Archival Report

Biological Psychiatry: CNNI

Increased Thalamocortical Connectivity in Schizophrenia Correlates With Sleep Spindle Deficits: Evidence for a Common Pathophysiology

Bengi Baran, Fikret Işık Karahanoğlu, Dimitrios Mylonas, Charmaine Demanuele, Mark Vangel, Robert Stickgold, Alan Anticevic, and Dara S. Manoach

ABSTRACT

BACKGROUND: Converging evidence implicates abnormal thalamocortical interactions in the pathophysiology of schizophrenia. This evidence includes consistent findings of increased resting-state functional connectivity of the thalamus with somatosensory and motor cortex during wake and reduced spindle activity during sleep. We hypothesized that these abnormalities would be correlated, reflecting a common mechanism: reduced inhibition of thalamocortical neurons by the thalamic reticular nucleus (TRN). The TRN is the major inhibitory nucleus of the thalamus and is abnormal in schizophrenia. Reduced TRN inhibition would be expected to lead to increased and less filtered thalamic relay of sensory and motor information to the cortex during wake and reduced burst firing necessary for spindle initiation during sleep.

METHODS: Overnight polysomnography and resting-state functional connectivity magnetic resonance imaging were performed in 26 outpatients with schizophrenia and 30 demographically matched healthy individuals. We examined the relations of sleep spindle density during stage 2 non–rapid eye movement sleep with connectivity of the thalamus to the cortex during wakeful rest.

RESULTS: As in prior studies, patients with schizophrenia exhibited increased functional connectivity of the thalamus with bilateral somatosensory and motor cortex and reduced sleep spindle density. Spindle density inversely correlated with thalamocortical connectivity, including in somotosensory and motor cortex, regardless of diagnosis.

CONCLUSIONS: These findings link two biomarkers of schizophrenia—the sleep spindle density deficit and abnormally increased thalamocortical functional connectivity—and point to deficient TRN inhibition as a plausible mechanism. If TRN-mediated thalamocortical dysfunction increases risk for schizophrenia and contributes to its manifestations, understanding its mechanism could guide the development of targeted interventions.

Keywords: Functional connectivity, Schizophrenia, Sleep, Sleep spindles, Thalamic reticular nucleus, Thalamus

https://doi.org/10.1016/j.bpsc.2019.04.012

Converging lines of evidence implicate abnormal communication of the thalamus with the cortex in the pathophysiology of schizophrenia. Resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) studies, for example, consistently report increased thalamic connectivity with somatosensory and motor cortex in schizophrenia (1–8) and in individuals at clinical high risk for psychosis, in whom it predicts conversion to full-blown illness (9). Findings of decreased sleep spindle activity in patients with schizophrenia and their first-degree relatives also implicate abnormal thalamocortical interactions [for reviews, see (10,11)]. Sleep spindles are a defining electroencephalogram (EEG) oscillation of non–rapid eye movement stage 2 sleep (N2) and depend on thalamocortical circuitry for their expression (12–16). The goal of the present study was to determine whether abnormally increased thalamocortical functional connectivity correlated with sleep spindle deficits in schizophrenia, which would be consistent with the hypothesis that they reflect a common pathophysiology.

Sleep spindles are initiated in the thalamic reticular nucleus (TRN) (17), a thin netlike structure around the thalamus that receives collaterals from corticothalamic and thalamocortical neurons. Sleep spindles depend on these thalamocortical feedback loops for their propagation and synchronization across the cortex (13,14,18,19). Sleep spindles facilitate the synaptic plasticity involved in memory (20,21); correlate with sleep-dependent memory consolidation, learning efficiency, and IQ in a large body of basic research (22); and can be manipulated to improve memory either pharmacologically (23,24) or using transcranial stimulation (25–27) in healthy

ISSN: 2451-9022

humans. Patients with schizophrenia show sleep spindle deficits (28–30) that are associated with impaired sleep-dependent memory consolidation (31–33). Reduced spindle activity that correlates with worse cognitive performance and lower IQ is also seen in early-course antipsychotic-naïve patients with schizophrenia and young nonpsychotic first-degree relatives. Collectively, this evidence suggests that reduced spindle activity is an endophenotype of schizophrenia that reflects the functional integrity of thalamocortical networks and contributes to cognitive deficits (10,34,35).

We hypothesized that the abnormal thalamocortical interactions that give rise to both hyperconnectivity and sleep spindle deficits in schizophrenia reflect reduced TRN inhibition of the thalamus. The TRN, which consists entirely of gamma-aminobutyric acid neurons (36), is the major inhibitory nucleus of the thalamus. Strategically positioned between thalamus and cortex, it powerfully inhibits glutamatergic thalamocortical neurons to gate the relay of information to cortex during wake and to initiate spindles during sleep (15). Sleep spindle initiation depends on powerful and prolonged inhibition of thalamocortical neurons by the TRN (12,37), particularly sensory projecting neurons (38). This inhibition is followed by rebound spike bursts in thalamocortical neurons that entrain cortical neurons to oscillate at spindle frequency (13). Postmortem studies provide evidence of TRN abnormalities in schizophrenia, including a reduction of parvalbumin neurons (39–41), which predominate in sensory relay nuclei (42). A consequent impairment of TRN-mediated inhibition of thalamocortical neurons in schizophrenia may increase the forwarding of sensory and motor information to the cortex, resulting in thalamic hyperconnectivity, and reduce the burst firing necessary for sleep spindle initiation, resulting in spindle deficits.

METHODS AND MATERIALS

Participants

Participants were 26 outpatients with schizophrenia, recruited from an urban mental health center, and 30 healthy control subjects, recruited from the community through poster and website advertisements. After exclusion for excessive motion during scanning (see description below), 22 patients and 29 control subjects were retained for group comparisons of functional connectivity. Group comparison of sleep spindle density was based on 26 patients and 29 control subjects after 1 control subject was excluded owing to technical problems with the sleep recording. Correlations of connectivity and spindle density included 22 patients and 28 control subjects. Patient and control groups did not differ in age, sex, handedness, mean years of parental education, or estimated premorbid verbal IQ (Table 1). Two patients were unmedicated, and the rest had been maintained on stable doses of antipsychotic and adjunctive medications for at least 6 weeks before enrollment (Supplemental Table S1). Diagnoses were confirmed with Structured Clinical Interview for DSM-IV (43), and symptoms were rated with the Positive and Negative Syndrome Scale (44). Healthy participants were screened to exclude individuals with a personal history of mental illness (Structured Clinical Interview for DSM-IV-TR, nonpatient edition) (45) or a family history of either schizophrenia spectrum disorder or psychosis.

Table 1. Participant Characteristics

	Patients With Schizophrenia (n = 22)	Healthy Control Subjects (n = 29)	t_{49}	p
Age, Years	31.7 ± 7.1	30.2 ± 6.3	0.80	.43
Sex, Female/Male, n	5/17	8/21	χ^2 = 0.64	.75
Handedness[a]	80 ± 24	65 ± 54	1.16	.25
Mean Parental Education, Years	14.3 ± 3	15.1 ± 3.4	−0.86	.40
Estimated Verbal IQ[b]	104 ± 9.3	108 ± 8.5	1.68	.10
Mean Residual Motion[c]	0.24 ± 0.06	0.23 ± 0.07	−0.39	.70
PANSS Total	69 ± 14.4 (Mild)			
PANSS Positive	17 ± 5.2 (Mild)			
PANSS Negative	19 ± 4.7 (Mild)			

Mean ± SD values and group comparisons of demographic data.
PANSS, Positive and Negative Syndrome Scale.
[a]Based on the modified Edinburgh Handedness Inventory (85,86). Laterality scores of −100 or +100 denote exclusive use of left or right hand, respectively.
[b]Based on standard scores on the reading subtest of the Wide Range Achievement Test 3 (87).
[c]Root mean square of translation in x, y, and z directions averaged across the 2 resting-state runs.

All participants were screened to exclude individuals with a diagnosed sleep disorder, treatment with sleep medications, a history of significant head injury or neurological disorder, a history of substance abuse or dependence within the past 6 months (based on interview, chart review, clinician report, and urine toxicological screening), and contraindications for MRI (e.g., metal in the body, pregnancy). All participants gave written informed consent. The study was approved by the Partners Human Research Committee.

Procedures

Overview. Participants had 4 nights of polysomnography (PSG) in the Massachusetts General Hospital Clinical Research Center as part of a double-blind, randomized, placebo-controlled clinical trial that involved adding 3 mg of eszopiclone to ongoing medications for the 2 treatment nights. Placebo and treatment visits were separated by 1 week and took place on 2 consecutive weeknights, with the first night of each visit serving as the baseline night and the second serving as the learning night. For the present study, we measured spindle activity during N2 on the baseline night of the placebo visit. MRI scans were acquired approximately 1 week after completion of the sleep visits.

Spindle Measurement and Analysis. PSG was acquired at 400 Hz using an Aura LTM64 acquisition system (Grass Technologies, Astro-Med Inc., Warwick, RI) and EasyCap EEG caps (EasyCap GmbH, Herrsching, Germany) with 58 EEG, 2 submental electromyography, and 2 electro-oculography channels. Each 30-second epoch of PSG was visually classified into stages (wake, N1, N2, N3, rapid eye movement sleep) according to standard criteria (46) by raters blinded to visit, group, and night. N2 EEG data were preprocessed and analyzed using BrainVision Analyzer 2.0 (Brain Products GmbH, Gilching,

Germany) and MATLAB R2014a (The MathWorks, Inc., Natick, MA), filtered at 0.3 to 35 Hz and notch filtered at 60 Hz. Channels displaying significant artifacts for more than 30 minutes of the recording were interpolated with spherical splines. After referencing to the average of all EEG channels, data were visually inspected, and 30-second epochs with artifacts were removed. Sleep spindles were automatically detected at 12 to 15 Hz at each channel using a wavelet-based algorithm that was previously validated against hand-counted spindles in both patients with schizophrenia and healthy individuals (32,47). The threshold for spindle detection, 9 times the median signal amplitude of artifact-free epochs, was chosen to maximize between-class (spindle vs. nonspindle) variance (48) in samples of patients with schizophrenia and control subjects from a previous study (32). The outcome measure was spindle density (spindles per minute) during N2 sleep.

Group comparisons of sleep spindle density were based on *t* tests at each electrode. A nonparametric clustering method optimized for EEG (49) and implemented in R (http://www.R-project.org/) was used to correct for multiple comparisons. Adjacent electrodes that met an uncorrected threshold of $p \leq .05$ were clustered, and within each cluster the *t* values were summed across electrodes. Cluster-level corrected *p* values were determined by estimating the likelihood that a cluster of that summed *t* value would be found by chance under the null distribution derived from 10,000 permutations with random group assignment.

MRI Acquisition. MRI scans were acquired with a 3T Siemens Trio TIM whole-body high-speed scanner (Siemens Healthcare, Erlangen, Germany) equipped for echo-planar imaging and a 32-channel head coil. Head stabilization was achieved with cushioning, and participants wore earplugs to attenuate noise. Autoalign was used for automatic slice positioning (50). Anatomical images were acquired with a three-dimensional multiecho magnetization prepared rapid acquisition gradient-echo sequence (T1-weighted) with echo-planar imaging–based volumetric navigators for real-time motion correction (repetition time = 2530 ms, flip angle = 7°, echo times = 1.7 ms/3.6 ms/5.5 ms/7.3 ms, integrated parallel imaging techniques = 2, field of view = 256 mm, 176 in-plane sagittal slices, voxel size = 1 mm^3 isotropic, scan duration = 6 minutes 12 seconds) (51). Two rs-fcMRI scans were obtained with a gradient-echo T2*-weighted sequence for blood oxygen level–dependent contrast (repetition time = 3000 ms, flip angle = 85°, echo time = 30 ms, field of view = 216 mm, 47 contiguous horizontal slices parallel to the intercommissural plane, voxel size = 3 mm^3, interleaved, scan duration = 6 minutes 12 seconds). rs-fcMRI sequences included prospective acquisition correction for head motion to adjust slice position and orientation during data acquisition (52). Participants were instructed to keep their eyes open for the duration of the resting-state scans.

MRI Preprocessing. rs-fcMRI data were preprocessed and analyzed using SPM8 (Wellcome Department of Cognitive Neurology, London, United Kingdom) implemented in MATLAB. Anatomical images were segmented into white matter, gray matter, and cerebrospinal fluid masks. Images were corrected for the time of slice acquisition, spatially realigned with respect to the reference image, resliced, and coregistered with the anatomical images. The volumes were normalized to the Montreal Neurological Institute template and spatially smoothed using a Gaussian kernel with a full width at half maximum of 6 mm.

MRI Data Quality. To minimize spurious correlations in rs-fcMRI data and to avoid artifactual group differences owing to head motion (53), we excluded data from 4 patients and 1 control subject based on high levels of residual motion—greater than 2 SD above the sample mean (root mean square of translation in x, y, and z directions averaged across the 2 runs). In the remaining participants, we identified and removed artifactual volumes using Artifact Detection Tools (http://www.nitrc.org/projects/artifact_detect/) based on whether head displacement in the x, y, or z direction was more than 1 mm from the previous frame or whether the global mean intensity of the volume was more than 3 SD above that of the entire functional scan. There were no group differences in residual motion ($t_{49} = 0.39$, $p = .70$) or the number of artifactual volumes ($t_{49} = 1.49$, $p = .14$) in the final sample.

Functional Connectivity Analyses. Analyses were implemented in CONN version 17 (54) using a component base noise reduction method, Anatomical CompCor (55), rather than global signal regression, to remove physiological and other noise (56). Preprocessing involved applying a temporal band-pass filter of 0.008 to 0.09 Hz to the time series. Residual head motion parameters (rotation and translations in x, y, and z directions and their first-order temporal derivatives) and artifactual volumes (flagged by Artifact Detection Tools) were regressed out in the model. Functional connectivity maps were generated for each participant by extracting the average time course of the blood oxygen level–dependent signal from the bilateral whole thalamus seed, which was defined using the probabilistic FSL Oxford thalamic connectivity atlas with a threshold of 25 (57,58) (Supplemental Figure S1), and correlating it with every other gray matter voxel. The resulting Pearson coefficients were transformed into Fisher's *z* values. This yielded a map for each resting-state run where the value at each voxel indexed connectivity with the thalamus. The two runs for each subject were averaged.

We examined group differences in thalamocortical functional connectivity with *t* tests at every voxel. We examined the relationships of sleep spindle density (averaged across electrodes) with thalamocortical connectivity using regression with group, spindle density, and group-by-spindle density interaction as predictors. Whole-brain correction for multiple comparisons was based on a voxel level uncorrected threshold of $p \leq .001$ and a false discovery rate–corrected cluster threshold of $p \leq .05$.

RESULTS

Thalamocortical Hyperconnectivity in Schizophrenia

As in prior studies, patients with schizophrenia exhibited significantly increased resting-state functional connectivity of the thalamus with bilateral motor and somatosensory cortex

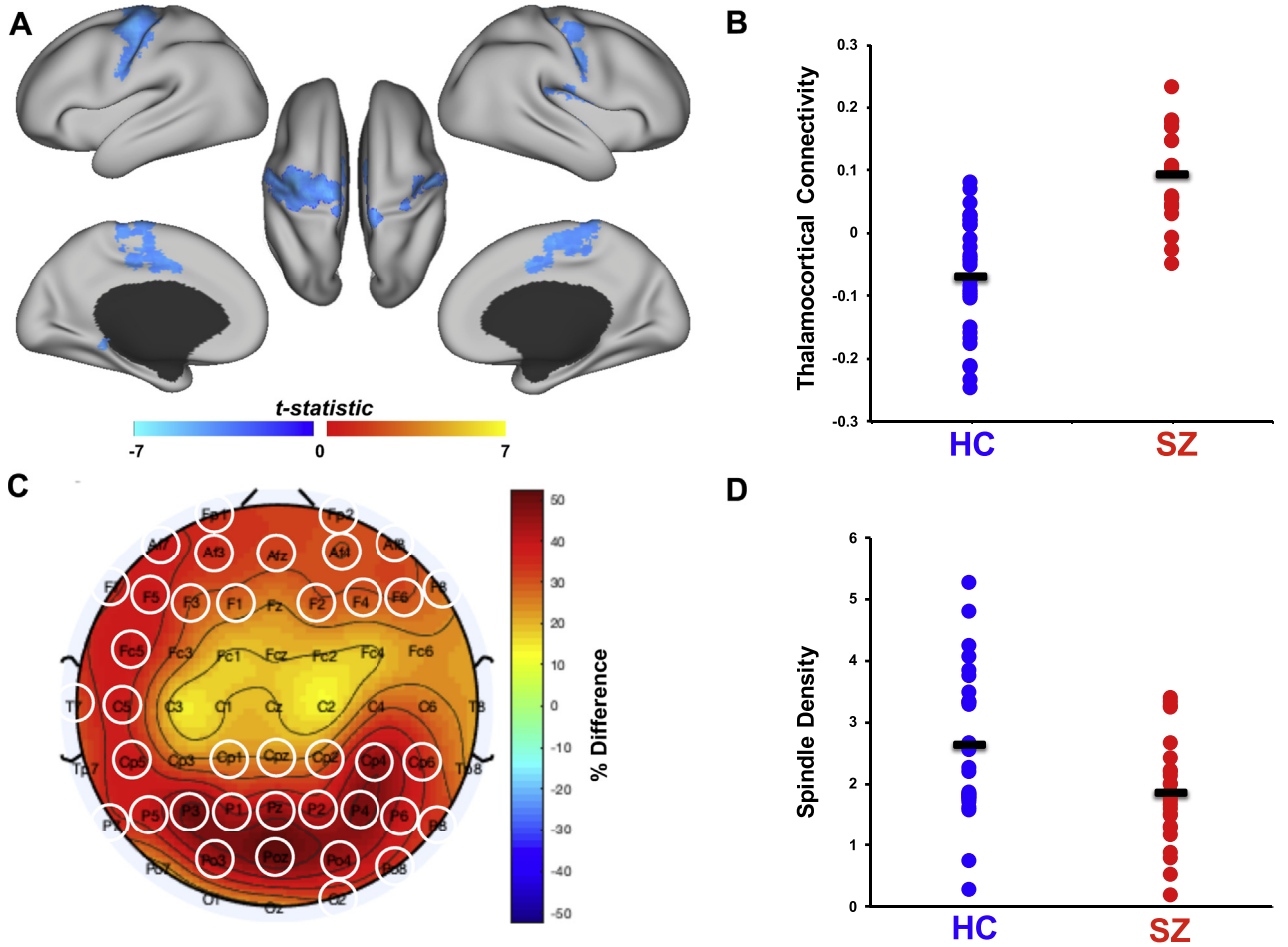

Figure 1. Group differences. **(A)** Statistical map of group differences in thalamocortical functional connectivity displayed on the cortical surface of the template brain at $p_{corrected} \leq .05$. Greater connectivity in patients with schizophrenia (SZ) is depicted in blue. There were no regions of significantly greater connectivity in healthy control subjects (HC). **(B)** Dot plot of averaged thalamocortical connectivity in the group difference mask. Black bars represent group means. **(C)** Topographical map of group differences in sleep spindle density. Warm colors represent higher spindle density in HC. The electrodes circled in white form a significant cluster. **(D)** Dot plot of averaged sleep spindle density in the cluster of electrodes with significantly reduced spindle density. Black bars represent group means.

and with the left parahippocampal gyrus (Figure 1A, B and Table 2). There were no regions of significantly reduced thalamic functional connectivity in schizophrenia (see Supplemental Figure S2 for unthresholded functional connectivity statistical maps for each group).

Reduced Spindle Density in Schizophrenia

We also replicated findings of reduced sleep spindle density in schizophrenia. High-density overnight PSG recordings revealed globally reduced spindle density (number per minute) during N2 sleep that reached significance in a large cluster (38 electrodes, $p_{corrected} = .009$) (Figure 1C, D).

Spindle Density Correlates With Thalamocortical Functional Connectivity

To test the hypothesis that both thalamocortical connectivity and spindle density reflect the functional integrity of TRN-mediated thalamocortical circuitry, we examined their relationships. A regression model with factors for spindle density (averaged across all electrodes), group, and their interaction showed that lower spindle density was significantly associated with greater thalamic connectivity in left motor and somatosensory cortex and left superior temporal gyrus (Figure 2A and Table 3). These relationships did not differ by group (Figure 2B).

Exploratory and Control Analyses

Based on recent evidence that thalamic input regulates local cortical functional connectivity (59), we questioned whether abnormally increased thalamic input in schizophrenia would disrupt local cortical interactions. To address this, we investigated the relationship of thalamocortical connectivity with intracortical connectivity in the regions that showed hyperconnectivity in schizophrenia. We quantified intracortical connectivity within the thalamocortical group difference mask by computing the average connectivity of each voxel with the

Table 2. Maxima and Locations of Clusters Showing Significant Group Differences in Functional Connectivity With the Thalamus

Region	Voxels	MNI Coordinates x	y	z	BA	t_{49}(max)
L Postcentral Gyrus	3624	−38	−20	46	2	−5.49
L precentral gyrus		−28	−20	70	4	
L postcentral gyrus		−37	−17	46	3	
L postcentral gyrus		−51	−6	35	6	
L cingulate gyrus		−10	−1	45	24	
L medial frontal gyrus		−3	−18	−52	6	
L paracentral lobule		−3	−7	46	31	
R Insula	1640	36	−34	22	13	−5.54
R precentral gyrus		42	−12	31	6	
R precentral gyrus		36	−13	37	4	
R postcentral gyrus		36	−16	41	3	
R Precentral Gyrus	207	54	−2	4	6	−5.17
L Parahippocampal Gyrus	194	−20	−46	−8	19	−4.52
L parahippocampal gyrus		−23	−49	−8	37	

All reported clusters have $p_{corrected} \leq .05$ based on correction for the entire brain. There were no clusters where control subjects showed significantly greater functional connectivity than patients. Local maxima within the clusters (indented) are listed only if they fell in a different Brodmann area (BA) than the global maximum.

L, left; MNI, Montreal Neurological Institute; R, right.

Table 3. Maxima and Locations of Clusters Showing Significant Relationships of Thalamocortical Functional Connectivity With Spindle Density

Region	Voxels	MNI Coordinates x	y	z	BA	t_{48}(max)
L Precentral Gyrus	181	−24	−16	64	4	−4.21
L postcentral gyrus		−40	−19	64	3	
L Superior Temporal Gyrus	169	−50	−10	−8	22	−4.88
L middle temporal gyrus		−56	−12	−8	21	
L Postcentral Gyrus	143	−30	−32	54	3	−5.20

Reported clusters have $p_{corrected} \leq .05$ based on correction for the entire brain. No clusters showed a significant positive correlation. Local maxima within the clusters (indented) are listed only if they fell in a different Brodmann area (BA) than the global maximum.

L, left; MNI, Montreal Neurological Institute.

averaged connectivity of the entire mask. We then correlated this measure of intracortical connectivity with the averaged thalamocortical connectivity of the mask. Intracortical connectivity within the group difference mask was significantly weaker in patients than in control subjects ($t_{49} = 2.8$, $p = .007$) (Figure 3A), and only control subjects showed a strong reciprocal relationship of intracortical connectivity with thalamocortical connectivity ($r = -.75$, $p = 2 \times 10^{-6}$; patients: $r = .19$, $p = .41$) (Figure 3B), a difference that was significant ($\beta = .84$, $p = 5 \times 10^{-6}$).

Several studies have examined correlations of thalamocortical hyperconnectivity with symptoms in schizophrenia, but the consistency and direction of these findings varies (60). In the present study, thalamic connectivity did not correlate with either positive or negative symptoms. In addition, hallucinations did not correlate with the connectivity of the thalamus with the superior temporal gyri, which are thought to be involved in their generation (61). Antipsychotic dosage measured in chlorpromazine equivalents (62) did not significantly correlate with either sleep spindle density ($r = -.30$, $p = .17$) or thalamocortical connectivity ($r = -.22$, $p = .35$).

DISCUSSION

We replicated previous findings of decreased spindle density and thalamic hyperconnectivity in schizophrenia and found that these two abnormalities were correlated. Both abnormalities reflect thalamocortical circuit dysfunction, and their correlation supports the hypothesis of a common underlying pathophysiology. We propose that these abnormalities reflect reduced inhibition of thalamocortical neurons by the TRN. This would be expected to lead to increased and less filtered relay of sensory and motor information during wake, corresponding to stronger functional connectivity of the thalamus with sensory and motor cortex, and to decreased sleep spindles. The present findings link two biomarkers of schizophrenia—the spindle density deficit and abnormally increased thalamocortical functional connectivity—and suggest deficient TRN inhibition as a mechanism.

The relationships of thalamocortical connectivity with spindle density were seen in both healthy control partcipants and patients with schizophrenia, and the slopes of these relationships were almost identical. Patients simply had lower spindle density that corresponded to higher connectivity. These findings support the hypothesis that both thalamocortical connectivity and spindle density index functional variation in TRN-mediated thalamocortical circuitry, which lies on a continuum, with patients having less robust TRN-mediated inhibition. This seemingly quantitative rather than qualitative difference, along with previous findings of normal spindle morphology in schizophrenia [e.g., (32)] may bode well for the prospects of therapy to normalize circuit function, increase spindles, and improve outcome. The relationship observed in control participants, who were not taking medications, suggests that medication is unlikely to be a confounding factor in these correlations.

As in prior studies, thalamocortical hyperconnectivity was seen primarily in motor and somatosensory cortex (1–6,9). This selectivity may reflect the organization of thalamocortical circuitry, which can be divided into core and matrix pathways (42). Thalamocortical neurons of the matrix pathway exhibit immunoreactivity to the calcium-binding protein calbindin, are widespread throughout the thalamus, and project diffusely to multiple cortical regions. Core neurons, in contrast, react to parvalbumin; are primarily found in sensory and motor nuclei; and have restricted, topographically organized projections to sensory cortical regions. The core pathway is thought to initiate focal spindles in sensory and motor regions, which have been associated with memory consolidation (63,64), whereas the matrix pathway is thought to play a greater role in initiating widely distributed spindles and in synchronizing spindles across the cortex (65,66). Thus, thalamocortical hyperconnectivity in sensory regions and a correlated reduction in spindle density in schizophrenia are most consistent with abnormalities of the core pathway.

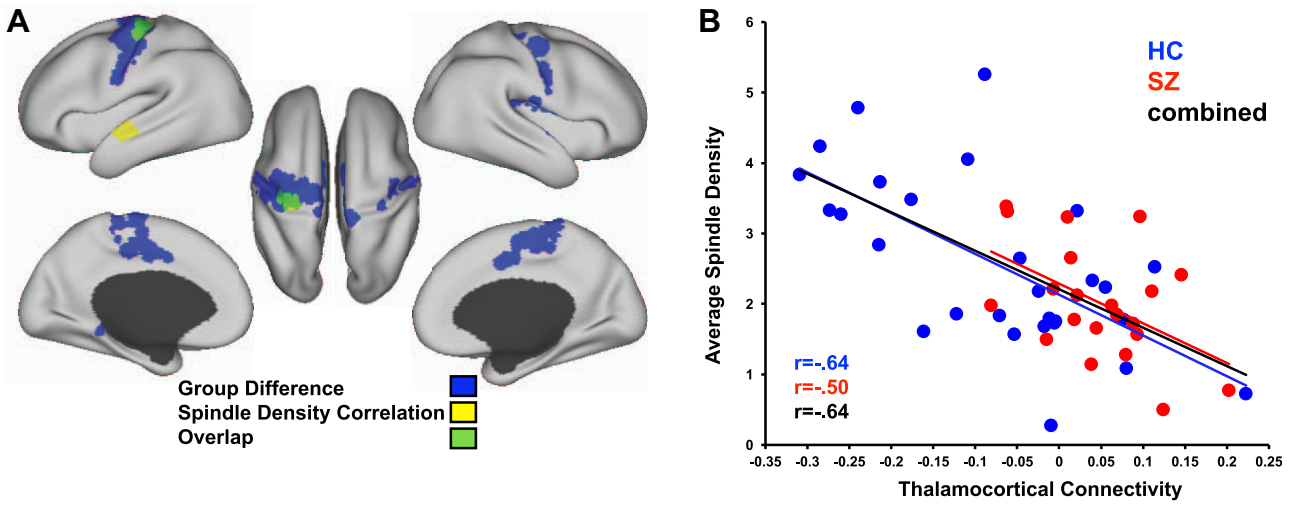

Figure 2. Relationships of sleep spindle density with thalamocortical connectivity. **(A)** Group differences in thalamocortical connectivity (blue), regions showing significant ($p_{corrected} \leq .05$) inverse correlations of average spindle density with thalamocortical connectivity (yellow) and their overlap (green) displayed on the cortical surface of the template brain. No regions showed significant positive correlations. **(B)** Thalamocortical connectivity in regions showing a significant inverse correlation [yellow and green in panel **(A)**] is plotted against average spindle density. HC, healthy control subjects; SZ, patients with schizophrenia.

Both spindle deficits and thalamocortical hyperconnectivity may reflect abnormal TRN function. Postmortem studies give evidence of TRN abnormalities in schizophrenia, including decreased nicotinic receptor binding (39), increased expression of excitatory amino acid transporters (40), and reduced parvalbumin neurons and perineuronal nets (41). These abnormalities may have a genetic origin. Risk genes for neurodevelopmental disorders, both schizophrenia and autism, affect TRN function and spindle expression, suggesting the possibility of a pathogenic role (67–70). During gestation, axons that connect the cortex and the thalamus pass through the TRN, which helps guide them to their terminations (71). As early as the first postnatal week in rodents, spindle bursts, a precursor to adult sleep spindles that are similar in shape, frequency, and origin (72), refine these reciprocal thalamocortical glutamatergic connections, particularly in somatosensory and motor cortex (73–76). These findings suggest mechanisms by which risk genes that affect the TRN early in neurodevelopment could disrupt the establishment of thalamocortical circuitry and contribute to vulnerability to schizophrenia and other neurodevelopmental

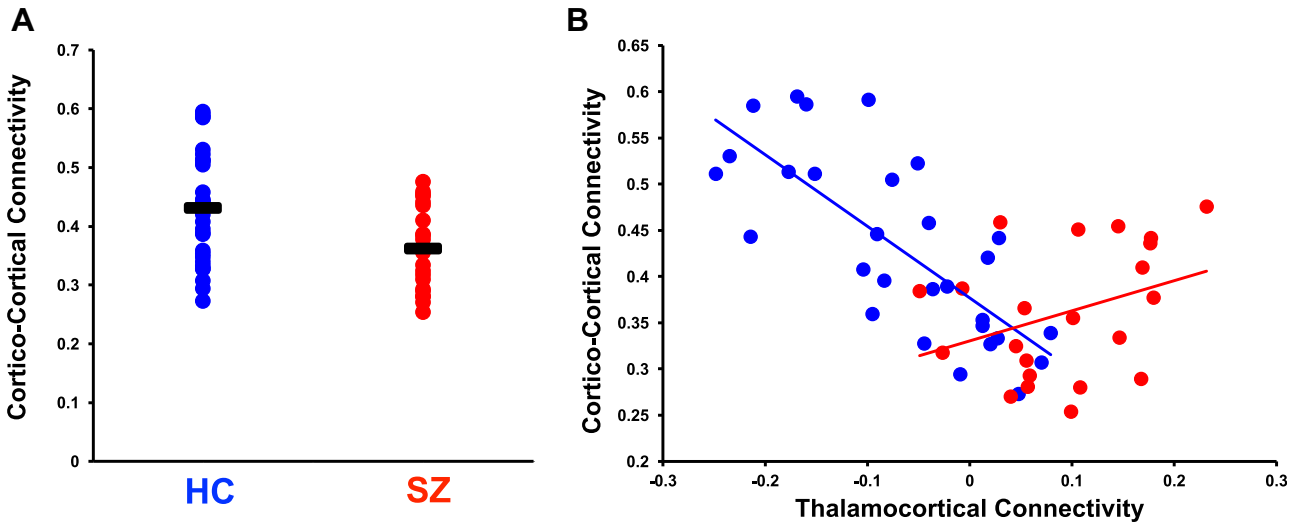

Figure 3. Relationships of thalamocortical connectivity with cortical connectivity. **(A)** Dot plot of the averaged corticocortical connectivity in the regions that show thalamocortical hyperconnectivity in schizophrenia. Black bars represent group means. **(B)** Thalamocortical connectivity is plotted against corticocortical connectivity within the same mask. The slopes of the relationships differ significantly between groups. HC, healthy control subjects; SZ, patients with schizophrenia.

disorders. While the neurodevelopmental literature strongly links TRN-generated spindle bursts to thalamocortical connectivity, we cannot exclude the possibility that a third factor mediates their relationship.

Dysfunction of TRN-mediated thalamocortical circuitry may contribute more broadly to the manifestations of schizophrenia. In larger studies, thalamocortical hyperconnectivity has been correlated with cognitive impairment, negative symptoms, and positive symptoms, including hallucinations (4,6,7). Abnormal perceptual experiences, which are also hypothesized to underlie delusions (77), may arise from increased and less filtered thalamic forwarding of sensory information to the cortex. Sensory gating deficits, impaired attentional filtering, and abnormal corollary discharge [i.e., reduced suppression of sensations resulting from one's own actions (2,78–81)] could similarly be attributed to deficient TRN inhibition of sensory relay. Reduced spindle activity also correlates with positive symptoms and cognitive dysfunction in patients with chronic schizophrenia taking medication, early-course antipsychotic-naïve patients with schizophrenia (28–33), and nonpsychotic first-degree relatives (34,35). In healthy young individuals, reduced spindle density correlates with both elevated proneness to psychosis and increased thalamic glutamine/glutamate levels, supporting a mechanistic link between spindles, symptoms, and heightened thalamic excitation (82). These findings are consistent with the hypothesis that both thalamocortical hyperconnectivity and spindle deficits reflect thalamocortical circuit dysfunction that may impair cognition and contribute to symptoms (9,10).

Motivated by recent evidence that thalamic input, in addition to relaying information, regulates local cortical functional connectivity to enhance information processing (59), we examined whether regions with abnormally increased thalamic input in schizophrenia would have disrupted local cortical interactions. Whereas control subjects showed a strong reciprocal relationship of thalamocortical connectivity with intracortical connectivity in these regions, patients showed no relationship and significantly reduced intracortical connectivity. Primary sensory and motor areas preferentially display local as opposed to long-range functional connectivity, which is thought to optimize area-specific information processing (83). The reduced intracortical connectivity in motor and somatosensory cortex seen in patients as well as lack of correlation with thalamocortical connectivity suggests that the balance between thalamic and local communication is disrupted. These are intriguing, but unexpected, findings that require replication and functional correlation to understand their significance.

Several limitations of the present study merit consideration. First, the relatively modest sample sizes limited our statistical power, and this may account for our failure to replicate previous findings of reduced connectivity of the thalamus with prefrontal cortex in schizophrenia seen in larger studies [for example, see (4)]. Relatedly, to maximize power in our analyses, we used the entire thalamus as a seed, which does not allow us to implicate specific thalamic regions in aberrant connectivity. Second, we used blood oxygen level–dependent functional MRI during wakeful rest to make inferences about connectivity. The strengths and weaknesses of this approach have been discussed elsewhere (84), and although fcMRI is not a direct measure of connectivity, it provides information about interregional communication. Although we found no correlations between antipsychotic dosage and our outcome variables, almost all participants with schizophrenia were taking medications that affect brain function. Sleep spindle deficits have also been reported in antipsychotic-naïve patients and first-degree relatives, and thalamocortical hyperconnectivity is also present in clinical high-risk individuals and is greater in individuals who eventually convert to psychosis. These findings indicate that neither sleep spindle deficits nor thalamocortical hyperconnectivity is a consequence of medications or chronicity. Moreover, the relationship of spindles with thalamocortical connectivity is not likely to be due to medications, as it was also seen in control participants. That spindle and connectivity abnormalities are also present in medicated patients suggests that they are not corrected by current medication regimens for schizophrenia, and to the degree that they impair function, treating them remains an unmet need. Finally, we relied on indirect measures to make inferences about TRN function. The TRN is challenging to study directly in humans because its size and location make it mostly inaccessible to neuroimaging.

By linking two biomarkers of schizophrenia, this work suggests that they share a common mechanism and neurodevelopmental origin. If spindle deficits and thalamocortical hyperconnectivity reflect a common TRN-mediated thalamocortical pathophysiology that increases risk for schizophrenia and contributes to its cognitive deficits and symptoms, understanding its mechanism could guide the development of interventions targeting TRN dysfunction to treat schizophrenia and possibly even prevent its onset.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (Grant No. T32HL007901-17 [to BB]), Swiss National Science Foundation (Grant No. P2ELP2_158891 [to FIK], National Institute of Mental Health (Grant No. R01 MH048832 [to RS], Grant No. R01 MH67720 [to DSM and RS], and Grant No. K24MH099421 [to DSM]), NIH Office of Research Infrastructure Programs (Grant Nos. 1S10RR023401, 1S10RR019307, and 1S10RR023043 [to Athinoula A. Martinos Center for Biomedical Imaging]), and NIH National Center for Research Resources (Grant No. UL1TR001102-01 [to Harvard Clinical and Translational Science Center]).

We thank Dr. Randy Buckner for consultation and Ben Seicol, Tessa Vuper, David Correll, Rachel Fowler, Elaine Parr, and Cameron Callahan for data acquisition and EEG preprocessing.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

From the Department of Psychiatry (BB, FIK, DM, CD, DSM) and Department of Biostatistics (MV), Massachusetts General Hospital, Harvard Medical School, Boston; Athinoula A. Martinos Center for Biomedical Imaging (BB, FIK, DM, CD, MV, DSM), Charlestown; Department of Psychiatry (RS), Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; and Department of Psychiatry (AA), Yale University, New Haven, Connecticut.

BB and FIK contributed equally to this work.

Address correspondence to Dara S. Manoach, Ph.D., Psychiatric Neuroimaging, Massachusetts General Hospital, 149 13th Street, Charlestown, MA 02129; E-mail: Dara.Manoach@mgh.harvard.edu.

Received Feb 6, 2019; revised Apr 6, 2019; accepted Apr 24, 2019.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2019.04.012.

REFERENCES

1. Woodward ND, Karbasforoushan H, Heckers S (2012): Thalamocortical dysconnectivity in schizophrenia. Am J Psychiatry 169:1092–1099.
2. Klingner CM, Langbein K, Dietzek M, Smesny S, Witte OW, Sauer H, Nenadic I (2014): Thalamocortical connectivity during resting state in schizophrenia. Eur Arch Psychiatry Clin Neurosci 264:111–119.
3. Anticevic A, Yang G, Savic A, Murray JD, Cole MW, Repovs G, *et al.* (2014): Mediodorsal and visual thalamic connectivity differ in schizophrenia and bipolar disorder with and without psychosis history. Schizophr Bull 40:1227–1243.
4. Anticevic A, Cole MW, Repovs G, Murray JD, Brumbaugh MS, Winkler AM, *et al.* (2014): Characterizing thalamo-cortical disturbances in schizophrenia and bipolar illness. Cereb Cortex 24:3116–3130.
5. Skatun KC, Kaufmann T, Brandt CL, Doan NT, Alnaes D, Tonnesen S, *et al.* (2018): Thalamo-cortical functional connectivity in schizophrenia and bipolar disorder. Brain Imaging Behav 12:640–652.
6. Ferri J, Ford JM, Roach BJ, Turner JA, van Erp TG, Voyvodic J, *et al.* (2018): Resting-state thalamic dysconnectivity in schizophrenia and relationships with symptoms. Psychol Med 48:2492–2499.
7. Chen P, Ye E, Jin X, Zhu Y, Wang L (2019): Association between thalamocortical functional connectivity abnormalities and cognitive deficits in schizophrenia. Sci Rep 9:2952.
8. Wang HL, Rau CL, Li YM, Chen YP, Yu R (2015): Disrupted thalamic resting-state functional networks in schizophrenia. Front Behav Neurosci 9:45.
9. Anticevic A, Haut K, Murray JD, Repovs G, Yang GJ, Diehl C, *et al.* (2015): Association of thalamic dysconnectivity and conversion to psychosis in youth and young adults at elevated clinical risk. JAMA Psychiatry 72:882–891.
10. Manoach DS, Pan JQ, Purcell SM, Stickgold R (2016): Reduced sleep spindles in schizophrenia: A treatable endophenotype that links risk genes to impaired cognition? Biol Psychiatry 80:599–608.
11. Manoach DS, Stickgold R (2019): Abnormal sleep spindles, memory consolidation and schizophrenia. Annu Rev Clin Psychol 15:451–479.
12. Steriade M (2003): The corticothalamic system in sleep. Front Biosci 8:d878–d899.
13. Contreras D, Steriade M (1996): Spindle oscillation in cats: The role of corticothalamic feedback in a thalamically generated rhythm. J Physiol 490(Pt 1):159–179.
14. Contreras D, Destexhe A, Sejnowski TJ, Steriade M (1996): Control of spatiotemporal coherence of a thalamic oscillation by corticothalamic feedback. Science 274:771–774.
15. Pinault D (2004): The thalamic reticular nucleus: Structure, function and concept. Brain Res Brain Res Rev 46:1–31.
16. Halassa MM, Siegle JH, Ritt JT, Ting JT, Feng G, Moore CI (2011): Selective optical drive of thalamic reticular nucleus generates thalamic bursts and cortical spindles. Nat Neurosci 14:1118–1120.
17. Guillery RW, Harting JK (2003): Structure and connections of the thalamic reticular nucleus: Advancing views over half a century. J Comp Neurol 463:360–371.
18. De Gennaro L, Ferrara M (2003): Sleep spindles: An overview. Sleep Med Rev 7:423–440.
19. Jacobsen RB, Ulrich D, Huguenard JR (2001): GABA(B) and NMDA receptors contribute to spindle-like oscillations in rat thalamus in vitro. J Neurophysiol 86:1365–1375.
20. Sejnowski TJ, Destexhe A (2000): Why do we sleep? Brain Res 886:208–223.
21. Rosanova M, Ulrich D (2005): Pattern-specific associative long-term potentiation induced by a sleep spindle-related spike train. J Neurosci 25:9398–9405.
22. Fogel SM, Smith CT (2011): The function of the sleep spindle: A physiological index of intelligence and a mechanism for sleep-dependent memory consolidation. Neurosci Biobehav Rev 35:1154–1165.
23. Kaestner EJ, Wixted JT, Mednick SC (2013): Pharmacologically increasing sleep spindles enhances recognition for negative and high-arousal memories. J Cogn Neurosci 25:1597–1610.
24. Mednick SC, McDevitt EA, Walsh JK, Wamsley E, Paulus M, Kanady JC, Drummond SP (2013): The critical role of sleep spindles in hippocampal-dependent memory: A pharmacology study. J Neurosci 33:4494–4504.
25. Lustenberger C, Boyle M, Alagapan S, Mellin J, Vaughn B, Frolich F (2016): Feedback-controlled transcranial alternating current stimulation reveals a functional role of sleep spindles in motor memory consolidation. Curr Biol 26:2127–2136.
26. Marshall L, Helgadottir H, Molle M, Born J (2006): Boosting slow oscillations during sleep potentiates memory. Nature 444:610–613.
27. Del Felice A, Magalini A, Masiero S (2015): Slow-oscillatory transcranial direct current stimulation modulates memory in temporal lobe epilepsy by altering sleep spindle generators: A possible rehabilitation tool. Brain Stimul 8:567–573.
28. Ferrarelli F, Huber R, Peterson MJ, Massimini M, Murphy M, Riedner BA, *et al.* (2007): Reduced sleep spindle activity in schizophrenia patients. Am J Psychiatry 164:483–492.
29. Ferrarelli F, Peterson MJ, Sarasso S, Riedner BA, Murphy MJ, Benca RM, *et al.* (2010): Thalamic dysfunction in schizophrenia suggested by whole-night deficits in slow and fast spindles. Am J Psychiatry 167:1339–1348.
30. Manoach DS, Thakkar KN, Stroynowski E, Ely A, McKinley SK, Wamsley E, *et al.* (2010): Reduced overnight consolidation of procedural learning in chronic medicated schizophrenia is related to specific sleep stages. J Psychiatr Res 44:112–120.
31. Goder R, Graf A, Ballhausen F, Weinhold S, Baier PC, Junghanns K, Prehn-Kristensen A (2015): Impairment of sleep-related memory consolidation in schizophrenia: Relevance of sleep spindles? Sleep Med 16:564–569.
32. Wamsley E, Tucker MA, Shinn AK, Ono KE, McKinley S, Ely AV, *et al.* (2012): Reduced sleep spindles and spindle coherence in schizophrenia: Mechanisms of impaired memory consolidation? Biol Psychiatry 71:154–161.
33. Seeck-Hirschner M, Baier PC, Sever S, Buschbacher A, Aldenhoff JB, Goder R (2010): Effects of daytime naps on procedural and declarative memory in patients with schizophrenia. J Psychiatr Res 44:42–47.
34. Manoach DS, Demanuele C, Wamsley EJ, Vangel M, Montrose DM, Miewald J, *et al.* (2014): Sleep spindle deficits in antipsychotic-naïve early course schizophrenia and in non-psychotic first-degree relatives. Front Hum Neurosci 8:762.
35. Schilling C, Schlipf M, Spietzack S, Rausch F, Eisenacher S, Englisch S, *et al.* (2017): Fast sleep spindle reduction in schizophrenia and healthy first-degree relatives: Association with impaired cognitive function and potential intermediate phenotype. Eur Arch Psychiatry Clin Neurosci 267:213–224.
36. Houser CR, Vaughn JE, Barber RP, Roberts E (1980): GABA neurons are the major cell type of the nucleus reticularis thalami. Brain Res 200:341–354.
37. Chen Z, Wimmer RD, Wilson MA, Halassa MM (2015): Thalamic circuit mechanisms link sensory processing in sleep and attention. Front Neural Circuits 9:83.
38. Halassa MM, Chen Z, Wimmer RD, Brunetti PM, Zhao S, Zikopoulos B, *et al.* (2014): State-dependent architecture of thalamic reticular subnetworks. Cell 158:808–821.
39. Court J, Spurden D, Lloyd S, McKeith I, Ballard C, Cairns N, *et al.* (1999): Neuronal nicotinic receptors in dementia with Lewy bodies and schizophrenia: Alpha-bungarotoxin and nicotine binding in the thalamus. J Neurochem 73:1590–1597.
40. Smith RE, Haroutunian V, Davis KL, Meador-Woodruff JH (2001): Expression of excitatory amino acid transporter transcripts in the thalamus of subjects with schizophrenia. Am J Psychiatry 158:1393–1399.
41. Steullet P, Cabungcal JH, Bukhari SA, Ardelt MI, Pantazopoulos H, Hamati F, *et al.* (2018): The thalamic reticular nucleus in schizophrenia and bipolar disorder: Role of parvalbumin-expressing neuron networks and oxidative stress. Mol Psychiatry 23:2057–2065.

42. Jones EG (1998): Viewpoint: The core and matrix of thalamic organization. Neuroscience 85:331–345.
43. First MB, Spitzer RL, Gibbon M, Williams JBW (1997): Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient Edition with Psychotic Screen (SCID-I/P W/PSY SCREEN). New York: Biometrics Research, New York State Psychiatric Institute.
44. Kay SR, Fiszbein A, Opler LA (1987): The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 13:261–276.
45. First MB, Spitzer RL, Gibbon M, Williams JBW (2002): Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Nonpatient Edition. New York: Biometrics Research, New York State Psychiatric Institute.
46. Iber C, Ancoli-Israel S, Chesson AL, Quan SF (2007): The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications. Westchester, IL: American Academy of Sleep Medicine.
47. Warby SC, Wendt SL, Welinder P, Munk EG, Carrillo O, Sorensen HB, *et al.* (2014): Sleep-spindle detection: crowdsourcing and evaluating performance of experts, non-experts and automated methods. Nat Methods 11:385–392.
48. Otsu N (1979): Time Frequency and Wavelets in Biomedical Signal Processing. Piscataway, NJ: Wiley-IEEE Press.
49. Maris E, Oostenveld R (2007): Nonparametric statistical testing of EEG- and MEG-data. J Neurosci Methods 164:177–190.
50. van der Kouwe AJ, Benner T, Fischl B, Schmitt F, Salat DH, Harder M, *et al.* (2005): On-line automatic slice positioning for brain MR imaging. Neuroimage 27:222–230.
51. Tisdall MD, Hess AT, Reuter M, Meintjes EM, Fischl B, van der Kouwe AJ (2012): Volumetric navigators for prospective motion correction and selective reacquisition in neuroanatomical MRI. Magn Reson Med 68:389–399.
52. Thesen S, Heid O, Mueller E, Schad LR (2000): Prospective acquisition correction for head motion with image-based tracking for real-time fMRI. Magn Reson Med 44:457–465.
53. Van Dijk KR, Sabuncu MR, Buckner RL (2012): The influence of head motion on intrinsic functional connectivity MRI. Neuroimage 59:431–438.
54. Whitfield-Gabrieli S, Nieto-Castanon A (2012): Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect 2:125–141.
55. Behzadi Y, Restom K, Liau J, Liu TT (2007): A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. Neuroimage 37:90–101.
56. Chai XJ, Castanon AN, Ongur D, Whitfield-Gabrieli S (2012): Anticorrelations in resting state networks without global signal regression. Neuroimage 59:1420–1428.
57. Behrens TE, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CA, Boulby PA, *et al.* (2003): Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat Neurosci 6:750–757.
58. Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, *et al.* (2003): Characterization and propagation of uncertainty in diffusion-weighted MR imaging. Magn Reson Med 50:1077–1088.
59. Schmitt LI, Wimmer RD, Nakajima M, Happ M, Mofakham S, Halassa MM (2017): Thalamic amplification of cortical connectivity sustains attentional control. Nature 545:219–223.
60. Giraldo-Chica M, Woodward ND (2017): Review of thalamocortical resting-state fMRI studies in schizophrenia. Schizophr Res 180:58–63.
61. Alderson-Day B, McCarthy-Jones S, Fernyhough C (2015): Hearing voices in the resting brain: A review of intrinsic functional connectivity research on auditory verbal hallucinations. Neurosci Biobehav Rev 55:78–87.
62. Woods SW (2003): Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 64:663–667.
63. Clemens Z, Fabo D, Halasz P (2006): Twenty-four hours retention of visuospatial memory correlates with the number of parietal sleep spindles. Neurosci Lett 403:52–56.
64. Johnson LA, Blakely T, Hermes D, Hakimian S, Ramsey NF, Ojemann JG (2012): Sleep spindles are locally modulated by training on a brain-computer interface. Proc Natl Acad Sci U S A 109:18583–18588.
65. Bonjean M, Baker T, Bazhenov M, Cash S, Halgren E, Sejnowski T (2012): Interactions between core and matrix thalamocortical projections in human sleep spindle synchronization. J Neurosci 32:5250–5263.
66. Piantoni G, Halgren E, Cash SS (2016): The contribution of thalamocortical core and matrix pathways to sleep spindles. Neural Plast 2016: 3024342.
67. Astori S, Wimmer RD, Prosser HM, Corti C, Corsi M, Liaudet N, *et al.* (2011): The Ca(V)3.3 calcium channel is the major sleep spindle pacemaker in thalamus. Proc Natl Acad Sci U S A 108:13823–13828.
68. Wells MF, Wimmer RD, Schmitt LI, Feng G, Halassa MM (2016): Thalamic reticular impairment underlies attention deficit in Ptchd1(Y/-) mice. Nature 532:58–63.
69. Andrade A, Hope J, Allen A, Yorgan V, Lipscombe D, Pan JQ (2016): A rare schizophrenia risk variant of CACNA1I disrupts CaV3.3 channel activity. Sci Rep 6:34233.
70. Krol A, Wimmer RD, Halassa MM, Feng G (2018): Thalamic reticular dysfunction as a circuit endophenotype in neurodevelopmental disorders. Neuron 98:282–295.
71. Mitrofanis J, Guillery RW (1993): New views of the thalamic reticular nucleus in the adult and the developing brain. Trends Neurosci 16:240–245.
72. Lindemann C, Ahlbeck J, Bitzenhofer SH, Hanganu-Opatz IL (2016): Spindle activity orchestrates plasticity during development and sleep. Neural Plast 2016:5787423.
73. Khazipov R, Sirota A, Leinekugel X, Holmes GL, Ben-Ari Y, Buzsaki G (2004): Early motor activity drives spindle bursts in the developing somatosensory cortex. Nature 432:758–761.
74. Cirelli C, Tononi G (2015): Cortical development, electroencephalogram rhythms, and the sleep/wake cycle. Biol Psychiatry 77:1071–1078.
75. Evrard A, Ropert N (2009): Early development of the thalamic inhibitory feedback loop in the primary somatosensory system of the newborn mice. J Neurosci 29:9930–9940.
76. Pinault D (2011): Dysfunctional thalamus-related networks in schizophrenia. Schizophr Bull 37:238–243.
77. Maher B (2003): Schizophrenia, abherrant utterance and delusions of control: The disconnection of speech and thought, and the connection of experience and belief. Mind Lang 18:1–22.
78. Mathalon DH, Ford JM (2008): Corollary discharge dysfunction in schizophrenia: Evidence for an elemental deficit. Clin EEG Neurosci 39:82–86.
79. Giraldo-Chica M, Woodward ND (2017): Review of thalamocortical resting-state fMRI studies in schizophrenia. Schizophr Res 180:58–63.
80. Vukadinovic Z (2011): Sleep abnormalities in schizophrenia may suggest impaired trans-thalamic cortico-cortical communication: Towards a dynamic model of the illness. Eur J Neurosci 34:1031–1039.
81. Vukadinovic Z (2012): Schizophrenia as a disturbance of cortical sensory maps. Transl Neurosci 3:388–398.
82. Lustenberger C, O'Gorman RL, Pugin F, Tushaus L, Wehrle F, Achermann P, Huber R (2015): Sleep spindles are related to schizotypal personality traits and thalamic glutamine/glutamate in healthy subjects. Schizophr Bull 41:522–531.
83. Sepulcre J, Liu H, Talukdar T, Martincorena I, Yeo BT, Buckner RL (2010): The organization of local and distant functional connectivity in the human brain. PLoS Comput Biol 6:e1000808.
84. Van Dijk KR, Hedden T, Venkataraman A, Evans KC, Lazar SW, Buckner RL (2010): Intrinsic functional connectivity as a tool for human connectomics: Theory, properties, and optimization. J Neurophysiol 103:297–321.
85. Oldfield RC (1971): The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9:97–113.
86. White K, Ashton R (1976): Handedness assessment inventory. Neuropsychologia 14:261–264.
87. Wilkinson GJ (1993): The Wide Range Achievement Test-Revision 3. Wilmington, DE: Jastak Associates.