlations with clinical and/or cognitive variables
Anticevic *et al.*, 2014 (72)	Seed-based functional activation	BPW > HC	BPW = 40; HC = 56	Anatomically defined MD and LGN (Oxford Thalamic Connectivity Atlas)	No reported significant correlations with clinical and/or cognitive variables
Anticevic *et al.*, 2015 (26)	Seed-based functional activation	CHR > HC	CHR = 243; HC = 154	Individual anatomically defined bilateral thalamus (FreeSurfer Segmentation)	Connectivity with all hyperconnected regions positively correlated with SOPS Positive symptoms
Lui *et al.*, 2015 (68)	Seed-based functional activation	SZ > HC	SZ = 37; HC = 59	Right thalamus ROI (18, −12, 9)	Connectivity with bilateral cuneus positively correlated with BACS score
Lui *et al.*, 2015 (68)	Seed-based functional activation	BPP > HC	BPP = 57; HC = 59	Right thalamus ROI (18, −12, 9)	Connectivity with sensorimotor, superior frontal, and insula areas positively correlated with PANSS Negative symptoms and BACS scores
Wang *et al.*, 2015 (74)	Seed-based functional activation	SZ > HC	SZ = 60; HC = 72	Anatomically defined bilateral thalamus (AAL)	No reported significant correlations with clinical and/or cognitive variables
Woodward and Heckers, 2016 (31)	Seed-based functional activation	EP > HC	EP = 53; HC = 105	Functionally defined motor thalamus (not reported)	No reported significant correlations with clinical and/or cognitive variables
Woodward and Heckers, 2016 (31)	Seed-based functional activation	CP > HC	CP = 95; HC = 105	Functionally defined motor thalamus (not reported)	No reported significant correlations with clinical and/or cognitive variables
Bernard *et al.*, 2017 (67)	Seed-based functional activation	SZ > HC	SZ = 82; HC = 88	Functionally defined sphere in left posterior thalamus (−18, −18, 16)	Mapwise thalamus-M1 connectivity correlated with positive symptoms
Iwabuchi and Palaniyappan, 2017 (36)	Seed-based GCA	SZ > HC	SZ = 62; HC = 71	Left thalamus ROI (−12, −18, 9)	No reported significant correlations with clinical and/or cognitive variables
Martino *et al.*, 2018 (71)	Seed-based functional activation	SZ > HC	SZ = 112; HC = 82	Left and right thalamus ROIs (Harvard-Oxford Atlas)	Connectivity with sensorimotor cortex correlated with PANSS Total
Ferri *et al.*, 2018 (27)	Seed-based functional activation	SZ > HC	SZ = 183; HC = 178	Anatomically defined bilateral thalamus (TD Atlas)	Increased connectivity with right middle temporal gyrus positively correlated with SAPS Total Positive symptoms
Hua *et al.*, 2018 (30)	Seed-based functional activation	SZ > HC	SZ = 14; HC = 14	7 anatomically defined thalamic subregions (Oxford Thalamic Connectivity Atlas)	No reported significant correlations with clinical and/or cognitive variables
Lencer *et al.*, 2018 (69)	Seed-based functional activation	PSY > HC	PSY = 88; HC = 50	Right thalamus ROI (−12, −12, 3, and 15, −12, 9)	No reported significant correlations with clinical and/or cognitive variables
Penner *et al.*, 2018 (70)	Seed-based functional activation	SZ > HC	SZ = 24; HC = 24	Right MD nucleus (6, −7, 8)	Reported nonsignificant mapwise correlations with SANS and SAPS
Tu *et al.*, 2018 (25)	Seed-based functional activation	SZ > HC	SZ = 100; HC = 160	Anatomically defined bilateral thalamus (not reported)	Thalamus connectivity with left superior temporal cortex positively correlated with PANSS Total

Table 1. Continued

Study	Connectivity Type	Experiment	*n*	Seed (Coordinates/Atlas)	Correlations
Tu *et al.*, 2018 (25)	Seed-based functional activation	BP1 > HC	BP1 = 100; HC = 160	Anatomically defined bilateral thalamus (not reported)	No reported significant correlations with clinical and/or cognitive variables
Tu *et al.*, 2018 (25)	Seed-based functional activation	BP2 > HC	BP2 = 88; HC = 160	Anatomically defined bilateral thalamus (not reported)	No reported significant correlations with clinical and/or cognitive variables
Yamamoto *et al.*, 2018 (37)	Seed-based functional activation	SZ > HC	SZ = 29; HC = 34	Functionally defined left thalamus (−6, −10, 0)	Mapwise thalamus-occipital cortex connectivity correlated with flanker task performance

AAL, Automated Anatomical Labeling Atlas; ALE, activation likelihood estimate; BACS, Brief Assessment of Cognition in Schizophrenia; BP1, bipolar I disorder; BP2, bipolar II disorder; BPP, bipolar disorder with psychosis; BPW, bipolar disorder without psychosis; CHR, clinical high risk; CP, chronic psychosis; EP, early psychosis; GAF, Global Assessment of Functioning; GCA, Granger causality analysis; HC, healthy control; LGN, lateral geniculate nucleus of the thalamus; M1, primary motor cortex; MD, medial dorsal nucleus of the thalamus; MFG, middle frontal gyrus; PANSS, Positive and Negative Syndrome Scale; PFC, prefrontal cortex; PSY, psychotic disorders; ROI, regions of interest; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SOPS, Scale of Prodromal Symptoms; SZ, schizophrenia; TD, Talairach Daemon.

DISCUSSION

The current results support a dysconnectivity hypothesis of psychosis, characterized by significant likelihood of activation in both hypoconnected (HC > PSY) and hyperconnected (PSY > HC) resting-state thalamocortical functional networks among patients with schizophrenia or bipolar disorder or individuals at clinical high risk for developing psychosis. These results are consistent with findings from a network-based approach conducted by Cheng *et al.* (22) that identified weakened thalamoprefrontal connections and increased thalamoprimary somatosensory connections in a large sample of patients with schizophrenia (n = 415). The convergence of the current findings with network-based approaches (22,44) further establishes the replicability of these thalamocortical dysconnectivity networks. In a subset of the experiments contributing to the current analyses, there was a strong negative relationship between the two thalamocortical deflections, suggesting that hypoconnections and hyperconnections from the thalamus likely arrive from a common mechanism. Also observed were small but significant effects measuring the relationship between hyperconnectivity and psychiatric symptoms, including positive, negative, and general symptoms. However, these analyses were based on very small sample sizes, which in some cases were conducted post hoc and were subject to sample heterogeneity and possible publication bias; therefore, they should be interpreted cautiously. Though further evidence to demonstrate the sensitivity and specificity of these networks will be required, these findings offer support for thalamocortical functional hyper- and hypoconnectivity as a plausible biomarker for psychosis spectrum disorders.

Consistent with previous functional (20) and structural (45) investigations, thalamocortical hypoconnections were observed in areas associated with cognitive control, including bilateral dorsolateral prefrontal cortex and the anterior cingulate cortex. These regions are implicated in aspects of working memory and executive functioning (46) and are well understood to show reduced functional activation in both schizophrenia (47) and bipolar disorder (48). The current findings

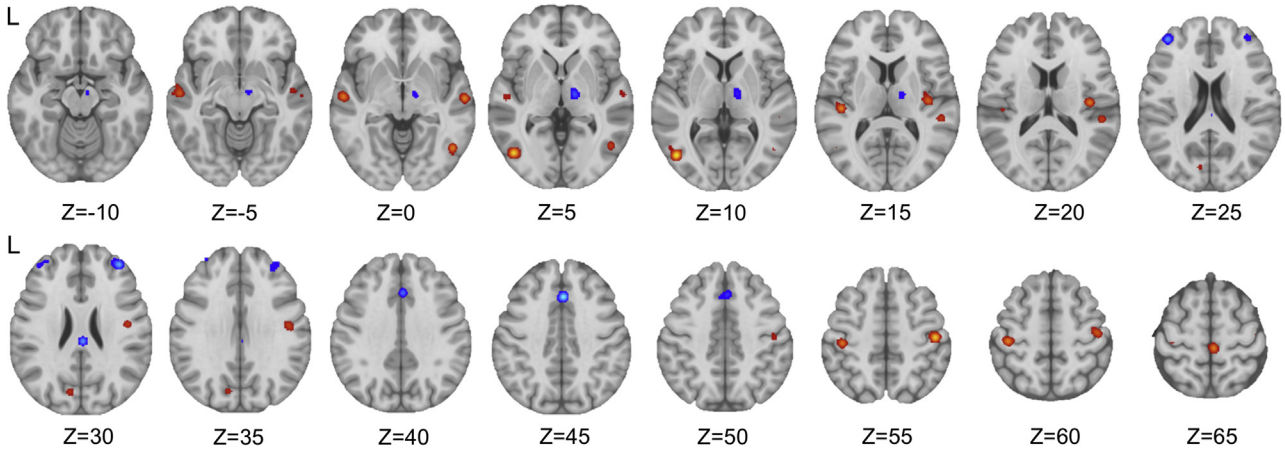

Figure 1. Thalamocortical hypoconnectivity and hyperconnectivity. Activation likelihood estimates of the thalamocortical hypoconnectivity network (blue) included regions of the bilateral middle frontal gyrus, anterior and posterior cingulate cortex, and right thalamus extending into the substantia nigra. Thalamocortical hyperconnectivity network (red = hot) revealed bilateral postcentral and sensory motor areas, bilateral temporal cortex, bilateral lateral occipital cortex, and right insula. L, left.

Table 2. MNI Coordinates of ALE Results

Cluster	Region	Brodmann Area	Volume (mm^3)	ALE Score (Extrema Value)	x	y	z
Hypoconnectivity (HC > PSY)							
1	Right thalamus	NA	1904	0.022939758	14	−14	0
	Right thalamus (ventral lateral nucleus)	NA		0.017444441	14	−10	10
	Right brainstem (substania nigra)	NA		0.014915778	8	−14	−14
2	Left anterior cingulate gyrus	32	1336	0.038475163	2	22	38
3	Right middle frontal gyrus	9	1312	0.033069264	38	48	24
4	Left middle frontal gyrus	10	1000	0.028804932	−40	48	22
5	Left posterior cingulate gyrus	23	640	0.028825257	2	−26	26
Hyperconnectivity (PSY > HC)							
1	Right postcentral gyrus	2	1680	0.037645694	48	−20	50
2	Left middle temporal gyrus	21	1592	0.031973608	−58	−12	-8
3	Left inferior temporal gyrus	37	1544	0.043373294	−46	−70	2
4	Right insula	13	1200	0.033475135	40	−16	12
	Right claustrum	NA		0.014680667	36	−8	8
5	Right paracentral lobule	6	1192	0.04256312	4	−28	64
6	Left postcentral gyrus	40	1184	0.03392417	−42	−26	52
7	Right superior temporal gyrus	22	1088	0.029271672	60	−14	−4
	Right superior temporal gyrus	22		0.015301475	52	−10	−10
8	Right middle temporal gyrus	37	952	0.030284904	48	−64	−4
9	Right precentral gyrus	6	792	0.023156233	46	−10	28
10	Left transverse temporal gyrus	41	744	0.02957679	−46	−24	10

All coordinates reported in MNI space.
ALE, activation likelihood estimate; HC, healthy control; MNI, Montreal Neurological Institute; NA, not applicable; PSY, psychotic disorders.

contextualize the thalamus's role in these previous observations, suggesting that thalamocortical feedback loops may be an important pathophysiological marker, and account for aspects of impaired cognition observed in psychotic disorders. However, despite being a theoretically plausible mechanism, very limited evidence demonstrates that thalamocortical prefrontal hypoconnectivity corresponds to deficits in cognition in psychosis. Only the Woodward and Heckers study (31) reported a small (r = .14), yet significant, effect relating thalamoprefrontal functional connectivity to a measure of global cognition, primarily driven by disruptions in verbal learning. Overall, it is unclear whether other studies either were unable to examine these relationships or did not report effects, making the relationship between thalamocortical connectivity and cognition a crucial area of further study.

Interestingly, the spatially largest ALE for the hypoconnectivity map was in the right thalamus itself. While this may have been a result of multiple studies seeding from a thalamic subregion or a unilateral functional ROI, it is worth noting that many studies seeding from the whole bilateral thalamus also observed hypoconnectivity to the thalamus itself (27,28). This may suggest that patients on the psychosis spectrum exhibit reduced local thalamic connectivity, which was demonstrated more directly by a recent study showing that short-distance functional disruptions in the thalamus are characteristic of patients with schizophrenia, bipolar disorder, and major depressive disorder (49). Thalamo-thalamo hypoconnectivity may also be accounted for by disruptions in corollary discharge (e.g., efference copies) observed in psychosis (50), wherein corticothalamic relays inefficiently exert ongoing communication with the thalamus (2), resulting in reduced synchronized activation. Another possibility is that thalamic hypoconnectivity reflects thalamic volume differences in patients with schizophrenia and other psychotic disorders (13), compared with HC subjects, such that reduced gray matter in specific thalamic subregions (i.e., medial dorsal thalamus) contributes less to the whole thalamic BOLD signal. It was also notable that there was no observed activation likelihood in cerebellar regions, despite numerous well-powered studies reporting thalamocortical hypoconnectivity with this structure more broadly. In the case of this ALE analysis, there may have been variability in the precise location of cerebellar connectivity or variability in spatial smoothing, and because this is a relatively large structure, consistent spatial activation was not observed from study to study.

In line with previous findings (22,51), thalamocortical hyperconnections identified in the ALE were observed in sensory regions including the motor cortex, somatosensory cortex, temporal cortex, and occipital cortex. Disruptions in motor functioning (52), auditory-sensory processing (53,54), and early visual processing (55,56) have all been observed previously in psychosis spectrum disorders and characterize aspects of the core features of psychotic disorders (57). Given the thalamus's critical role in sensory integration and subsequent cognitive processing (3), these observed hyperconnections may reflect source-monitoring deficits (58), resulting in aberrant sensory experiences in the form of hallucinations, delusional ideation, or disorganized thinking. In support of this explanation, the meta-analyses examining the relationship between psychiatric symptoms and thalamic hyperconnectivity to sensory regions showed small but significant relationships, wherein greater thalamosensory hyperconnectivity correlated with higher

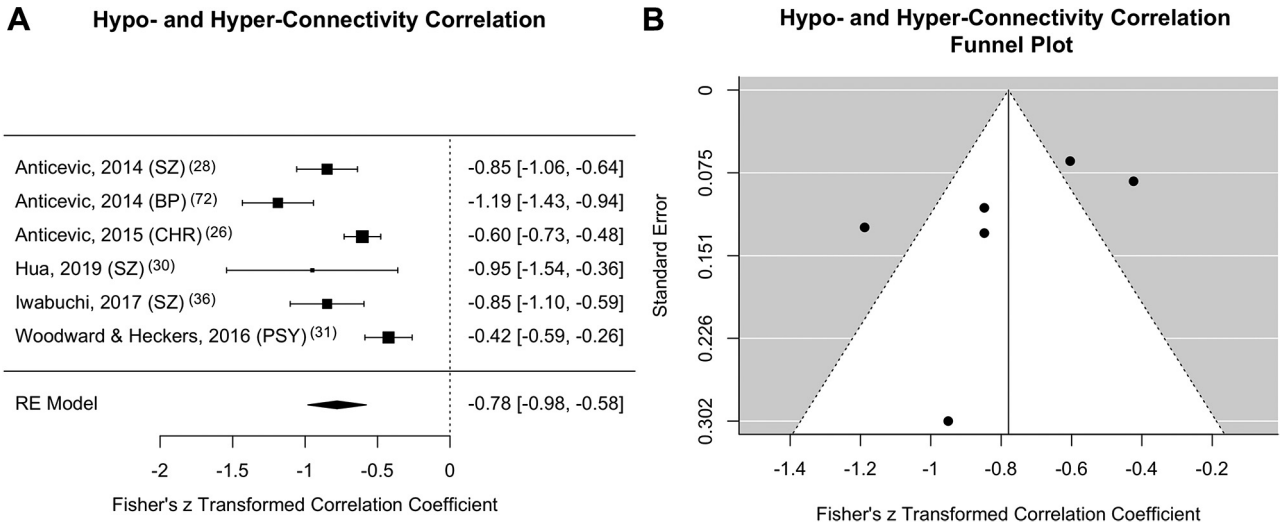

Figure 2. Meta-analysis of hypoconnectivity and hyperconnectivity correlations. **(A)** Forest and **(B)** funnel plots for the relationship between hypoconnectivity and hyperconnectivity in six experiments (patient population in parenthesis). BP, bipolar disorder; CHR, clinical high risk; PSY, psychotic disorder; RE, random-effects; SZ, schizophrenia.

positive, negative, and general symptom ratings. However, these effects remained small, variable, and largely nonspecific, and they should be interpreted cautiously given the small sample size and the fact that many studies likely did not report null findings. Nonetheless, this result may suggest that instead of being a primary mechanism underlying symptomology, thalamocortical connectivity reflects a general liability for psychosis symptoms more broadly or may be a contributing or secondary factor. One possibility is that thalamocortical dysconnections reflect *N*-methyl-D-asparate receptor dysfunction, which has been hypothesized to account for aberrant brain functioning and psychosis symptomology in disorders such as schizophrenia (59). Notably, drugs that block *N*-methyl-D-asparate functioning such as ketamine result not only in psychomimetic symptoms, but also have been shown to induce thalamocortical dysconnectivity (60,61), similar to that observed in the current ALE analysis.

Though few studies reported on the relationship between hypoconnectivity and hyperconnectivity, the studies that did reported a consistently strong negative relationship, suggesting that these intrinsic thalamocortical deflections are reciprocal and arise from a common mechanism. This interaction may be explained by an imbalance in top-down control (62), where thalamoprefrontal networks inefficiently regulate aspects of thalamosensory processing resulting in a range of positive, negative, and cognitive symptoms characteristic of psychosis. Another unifying hypothesis could be that thalamocortical dysconnectivity reflects aberrant predictive coding. Such an account proposes that in disorders such as schizophrenia, a mismatch between sensory experiences and prior expectations may result in the constellation of hallucinations, delusions, and cognitive deficits exhibited in psychotic disorders (63). Indeed, sensorimotor control may play an important role in this, with downstream effects on aspects of decision making and symptom expression (64). These results also introduce thalamocortical circuitry as a viable treatment target, wherein by enhancing or otherwise modulating these circuits, patients may show reductions in symptoms and subsequent improved functioning. Such an effect has been demonstrated in an animal model of psychosis, where enhanced thalamoprefrontal connectivity reflected improvements in working memory (33). In adults with schizophrenia, working memory–focused cognitive training was shown to enhance thalamoprefrontal connectivity and to coincide with improvements in global cognition (65). This suggests that thalamocortical deflections may be neuroplastic and possibly responsive to targeted training, targeted pharmacotherapy, or other neuromodulatory interventions such as transcranial electrical stimulation or transcranial magnetic stimulation.

Another noteworthy observation related to the effects of medication status and whether exposure or dose of antipsychotic medication may influence thalamocortical connectivity. Previous work has established that antipsychotic medications can influence neural activation and subsequent connectivity (66), leading to hypotheses about its effects on thalamocortical circuitry. Numerous experiments included in the current study controlled for the effects of medication, reporting no changes in the observed thalamocortical network (25,27,28,67), while others directly examined the relationship between chlorpromazine equivalents and thalamocortical connectivity, revealing no significant relationships (30,36,37,68–70). While unable to empirically test the relationships between antipsychotic medication status and thalamocortical connectivity, review of the findings among these studies suggests that aberrant thalamocortical connectivity reflects an illness state as opposed to an effect of anticholinergic burden. Further reinforcing this notion, consistent thalamocortical dysconnectivity patterns were observed in the study performed by Martino *et al.* (71), which examined treatment-naïve patients.

Study Limitations

The current findings are promising but were limited by a relatively small, but growing, body of studies contributing to the

sample size. Recent work suggests that a minimum of 17 experimental entries are required to be sufficiently powered to observe reliable ALEs (41), and though this study exceeds that minimum threshold, continued examination will likely be necessary to characterize these effects. To that end, this study was underpowered to examine either schizophrenia or bipolar disorder alone and was also not powered to compare these samples. However, in a post hoc comparison between the schizophrenia and bipolar groups, no significant ALEs were observed in a contrast. Relatedly, only a small subset of studies reported the relationship between thalamocortical deflections or the relationship between connectivity and symptoms or cognition. Multiple studies observed nonsignificant findings related to symptoms but did not report their test statistics. This obviously biases the results, limits the meta-analytic inferences to be drawn from these findings, and highlights an important gap in this area of research. Another limitation related to the imaging modalities summarized in these ALEs. While all included studies measured seed-based functional BOLD connectivity, a subset focused on regional cerebral blood flow or used a Granger causality approach. Because of the limited number of studies examining thalamocortical connectivity in psychosis, these studies were pooled. As the literature in this area grows, it will be important to replicate and expand on these findings among studies using comparable methods.

There were also limitations related to the variability in thalamic seeds used across experiments. While many studies relied on whole bilateral thalamic seeds, others used functional ROIs or seeds from specific thalamic nuclei. Given that the thalamus is not a unitary structure, but instead comprises a series of thalamic nuclei with specialized projections to different cortical, subcortical, and cerebellar regions (2), seeds in specific nuclei may have biased the current findings. For example, Anticevic *et al.* (72) specifically examined the medial dorsal and lateral geniculate nuclei, given their hypotheses about explicit connections to the prefrontal and visual cortex, respectively. Similarly, Woodward and Heckers (31) examined subregions of the thalamus found to be connected to the prefrontal or somatosensory cortex, highlighting similar networks. Both studies showed the expected hypoconnectivity and hyperconnectivity relationships in these regions, suggesting that these thalamocortical deflections may be localized to efferent projections from specific thalamic nuclei and may therefore better explain the specific roles of the thalamus in this context. This is consistent with other studies that have also demonstrated that different subthalamic seeds are likely to yield different functional networks (29). In this case, it may be that by combining whole and subthalamic ROIs in this meta-analysis, the individual connective contributions from subthalamic regions are being blurred by whole thalamic functional dysconnections. However, the current ALE was underpowered to compare specific thalamic nuclei connectivity to studies relying on a whole thalamus ROI. With improvements in the resolution of functional magnetic resonance imaging, as well as the prevalence of multimodal approaches (perhaps combining functional and structural/diffusion-weighted imaging modalities) to improve the spatial definition of thalamic nuclei, future studies may examine these relationships more closely, allowing for meta-analyses that will be better poised to determine whether specific thalamic subregions may be driving thalamocortical dysconnectivity. Lastly, there was limited ability to perform reliability checks on the literature search and coordinate extraction as ISR served as a solo author.

Conclusions

Thalamocortical dysconnectivity in psychotic disorders is consistently characterized by functional hypoconnectivity in prefrontal and thalamic regions and hyperconnectivity in sensory regions including motor, visual, and occipital cortex. These deflections may characterize a viable biomarker for psychosis illnesses including schizophrenia and bipolar disorder and for individuals at clinical high risk and may also relate to aspects of psychiatric symptoms and course. Further evidence of the sensitivity and specificity of this circuit will be necessary to definitively clarify this biomarker status or to otherwise demonstrate whether thalamocortical dysconnections characterize the psychosis spectrum or psychiatric illness more broadly. Finally, given its relationship to psychosis symptoms, as well as preliminary evidence of neuroplasticity in this circuit, thalamocortical dysconnectivity may be a crucial treatment target. Future work will be required to investigate the underlying mechanisms of this aberrant circuitry, both to better understand the role of thalamocortical connectivity in psychotic disorders and to develop novel interventions.

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ARTICLE INFORMATION

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