Biological Psychiatry

Archival Report

Thalamocortical Structural Covariation Networks Are Related to Familial Risk for Schizophrenia in the Context of Lower Nuclei Volume Estimates in Patients: An ENIGMA Study

Annalisa Lella, Linda A. Antonucci, Roberta Passiatore, Loredana Bellantuono, Pierluigi Selvaggi, Teresa Popolizio, Guido Di Sciascio, Alessandro Saponaro, Patrizia Ricci, Mario Altamura, Giuseppe Blasi, Antonio Rampino, Chris Vriend, Vince D. Calhoun, Kelly Rootes-Murdy, Aaron L. Goldman, Inmaculada Baeza, Josefina Castro-Fornieles, Gisela Sugranyes, Elena De la Serna, Edith Pomarol-Clotet, Mar Fatjó-Vilas, Raymond Salvador, Andriana Karuk, Paola Fuentes-Claramonte, David C. Glahn, Amanda L. Rodrigue, John Blangero, Lei Wang, Taeyoung Lee, Karolin E. Einenkel, Saskia Hamers, Oliver Gruber, Adrian Preda, Young-Chul Chung, Soyolsaikhan Odkhuu, Corentin Vallée, Paola Dazzan, Machteld Marcelis, Stijn Michielse, Katharina Brosch, Frederike Stein, Igor Nenadić, Benjamin Straube, Florian Thomas-Odenthal, Tilo Kircher, Sean Carruthers, Susan L. Rossell, Phillip J. Sumner, Tamsyn E. Van Rheenen, Caroline Demro, Ian S. Ramsay, Scott R. Sponheim, Rebekka Lencer, Susanne Meinert, Tim Hahn, Udo Dannlowski, Dominik Grotegerd, Mariateresa Ciccarelli, Felice Iasevoli, Giuseppe Pontillo, Godfrey D. Pearlson, Derin Cobia, Fabrizio Piras, Nerisa Banaj, Daniela Vecchio, Marjolein E.A. Barendse, Neeltje E.M. van Haren, Hang Joon Jo, Kang Sim, Yann Quidé, Melissa J. Green, Rachael Slate, Giacomo Cecere, Wolfgang Omlor, Stephanie Homan, Philipp Homan, Sophia I. Thomopoulos, The Apulian Network on Risk for Psychosis, Jessica A. Turner, Theo G.M. van Erp, Paul M. Thompson, Alessandro Bertolino, and Giulio Pergola

ABSTRACT

BACKGROUND: Structural brain differences in the thalamus and the cortex have been widely reported in schizophrenia (SCZ) relative to neurotypical control individuals (NCs). Most previous studies examined the thalamus as a whole as a single region of interest. In addition, findings in individuals at familial high risk for SCZ (FHRs) remain inconclusive. Here, we investigated whether local and network-wide thalamic-related structural alterations vary as a function of familial risk for SCZ.

METHODS: Structural magnetic resonance imaging scans were obtained from 5197 participants (NC, n = 3409; FHR, n = 257; SCZ, n = 1531) across 32 cross-sectional samples within the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) Consortium. Random-effects meta-analyses and network analyses were conducted on 1) local thalamic alterations (volume estimates of 7 thalamic subdivisions) and 2) network-wide thalamic alterations (thickness and surface-related thalamocortical/corticocortical covariation patterns) across groups (NC, FHR, SCZ).

RESULTS: Individuals with SCZ showed significantly lower gray matter volume estimates in the anterior, pulvinar, medial, posterior, and ventral thalamic subdivisions compared with NCs (false discovery rate–corrected q [q_{FDR}] $< .05$). FHRs did not differ from NCs. At the network-wide level, thalamocortical covariations discriminated FHRs from NCs ($q_{FDR} < .05$), with FHRs showing intermediate covariation between individuals with SCZ and NCs. Corticocortical covariation patterns revealed that individuals with SCZ and FHRs shared similarly disconnected clustering configurations, distinct from NCs ($q_{FDR} < .05$).

CONCLUSIONS: Results revealed lower thalamic volume estimates in individuals with SCZ but not in FHRs, hence yielding no evidence of a familial risk trait, whereas thalamocortical and corticocortical covariation estimates were associated with familial risk for SCZ. These findings suggest that, once the thalamus is parsed into subdivisions, network-wide thalamocortical features may identify trait-dependent, neurobiological correlates of genetic risk for SCZ.

https://doi.org/10.1016/j.biopsych.2025.03.027

ISSN: 0006-3223

The thalamus facilitates the bidirectional flow of neuronal signals between cortical and subcortical regions and among different cortical regions (1). Suboptimal thalamocortical connectivity may detrimentally affect cortical development (2), especially after early-life brain insults (3). The developmental relationship between the human thalamus and cortex is relevant to schizophrenia (SCZ) pathophysiology (4), given that heritable neurodevelopmental alterations may interact with early environmental risk factors and brain maturational processes before clinical symptoms emerge (5–7).

Patients with SCZ reportedly have lower thalamic (8–10) and larger ventricular (11) volume estimates. These alterations characterize the early stage of SCZ but may also be affected by antipsychotic treatment (5,12). Therefore, it remains unclear whether thalamic alterations are related to illness state or whether they represent a trait shared by individuals at genetic risk for the disorder, potentially suggesting thalamic involvement in etiopathogenic mechanisms. Meta-analyses of data from individuals with a familial high risk for SCZ (FHRs, i.e., first-degree relatives of patients) suggest lower thalamic gray matter volumes in FHR (13,14). However, the evidence in this regard is mixed (15,16). Notably, most published studies focused on the thalamus as a whole, disregarding the functional and anatomical segregation of its nuclei (9,17). Indeed, thalamic nuclei are not interconnected and have distinct patterns of connections with other brain structures, which define their functional role (Figure 1) (8). The mediodorsal and pulvinar nuclei have been repeatedly associated with SCZ (8,9), with sparser evidence for intralaminar and anterior nuclei (9,18,19). Findings on thalamic subdivisions in FHR are inconclusive. Twin studies have established the heritability of structural gray matter estimates for both the cortex and thalamus (20), hence motivating investigations at the thalamocortical network level in FHR. However, small sample sizes and the varying definitions of FHRs, e.g., including individuals with

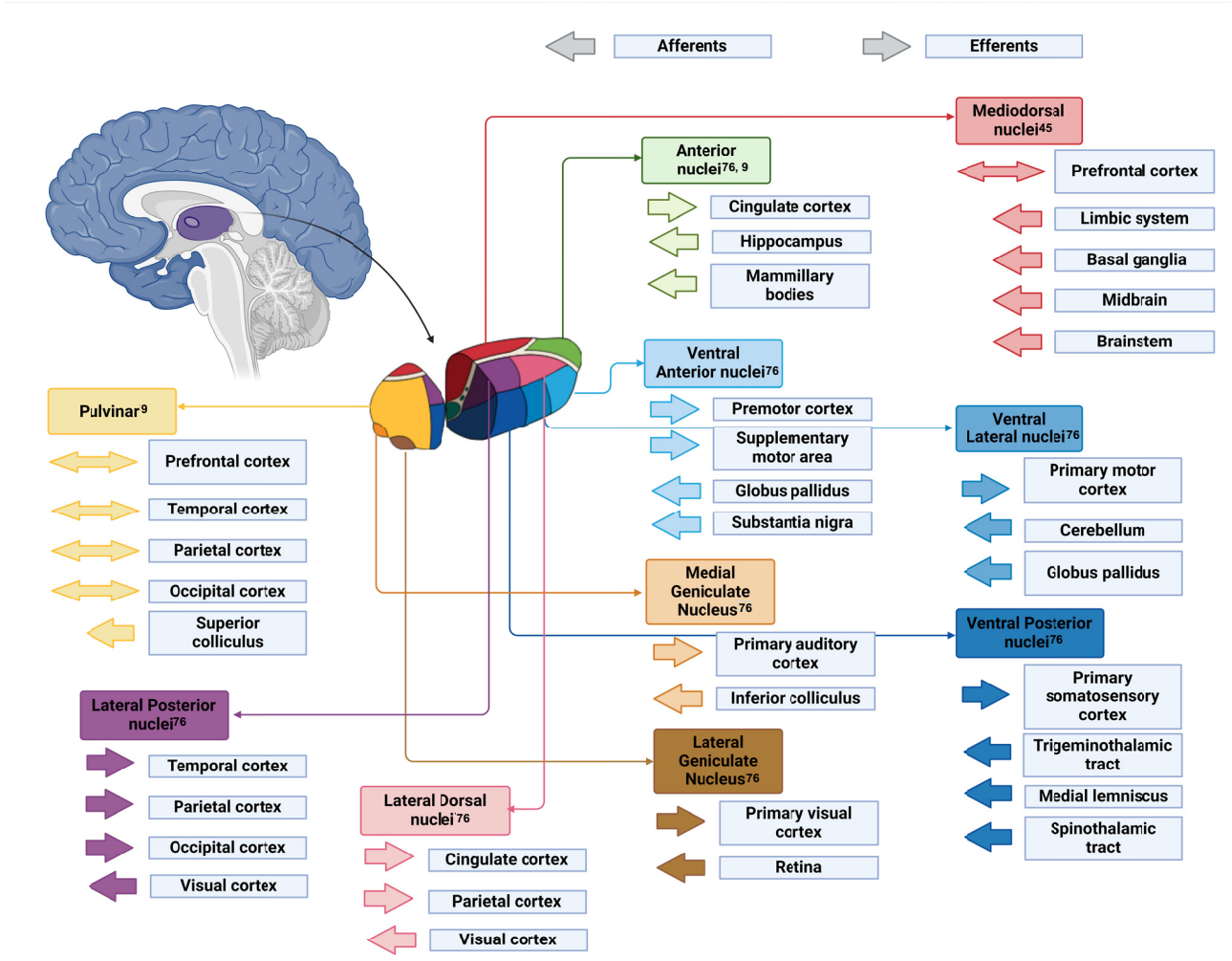

Figure 1. Connections between thalamic nuclei and cortex. Major connections between thalamic nuclei and cortical or subcortical regions are shown using corresponding colors. Each nucleus is shown with its main afferents and efferents. (Image created with BioRender.)

familial high risk for psychosis and not only SCZ (14,15), have hindered reproducibility. Potential confounders also require investigation (11,21,22), given that smaller gray matter estimates are often accompanied by third ventricle enlargement (21). Indeed, ventricular enlargement, commonly associated with SCZ, has also been reported in FHRs (23). Enlarged lateral or third ventricles can affect the shape of the thalamus and, hence, hinder accurate thalamic segmentation, affecting especially medial and dorsal thalamic nuclei owing to their proximity to the ventricles (24–26). Consequently, failing to consider ventricular volumes might lead to overestimating gray matter alterations associated with the disorder.

Structural alterations localized in thalamic nuclei are compounded by network-wide thalamocortical deficits (2). In support of thalamic parcellation efforts, Prasad *et al.* (27) suggested that different thalamocortical covariation patterns are not apparent at the whole thalamus level but can be detected at the subdivision level (28–30). Indeed, structural alterations in SCZ are not randomly distributed in the brain but follow network-wide patterns of co-alteration (31–33), in which the thalamus is pivotal.

Here, we aimed to investigate the potential association between SCZ risk and 1) local alterations, i.e., volume estimates of 7 thalamic subdivisions; 2) network-wide alterations, i.e., the structural covariation between thalamic subdivisions and cortical thickness and surface; and 3) corticocortical similarity profiles, i.e., corticocortical covariation networks derived from thalamocortical covariation patterns resulting from aim 2.

Based on previous findings (4,8), we hypothesized lower volumes in the medial, pulvinar, and anterior thalamic subdivisions in both FHR and SCZ. We also expected FHRs and individuals with SCZ to have different thalamocortical covariation patterns and corticocortical covariation profiles compared with neurotypical control individuals (NCs). Finally, we addressed the potential confounding effect of ventricle volume estimates, considering that larger brain ventricles may disproportionately affect medial more than lateral thalamic subdivisions.

METHODS AND MATERIALS

Study Samples

Thirty-two worldwide cross-sectional study samples (34) (Figure S1) totaling 5197 participants—1531 individuals with SCZ, 257 FHRs, and 3409 NCs—part of the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) Consortium-Schizophrenia Working Group (35)—contributed to the collaborative analysis of thalamic brain volumes and thalamocortical structural covariation (Supplement, Section 1; Tables S1 and S2). The sample-size weighted mean age across samples for NC was 32.8 ± 10.03 years, for FHRs, 33.4 ± 7.5 years, and for SCZ, 34.4 ± 11.4 years. The percentage of males for NC was 42%, for FHRs, 45%, and for SCZ, 65%. The sample-size weighted means for Positive and Negative Syndrome Scale (PANSS) for SCZ were 15.81 ± 5.65 for positive and 16.07 ± 5.89 for negative symptoms. The weighted mean age at onset and duration of illness for the SCZ group were 23.1 ± 7.3 and 13.8 ± 9.4 years, respectively. The sample-size weighted mean chlorpromazine dose equivalent (CPZeq) was 431.32 ± 428.38 mg. Each study sample was collected with participants' written informed consent approved by local institutional review boards and ethics committees. For all samples, T1-weighted structural brain scans were acquired using 3T magnetic resonance imaging (MRI) scanners (detailed acquisition and processing procedures are presented in Supplement, Section 2 and Table S2). Thalamic volumes underwent segmentation procedures into 7 subdivisions (anterior, intralaminar, medial, posterior, pulvinar, ventral-posterior, and ventral). Quality control procedures aligned with the ENIGMA OCD ThalamicNuclei pipeline. The detailed procedure is presented in Supplement, Section 2 and Tables S3–S6.

Local Thalamus-Related Analyses on Thalamic Subdivisions' Volumes

To investigate the effects of group (NC, FHR, SCZ), thalamic subdivision, and their interaction on thalamic volume estimates, we used repeated-measures analyses of covariance (false discovery rate–corrected q [q_{FDR}] $< .05$), after regressing out relevant covariates (sex, age, quadratic age, ventricular and intracranial volume) (R's *car* package; Figure 2). Pairwise random-effect meta-analysis was performed using the Sidik-Jonkman method with Hartung-Knapp adjustment to generate cumulative effect sizes (pooled standardized mean differences [SMDs]), Hedges' g, $p < .05$) (R's *meta* package) (36) and to account for uncertainty in the estimation of between-study variance in the random-effects meta-analysis. SMDs with 95% CIs were calculated for each thalamic subdivision and the whole thalamus, summarizing pairwise differences in thalamic volume estimates across groups (NC vs. FHR, FHR vs. SCZ, and NC vs. SCZ). Effect sizes for left and right hemisphere thalamic subdivisions were examined separately. Heterogeneity was assessed by the Cochran Q statistic and quantified with the I^2 statistic (37). We performed the same analyses without the estimated ventricular volumes as a covariate to assess the possible influence of ventricle enlargement in SCZ on these effects.

The effect of nuisance covariates on thalamic volume estimates was assessed through moderator analyses (Supplement, Section 3). We considered sample demographics (mean age at onset, duration of illness); CPZeq (38); proportion of typical, atypical, and both types of antipsychotic medication; severity of positive and negative symptoms; and methodology (FreeSurfer version and thalamic segmentation FreeSurfer version).

Network-Wide Thalamus-Related Analyses on Morphological Covariation Matrices

To investigate the effect of group on structural thalamocortical covariation patterns, we computed, for each site, 2 bilateral matrices of Kendall correlations between thalamic volumes and morphometric measures (cortical surface and thickness), after regressing out nuisance covariates (sex, age, quadratic age, ventricular and intracranial volumes) (Figure 2). The resulting 2 correlation matrices (correlations between thalamic volumes/cortical thickness and thalamic volumes/cortical surface), collected for each site, were then summarized in 2 meta-analytic matrices through random-effect meta-analyses (R's *metacor* package). Subsequently, these 2 meta-analytic matrices calculated for each group (NC, FHR, SCZ) were vectorized to assess the group effect via analysis of variance (ANOVA) ($q_{FDR} < .05$). In addition, we conducted pairwise comparisons of corresponding meta-analytic correlation coefficients among different groups (NC vs. FHR, FHR vs. SCZ, NC vs. SCZ). These comparisons were performed using Fisher's test and FDR

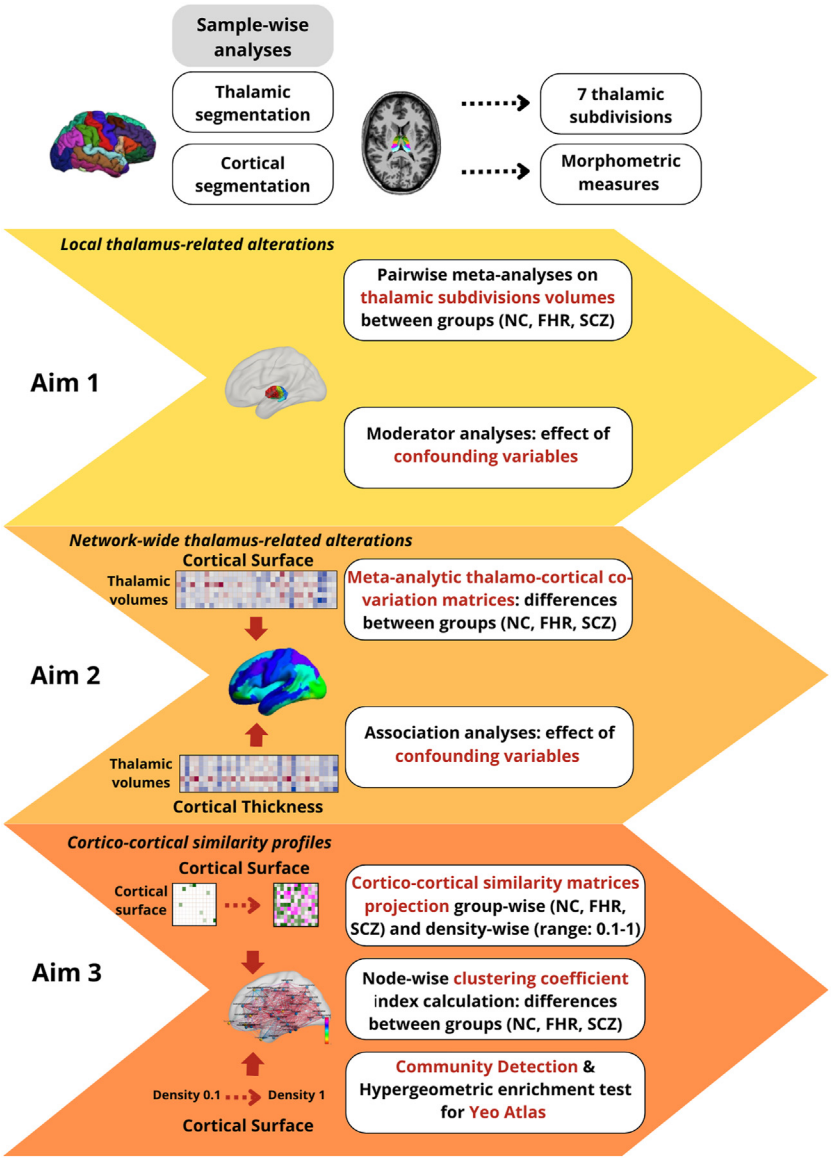

Figure 2. Workflow of the statistical analyses on local thalamus-related alterations (aim 1), network-wide thalamus-related alterations (aim 2), and corticocortical similarity profiles (aim 3). FHR, familial high risk for schizophrenia; NC, neurotypical control; SCZ, schizophrenia.

corrected for the number of tested correlation coefficients. We also explored uncorrected thresholds (nominal $p < .05$ and .005), as reported elsewhere (28,29).

To keep the local and network-wide analyses consistent, we assessed the effects of the same nuisance covariates previously considered in relation to thalamic volume estimates (i.e., sample demographics and methodology variables) on thalamocortical covariation matrices, using association analyses (Supplement, Section 4).

Network-Wide Thalamus-Related Analyses on Corticocortical Covariation Similarity Profiles

We transformed each of the 2 thalamocortical covariation meta-analytic matrices (i.e., thalamic volumes/cortical thickness, thalamic volumes/cortical surface) calculated for each group (NC, FHR, SCZ) into a corticocortical similarity matrix (i.e., cortical thickness/cortical thickness, cortical surface/cortical surface), reporting the similarities for each corticocortical pair with respect to the thalamocortical associations (Figure 2). For each corticocortical similarity matrix and each group (NC, FHR, SCZ), we calculated the clustering coefficient for each node across different densities, from 0.1 (the sparsest matrix) to 1 (the full matrix). We tested the effect of group on the clustering coefficients of each corticocortical matrix via ANOVA with a permutation test based on 1000 iterations ($q_{FDR} < .05$), which returned a permutation-based p value. Further details are presented in Supplement, Section 5.

We used the spin-glass algorithm (39) on the corresponding corticocortical similarity matrices to identify nodes clustering in distinct patterns for each group (NC, FHR, SCZ). As a result, each node was assigned to a particular

cluster. To assess group differences on the corticocortical similarity matrices-related clustering configurations, we performed a pairwise normalized variation of information (NVI) calculation, a measure of the distance between 2 partitions of clusters across groups (NC-FHR, FHR-SCZ, NC-SCZ). Pairwise NVI calculation was repeated for 1000 permuted networks ($p < .05$) to obtain an empirical p value. Finally, we performed a hypergeometric enrichment test in R, using the *phyper* function, to determine whether specific Yeo functional networks were significantly overrepresented within the different corticocortical similarity clustering profiles ($q_{FDR} < .05$) (see Supplement, Section 9).

RESULTS

Local Thalamus-Related Alterations: Main Effect of Group on Thalamic Subdivisions' Volumes

Individuals with SCZ showed significantly lower gray matter estimates for bilateral anterior, medial, ventral, posterior, pulvinar, and left ventral–posterior thalamic subdivisions compared with NC (Figure 3A–C; Table S7) ($q_{FDR} < .05$, 2 tailed). Site-wise effect sizes are presented in Figure S3. No differences were significant between FHR and NC (all $q_{FDR} > .05$) (Table S8). Compared with FHR, individuals with SCZ showed significantly smaller left medial thalamic subdivisions

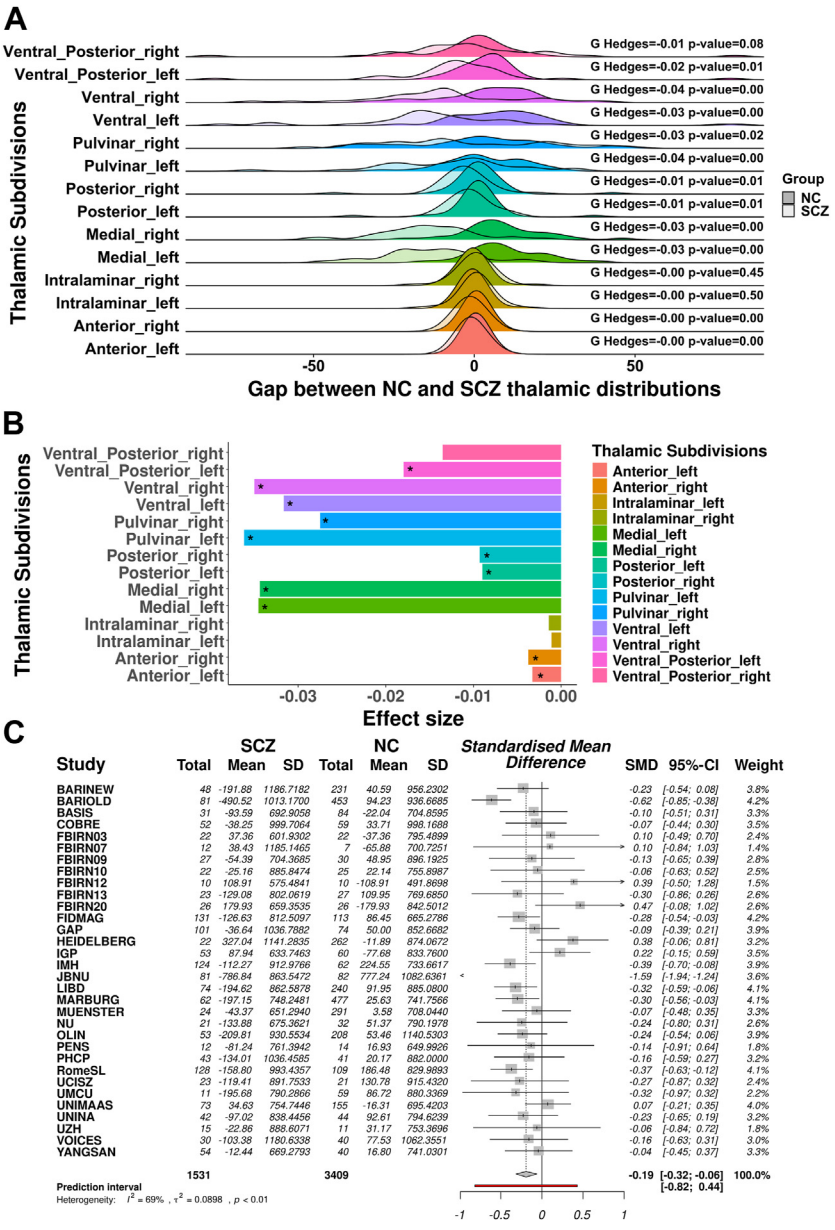

Figure 3. Hedges' g effect sizes for differences in thalamic subdivisions' volumes between neurotypical control individuals (NCs) and patients with schizophrenia (SCZ). **(A, B)** Hedges' g effect sizes for differences in thalamic subdivisions' volumes between individuals with SCZ and NCs. Effect sizes for all thalamic subdivision volumes depicted were corrected for nuisance covariates (i.e., sex, age, quadratic age, ventricles, and intracranial volume [ICV]). **(C)** Forest plot showing group effect (NC vs. SCZ) on whole thalamus volumes. The dotted vertical line indicates the combined (overall) estimates. Standardized mean differences (SMDs) (95% CI) denotes weighted estimates (Hedges' g), which are SMDs between NC and SCZ with their 95% CIs based on the variance in each individual study. BARI, University of Bari Aldo Moro, Bari, Italy; BASIS, August Pi i Sunyer Biomedical Research Institute, Barcelona, Spain; FBIRN, Function Biomedical Informatics Research Network, University of California, Irvine, Irvine, California; FIDMAG, FIDMAG Germanes Hospitalàries, Barcelona, Spain; GAP, National Institute of Health Research Biomedical Research Centre Genetics and Psychosis, South London, United Kingdom; GSU, Georgia State University, Atlanta, Georgia; HEIDELBERG, Heidelberg University Hospital, Heidelberg, Germany; IGP, Imaging Genetics in Psychosis, the University of New South Wales, Sydney, New South Wales, Australia; IMH, Institute of Mental Health, Buangkok, Singapore; JBNU, Jeonbuk National University Hospital, Jeonju, Korea; LIBD, Lieber Institute for Brain Development, Johns Hopkins Medical Campus, Baltimore, Maryland; MARBURG, University of Marburg, Marburg, Germany; MUENSTER, University of Münster, Germany; NU, Northwestern University, Evanston, Illinois; OLIN, Olin Neuropsychiatry Research Center, Institute of Living, Hartford, Connecticut; PENS, University of Minnesota, Minneapolis, Minnesota; PHCP, University of Minnesota, Minneapolis, Minnesota; RomeSL, the IRCCS Santa Lucia Foundation of Rome study, Rome, Italy; SEOUL, Seoul National University Hospital, Seoul, South Korea; UCISZ, University of California, Irvine, Irvine, California; UMCU, University Medical Center Utrecht, Utrecht, the Netherlands; UNIMAAS, Maastricht University, Maastricht, the Netherlands; UNINA, University of Naples Federico II, Naples, Italy; UZH, University of Zurich, Zurich, Switzerland; VOICES, University of Melbourne, Melbourne, Victoria, Australia.

($q_{FDR} < .05$) (Table S9). Results were similar, with larger effect sizes, when not accounting for ventricular volume estimates (Tables S10 and S11). We also found a negative effect for CPZeq, age of SCZ onset, and thalamic segmentation version (v11, v12) on several thalamic subdivisions (Supplement, Section 6), whereas we did not detect significant effects of illness duration, proportion of antipsychotic medication, symptom severity, and FreeSurfer version (versions 5.3, 6.0.1, 7.1.1.0, 7.1.1, 7.2.0, and 7.3.0).

Network-Wide Thalamus-Related Alterations: Main Effect of Group on Morphological Covariation Matrices

In the network-related comparisons of thalamocortical covariation, group effects were significant for the structural covariation between thalamic volumes and cortical thickness ($F_{2,711} = 26.5$, $p \leq .001$) as well as cortical surface ($\chi^2_{2,711} = 99.403$, $p < .001$) (Table S16). In particular, post hoc comparisons showed that thalamic covariations with cortical surface area for FHR were in an intermediate position between SCZ and NC, with surface-related structural covariation higher compared with NC but lower compared with SCZ ($z_{FHR-SCZ} = -5.003$; $z_{NC-SCZ} = -9.970$; $z_{NC-FHR} = -4.977$; all $q_{FDR} < .05$); both differences were significant (Figure 4A–C; Table S16). In contrast, thalamic covariations with thickness for both SCZ and FHR were significantly lower compared with NC ($z_{NC-FHR} = 3.467$; $z_{NC-SCZ} = 2.594$; all $q_{FDR} < .05$), whereas no significant differences were found between FHR and SCZ (Figure 4A–C; Table S16). Regarding confounding variables, there were no significant findings when considering sample demographics and methodological variables (Supplement, Section 7). The edge-related covariation analyses are presented in Supplement, Section 8.

Network-Wide Thalamus-Related Alterations: Main Effect of Group on Corticocortical Covariation Similarity Profiles

In the network-related comparisons of corticocortical trans-thalamic morphological measures, we found a group effect on

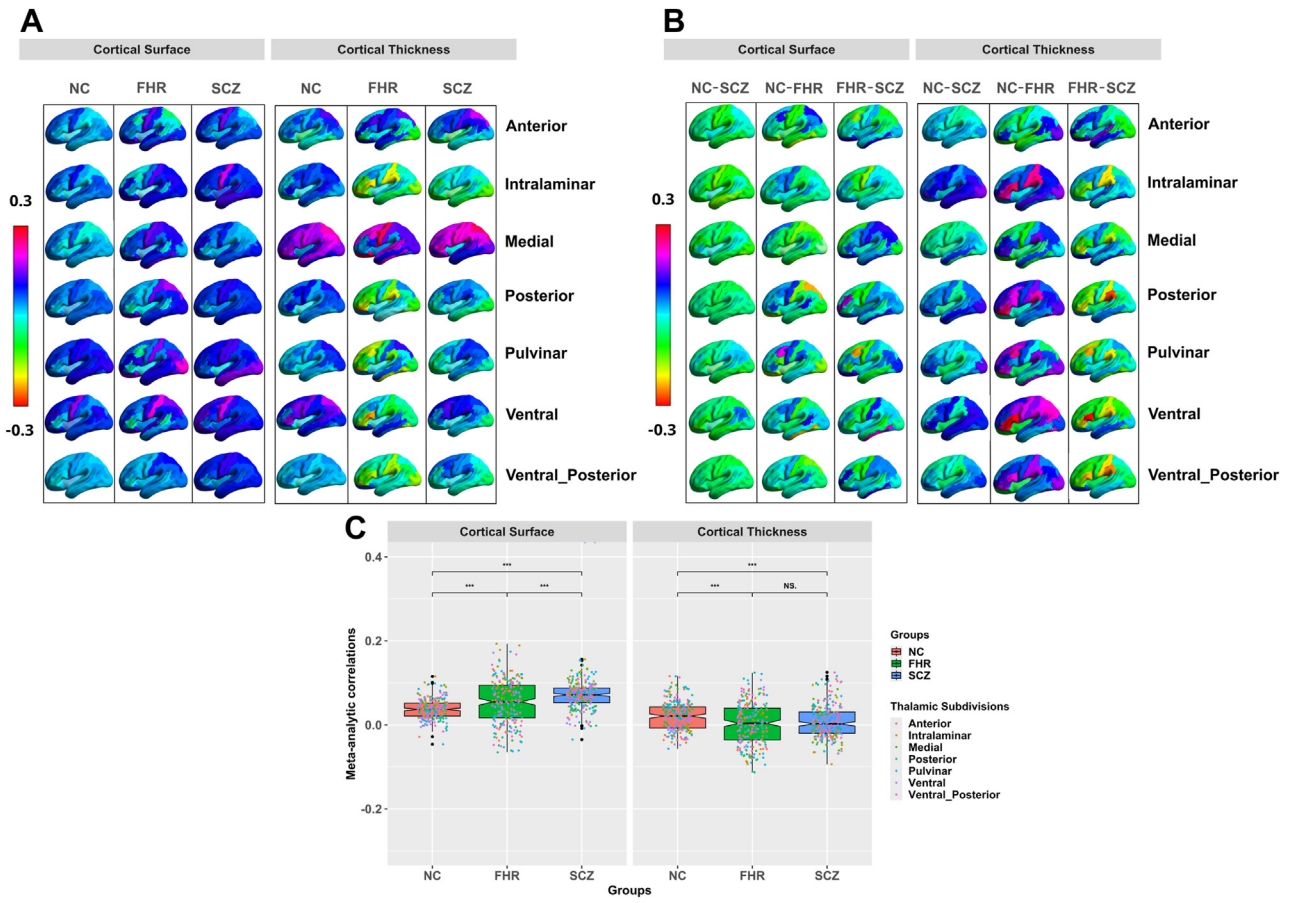

Figure 4. Differences in morphometric thalamocortical covariation across groups (Benjamini–Hochberg post hoc test: all $p < .05$). **(A)** Brain surface mapping showing standardized group average meta-analytic correlation coefficients between each thalamic subdivision and each cortical value. **(B)** Brain surface mapping showing differences across groups (neurotypical control [NC], familial high risk for schizophrenia [FHR], schizophrenia [SCZ]) related to the standardized meta-analytic correlation coefficients between each thalamic subdivision and each cortical value. **(C)** Box plot showing differences in thalamocortical covariation matrices across groups (NC, FHR, SCZ). Each data point represents the correlation between thalamic volumes and morphometric measures (from left to right, respectively, cortical surface and cortical thickness). NS, not significant. ***$p < .05$.

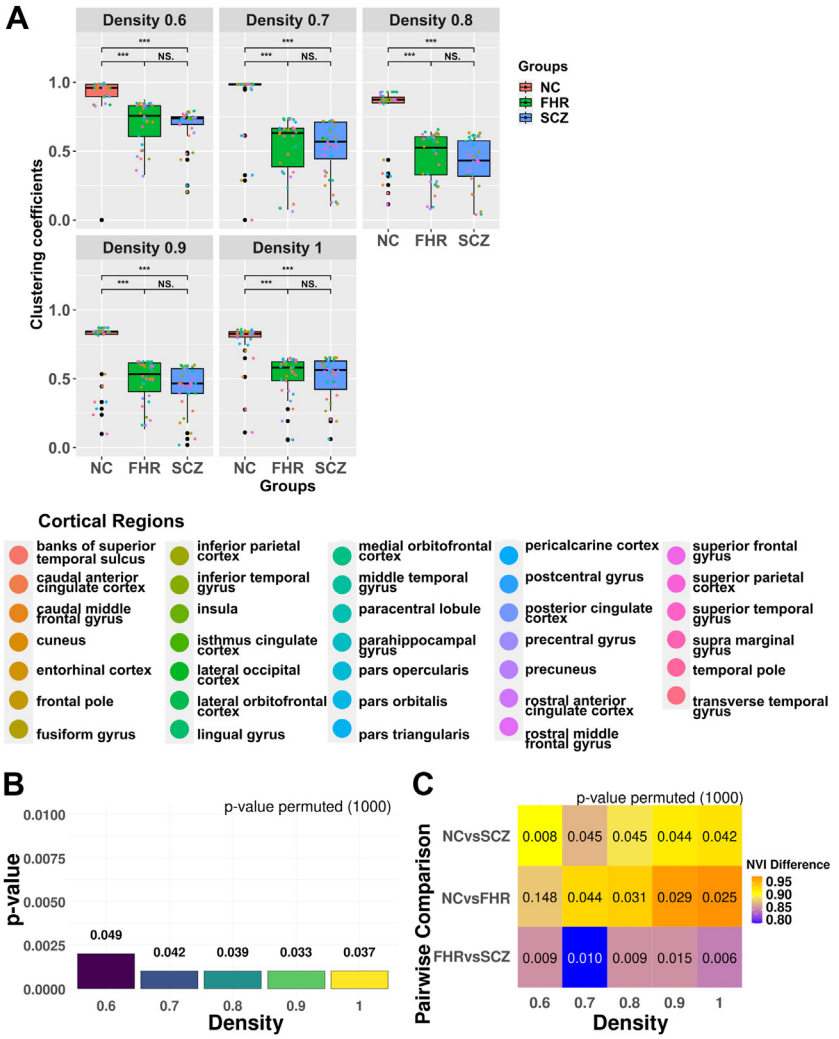

Figure 5. Differences in cluster coefficients related to surface-based corticocortical covariation across groups and densities (from 0.6 to 1). **(A)** Box plots showing the significant differences in cluster coefficients related to surface-based corticocortical covariation across groups and densities (from 0.6 to 1). Pairwise comparisons within groups were corrected for multiple comparisons using the Benjamini–Hochberg procedure (all $p < .05$). Each data point represents the cluster coefficient of a specific cortical region. **(B)** Group effects on surface-related corticocortical covariation. Analysis of variance with permutation test (1000 iterations, $p < .05$). **(C)** Pairwise normalized variation of information (NVI) related to surface-based corticocortical covariation cluster configurations. Permutation test (1000 iterations, $p < .05$). Familial high risk for schizophrenia (FHR) clustering configurations showed the highest NVI (which means more different cluster configurations) compared with neurotypical control (NC) cluster configurations and the lowest NVI (which means more similar cluster configurations) compared with schizophrenia (SCZ) cluster configurations (permuted $p < .05$). SCZ cluster configurations were revealed to be more similar to FHR than to NC (permuted $p < .05$). NS, not significant.

the surface-related corticocortical covariation matrices, evident and consistent for all networks with a density of >0.6 (all $p < .001$, all permuted $p < .05$): the clustering coefficients were significantly higher in NC compared with FHR and SCZ, whereas no significant difference was detected between FHR and SCZ (Figure 5A, B; Table S19).

Community detection revealed different cluster configurations among NC, FHR, and SCZ. Both NC's and SCZ's corticocortical surface-based covariation matrices clustered into 2 communities, whereas FHR's corticocortical surface-based covariation matrices clustered into 3. However, for FHR and SCZ, the same cortical nodes tended to cluster together, across the densities ranging from 0.6 to 1, indicating a more similar cluster configuration compared with NC, as further confirmed by NVI analyses ($NVI_{NC-FHR} > NVI_{NC-SCZ} > NVI_{FHR-SCZ}$ permuted $p < .05$) (Figure 5C; Table S20).

Yeo networks represented within FHR and SCZ cluster configurations were more similar to each other than to NC ($q_{FDR} < .005$) (Figure 6A, B; Tables S21 and S22). In particular, both FHR's and SCZ's cluster 1 (visual B, temporal-parietal, control B, $q_{FDR} < .05$) (Table S22) comprised cortical association areas engaged in visual processing, temporal-parietal functions, and cognitive control. FHR's clusters 2 (visual A, salience+ventral attention A, default C, somatomotor B, $q_{FDR} < .05$) (Figure 6A) and 3 (default A, somatomotor A, dorsal attention B, $q_{FDR} < .05$) (Figure 6B), which covered default mode and somatomotor and ventral functions, converged into SCZ's cluster 2. Notably, visual A and dorsal attention B, which were, respectively, encompassed in clusters 2 and 3 of FHR, did not fit this trend and were not included in SCZ's cluster 2. In contrast, both networks were strongly associated with NC's cluster 1 ($q_{FDR} < .001$), whereas salience+ventral attention A was solely associated with FHR and SCZ (for both, cluster 2). Instead, NC's cluster 1 comprised regions involved in visual processing, somatomotor functions, temporal and parietal functions, dorsal attention, cognitive control, default mode, and limbic functions, indicating a broader and more diverse cluster configuration in NC that mixed sensory, motor, and associative cortices. NC's cluster 2 encompassed regions related to somatomotor and limbic functions. Moreover, no significant group effects were observed in the thickness similarity profiles, indicating that the observed differences were specific to surface-related measures.

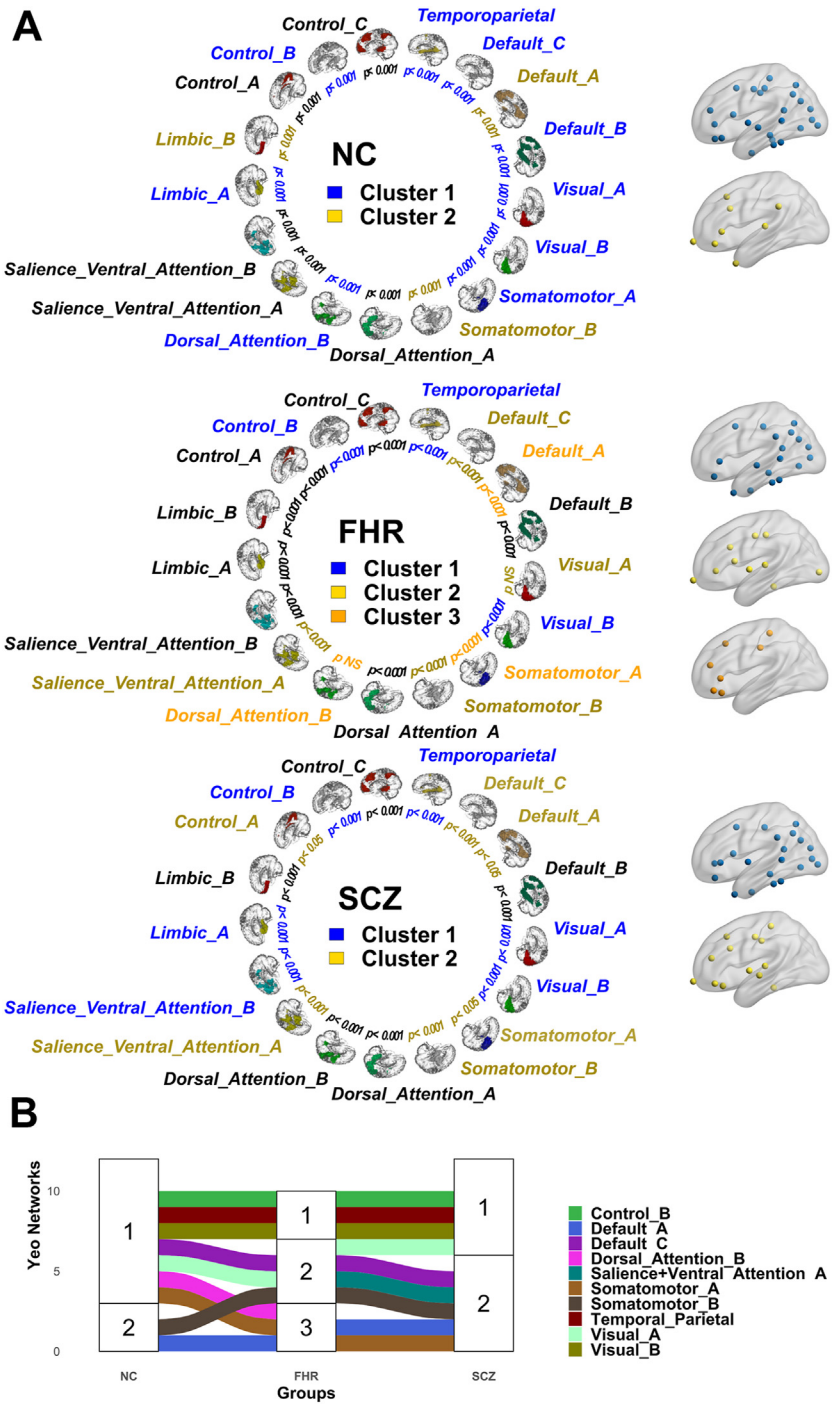

Figure 6. Hypergeometric enrichment test. Yeo networks are significantly represented within surface-related corticocortical similarity clustering profiles. **(A)** Chord diagrams showing surface-related corticocortical covariation clusters enriched for the 17 Yeo networks for each group (neurotypical control [NC], familial high risk for schizophrenia [FHR], schizophrenia [SCZ]). Yeo networks enriched for a specific cluster were represented with the same color as the associated cluster. Black color indicates that a specific Yeo network is not associated with any cluster. *p* values reported were corrected for multiple comparisons using the Benjamini–Hochberg procedure (all $p > .05$ are indicated as not significant [NS]). The right images show the brain surface mapping of cluster partitions for each group, with the same color coding as in the corresponding left diagrams, identifying distinct clusters. **(B)** The alluvial diagram illustrates changes in community assignments of enriched Yeo networks across groups (NC, FHR, SCZ). Each block represents a surface-related corticocortical community and each line corresponds to a Yeo network. Yeo networks not surviving multiple comparisons were not represented. For example, NC's cluster 1 fragmented into 2 parts, one of which joined cluster 2 in FHR and another one of which joined cluster 3 in FHR. Yeo networks: Visual_A, Visual_B, Somatomotor_A, Somatomotor_B, Temporal_Parietal, Dorsal_Attention_A, Dorsal_Attention_B, Salience+Ventral_Attention_A, Salience+Ventral_Attention_B, Control_A, Control_B, Control_C, Default_A, Default_B, Default_C, Limbic_A, and Limbic_B.

DISCUSSION

We investigated the association between local and network-wide thalamus-related structural patterns and familial risk for SCZ in the largest sample to date. We found that 1) individuals with SCZ had significantly smaller whole thalamus volume estimates than NCs, and this effect was also significant at the level of medial, ventral, posterior, anterior, pulvinar, and left ventral–posterior thalamic subdivisions; 2) thalamic covariation with cortical surface was stronger in individuals with SCZ and FHRs compared with NCs, whereas thalamic covariation with cortical thickness was weaker in both individuals with SCZ and

FHRs compared with NCs; and 3) individuals with SCZ and FHRs showed similar corticocortical surface-based similarities profiles, in which associative cortical configurations seemed more similar and more distant from sensory cortices compared with NC.

Volume Estimates of Thalamic Subdivisions

Patients with SCZ showed lower whole thalamus volume estimates compared with NCs, corroborating previous studies (11,40). Subdivision-level findings align with previous voxel-based morphometry (VBM) studies and postmortem evidence regarding the anterior, mediodorsal, posterior, pulvinar, and midline nuclei in individuals with SCZ compared with NCs (8,9,41). Postmortem studies reported that the greatest thalamic gray matter reduction can be observed in the medial subdivision (encompassing the mediodorsal and the midline nuclei) and in the pulvinar, i.e., nuclei largely projecting to the frontal, temporal, and parietal cortices (42). Thus, thalamocortical dysfunction might stem, at least in part, from structural alterations within the thalamus (43). Consistently, previous VBM analyses attributed the gray matter focal deficits in SCZ preeminently to these nuclei (8,9,44). The mediodorsal thalamus may be dysfunctional in SCZ (45), consistent with its strong prefrontal connections (46) and involvement in higher-order cognitive processes (47,48).

The small effect sizes of the volumetric differences observed should be interpreted in light of the confounding variables we considered. Unlike previous studies (11,13,22), we included ventricular volume estimates as nuisance covariates when comparing NC and SCZ. All effect sizes were systematically larger in our control analysis without this covariate. Therefore, ventricle size may explain a portion of the variance in thalamic volumetric differences between patients and controls. The same may apply to other periventricular regions, such as the hippocampus. Other factors contributing to these findings may include the small size of thalamic subdivisions and the heterogeneity between patients (32,49).

The negative association between volume estimates and CPZeq aligns with prior studies (12,50); the FreeSurfer version used for thalamic segmentation also affected several thalamic subdivisions. These findings highlight that drug effects and neuroimaging pipelines may affect inferences drawn from structural MRI studies (51). We also found a negative association between the SCZ onset age and all thalamic subdivision volumes, except for the medial ones, suggesting that with the unitary increase of age at onset, the differences between NCs and individuals with SCZ become smaller. These results align with previous studies reporting smaller thalamic volume estimates in earlier-onset SCZ (52). The lack of an association between illness duration and thalamic volume estimates, combined with the observed negative relationship with antipsychotics, suggests that the thalamic volume deficiencies are unlikely to be explained by chronicity or long-term treatment effects. Accordingly, previous studies showed smaller thalamic volume estimates in untreated SCZ patients relative to controls (43,50).

We found no significant differences in thalamic volume or subdivisions between FHRs and NCs, consistent with other studies (12,15,16,53). In contrast, a recent ENIGMA-Relatives meta-analysis found structural alterations in the whole thalamus in FHRs compared with NCs, reporting a Cohen's *d* of −0.12. The divergent findings with our meta-analyses in FHRs may be related to sample-size differences, the heterogeneity among FHR samples, and covariates used, e.g., including ventricular volume estimates. Although some studies reported lower thalamus gray matter estimates in FHRs compared with NCs (13,14,22), the construct of familial risk for SCZ has been variably defined (e.g., including also second-degree relatives or different types of first-degree relatives, such as offspring, parents, and siblings) (14). In summary, our results support that patients with SCZ have lower thalamic volume estimates than NCs, albeit with smaller effect sizes than previous estimates, but provide no support for abnormal volume estimates in FHRs.

Thalamocortical Structural Covariation

When assessing network-wide differences in thalamocortical covariation, we found higher thalamic positive covariation with cortical surface in patients with SCZ compared with NCs, with FHRs in an intermediate position. Moreover, both patients with SCZ and FHRs showed lower thalamic covariation with cortical thickness compared with NCs, indicating a shared feature between patients with SCZ and FHRs. Interestingly, covariation with cortical surface points to widespread higher correlations in SCZ and FHR compared with NC. Given that individuals with SCZ had lower thalamic subdivision volume estimates than NCs, results suggest lower cortical surface estimates in SCZ and FHR. This result is consistent with a previous ENIGMA study reporting widespread cortical surface alterations in SCZ (54). Only a few regions are an exception to this pattern. In particular, the rostral-middle frontal and postcentral gyrus involved in higher-order cognitive processes and sensory integration (55) showed higher correlations in FHR compared with NC and, to a lesser extent, in SCZ. Conversely, the caudal-middle frontal and precentral gyrus exhibited an opposite covariation pattern, especially related to pulvinar, ventral, posterior, and ventral-posterior subdivisions, which are mostly involved in attentional and motor domains (Table S17A–C for nominally significant differences).

In contrast, cortical thickness showed smaller correlations with thalamic subdivision volume estimates in both FHR and SCZ: mean covariation estimates were closer to zero in these groups. In line with previous literature (54), thickness-related covariation exhibited regional specificity. Most regions still show a positive covariation in both FHR and SCZ with the largest differences between FHR and NC at the level of the intralaminar, ventral, and posterior thalamic subdivisions in their relationship with the frontal lobe. Previous reports also showed regional differences with either thicker or thinner cortex (especially within frontal and temporal regions) in SCZ and genetic or familial SCZ risk (54,56,57). Notably, some regions, such as precentral, postcentral, supramarginal, inferior frontal gyrus, and caudal frontal gyrus, showed an opposite thickness-related covariation with thalamic subdivisions (specifically related to intralaminar, posterior, pulvinar, ventral and ventral-posterior subdivisions) in FHR versus SCZ (Table S17A–C for nominally significant differences). A mix of regional thinner and thicker cortex alterations has previously

been associated with FHR (58–61), especially in sensorimotor areas, which showed opposite patterns in SCZ (59,62). Thinner cortex in several brain areas in FHR has been linked to motor control and cognitive processes (13,63,64). Conversely, a thicker cortex has been associated with higher education levels and stronger verbal abilities (60,65). Sometimes the thicker cortex has been interpreted as a compensatory factor protecting against progression to clinical states (60,64,66). However, caution is required when interpreting these results, considering that FHRs who are not diagnosed as having SCZ are not always free of other psychiatric conditions.

Transthalamic Cortical Covariation

Finally, we found similar corticocortical surface-based clustering configurations between FHR and SCZ. Thus, cortical regions linked to the same thalamic subdivision tend to exhibit similar covariation patterns and cluster together in both FHR and SCZ, reflecting shared network-wide alterations between these groups. This convergence between FHR and SCZ suggests a potential familial risk overlap, possibly linked to attention, motor control, sensory integration, and cognitive processes relevant to SCZ. Particularly, the salience+ventral attention Yeo network, encompassing neural circuits responsible for salient stimuli detection and attentional resources allocation, was exclusively associated with FHR and SCZ (both in cluster 2). This pattern of results is consistent with abnormalities in salience and attention circuits in individuals at familial risk for this disorder (67,68).

We observed a distinct pattern in the clustering of cortical regions associated with similar thalamic subdivisions: a broader frontoparietal control-related Yeo network in NC, involving several associative and somatomotor areas, and clear distinctions between dorsal and ventral/somatomotor-related networks in FHR and SCZ. Previous reports found structural alterations among the thalamus, prefrontal cortex, and sensorimotor networks (45,69,70), interpreted as reflecting altered synaptic pruning (52). Particularly, a study by Kebets *et al.* (71) found dysconnectivity within the somatosensory-motor Yeo network, as well as between the somatosensory-motor Yeo network and subcortical structures, along with cortical executive networks in SCZ and psychosis. Thus, the disrupted covariation we found between dorsal and ventral/somatomotor-related networks in FHR and SCZ may reflect impaired frontothalamic connectivity and stronger somatosensory-thalamic coupling, tying in with functional connectivity reports in SCZ (9,45,72–74). Our findings on altered cortical-thalamic-cortical circuitries, implied in coordinating both motor and cognitive activity, are consistent with the idea that thalamocortical developmental trajectories are associated with cognitive deficits in SCZ, i.e., the hypothesis of cognitive dysmetria (75). The lack of local thalamic alterations in FHR, in the presence of significant alterations in thalamocortical and corticocortical measures, might suggest that the primary alterations in SCZ and FHR occur at a cortical, rather than subcortical, level. This notion is in line with emerging evidence suggesting that local thalamic alterations, particularly in the mediodorsal nucleus, are a psychosis state marker, whereas altered thalamus-related networks may represent a trait and vulnerability marker (76).

Limitations

The main limitation of this study is the small FHR cohort compared with NCs and patients with SCZ. In addition, we conducted a meta-analysis on retrospective data, facing limitations from inherent sources of variation such as different scanners, diagnostic methods, and medication treatments, among others. Even though meta-analyses can control for these differences by summarizing within-site effects and providing average effect sizes, they do not account for all possible sources of variation in assessment methods, potentially reducing sensitivity. In addition, meta-analytic findings aggregate results across studies, potentially obscuring individual-level variability. For example, we cannot infer that the observed group-level covariation patterns are present at the individual subject level. Heterogeneity is another limitation: we applied a random-effects model to account for sample size variability across sites and used the I^2 statistic to assess pairwise heterogeneity between groups. Although I^2 showed generally moderate to low heterogeneity, this statistic is not specific to each group considered. Given that the FHR group had the lowest sample size, comparisons between this group and others had the highest group heterogeneity.

Conclusions

We found lower thalamic gray matter volume estimates in SCZ, but not in FHR. The current results remain inconclusive with respect to local thalamic effects in FHR. Instead, altered thalamocortical structural covariation significantly differed from NCs in both FHRs and patients with SCZ. Our findings suggest that extending the morphometric study beyond the thalamus to include its whole-brain network may provide a sensitive approach to detecting familial risk effects. Therefore, these findings suggest that alterations in network-wide cortico-thalamocortical alterations play a more significant role than primary structural thalamic alterations in familial risk for SCZ.

ACKNOWLEDGMENTS AND DISCLOSURES

The UNIBA (University of Bari Aldo Moro) study was supported by #NEXTGENERATIONEU and funded by the Ministry of University and Research, National Recovery and Resilience Plan, "MNESYS, A multiscale integrated approach to the study of the nervous system in health and disease" (PE0000006)—(DN 1553 11.10.2022 [to GB, AR, AB, and GPe]); by the funding initiative Horizon Europe Seeds 2021 (Next generation 8 EU–European Union—Ministero dell'università e della Ricerca Decreto Ministeriale 737/2021) for the project S68 CUP H99J21017550006 (to LAA, LB, GB, AR, AB and GPe); by the Apulian regional government for the project: "Early Identification of Psychosis Risk" (to AB); and by RIPARTI (assegni di RIcerca per riPARTire con le Imprese) initiative, APULIA REGION (POC PUGLIA FESR-FSE 2014/2020), Project Code 79ed97ad (to GPe).

The PENS and PHCP studies were supported by National Institutes of Health (NIH) (Grant Nos. U01MH108150, P50MH119569, and I01CX000227 [to SRS]).

The YANGSAN study by the National Research Foundation of Korea (Grant No. 2021R1A2C1006718 [to TYL and HJJ]) was supported by the National Research Foundation of Korea grant funded by the Korea government (MSIT) (Grant Nos. 2022R1A2C1092667 and 2021R1F1A1061631).

The IGP study was supported by project grants from the Australian National Health and Medical Research Council (NHMRC) (Grant Nos. APP630471 and APP1081603) and the Macquarie University's ARC Centre of Excellence in Cognition and its Disorders (CE 110001021). MJG was supported by an Australian Research Council Future Fellowship

(FT0991511; 2009–2013) and an RD Wright Biomedical Career Development Award from the NHMRC (1061875; 2014–2017).

For VOICES sample, TVR was supported by an Al and Val Rosenstrauss Fellowship from the Rebecca L. Cooper Medical Research Foundation; SR was supported by an NHMRC Senior Fellowship; and SC was supported by the Brain and Behaviour Research Foundation and the Barbara Dick Brain Sciences Foundation.

The MARBURG study was funded in part by the consortia grants from the German Research Foundation (DFG) FOR 2107 (Grant Nos. FOR2107 KI588/14-1, KI588/14-2, KI588/20-1, and KI588/22-1) and SFB/TRR 393 (Grant No. 521379614 [to TK]); by DFG (Grant Nos. FOR2107 NE2254/1-2, NE2254/2-1, NE2254/3-1, and NE2254/4-1 [to IN]); and by the DFG (Grant No. FOR2107 STR1146/18-1 [to BS]). Biosamples and corresponding data were sampled, processed, and stored in the Marburg Biobank Comprehensive Biomaterial Bank Marburg (CBBMR). Ethics approval was obtained from the ethics committees of the Medical Schools of the Universities of Marburg (approval identifier Studie 07/2014) and Münster, respectively, in accordance with the Declaration of Helsinki. All subjects volunteered to participate in the study and provided written informed consent.

The RomeSL study was supported by the Italian Ministry of Health, Ricerca Corrente 23.

The BASIS study authors thank the Pons-Bartran legacy (FRCB_IPB2-2023, FCRB_PB1_2018), the Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III (Grant No. PI17/00741, PI21/00519, PI21/01694, PI2100330, PI23/00625, FORT23/00002_SUGR_G6), European Commission (Grant No. 101057529), and INVESTIGO-AGAUR (Next Generation Funds, Generalitat de Catalunya). This study was also supported by Consorcio Centro de Investigación Biomédica en Red, cofinanced by the European Union and European Regional Development Fund from the European Commission, "A way of making Europe," financed by the European Union—NextGeneration EU, Fundació Marató TV3 (Grant No. 202210-10, 202232-30-31), and Fundación Alicia Koplowitz.

The JBNU study was supported by HL19C0015 and HR18C0016.

The FIDMAG (FIDMAG Hermanas Hospitalarias Research Foundation) study was supported by a Miguel Servet contract (ISCIII—CP20/00072) to MF-V. PF-C was supported by "la Caixa" Junior Leader Fellowship (Grant No. LCF/BQ/PR22/11920017).

The IMH study was supported by research grants from the National Healthcare Group, Singapore (Grant Nos. SIG/05004 and SIG/05028) and the Singapore Bioimaging Consortium (Grant No. RP C009/2006 [to KS]).

FBRIN and UCISZ studies were supported by the National Center for Research Resources at the NIH (Grant Nos. NIH 1 U24 RR021992 [Function Biomedical Informatics Research Network] and NIH 1 U24 RR025736-01 [Biomedical Informatics Research Network Coordinating Center; http://www.birncommunity.org]); the National Center for Research Resources and the National Center for Advancing Translational Sciences, NIH (Grant No. UL1 TR000153); and the NIMH (Grant No. R21MH097196).

For the COBRE study, JAT was supported by the NIMH (Grant Nos. 5R01MH094524 and 5R01MH121246), and VDC was supported by NIMH (Grant Nos. 3R01MH121246, 1P20RR021938, and 5R01MH121246).

The MUNSTER study was funded by the DFG (cospeaker FOR2107, DA 1151/5-1, DA 1151/5-2, Grant Nos. DA1151/9-1, DA1151/10-1, and DA1151/11-1 [to UD]) and the Interdisciplinary Center for Clinical Research of the medical faculty of Münster (Grant No. Dan3/022/22 [to UD]). This study was supported in part by the CRC/TRR 393 consortium from the DFG (project: A04) and by the Else Kröner-Fresenius-Stiftung (Grant No. 2023_EKEA.153).

The OLIN study was supported by NIMH (Grant Nos. MH106324, MH127158, and MH124802).

The UNIMAAS was supported by the Geestkracht program of the Netherlands Organization for Health Research and Development (Grant No. 10-000-1002).

The NU study was supported by NIH (Grant No. P50MH071616).

The UMCU study was supported by NIH (Grant No. R01MH114152).

This paper reflects only the authors' views, and the European Union and Research Executive Agency are not liable for any use that may be made of the information contained herein. No funding body intervened in the manuscript preparation.

We also acknowledge the contribution of the members of The Apulian Network on Risk for Psychosis: Anna Manzari (Department of Mental Health, Mental Health Center District 3 of Ceglie Messapica, ASL Brindisi, Brindisi, Italy) and Antonello Bellomo (Department of Mental Health, ASL Foggia, Foggia, Italy). None of the members of this group has relevant financial disclosures or conflicts of interest to declare.

We thank Dr. Barbara Gelao, Dr. Marina Mancini, Dr. Annamaria Porcelli, Teresa Pennacchio, Martina Asselti, Dr. Alessandra Raio, and Dr. Leonardo Fazio for UNIBA data acquisition in Bari. We gratefully acknowledge the work of Alba Quarato and Biancamaria Di Bello, who contributed to the quality checking of UNIBA MRI images. We gratefully acknowledge the significant contributions of Prof. Gianfranco Spalletta (RomeSL) to this research, who passed away during the preparation of this manuscript. Finally, we thank all the volunteers who took part in the study.

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

ARTICLE INFORMATION

From the Department of Translational Biomedicine and Neuroscience–University of Bari Aldo Moro, Bari, Italy (AK, LAA, RP, LB, PS, GB, AR, AB, GPe); Lieber Institute for Brain Development, Johns Hopkins Medical Campus, Baltimore, Maryland (RP, ALG, GPe); Istituto Nazionale di Fisica Nucleare, Bari, Italy (LB); Azienda Ospedaliero-Universitaria Consorziale Policlinico, Bari, Italy (PS, GB, AR, AB); Neuroradiology Unit, Scientific Institute for Research, Hospitalization and Health Care, San Giovanni Rotondo, Foggia, Italy (TP); Department of Mental Health, Azienda Sanitaria Locale Bari, Bari, Italy (GDS); Department of Mental Health, Azienda Sanitaria Locale Brindisi, Brindisi, Italy (AS); Department of Mental Health, Azienda Sanitaria Locale Barletta Andria Trani, Barletta-Andria-Trani, Italy (PR); Department of Clinical and Experimental Medicine, University of Foggia, Foggia, Italy (MA); Amsterdam University Medical Center, Vrije Universiteit Amsterdam, Department of Psychiatry and Department of Anatomy and Neuroscience, Amsterdam, the Netherlands (CV); Compulsivity, Impulsivity and Attention, Amsterdam Neuroscience, Amsterdam, the Netherlands (CV); Tri-Institutional Center for Translational Research in Neuroimaging and Data Science, Georgia Institute of Technology, Georgia State University, Emory University, Atlanta, Georgia (VDC, KR-M); Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, Hospital Clínic Barcelona, University of Barcelona, Spain (IB, JC-F, GS, EDLS); Institut d'Investigacions Biomèdiques August Pi i Sunyer, Centro de Investigación Biomédica en Red de Salud Mental, Barcelona, Spain (IB, JC-F, GS, EDLS); FIDMAG Germanes Hospitalàries Research Foundation, Centro de Investigación Biomédica en Red de Salud Mental Instituto de Salud Carlos III, Barcelona, Spain (EP-C, MF-V, RS, AK, PF-C); Department of Psychiatry and Behavioral Sciences, Boston Children's Hospital, Boston Massachusetts (DCG, ALR); Department of Psychiatry, Harvard Medical School, Boston, Massachusetts (DCG, ALR); Olin Neuropsychiatry Research Center, Institute of Living, Hartford, Connecticut (DCG, GDP); Department of Human Genetics and South Texas Diabetes and Obesity Institute, School of Medicine at University of Texas Rio Grande Valley, Brownsville, Texas (JB); Department of Psychiatry and Behavioral Health, Neuroscience, Ohio State University Wexner Medical Center, Columbus, Ohio (LW); Department of Psychiatry, Kyungpook National University School of Medicine, Daegu, South Korea (TL); Department of Psychiatry, Kyungpook National University Hospital, Daegu, South Korea (TL); Department of Biomedical Engineering, Graduate School of Biomedical Sciences and Engineering, Hanyang University, Seoul, South Korea (TL, HJJ); Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Heidelberg University, Heidelberg, Germany (KEE, SH, OG); Division of Clinical Psychology and Sexual Medicine, Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School, Hannover, Germany (SH); Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, California (AP); Department of Psychiatry, Jeonbuk National University, Medical School, Jeonju, South Korea (Y-CC, SO); Department of Psychiatry, Jeonbuk National University Hospital, Jeonju, Korea (Y-CC); Research Institute of Clinical Medicine of Jeonbuk National University-, Biomedical Research Institute of Jeonbuk National University Hospital, Jeonju, Korea (Y-CC, SO); Department of Psychological Medicine, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, United Kingdom (CV, PD); National Institute for Health and Care

Research Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust, London, United Kingdom (PD); Department of Psychiatry and Neuropsychology, Mental Health and Neuroscience Research Institute, Maastricht University, Maastricht, the Netherlands (MM, SM); Department of Psychiatry and Psychotherapy, University of Marburg, Marburg, Germany (KB, FS, IN, BS, FT-O, TK); Institute of Behavioral Science, Feinstein Institutes for Medical Research, Manhasset, New York (KB); Centre for Mental Health and Brain Sciences, Swinburne University, Melbourne, Victoria, Australia (SC SLR, PJS, TEVR); Department of Psychiatry, University of Melbourne, Melbourne, Victoria, Australia (TEVR); Minneapolis Veterans Affairs Health Care System, Minneapolis, Minnesota (SRS); Department of Psychiatry & Behavioral Sciences, University of Minnesota, Minneapolis, Minnesota (CD, ISR, SRS); Institute for Translational Psychiatry, University of Münster, Münster, Germany (RL, SM, TH, UD, DG); Section of Psychiatry, Department of Neuroscience, Reproductive Sciences, and Dentistry, University School of Medicine Federico II, Naples, Italy (MC, FI); Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy (GPo); Department of Electrical Engineering and Information Technology, University "Federico II," Naples, Italy (GPo); Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (GDP); Department of Psychology and Neuroscience Center, Brigham Young University, Provo, Utah (DC); Laboratory of Neuropsychiatry, Scientific Institute for Research, Hospitalization and Healthcare, Santa Lucia Foundation, Rome, Italy (FP, NB, DV); Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Center, Rotterdam, the Netherlands (MEAB, NEMvH); Department of Physiology, College of Medicine, Hanyang University, Seoul, South Korea (HJJ); West Region, Institute of Mental Health, Singapore, Singapore (KS); School of Psychology, University of New South Wales, Sydney, New South Wales, Australia (YQ); Neuroscience Research Australia, Randwick, New South Wales, Australia (YQ, MJG); School of Clinical Medicine, Discipline of Psychiatry and Mental Health, UNSW Sydney, Sydney, New South Wales, Australia (MJG); Department of Psychiatry, Department of Physical Medicine and Rehabilitation, University of Toledo, Toledo, Ohio (RS); Psychiatric Hospital, University of Zurich, Zurich, Switzerland (GC, WO, SH, PH); Imaging Genetics Center, Stevens Neuroimaging & Informatics Institute, Keck School of Medicine of University of Southern California, Los Angeles, California (SIT, PMT); Department of Psychiatry and Behavioral Health, Ohio State Wexner Medical Center, Columbus, Ohio (JAT); Clinical Translational Neuroscience Laboratory, Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, California (TGMvE); Center for the Neurobiology of Learning and Memory, University of California Irvine, Irvine, California (TGMvE); and Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland (GPe).

The members of The Apulian Network on Risk for Psychosis who meet authorship criteria are Anna Manzari (Department of Mental Health, Mental Health Center District 3 of Ceglie Messapica, ASL Brindisi, Brindisi, Italy) and Antonello Bellomo (Department of Mental Health, ASL Foggia, Foggia, Italy).

Address correspondence to Giulio Pergola, Ph.D., at giulio.pergola@uniba.it.

Received Aug 2, 2024; revised Feb 11, 2025; accepted Mar 19, 2025.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2025.03.027.

REFERENCES

1. Liu J, Lee HJ, Weitz AJ, Fang Z, Lin P, Choy M, *et al.* (2015): Frequency-selective control of cortical and subcortical networks by central thalamus. eLife 4:e09215.
2. Jones EG (1997): Cortical development and thalamic pathology in schizophrenia. Schizophr Bull 23:483–501.
3. Krol A, Wimmer RD, Halassa MM, Feng G (2018): Thalamic reticular dysfunction as a circuit endophenotype in neurodevelopmental disorders. Neuron 98:282–295.
4. Byne W, Hazlett EA, Buchsbaum MS, Kemether E (2009): The thalamus and schizophrenia: Current status of research. Acta Neuropathol 117:347–368.
5. Sullivan EV, Rosenbloom MJ, Serventi KL, Deshmukh A, Pfefferbaum A (2003): Effects of alcohol dependence comorbidity and antipsychotic medication on volumes of the thalamus and pons in schizophrenia. Am J Psychiatry 160:1110–1116.
6. Gottesman II, Shields J (1973): Genetic theorizing and schizophrenia. Br J Psychiatry 122:15–30.
7. Weinberger DR (1987): Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 44:660–669.
8. Pergola G, Selvaggi P, Trizio S, Bertolino A, Blasi G (2015): The role of the thalamus in schizophrenia from a neuroimaging perspective. Neurosci Biobehav Rev 54:57–75.
9. Steullet P (2020): Thalamus-related anomalies as candidate mechanism-based biomarkers for psychosis. Schizophr Res 226:147–157.
10. Adriano F, Spoletini I, Caltagirone C, Spalletta G (2010): Updated meta-analyses reveal thalamus volume reduction in patients with first-episode and chronic schizophrenia. Schizophr Res 123:1–14.
11. Van Erp TG, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, *et al.* (2016): Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol Psychiatry 21:547–553.
12. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S (2013): Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. Neurosci Biobehav Rev 37:1680–1691.
13. Zhang W, Sweeney JA, Yao L, Li S, Zeng J, Xu M, *et al.* (2020): Brain structural correlates of familial risk for mental illness: A meta-analysis of voxel-based morphometry studies in relatives of patients with psychotic or mood disorders. Neuropsychopharmacology 45:1369–1379.
14. Cooper D, Barker V, Radua J, Fusar-Poli P, Lawrie SM (2014): Multimodal voxel-based meta-analysis of structural and functional magnetic resonance imaging studies in those at elevated genetic risk of developing schizophrenia. Psychiatry Res 221:69–77.
15. Saarinen AIL, Huhtaniska S, Pudas J, Björnholm L, Jukuri T, Tohka J, *et al.* (2020): Structural and functional alterations in the brain gray matter among first-degree relatives of schizophrenia patients: A multimodal meta-analysis of fMRI and VBM studies. Schizophr Res 216:14–23.
16. Niu Y, Li Z, Cheng R, Peng B, Liu B, Ma Y (2017): Altered gray matter and brain activity in patients with schizophrenia and their unaffected relatives: A multimodal meta-analysis of voxel-based structural MRI and resting-state fMRI studies. Int J Clin Exp Med 10:1866–1878.
17. Boelens Keun JT, van Heese EM, Laansma MA, Weeland CJ, de Joode NT, van den Heuvel OA, *et al.* (2021): Structural assessment of thalamus morphology in brain disorders: A review and recommendation of thalamic nucleus segmentation and shape analysis. Neurosci Biobehav Rev 131:466–478.
18. Di Carlo P, Pergola G, Antonucci LA, Bonvino A, Mancini M, Quarto T, *et al.* (2020): Multivariate patterns of gray matter volume in thalamic nuclei are associated with positive schizotypy in healthy individuals. Psychol Med 50:1501–1509.
19. Pergola G, Trizio S, Di Carlo P, Taurisano P, Mancini M, Amoroso N, *et al.* (2017): Grey matter volume patterns in thalamic nuclei are associated with familial risk for schizophrenia. Schizophr Res 180:13–20.
20. Hulshoff Pol HEH, Schnack HG, Mandl RCW, Brans RGH, van Haren NEM, Baaré WFC, *et al.* (2006): Gray and white matter density changes in monozygotic and same-sex dizygotic twins discordant for schizophrenia using voxel-based morphometry. Neuroimage 31:482–488.
21. Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L (1976): Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet 2:924–926.
22. De Zwarte SMC, Brouwer RM, Agartz I, Alda M, Aleman A, Alpert KI, *et al.* (2019): The association between familial risk and brain abnormalities is disease specific: An ENIGMA-relatives study of schizophrenia and bipolar disorder. Biol Psychiatry 86:545–556.
23. Mai JK, Majtanik M (2018): Toward a common terminology for the thalamus. Front Neuroanat 12:114.
24. Akudjedu TN, Tronchin G, McInerney S, Scanlon C, Kenney JPM, McFarland J, *et al.* (2020): Progression of neuroanatomical abnormalities after first-episode of psychosis: A 3-year longitudinal sMRI study. J Psychiatr Res 130:137–151.

25. Cobia DJ, Smith MJ, Wang L, Csernansky JG (2012): Longitudinal progression of frontal and temporal lobe changes in schizophrenia. Schizophr Res 139:1–6.
26. Gaser C, Nenadic I, Buchsbaum BR, Hazlett EA, Buchsbaum MS (2004): Ventricular enlargement in schizophrenia related to volume reduction of the thalamus, striatum, and superior temporal cortex. Am J Psychiatry 161:154–156.
27. Prasad K, Rubin J, Mitra A, Lewis M, Theis N, Muldoon B, *et al.* (2022): Structural covariance networks in schizophrenia: A systematic review Part I. Schizophr Res 240:1–21.
28. Mitelman SA, Brickman AM, Shihabuddin L, Newmark R, Chu KW, Buchsbaum MS (2005): Correlations between MRI-assessed volumes of the thalamus and cortical Brodmann's areas in schizophrenia. Schizophr Res 75:265–281.
29. Mitelman SA, Byne W, Kemether EM, Hazlett EA, Buchsbaum MS (2006): Correlations between volumes of the pulvinar, centromedian, and mediodorsal nuclei and cortical Brodmann's areas in schizophrenia. Neurosci Lett 392:16–21.
30. Kim J-J, Kim D-J, Kim T-G, Seok J-H, Chun JW, Oh M-K, Park H-J (2007): Volumetric abnormalities in connectivity-based subregions of the thalamus in patients with chronic schizophrenia. Schizophr Res 97:226–235.
31. Prasad K, Rubin J, Mitra A, Lewis M, Theis N, Muldoon B, *et al.* (2022): Structural covariance networks in schizophrenia: A systematic review Part II. Schizophr Res 239:176–191.
32. Wolfers T, Doan NT, Kaufmann T, Alnæs D, Moberget T, Agartz I, *et al.* (2018): Mapping the heterogeneous phenotype of schizophrenia and bipolar disorder using normative models. JAMA Psychiatry 75:1146–1155.
33. Cauda F, Nani A, Costa T, Palermo S, Tatu K, Manuello J, *et al.* (2018): The morphometric co-atrophy networking of schizophrenia, autistic and obsessive spectrum disorders. Hum Brain Mapp 39:1898–1928.
34. Gollub RL, Shoemaker JM, King MD, White T, Ehrlich S, Sponheim SR, *et al.* (2013): The MCIC collection: A shared repository of multi-modal, multi-site brain image data from a clinical investigation of schizophrenia. Neuroinformatics 11:367–388.
35. Christoforou A, Le Hellard S, Giddaluru S, Steen VM, Consortium E, *et al.* (2014): The ENIGMA Consortium: large-scale collaborative analyses of neuroimaging and genetic data. Brain Imaging Behav 8:153–182.
36. Sidik K, Jonkman JN (2005): Simple heterogeneity variance estimation for meta-analysis. J R Stat Soc C 54:367–384.
37. Higgins JPT, Thompson SG (2002): Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539–1558.
38. Leucht S, Samara M, Heres S, Davis JM (2016): Dose equivalents for antipsychotic drugs: The DDD method. Schizophr Bull 42(suppl 1): S90–S94.
39. Eaton E, Mansbach R, editors. (2021). A spin-glass model for semi-supervised community detection. AAAI 26:900–906.
40. Okada N, Fukunaga M, Yamashita F, Koshiyama D, Yamamori H, Ohi K, *et al.* (2016): Abnormal asymmetries in subcortical brain volume in schizophrenia. Mol Psychiatry 21:1460–1466.
41. Janssen J, Alemán-Gómez Y, Reig S, Schnack HG, Parellada M, Graell M, *et al.* (2012): Regional specificity of thalamic volume deficits in male adolescents with early-onset psychosis. Br J Psychiatry 200:30–36.
42. Segobin S, Haast RAM, Kumar VJ, Lella A, Alkemade A, Bach Cuadra M, *et al.* (2024): A roadmap towards standardized neuroimaging approaches for human thalamic nuclei. Nat Rev Neurosci 25:792–808.
43. Dorph-Petersen K-A, Lewis DA (2017): Postmortem structural studies of the thalamus in schizophrenia. Schizophr Res 180:28–35.
44. Huang AS, Rogers BP, Sheffield JM, Jalbrzikowski ME, Anticevic A, Blackford JU, *et al.* (2020): Thalamic nuclei volumes in psychotic disorders and in youths with psychosis spectrum symptoms. Am J Psychiatry 177:1159–1167.
45. 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.
46. Pergola G, Danet L, Pitel A-L, Carlesimo GA, Segobin S, Pariente J, *et al.* (2018): The regulatory role of the human mediodorsal thalamus. Trends Cogn Sci 22:1011–1025.
47. Antonucci LA, Penzel N, Pigoni A, Dominke C, Kambeitz J, Pergola G (2021): Flexible and specific contributions of thalamic subdivisions to human cognition. Neurosci Biobehav Rev 124:35–53.
48. Hwang K, Bertolero MA, Liu WB, D'Esposito M (2017): The human thalamus is an integrative hub for functional brain networks. J Neurosci 37:5594–5607.
49. Pergola G, Suchan B, Koch B, Schwarz M, Daum I, Güntürkün O (2013): Quantitative assessment of chronic thalamic stroke. AJNR Am J Neuroradiol 34:E51–E55.
50. Haijma SV, Van Haren N, Cahn W, Koolschijn PCM, Hulshoff Pol HE, Kahn RS (2013): Brain volumes in schizophrenia: A meta-analysis in over 18 000 subjects. Schizophr Bull 39:1129–1138.
51. Weinberger DR, Radulescu E (2016): Finding the elusive psychiatric "lesion" with 21st-century neuroanatomy: A note of caution. Am J Psychiatry 173:27–33.
52. Benoit LJ, Canetta S, Kellendonk C (2022): Thalamocortical development: A neurodevelopmental framework for schizophrenia. Biol Psychiatry 92:491–500.
53. Dietsche B, Kircher T, Falkenberg I (2017): Structural brain changes in schizophrenia at different stages of the illness: A selective review of longitudinal magnetic resonance imaging studies. Aust N Z J Psychiatry 51:500–508.
54. Van Erp TGM, Walton E, Hibar DP, Schmaal L, Jiang W, Glahn DC, *et al.* (2018): Cortical brain abnormalities in 4474 individuals with schizophrenia and 5098 control subjects via the enhancing neuro imaging genetics through meta analysis (ENIGMA) consortium. Biol Psychiatry 84:644–654.
55. Callicott JH, Bertolino A, Mattay VS, Langheim FJ, Duyn J, Coppola R, *et al.* (2000): Physiological dysfunction of the dorsolateral prefrontal cortex in schizophrenia revisited. Cereb Cortex 10:1078–1092.
56. Venkatasubramanian G, Jayakumar PN, Gangadhar BN, Keshavan MS (2008): Automated MRI parcellation study of regional volume and thickness of prefrontal cortex (PFC) in antipsychotic-naïve schizophrenia. Acta Psychiatr Scand 117:420–431.
57. Crespo-Facorro B, Roiz-Santiáñez R, Pérez-Iglesias R, Rodriguez-Sanchez JM, Mata I, Tordesillas-Gutierrez D, *et al.* (2011): Global and regional cortical thinning in first-episode psychosis patients: Relationships with clinical and cognitive features. Psychol Med 41:1449–1460.
58. Li G, Wang L, Shi F, Lyall AE, Ahn M, Peng Z, *et al.* (2016): Cortical thickness and surface area in neonates at high risk for schizophrenia. Brain Struct Funct 221:447–461.
59. Goghari VM, Rehm K, Carter CS, MacDonald AW 3RD (2007): Regionally specific cortical thinning and gray matter abnormalities in the healthy relatives of schizophrenia patients. Cereb Cortex 17:415–424.
60. Goghari VM, Truong W, Spilka MJ (2015): A magnetic resonance imaging family study of cortical thickness in schizophrenia. Am J Med Genet B Neuropsychiatr Genet 168:660–668.
61. Bois C, Whalley HC, McIntosh AM, Lawrie SM (2015): Structural magnetic resonance imaging markers of susceptibility and transition to schizophrenia: A review of familial and clinical high risk population studies. J Psychopharmacol 29:144–154.
62. Rasser PE, Ehlkes T, Schall U (2024): Fronto-temporal cortical grey matter thickness and surface area in the at-risk mental state and recent-onset schizophrenia: A magnetic resonance imaging study. BMC Psychiatry 24:33.
63. Jung WH, Kim JS, Jang JH, Choi J-S, Jung MH, Park J-Y, *et al.* (2011): Cortical thickness reduction in individuals at ultra-high-risk for psychosis. Schizophr Bull 37:839–849.
64. Van Haren NEM, Schnack HG, Cahn W, Van Den Heuvel MP, Lepage C, Collins L, *et al.* (2011): Changes in cortical thickness during the course of illness in schizophrenia. Arch Gen Psychiatry 68:871–880.

65. Shaw P, Greenstein D, Lerch J, Clasen L, Lenroot R, Gogtay N, *et al.* (2006): Intellectual ability and cortical development in children and adolescents. Nature 440:676–679.
66. Kirschner M, Hodzic-Santor B, Antoniades M, Nenadic I, Kircher T, Krug A, *et al.* (2022): Cortical and subcortical neuroanatomical signatures of schizotypy in 3004 individuals assessed in a worldwide ENIGMA study. Mol Psychiatry 27:1167–1176.
67. Howes OD, Hird EJ, Adams RA, Corlett PR, McGuire P (2020): Aberrant salience, information processing, and dopaminergic signaling in people at clinical high risk for psychosis. Biol Psychiatry 88:304–314.
68. Kapur S (2003): Psychosis as a state of aberrant salience: A framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 160:13–23.
69. Woodward ND, Heckers S (2016): Mapping thalamocortical functional connectivity in chronic and early stages of psychotic disorders. Biol Psychiatry 79:1016–1025.
70. Cheng W, Palaniyappan L, Li M, Kendrick KM, Zhang J, Luo Q, *et al.* (2015): Voxel-based, brain-wide association study of aberrant functional connectivity in schizophrenia implicates thalamocortical circuitry. npj Schizophr 1:15016.
71. Kebets V, Holmes AJ, Orban C, Tang S, Li J, Sun N, *et al.* (2019): Somatosensory-motor dysconnectivity spans multiple transdiagnostic dimensions of psychopathology. Biol Psychiatry 86:779–791.
72. Fröhlich F, Lustenberger C (2020): Neuromodulation of sleep rhythms in schizophrenia: Towards the rational design of non-invasive brain stimulation. Schizophr Res 221:71–80.
73. Antonucci LA, Di Carlo P, Passiatore R, Papalino M, Monda A, Amoroso N, *et al.* (2019): Thalamic connectivity measured with fMRI is associated with a polygenic index predicting thalamo-prefrontal gene co-expression. Brain Struct Funct 224:1331–1344.
74. Antonucci LA, Taurisano P, Fazio L, Gelao B, Romano R, Quarto T, *et al.* (2016): Association of familial risk for schizophrenia with thalamic and medial prefrontal functional connectivity during attentional control. Schizophr Res 173:23–29.
75. Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M (1999): Defining the phenotype of schizophrenia: Cognitive dysmetria and its neural mechanisms. Biol Psychiatry 46:908–920.
76. Hwang WJ, Kwak YB, Cho KIK, Lee TY, Oh H, Ha M, *et al.* (2022): Thalamic connectivity system across psychiatric disorders: Current status and clinical implications. Biol Psychiatry Glob Open Sci 2:332–340.