Severe neuropsychiatric conditions, such as schizophrenia, affect distributed neural computations. One candidate system profoundly altered in chronic schizophrenia involves the thalamocortical networks. It is widely acknowledged that schizophrenia is a neurodevelopmental disorder that likely affects the brain before onset of clinical symptoms. However, no investigation has tested whether thalamocortical connectivity is altered in individuals at risk for psychosis or whether this pattern is more severe in individuals who later develop full-blown illness.

To determine whether baseline thalamocortical connectivity differs between individuals at clinical high risk for psychosis and healthy controls, whether this pattern is more severe in those who later convert to full-blown illness, and whether magnitude of thalamocortical dysconnectivity is associated with baseline prodromal symptom severity.

In this multicenter, 2-year follow-up, case-control study, we examined 397 participants aged 12-35 years of age (243 individuals at clinical high risk of psychosis, of whom 21 converted to full-blown illness, and 154 healthy controls). The baseline scan dates were January 15, 2010, to April 30, 2012.

Whole-brain thalamic functional connectivity maps were generated using individuals' anatomically defined thalamic seeds, measured using resting-state functional connectivity magnetic resonance imaging.

Using baseline magnetic resonance images, we identified thalamocortical dysconnectivity in the 243 individuals at clinical high risk for psychosis, which was particularly pronounced in the 21 participants who converted to full-blown illness. The pattern involved widespread hypoconnectivity between the thalamus and prefrontal and cerebellar areas, which was more prominent in those who converted to full-blown illness ($t_{173} = 3.77, P < .001$, Hedge $g = 0.88$). Conversely, there was marked thalamic hyperconnectivity with sensory motor areas, again most pronounced in those who converted to full-blown illness ($t_{173} = 2.85$, $P < .001$, Hedge $g = 0.66$). Both patterns were significantly correlated with concurrent prodromal symptom severity ($r = 0.27, P < 3.6 \times 10^{-8}$, Spearman $\rho = 0.27, P < 4.75 \times 10^{-5}$, 2-tailed).

Thalamic dysconnectivity, resembling that seen in schizophrenia, was evident in individuals at clinical high risk for psychosis and more prominently in those who later converted to psychosis. Dysconnectivity correlated with symptom severity, supporting the idea that thalamic connectivity may have prognostic implications for risk of conversion to full-blown illness.
Schizophrenia is characterized as a neurodevelopmental disorder of distributed brain dysconnectivity, emerging from complex biological alterations that affect large-scale neural systems. Its symptoms are correspondingly pervasive, leading to lifelong disability for most patients and profound economic consequences. Understanding neural disturbances in schizophrenia constitutes a critical research goal that necessitates identification of pathophysiologic mechanisms and biomarkers that aid risk prediction. Growing sophistication in noninvasive neuroimaging offers a way to characterize large-scale neural system disturbances in psychiatric illness by studying low-frequency fluctuations in the blood oxygenation level-dependent (BOLD) signal at rest (i.e., via resting-state functional connectivity magnetic resonance imaging [rs-fcMRI]). This technique is increasingly applied to the study of neuropsychiatric conditions given its brief acquisition time, cost-effectiveness, and reproducibility based on the hypothesis that conditions such as schizophrenia are brain disorders that affect exchange of information across large-scale neural networks.

One such neural system, repeatedly implicated in schizophrenia, involves thalamocortical loops through which most neural computations flow. Thalamocortical systems have been studied extensively in humans using noninvasive neuroimaging. Both rs-fcMRI and structural diffusion studies in humans revealed that the thalamus is organized into parallel pathways that form information routes with the neocortex. This property makes the thalamus an ideal starting point and a possible lens into large-scale neural system disruptions in schizophrenia.

Indeed, several groups have recently reported disrupted thalamocortical functional connectivity in chronic schizophrenia. However, schizophrenia is a neurodevelopmental illness associated with brain abnormalities that likely occur before onset of all clinical symptoms. Currently, it is unknown whether thalamocortical dysconnectivity emerges exclusively in association with chronic illness or whether high clinical risk (CHR) and subsequent longitudinal conversion to full-blown illness (CHR-C), as opposed to nonconversion (CHR-NC), are also associated with functional thalamocortical disruptions. It is vital to address this question for 3 reasons: (1) to elucidate how incipient pathophysiologic stages of putative schizophrenia affect large-scale neural systems before full-blown symptoms emerge; (2) to establish whether disruptions in thalamocortical connectivity could provide viable neural markers associated with clinical risk before conversion; and (3) to extend recent discoveries while bypassing typical confounds associated with chronic illness (e.g., years of medication exposure).

In this study, we examined resting-state thalamocortical connectivity in the North American Prodromal Longitudinal Study (NAPLS) clinical high-risk sample. After obtaining baseline images, we longitudinally studied 243 CHR patients (21 CHR-C patients and 222 CHR-NC patients) and 154 healthy controls who were demographically similar to the clinical group. We tested the following 3 questions: (1) “Is CHR associated with thalamocortical dysconnectivity?” (2) “Is thalamocortical dysconnectivity more severe in CHR-C compared with CHR-NC patients?” and (3) “Is thalamocortical dysconnectivity associated with severity of psychotic symptoms at baseline?”

Methods

Participants

Our final sample included 243 CHR individuals (21 in the CHR-C group and 222 in the CHR-NC group) and 154 controls. All participants were recruited as part of the NAPLS 2 cohort and underwent rs-fcMRI at their baseline evaluations (eTable 1 in the Supplement). The study protocol and consent form were reviewed and approved by the institutional review boards at each of the 8 participating data collection sites (University of California, Los Angeles, Emory University, Harvard Medical School, Zucker Hillside Hospital, University of North Carolina, University of California, San Diego, University of Calgary, and Yale University). All participants provided written informed consent. All recruitment, symptom assessment, and longitudinal evaluation details are presented in eTable 1 in the Supplement.

All participants were between 12-35 years of age with IQ >70, no history of central nervous system disorders and no substance dependence in the past 6 months. The CHR sample met the Criteria of Prodromal Syndromes (COPS) following assessment with the Structured Interview for Prodromal Syndromes (SIPS) by experienced MA/PhD level clinicians. Participants were excluded for current or past diagnosis with Axis I psychotic disorders, including affective psychoses, as determined by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV (SCID). Other comorbid Axis I diagnoses, such as mood or anxiety disorders, were not exclusionary provided they did not account for the subject’s prodromal symptoms. There were no significant differences in substance use, anxiety, or age between CHR subjects who converted and those who did not. HCS were excluded if they met criteria for any prodromal syndrome, current or past psychotic disorder, or Cluster A personality disorder. HCS were also excluded for family history (first-degree relatives) of any disorder involving psychotic symptoms and for current use of psychotropic medication.

Neuroimaging Data Acquisition

Neuroimaging was performed at 8 sites. Five sites (University of California, Los Angeles, Emory University, Harvard University, University of North Carolina, and Yale University) used Siemens-Trio 3-T scanners (Siemens), 2 sites (Zucker Hillside Hospital and University of California, San Diego) used General Electric HDx Signa scanners (General Electric), and 1 site (University of Calgary) used a General Electric Discovery scanner (General Electric). All neuroimaging and functional connectivity analyses followed prior work and best practices in the clinical connectivity literature with details presented in the eAppendix in the Supplement.

Seed-Based Functional Connectivity Analysis Based on Thalamic Anatomy

Our seed-based approach followed a prior study using anatomically defined thalamic nuclei. In-house Matlab tools were used to examine thalamus connectivity with all gray matter voxels. We computed a seed-based thalamus correlation
map by extracting mean time series across all voxels in each participant’s bilateral thalamus (anatomically defined through Freesurfer-based segmentation\textsuperscript{[25,26]}. This entire thalamic signal was then correlated with each gray matter voxel, and the computed Pearson correlation values were transformed to Fisher z values using a Fisher r-to-z transformation, providing a map for each participant that was entered into second-level analyses in which each voxel’s value represented its connectivity with the whole thalamus (eAppendix in the Supplement). To examine between-group differences, all individual-subject maps were entered into appropriate second-level tests (either independent samples t-test or 1-way ANOVA) using a threshold-free cluster enhancement (TFCE) using a permutations. Type I error correction was determined via Fisher’s Randomize tool with 10,000 permutations for three between-group levels ([CHR-NC, CHR-C, HCS]), which were computed within FSL’s Randomize tool with 10,000 permutations. Type I error correction was determined via threshold-free cluster enhancement (TFCE) using a permutations. Type I error correction was determined via

**Results**

**Association of Psychosis Risk and Thalamic Dysconnectivity**

We tested whether the risk of psychosis was associated with thalamocortical dysconnectivity across the 21 participants in the CHR-C group, 222 participants in the CHR-NC group, and the 154 participants in the control group (computed via t-tests that the 2 disruptions represent shared disturbances whereby individuals with most severe thalamic-sensory perturbations also have the greatest thalamo-prefrontal-cerebellar dysconnectivity. To test this hypothesis, we correlated the strength of connectivity from regions with reduced thalamic connectivity with regions with increased thalamic connectivity, explicitly following approaches in our prior work (Figure 2).\textsuperscript{12}

Across all participants, there was a highly significant negative relationship (N = 397, r = −0.58, P < 4.1 × 10\textsuperscript{−38}) between the 2 findings, which held for the CHR group (N = 242, r = −0.53, P < 1.2 × 10\textsuperscript{−39}): individuals with the most severe thalamic-sensory hyperconnectivity had the greatest thalamo-prefrontal-cerebellar hypoconnectivity. This pattern indicates that the 2 disruptions represent shared thalamocortical alterations, consistent with schizophrenia findings.\textsuperscript{12}

**Association Between Baseline Symptoms and Thalamic Dysconnectivity**

Next, to provisionally test the clinical significance of thalamic dysconnectivity, we examined its association with symptoms. We examined the composite score using the Scale of Prodromal Symptoms (SOPS; composite positive symptoms\textsuperscript{33} for 2 reasons. First, prior work\textsuperscript{12} in chronic schizophrenia identified a significant association between positive symptoms and thalamic-sensory-motor hyperconnectivity, providing strong a priori predictions. Second, we sought to circumvent stringent type I error correction arising from many exploratory comparisons. We correlated symptoms with connectivity measures separately for areas with reduced vs increased thalamic connectivity (ie, aggregate signal across yellow vs blue foci in Figure 1). We examined this association across all participants to remain maximally powered and motivated by a Research Domain Criteria\textsuperscript{33} strategy because low SOPS scores may exist even in the general population (eTable 1 in the Supplement). We identified a significant negative correlation between regions with thalamic hypoconnectivity and symptoms (r = −0.31, P < 9.54 × 10\textsuperscript{−10}, Spearman ρ = −0.32, P < 1.36


Figure 1. Regions With Between-Group Differences in Thalamic Connectivity

Significant between-group effects were found for 5 regions of interest (ROIs) after a 1-way analysis of variance F test using cluster protection after 10,000 permutations (see Methods). Results were visualized using surface-based and volume maps. All displayed foci revealed significant between-group effects within the thalamocortical masks identified in our prior work (in which patients with chronic illness exhibited robust thalamocortical disruptions; eAppendix and eTables 3 and 4 in the Supplement). Blue and yellow areas indicate regions where the F test is driven by a reduction or increase, respectively, in thalamic connectivity in the clinical high risk for psychosis (CHR) groups. Magnitudes (left) and distributions (right) across groups for each of the identified regions qualitatively illustrate the direction of the effect. Effect sizes (Hedge g [Hg]) reflect the shift for the CHR converted to full-blown illness (CHR-C) group relative to controls. For a complete list of regions and statistics, see the Table. We used the Hg as a measure of effect size to account for differences in sample size between the CHR-C and CHR-nonconversion (CHR-NC) groups. Error bars indicate ±1 SEM. The histograms are based on the data extracted from the F map presented in the surface view panel. We present reduced-threshold pairwise effects in the eAppendix in the Supplement.

Association Between Medication and Thalamic Dysconnectivity

Last, we tested whether identified thalamic dysconnectivity was related to medication dose and/or status. We first correlated medication level (calculated via chlorpromazine equivalents) with magnitude of thalamic hyperconnectivity and hypoconnectivity across participants (×10^{-9} 2-tailed), which also held when we restricted analyses to those individuals who presented with symptoms (r = −0.21, P < .001, Spearman ρ = −0.22, P < .001, 2-tailed) and only to CHR patients (r = −0.14, P = .03, Spearman ρ = −0.32, P = .04, 2-tailed; eFigures 6 and 7 in the Supplement). There was also a significant positive correlation between SOPS scores and hyperconnectivity across participants (r = 0.21, P < 4.1 × 10^{-5}, Spearman ρ = 0.21, P < 4.8 × 10^{-5}; Figure 3), which did not survive when we restricted the analysis to symptomatic participants or CHR patients (eFigure 7 in the Supplement). To confirm that the 2 disturbances are related, we calculated the difference in magnitude of hyperconnectivity vs hypoconnectivity for each participant (ie, difference in connectivity for yellow vs blue foci in Figure 1). We correlated the magnitude of this connectivity difference with symptoms, which also revealed a significant association (r = 0.27, P < 3.6 × 10^{-6}, Spearman ρ = 0.27, P < 4.75 × 10^{-5}, 2-tailed), which held when we restricted analyses to those individuals who presented with symptoms (r = 0.17, P < .001, Spearman ρ = 0.14, P < .001, 2-tailed) but did not survive when restricted to CHR patients (eFigure 7 in the Supplement). Of note, we did not identify a significant association between identified thalamic dysconnectivity and SOPS scores at the 2-year follow-up.

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This analysis revealed no significant association, although there were modest trends (thalamic hyperconnectivity: \( r = 0.19, P = .19 \); thalamic hypoconnectivity: \( r = -0.2, P = .16 \); \( n = 50 \) medicated patients). The set trends simply that individuals who received higher doses of medication had greater thalamocortical dysconnectivity at baseline. Next, we tested whether effects differed as a function of medication status (because some individuals were medicated even at their baseline scans\(^\text{34} \)) (Figure 4). This analysis revealed that unmedicated patients in the CHR-C group (\( n = 17 \)) exhibited the most profound thalamic-sensory-motor hyperconnectivity (Figure 4), which significantly differed from the controls (\( t_{169} = 3.7, P < .001, 2\)-tailed, Hedge g = 0.81). This effect is the opposite of what one would expect if a medication confound were driving thalamic hyperconnectivity because medicated individuals had a milder profile. Medicated and unmedicated patients in the CHR-C group exhibited thalamic hypoconnectivity of similar magnitude (Figure 4). Again, the unmedicated patients in the CHR-C group significantly differed from the controls (\( t_{169} = 2.34, P = .02, 2\)-tailed, Hedge g = 0.31). These secondary medication analyses rule out the possibility that medication is driving the observed patterns.

### Discussion

Thalamic circuits feature prominently in theoretical models of schizophrenia\(^\text{17,35} \) and are implicated in empirical schizo-
Thalamic connectivity and conversion to psychosis

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Figure 3. Association Between Prodromal Schizophrenia Symptoms and Thalamic Dysconnectivity

Regions showing reduced (blue) and increased (yellow) thalamic connectivity. Significant positive association was found between thalamic connectivity across all areas showing increased connectivity (yellow regions) and composite positive symptoms on the Scale of Prodromal Symptoms (SOPS) across all participants \( (r = 0.21, P < 4.1 \times 10^{-5}, \text{Spearman } \rho = 0.21, P < 4.8 \times 10^{-5}) \). A significant negative association was found between thalamic connectivity across all areas showing reduced connectivity (blue regions) and composite positive symptoms on the SOPS across all participants \( (r = -0.31, P < 9.54 \times 10^{-10}, \text{Spearman } \rho = -0.32, P < 1.36 \times 10^{-9}, \text{2-tailed}) \). We computed a difference score between the regions showing hyperconnectivity (yellow) and hypoconnectivity (blue). The purpose of this calculation was to establish that the total magnitude of connectivity disruptions in either direction still relates to psychotic symptoms as opposed to these 2 patterns capturing independent sources of variability. We found a significant association between thalamic connectivity difference score and composite positive symptoms on the SOPS across all participants \( (r = 0.27, P < 3.6 \times 10^{-8}, \text{Spearman } \rho = 0.27, P < 4.75 \times 10^{-5}, \text{2-tailed}) \). For a figure presenting clinical high risk (CHR) patients only, see eFigure 7 in the Supplement. CHR-C indicates clinical high risk of psychosis converted to full-blown illness; CHR-NC, clinical high risk of psychosis not converted to full-blown illness; L indicates left; and R, right.

Risk for Psychosis and Thalamocortical Dysconnectivity

Schizophrenia is a neurodevelopmental disorder associated with genetic risk factors. However, indicators of its emerging pathophysiologic conditions remain poorly understood, with few viable neural markers that predict illness development and subsequent frank onset. This lack of at-risk endophenotypes for schizophrenia is compounded by the scarcity of well-established neural markers of chronic illness. The field has made progress in defining neural markers of cortical and subcortical dysfunction in schizophrenia through a combination of postmortem and neuroimaging studies examining structure, task-based activation, and functional and structural connectivity. This work has been enriched by resting-state studies mapping large-scale network disturbances in schizophrenia, during the past year, several groups independently replicated prominent thalamocortical disturbances in chronic schizophrenia. Although promising, this work has not addressed 2 vital questions. First, “Are the observed thalamocortical connectivity disturbances in part related to long-term medication effects?” Second, from a clinical standpoint, “Are these thalamocortical connectivity disturbances an exclusive feature of long-standing illness, or...
do they emerge during early illness stages?” The second question is particularly important for identifying neural markers that appear before progression to chronic illness.

We found that thalamocortical dysconnectivity was present in the CHR state before full-blown psychosis. The effects followed previously reported hyperconnectivity with sensory motor areas and hypoconnectivity with PFC and cerebellum (note that hyperconnectivity with other auditory and visual sensory regions was evident, although these regions did not survive more stringent thresholding). Both patterns were more severe for CHR-C patients, suggesting pathophysiologic relevance to the pathogenic cascade that culminates in psychosis. These effects address the limitations of prior long-term studies: because thalamocortical dysconnectivity in CHR patients closely mirrors effects reported in patients with chronic illness and these patterns were observed in unmedicated patients, it is unlikely that these alterations are driven by long-term pharmacotherapy. However, our analyses provisionally imply that medication may exert a beneficial effect by reducing thalamocortical hyperconnectivity.

Follow-up analyses revealed similar effects even at lower statistical thresholds (Figure 2). Furthermore, thalamic hyperconnectivity and hypoconnectivity were highly related across participants, suggesting a common system-wide disturbance (as reported in chronic schizophrenia10-12). Finally, the magnitude of thalamic dysconnectivity in both hyperconnected and hypoconnected regions predicted symptoms. The difference in magnitude between hyperconnectivity and hypoconnectivity also correlated with symptoms, supporting the hypothesis that the 2 effects constitute a shared, system-wide thalamic abnormality. By linking thalamic dysconnectivity with symptom levels before illness onset, these results support the hypothesis that the 2 effects constitute a shared, system-wide thalamic abnormality. By linking thalamic dysconnectivity with symptom levels before illness onset, these results support the hypothesis that the 2 effects constitute a shared, system-wide thalamic abnormality.

Regions with reduced (blue) and increased (yellow) thalamic connectivity, driven by the clinical high risk of psychosis (CHR) converted to full-blown illness (CHR-C). The association between medication status and thalamic hyperconnectivity indicated that CHR-C patients who remained unmedicated (CHR-C-UM) exhibited the most severe hyperconnectivity, significantly differing from controls (t_{Hedge} = 3.7, P < .001, 2-tailed, Hedge g = 0.81) and CHR patients who did not convert (CHR-NC) without medication (CHR-NC-UM) (t_{Hedge} = 2.27, P = .02, 2-tailed, Hedge g = 0.53). However, no significant difference was found between medicated (CHR-C-M and CHR-NC-M) and CHR-C-UM and CHR-NC-UM patients (t_{Hedge} = 0.46, P = .76). Again, CHR-C-UM patients exhibited significant reductions in thalamic connectivity with prefrontal cortex and cerebellar nodes relative to controls (t_{Hedge} = 3.34, P = .02, 2-tailed, Hedge g = 0.31) but not the other clinical groups. We used Hedge g as a measure of effect size to account for differences in sample sizes. Error bars indicate ±1 SEM. L indicates left; and R, right.

P < .05.

P < .001.

Implications for the Neurobiology of Schizophrenia Onset

Present findings are correlational given the indirect neuroimaging measure (BOLD fcMRI) and therefore cannot ad-
Thalamic Dysconnectivity and Conversion to Psychosis

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Thalamic Dysconnectivity and Conversion to Psychosis

Conclusions
This study establishes that thalamocortical dysconnectivity is present in CHR states before psychosis onset. We found that sensory motor and prefrontal-cerebellar thalamic dysconnectivity was more severe in the CHR-C patients. These effects are congruent with recent discoveries in patients with chronic illness, suggesting that brain-wide thalamocortical dysconnectivity is apparent even during incipient illness stages and may provide a sensitive marker for elevated clinical risk of full illness onset.

Dress upstream causal mechanisms. To map such upstream cellular mechanisms, translational research from animal experiments,56 experimental pharmacologic neuroimaging studies,56 and computational models can generate mechanistic and testable predictions.17,59-61 Schizophrenia likely involves alterations in glutamatergic, dopaminergic, and inhibitory gamma-aminobutyric acid (GABA) neurotransmission.3,38,39,59-62 Theoretical models of the illness repeatedly implicate these neurotransmitter systems in thalamo-striatal-cortical circuits, which may contribute to the observed alterations. It currently remains unknown which upstream mechanisms and at which locus (subcortical or cortical) produce such widespread thalamic dysconnectivity. One possibility may involve dysfunction of the N-methyl-D-aspartate receptor,63 hypothesized to occur in inhibitory interneurons.38-39,62 which affects the balance of neural excitation and inhibition64 in cortical circuits, producing brain-wide disturbances in thalamocortical information flow.

Limitations
Although medication effects were largely ruled out, some CHR patients were medicated. Thus, we correlated medication levels with magnitude of thalamocortical dysconnectivity, which did not reveal significant effects. Furthermore, we compared medicated and unmedicated CHR patients: although hypoconnectivity did not vary as a function of medication status, the hyperconnectivity profile was actually worse for unmedicated CHR patients, suggesting that medication did not drive primary effects. Another concern, present in all clinical connectivity studies, relates to head movement. We used careful movement-censoring methods for all data and used movement (percentage of frames scrubbed) as a covariate in the analysis, which did not alter effects (eAppendix in the Supplement). Movement levels did not significantly differ between CHR-NC and CHR-C patients (Table), increasing confidence that head movement did not drive effects. The data were pooled from multiple sites and scanners, introducing possible scanner bias and other site-specific effects on cohort recruitment and assessment. To mitigate this concern, we conducted 2 analyses: we confirmed that results remained despite using site as a covariate in the reported analysis (of note, there was a slight deviation from expected proportions revealed by a χ² test; eTable 2 in the Supplement). Another issue relates to the definition of risk: here, we studied individuals who were clinically symptomatic and seeking help and therefore presented with clinical elevated risk for psychosis conversion. Consequently, these findings cannot directly address whether genetic liability for schizophrenia is associated with the same pattern of thalamic dysconnectivity. We observed reported effects within a priori masks exhibiting thalamocortical dysconnectivity in our prior work25 but not at the whole-brain level. This finding may reflect restricted power because of the relatively smaller CHR-C group but also the possibility that the CHR state may be associated with weaker effects relative to the more robust patterns found in patients with chronic illness.5 In addition, although starting from the entire thalamus may be a well-justified first-pass approach (to remain sensitive to pan-thalamic disruptions), there may be important discrepancies across thalamic subnuclei that the current analysis did not consider.10,65

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