WILEY

A meta-analysis of deep brain structural shape and asymmetry abnormalities in 2,833 individuals with schizophrenia compared with 3,929 healthy volunteers via the ENIGMA Consortium

Boris A. Gutman[1,2] | Theo G.M. van Erp[3,4] | Kathryn Alpert[5] |
Christopher R. K. Ching[6] | Dmitry Isaev[7] | Anjani Ragothaman[8] |
Neda Jahanshad[6] | Arvin Saremi[6] | Artemis Zavaliangos-Petropulu[6] |
David C. Glahn[9] | Li Shen[10] | Shan Cong[10] | Dag Alnæs[11] |
Ole Andreas Andreassen[11] | Nhat Trung Doan[11] | Lars T. Westlye[11,12] |
Peter Kochunov[13] | Theodore D. Satterthwaite[14] | Daniel H. Wolf[14] |
Alexander J. Huang[3] | Charles Kessler[3] | Andrea Weideman[3] | Dana Nguyen[15] |
Bryon A. Mueller[16] | Lawrence Faziola[17] | Steven G. Potkin[17] | Adrian Preda[17] |
Daniel H. Mathalon[18,19] | Juan Bustillo[20] | Vince Calhoun[21,22] |
Judith M. Ford[19,23] | Esther Walton[24] | Stefan Ehrlich[25] | Giuseppe Ducci[26] |
Nerisa Banaj[27] | Fabrizio Piras[27] | Federica Piras[27] | Gianfranco Spalletta[27,28] |
Erick J. Canales-Rodríguez[29] | Paola Fuentes-Claramonte[29] |
Edith Pomarol-Clotet[29] | Joaquim Radua[29,30] | Raymond Salvador[29] |
Salvador Sarró[29] | Erin W. Dickie[31] | Aristotle Voineskos[31] |
Diana Tordesillas-Gutiérrez[32] | Benedicto Crespo-Facorro[33] | Esther Setién-Suero[34] |
Jacqueline Mayoral van Son[33] | Stefan Borgwardt[35,36] |
Fabienne Schönborn-Harrisberger[35] | Derek Morris[37] | Gary Donohoe[38] |
Laurena Holleran[38] | Dara Cannon[39] | Colm McDonald[39] | Aiden Corvin[40,41] |
Michael Gill[40,41] | Geraldo Busatto Filho[42] | Pedro G. P. Rosa[42] |
Mauricio H. Serpa[42] | Marcus V. Zanetti[42,43] | Irina Lebedeva[44] | Vasily Kaleda[45] |
Alexander Tomyshev[44] | Tim Crow[46] | Anthony James[46] | Simon Cervenka[47] |
Carl M Sellgren[48] | Helena Fatouros-Bergman[47] | Ingrid Agartz[11] |
Fleur Howells[49,50] | Dan J. Stein[49,50,51] | Henk Temmingh[49] | Anne Uhlmann[49,52] |
Greig I. de Zubicaray[53] | Katie L. McMahon[54] | Margie Wright[55] |
Derin Cobia[5,56] | John G. Csernansky[5] | Paul M. Thompson[6] | Jessica A. Turner[57] |
Lei Wang[5,58]

[1]Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, Illinois

[2]Institute for Information Transmission Problems (Kharkevich Institute), Moscow, Russia

[3]Clinical Translational Neuroscience Laboratory, Department of Psychiatry and Human Behavior, University of California Irvine, Irvine, California

[4]Center for the Neurobiology of Learning and Memory, University of California Irvine, Irvine, California

[5]Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, Illinois

[6]Imaging Genetics Center, Mark & Mary Stevens Neuroimaging & Informatics Institute, Keck School of Medicine, University of Southern California, Los Angeles, California

[7]Department of Biomedical Engineering, Duke University, Durham, North Carolina

[8]Department of biomedical engineering, Oregon Health and Science university, Portland, Oregon

[9]Department of Psychiatry, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts

[10]Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania, Philadelphia, Pennsylvania

[11]NORMENT, Division of Mental Health and Addiction, Oslo University Hospital & Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[12]Department of Psychology, University of Oslo, Oslo, Norway

[13]Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland

[14]Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania

[15]Department of Pediatrics, University of California Irvine, Irvine, California

[16]Department of Psychiatry and Behavioral Sciences, University of Minnesota, Minneapolis, Minnesota

[17]Department of Psychiatry and Human Behavior, University of California Irvine, Irvine, California

[18]Department of Psychiatry and Weill Institute for Neurosciences, University of California San Francisco, San Francisco, California

[19]Judith Ford Mental Health, VA San Francisco Healthcare System, San Francisco, California

[20]Departments of Psychiatry & Neuroscience, University of New Mexico, Albuquerque, New Mexico

[21]Tri-institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS) [Georgia State University, Georgia Institute of Technology], Emory University, Atlanta, Georgia

[22]Department of Electrical and Computer Engineering, The University of New Mexico, Albuquerque, New Mexico

[23]Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, California

[24]Department of Psychology, University of Bath, Bath, UK

[25]Division of Psychological & Social Medicine and Developmental Neurosciences, Faculty of Medicine, TU-Dresden, Dresden, Germany

[26]Mental Health Department, ASL Roma1 DSM, Rome, Italy

[27]Laboratory of Neuropsychiatry, IRCCS Santa Lucia Foundation, Rome, Italy

[28]Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Texas

[29]FIDMAG Germanes Hospitalàries Research Foundation, CIBERSAM, Barcelona, Spain

[30]Institut d'Investigacions Biomdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

[31]Centre for Addiction and Mental Health (CAMH), Toronto, Canada

[32]Department of Radiology, IDIVAL, Marqués de Valdecilla University Hospital, Santander, Spain

[33]University Hospital Virgen del Rocio, IBiS, University of Sevilla, CIBERSAM, Sevilla, Spain

[34]University Hospital Marqués de Valdecilla, IDIVAL, CIBERSAM, Santander, Spain

[35]Department of Psychiatry, University of Basel, Basel, Switzerland

[36]Department of Psychiatry and Psychotherapy, University of Lübeck, Lübeck, Germany

[37]Centre for Neuroimaging and Cognitive Genomics, Discipline of Biochemistry, National University of Ireland Galway, Galway, Ireland

[38]Centre for Neuroimaging and Cognitive Genomics, School of Psychology, National University of Ireland Galway, Galway, Ireland

[39]Clinical Neuroimaging Laboratory, Centre for Neuroimaging and Cognitive Genomics, National University of Ireland Galway, Galway, Ireland

[40]Neuropsychiatric Genetics Research Group, Department of Psychiatry, Trinity College Dublin, Dublin, Ireland

[41]Trinity College Institute of Neuroscience, Trinity College Dublin, Dublin, Ireland

[42]Laboratory of Psychiatric Neuroimaging (LIM-21), Departamento e Instituto de Psiquiatria, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Sao Paulo, SP, Brazil

[43]Hospital Sirio-Libanes, Sao Paulo, SP, Brazil

[44]Laboratory of Neuroimaging and Multimodal Analysis, Mental Health Research Center, Moscow, Russia

[45]Department of Endogenous Mental Disorders, Mental Health Research Center, Moscow, Russia

[46]Department of Psychiatry, University of Oxford, Oxford, UK

[47]Centre for Psychiatry Reserach, Department of Clinical Neuroscience, Karolinska Institutet, & Stockholm Health Care Services, Region Stockholm, Stockholm, Sweden

[48]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden

[49]Department of Psychiatry and Mental Health, Faculty of Health Sciences, University of Cape Town, Cape Town, WC, South Africa

[50]Neuroscience Institute, University of Cape Town, Cape Town, WC, South Africa

[51]SA MRC Unit on Risk & Resilience in Mental Disorders, University of Cape Town, Cape Town, WC, South Africa

[52]Department of Child and Adolescent Psychiatry, TU Dresden, Germany

[53]School of Psychology, Faculty of Health, Queensland University of Technology (QUT), Brisbane, QLD, Australia

[54]School of Clinical Sciences, Queensland University of Technology (QUT), Brisbane, QLD, Australia

[55]Queensland Brain Institute, University of Queensland, Brisbane, QLD, Australia

[56]Department of Psychology and Neuroscience Center, Brigham Young University, Provo, Utah

[57]Psychology & Neuroscience, Georgia State University, Atlanta, Georgia

[58]Department of Psychiatry and Behavioral Health, Ohio State University Wexner Medical Center, Columbus, Ohio

Correspondence
Lei Wang, Northwestern University Feinberg School of Medicine, Department of Psychiatry and Behavioral Sciences, 710 N. Lake Shore Drive, Abbott Hall 1322, Chicago, IL 60611.
Email: leiwang1@northwestern.edu

Abstract

Schizophrenia is associated with widespread alterations in subcortical brain structure. While analytic methods have enabled more detailed morphometric characterization, findings are often equivocal. In this meta-analysis, we employed the harmonized ENIGMA shape analysis protocols to collaboratively investigate subcortical brain structure shape differences between individuals with schizophrenia and healthy control participants. The study analyzed data from 2,833 individuals with schizophrenia and 3,929 healthy control participants contributed by 21 worldwide research groups participating in the ENIGMA Schizophrenia Working Group. Harmonized shape analysis protocols were applied to each site's data independently for bilateral hippocampus, amygdala, caudate, accumbens, putamen, pallidum, and thalamus obtained from T1-weighted structural MRI scans. Mass univariate meta-analyses revealed more-concave-than-convex shape differences in the hippocampus, amygdala, accumbens, and thalamus in individuals with schizophrenia compared with control participants, more-convex-than-concave shape differences in the putamen and pallidum, and both concave and convex shape differences in the caudate. Patterns of exaggerated asymmetry were observed across the hippocampus, amygdala, and thalamus in individuals with schizophrenia compared to control participants, while diminished asymmetry encompassed ventral striatum and ventral and dorsal thalamus. Our analyses also revealed that higher chlorpromazine dose equivalents and increased positive symptom levels were associated with patterns of contiguous convex shape differences across multiple subcortical structures. Findings from our shape meta-analysis suggest that common neurobiological mechanisms may contribute to gray matter reduction across multiple subcortical regions, thus enhancing our understanding of the nature of network disorganization in schizophrenia.

KEYWORDS
schizophrenia, structure, subcortical shape

1 | INTRODUCTION

Deep-brain nuclei are implicated in a range of emotional, cognitive, motor, and sensory processes (Haijma et al., 2013; Levitt, Bobrow, Lucia, & Srinivasan, 2010; van Erp et al., 2016), with perturbations resulting in a host abnormal behavioral features (Bonelli & Cummings, 2007). Schizophrenia is associated with abnormalities in volume (Haijma et al., 2013; Levitt et al., 2010; van Erp et al., 2016) and shape measures (Csernansky et al., 1998; Gutman et al., 2015; Harms et al., 2007; Lee et al., 2004; Mamah et al., 2007; McClure et al., 2013; Narr et al., 2001; Roalf et al., 2015) of these subcortical structures, as well as their asymmetry (Okada et al., 2016; L. Wang, Joshi, Miller, & Csernansky, 2001). However, substantial heterogeneity in reported findings (see, e.g., Levitt et al., 2010 for a review) has inspired efforts to harmonize studies via collaborative meta-analyses. Meta-analyses aim to distill true effects from heterogeneous findings, a crucial task for advancing existing theories and for hypothesis generation (Berman & Parker, 2002). Prospective meta-analyses allow for collaborative and harmonized analyses across diverse data sets (Jahanshad & Thompson, 2017; Thompson et al., 2014; van Erp et al., 2016). Using this approach, a recent meta-analysis investigated subcortical volumes in over 4,500 individuals from 15 data sets, and found that schizophrenia patients had smaller hippocampus, amygdala, thalamus and nucleus accumbens, and larger pallidum as compared to healthy control participants, whereas caudate and putamen did not show group differences (van Erp et al., 2016).

Given the anatomical complexity of subcortical structures, studies of shape—defined as the inward and outward variations of surface-based structural boundaries, as well as their curvatures, expansions, and contractions—can detect and characterize more nuanced disease-related structural morphometry patterns relative to whole-structure volume (Levitt et al., 2010). In particular, subcortical structural shape is consistently altered in subtle, yet significant, ways in individuals with schizophrenia (Csernansky, Wang, Joshi, Ratnanather, & Miller, 2004; Mamah, Alpert, Barch, Csernansky, & Wang, 2016; Yang et al., 2012). However, inconsistent findings for specific nuclei have been observed, likely due to the small sample sizes of individual studies as well as investigators' preferred choices of atlases, computational methods, statistical models, and specialized quantitative phenotypes.

For example, a review of shape analysis research in psychosis-spectrum disorders reveals patient sample sizes and types ranging from 20 (Li et al., 2015) to 126 (Qiu et al., 2010) in "strict" schizophrenia samples, 28 (Qiu, Gan, Wang, & Sim, 2013) to 35 (Coscia et al., 2009) in first-episode samples, 60 in an antipsychotic-naïve schizophrenia sample, and another study of 86 early-onset subjects (Chakravarty et al., 2015). While the choices for computational approaches in shape analysis are not as varied relative to volumetric procedures, there still exists some variability including: the radial distance method (Coscia et al., 2009; Thompson et al., 2003); FSL FIRST (Danivas, Kalmady, Venkatasubramanian, & Gangadhar, 2013; Li et al., 2015; Smith et al., 2004); large deformation diffeomorphic metric mapping (LDDMM; (Csernansky et al., 2004; Khan, Wang, & Beg, 2008; Qiu et al., 2010; Qiu et al., 2013; Qiu & Miller, 2008; Vaillant, Qiu,

Glaunes, & Miller, 2007; Wang et al., 2008; Womer et al., 2014); and the MAGeT automatic segmentation method (Chakravarty et al., 2013) with a modified surface-based approach (Chakravarty et al., 2015; Lerch et al., 2008). The heterogeneity in these approaches has yielded both consistent (e.g., thalamus: Coscia et al., 2009; Csernansky, Schindler, et al., 2004; Danivas et al., 2013; Harms et al., 2007; basal ganglia: Chakravarty et al., 2015; Mamah et al., 2016; Wang et al., 2008; hippocampus: Qiu et al., 2013; Wang et al., 2001) and inconsistent findings (e.g., Li et al., 2015), suggesting a need for synthesizing the literature to better capture the global effects of psychosis on these important brain regions.

Given the variability described above, a new approach to meta-analysis of structural shape is needed to overcome the limitations of a traditional, retrospective meta-analysis to characterize subcortical structural shape alterations in schizophrenia. The ENIGMA consortium (Thompson et al., 2020) recently developed a prospective shape meta-analysis approach by harmonizing atlases, computational methods, and statistical models prior to hypothesis testing (Gutman et al., 2015; Gutman, Wang, Rajagopalan, Toga, & Thompson, 2012; Roshchupkin et al., 2016). Here we report the first, large prospective subcortical shape meta-analysis comparing individuals with schizophrenia and healthy control participants using standardized normalization to a common surface-based subcortical atlas, harmonized quality assurance procedures, and a common set of linear statistical models. In this approach, shape analysis was first independently performed for each data set, followed by a meta-analysis on the aggregated group-level results. Two measures of shape were computed; the first was a measure of distance from the medial axis of each structure which we called *thickness*, while the second was a measure of surface *contraction* or *expansion* as calculated by the log Jacobian determinant.

Based on previous literature findings, we hypothesized a predominance of concordant reductions in thickness and contractions across the surfaces of the hippocampus, amygdala, nucleus accumbens, and thalamus. Furthermore, we hypothesized a predominance of concordant increases in thickness and expansions across the surfaces of the putamen and pallidum, in individuals with schizophrenia as compared with control participants. Since atypical antipsychotic drugs have been associated with both increases (Haijma et al., 2013; Konradi & Heckers, 2001; Roiz-Santianez, Suarez-Pinilla, & Crespo-Facorro, 2015) and reductions (Dorph-Petersen et al., 2005; Ho, Andreasen, Ziebell, Pierson, & Magnotta, 2011; Li et al., 2018; Roiz-Santianez et al., 2014; Roiz-Santianez et al., 2015) in subcortical volumes, as well as shape alterations (Mamah et al., 2012), we also attempted to resolve these disparate findings by testing for effects of antipsychotic drug exposure (using chlorpromazine dose equivalents) on shape.

2 | MATERIALS AND METHODS

Twenty-four worldwide cross-sectional study samples from 21 institutions (Figure S1)—2,833 individuals with schizophrenia and 3,929 healthy control participants—contributed to the collaborative shape

meta-analysis via the ENIGMA Schizophrenia Working Group. Each study sample was collected with participants' written informed consent approved by local Institutional Review Boards. The characteristics of these cohorts are provided in Table 1 including weighted age, age of illness onset, duration of illness, and symptom severity. The weighted total scores for positive and negative syndrome scale (PANSS), scale for the assessment of negative symptoms (SANS), and scale for the assessment of positive symptoms (SAPS) across data sets were 16.6 (range of means across data sets: 13.7–22.9), 21.3 (range: 5.5–38.9) and 17.1 (range: 9.0–23.2), respectively. For data sets that recorded current antipsychotic type and dose, we determined the percentage of patients on second-generation (atypical; 77%), first-generation (typical; 15%), both (3%) or none (5%), and chlorpromazine dose equivalents (from 11 data sets) based on Woods (2003) (http://www.scottwilliamwoods.com/files/Equivtext.doc).

To assess subcortical shape measures, we followed the validated ENIGMA-Shape pipeline (http://enigma.usc.edu/ongoing/enigma-shape-analysis/) (Ching et al., 2020; Chye et al., 2020; T. C. Ho et al., 2020; Roshchupkin et al., 2016). A set of standardized scripts to compute mass univariate statistics was distributed to all sites performing the analysis locally via the ENIGMA-Git webpage (https://github.com/ENIGMA-git/ENIGMA/tree/master/WorkingGroups). To harmonize analysis across sites, the distributed script accessed a static online list of models agreed upon by the ENIGMA-Schizophrenia Working Group. Below, we summarize the pipeline.

1. FreeSurfer parcellation. Left and right thalamus, caudate, putamen, pallidum, accumbens, hippocampus and amygdala parcellations, their volumes, and intracranial volumes (ICVs), were obtained with FreeSurfer (http://surfer.nmr.mgh.harvard.edu) from high-resolution T1-weighted structural brain scans. For details on study type (single site or multisite), scanner vendor/strength/sequence, acquisition parameters, FreeSurfer versions, and parcellation quality control, we refer the reader to van Erp et al. (2016) table S3b.

2. Surface triangulation. The boundary of each individual FreeSurfer-parcellated subcortical region was represented by a triangulated surface model. The surface was spherically inflated and registered to a region-specific average model by matching local geometric features (Wang et al., 2011). In this way, each subject was represented by a set of shapes with vertex-to-vertex correspondence to a standard template surface. Visual quality control of the surfaces was performed by individual raters according to the ENIGMA-Shape Quality Control guide (http://enigma.ini.usc.edu/ongoing/enigma-shape-analysis/). Beyond the guide, sites performed local quality control, assisted by experienced raters at the University of Southern California Imaging Genetics Center for particularly difficult cases. More information on shape quality control and failure rates is available in Supplementary Materials.

3. Surface registration. A single template—the default ENIGMA shape atlas—was used by all ENIGMA-Schizophrenia sites participating in the shape project. The ENIGMA-Shape atlas was constructed by averaging surface models of 200 unrelated individuals (100 M/100 F, mean age: 22.9 [2.8] years) from the Queensland Twin Imaging Study (QTIM, Renteria et al., 2014). QTIM data were not used in this study beyond atlas construction.

4. Shape and asymmetry computation. Following registration, a medial curve was computed for the individual shape models (Gutman et al., 2012), and their registrations were further refined (Gutman et al., 2012). Two measures of shape were calculated at each vertex (Wang et al., 2011). The first, which we called "thickness," was the distance to the medial curve. For a cylindrical structure, the medial curve is its center axis, and our measure of thickness measures the length of the radius of each circular cross-section. The second quantity was the Jacobian determinant, which we called "contraction or expansion," was defined as the ratio of the triangular area relative to the triangular area in the template at corresponding vertices. As the Jacobian tends to be non-Gaussian, we used its logarithm transform in all analyses. Vertex-wise maps were then compared to test for group differences (see below). We reasoned that when significant thinning and contraction (or thickening and expansion) occurred concordantly in the same vertices, subvolume changes were likely occurring nearer the structural surface. In contrast, when measures of thickness and contraction/expansion were present in a discordant fashion, we reasoned that subvolume changes could be occurring farther from the surface and closer to the medial curve. We computed the degree of concordance for each of the structures. Finally, the ENIGMA-Shape atlas contains corresponding vertices across the left and right hemispheres allowing calculation of asymmetry indices for the absolute difference between left and right thickness and the log Jacobian determinant at each vertex.

5. Statistical analysis. Vertex-wise mass univariate analysis per shape/asymmetry measure was independently performed first for each data set. Resulting group-level maps of effect sizes (Cohen's

TABLE 1 Sample characteristics

Mean (range of means)	Schizophrenia	Healthy control
N	2,833	3,929
% male	66.9% (54.4–100%)	54.9% (38.6–100%)
Age, years	35.1 (16.3–43.9)	33.2 (16.2–43.6)
Age at onset, years	23.9 (20.7–28.9)	-
Duration of illness, years	11.3 (0.7–31.5)	-
PANSS total	16.6 (13.7–22.9)	-
SANS total	21.3 (5.5–38.9)	-
SAPS total	17.1 (9.0–23.2)	-
Chlorpromazine dose equivalent	376 (166.1–634.6)	-

Note: Age, age at onset and duration of illness, total PANSS (Positive and Negative Syndrome Scale), SANS (Scale for the Assessment of Negative Symptoms), SAPS (Scale for the Assessment of Positive Symptoms), and chlorpromazine dose equivalents were all weighted by sample size. Range is reported on range of means across the data sets. The 100% extreme in % male was due to the all-male sample from the Mental Health Research Center, Moscow.

d; Cohen, 1992), regression parameters, and confidence intervals were then aggregated for mass univariate meta-analysis. We followed the same meta-analytic strategy as in van Erp et al. (2016), using inverse variance-based mixed effects sample weighting with as implemented in the R *metafor* package. Further details are available in Supplementary Materials. The following effects were tested using linear models: effect of diagnosis on thickness (Model 1), log Jacobian determinant (Model 2), asymmetry index of thickness (Model 3), asymmetry index of log Jacobian determinant (Model 4), and effect of chlorpromazine dose equivalents in individuals with schizophrenia (Model 5). In all models, sex and age were accounted for by including their linear, quadratic, and interaction terms: sex, age, age x sex, age^2, and age^2 x sex. Intracranial Volume (ICV) was also included in all models as a covariate. Maps of *p*-values resulting from the meta-analysis were corrected for multiple comparisons (number of structures, vertices, and measures) using a modified searchlight false discovery rate (FDR) procedure (Kriegeskorte, Goebel, & Bandettini, 2006; Langers, Jansen, & Backes, 2007). The correction was applied globally across all structures and measures for each linear model. Distance in the searchlight procedure was defined as the Euclidean distance between atlas vertices, with distance between vertices of different structures set to infinity. We note that this is a more conservative correction than one that assumes spatial correlation between boundaries of different structures, though less conservative than the original Benjamini and Hochberg procedure (Hochberg & Benjamini, 1990).

3 | RESULTS

3.1 | Effect of diagnosis on bilateral shape features

Patterns of predominant concave shape differences were observed across multiple, neighboring subcortical structures. An examination of the aggregate surfaces of the hippocampus, amygdala, accumbens, and the thalamus indicate a predominance of regions showing thinning (Cohen's *d* range = −.03 to −.17; Figure 1a) and surface contractions (Cohen's *d* range = −.01 to −.04; Figure 1b) in individuals with schizophrenia as compared with control subjects. In contrast, an examination of the aggregate surfaces of the caudate, putamen and the pallidum, indicate a predominance of regions showing thickening (Cohen's *d* range = .03 to .17; Figure 1a) and surface expansions (Cohen's *d* range = .01 to .04; Figure 1b). The magnitude of size for all above comparisons are characterized as small effects (Cohen, 1992).

Group differences in the two shape measures did not always overlap with each other. For example, surface contraction without thinning was observed in the superior portions of the hippocampal body (i.e., close to the CA2-4 + DG subfields, Figure S2). In addition, the caudate showed thinning along with surface expansion in its medial regions (Figure S7A,B). Nonetheless, the proportion of concordance of these two measures accounted for the majority of shape differences. A more detailed description of the spatial patterns and the degree of concordance of shape measures for each individual structure can be found in the Supplementary Materials.

We assessed an overall effect size for thinning/thickening and surface contraction/expansion for each subcortical structure collapsed across the hemispheres. We did this by first obtaining surface indices for which the above linear models were significant on measures of interhemispheric means, then separately computing an average for vertices carrying positive effect sizes and an average for negative effect sizes (see Cohen's *d*, Figure 2a,b). With regard to thinning vs. thickening (Figure 2a), only the amygdala and accumbens showed thinning (i.e., negative effect sizes only) in schizophrenia participants. For the hippocampus and thalamus, surface regions with thinning were larger in extent (based on effect size) compared with regions showing thickening. The caudate, putamen, and pallidum showed more thickening than thinning. With regard to surface contraction vs. expansion (Figure 2b), only the hippocampus and accumbens showed surface contraction in schizophrenia participants. Surface regions with larger contraction relative to expansion (based on effect size) included the amygdala and thalamus. The caudate and putamen showed more expansion than contraction, and the pallidum showed only expansion compared to control participants. See Supplementary Materials for more detailed descriptions. Again, the magnitude of all effects above were characterized as small in size.

3.2 | Effect of diagnosis on shape asymmetry

Significant group differences in asymmetry patterns were also observed for both shape measures. Our interpretation of shape asymmetry was based on how the asymmetry index was calculated, which was the absolute difference in effect size for the structures between left and right hemispheres. The asymmetry index for thinning/thickening (Figure 3a) was greater for individuals with schizophrenia as compared to control subjects for the hippocampus, amygdala, nucleus accumbens, and putamen (see *red color* on the surfaces, Cohen's *d* = .05 to .1). For the thalamus, the index was predominantly smaller, as seen in *blue color* (Cohen's *d* = −0.05 to −0.15). For the pallidum and the caudate nucleus, group differences in the asymmetry index was negligible. The asymmetry index of surface contraction/expansion (Figure 3b) was greater for individuals with schizophrenia as compared with control subjects for the hippocampus, amygdala, putamen, and nucleus accumbens (Cohen's *d* = .01 to .04). For the thalamus, the index was predominantly greater for individuals with schizophrenia as compared with control subjects, with smaller proportions of the surface showing smaller indices (Cohen's *d* = −.01 to −.03). For the pallidum and caudate nucleus, group differences in the asymmetry index was negligible.

Consistent with the shape difference maps, patterns of shape asymmetry differences also demonstrated continuity across multiple, neighboring structures. For example, one pattern extended across the hippocampus, amygdala, to the thalamus, showing predominantly exaggerated asymmetry for individuals with schizophrenia as compared with control subjects (Figure 3b, *bottom and front views*), and
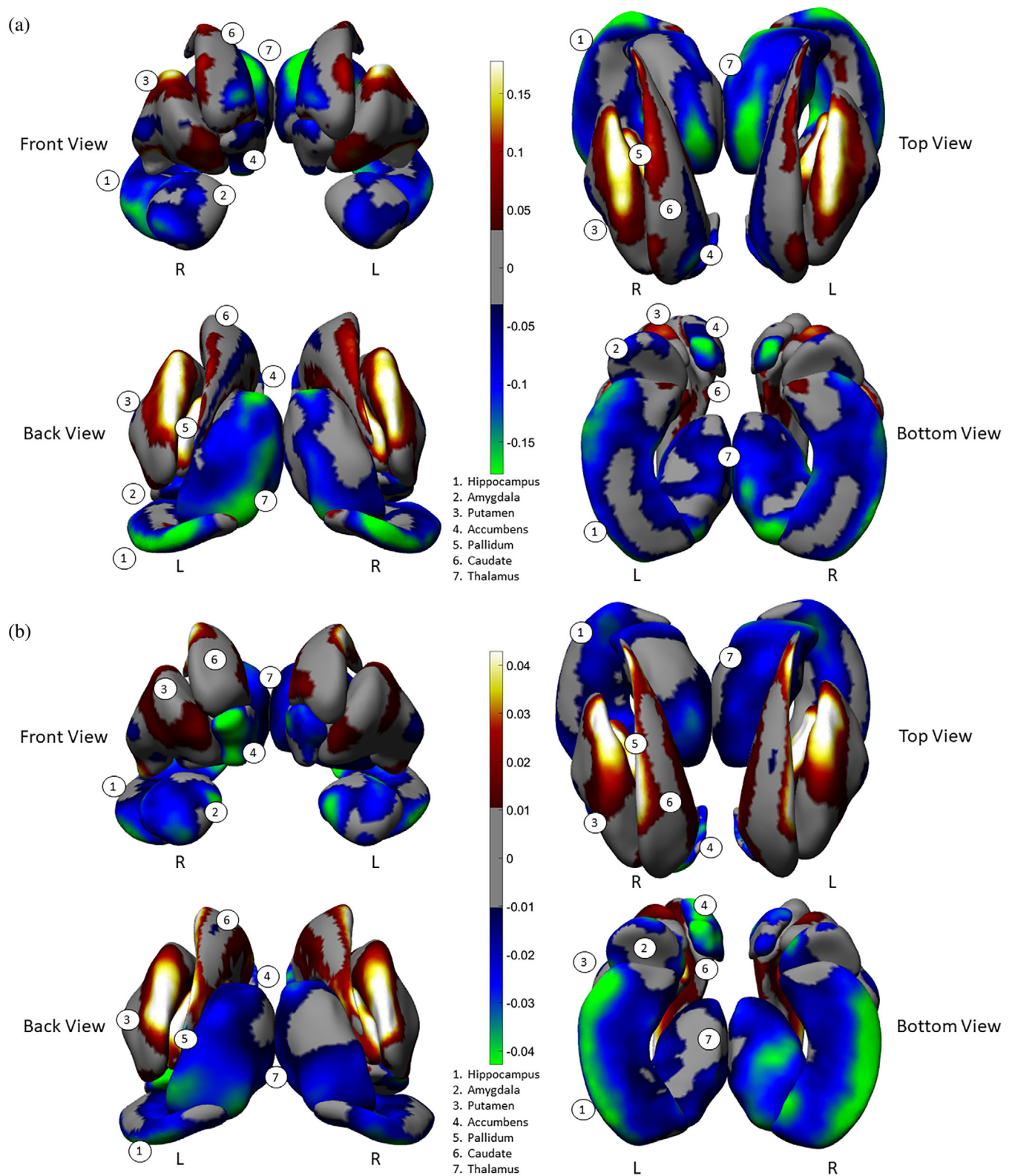
FIGURE 1 Vertex-wise effects of diagnosis (i.e., schizophrenia vs. control) on each hemisphere for (a) thickness, (b) surface dilation/contraction (log Jacobian determinant). The effects are tested in models that included diagnosis sex, age, age x sex, age^2, age^2 x sex, and ICV. Vertex-wise effect sizes (Cohen's *d*, see text) are visualized on subcortical surfaces. The subcortical structures—1. hippocampus, 2. amygdala, 3. putamen, 4. accumbens, 5. pallidum, 6. caudate, and 7. thalamus—are shown as a group situated in template space, from front, back, top, and bottom viewpoints of the brain. L = left hemisphere. R = right hemisphere. Color scale indicates the intensity of effect sizes. Cooler colors (i.e., negative effect sizes) indicate thinning, surface contraction for schizophrenia as compared to controls, and warmer colors (i.e., positive effect sizes) indicate thickening, surface dilation. Gray color indicates nonsignificant surface vertices after multiple comparison correction
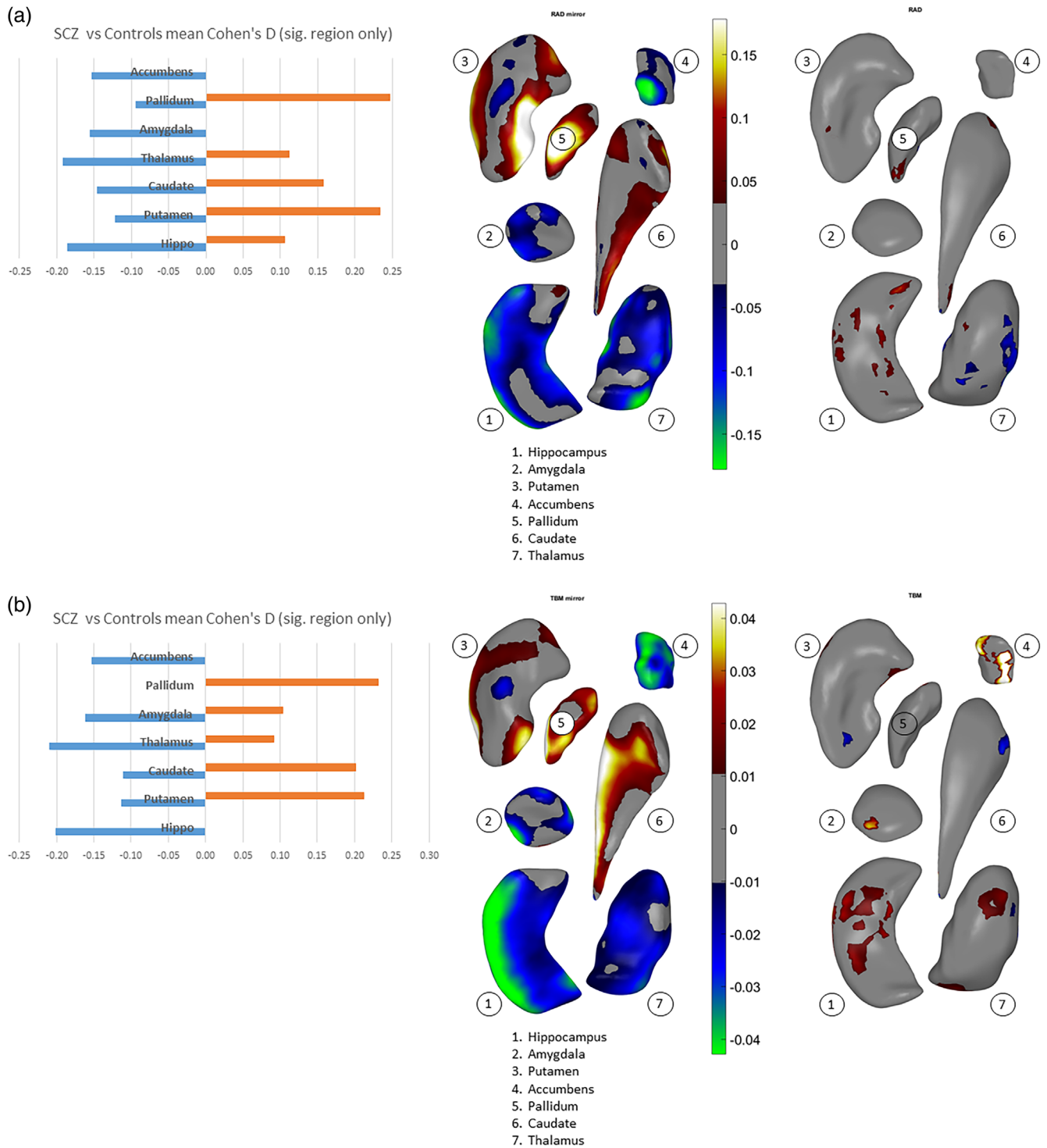
FIGURE 2 Overall and vertex-wise effects of diagnosis (i.e., schizophrenia vs. control) across hemispheres for (a) thickness, (b) surface dilation/contraction (log Jacobian determinant). The effects are tested in models that included diagnosis sex, age, age x sex, age^2, age^2 x sex, and ICV. In the left column, mean positive effect sizes and mean negative effect sizes across each subcortical structure surface (see text) are shown as bar plots. The middle column shows the vertex-wise effects of diagnosis on interhemispheric means (see text). The right column shows the vertex-wise effects of diagnosis on interhemispheric absolute differences (reproduced from Figure 3a,b right columns). The subcortical structures—1. hippocampus, 2. amygdala, 3. putamen, 4. accumbens, 5. pallidum, 6. caudate, and 7. thalamus—are positioned generally from a bottom viewpoint, with some slightly rotated about their own principal axis to be oblique, for better exposure: caudate—pi/7 or about 25°, accumbens—pi/10 or 18°, pallidum—pi/3 or 60°. Color scale indicates the intensity of effect sizes. Cooler colors (i.e., negative effect sizes) indicate reduced asymmetry for schizophrenia as compared to controls, and warmer colors (i.e., positive effect sizes) indicate exaggerated asymmetry. Gray color indicates nonsignificant surface vertices after multiple comparison correction

another encompassed the ventral striatum and ventral and dorsal thalamus, revealing predominantly diminished normal asymmetry for individuals with schizophrenia (Figure 3b, *front view*). Additionally, the determination that these asymmetry differences indicated a leftward versus rightward, or an exaggerated versus diminished normal asymmetry, was made in the context of group differences across both hemispheres; please see Supplementary Materials for these observations.
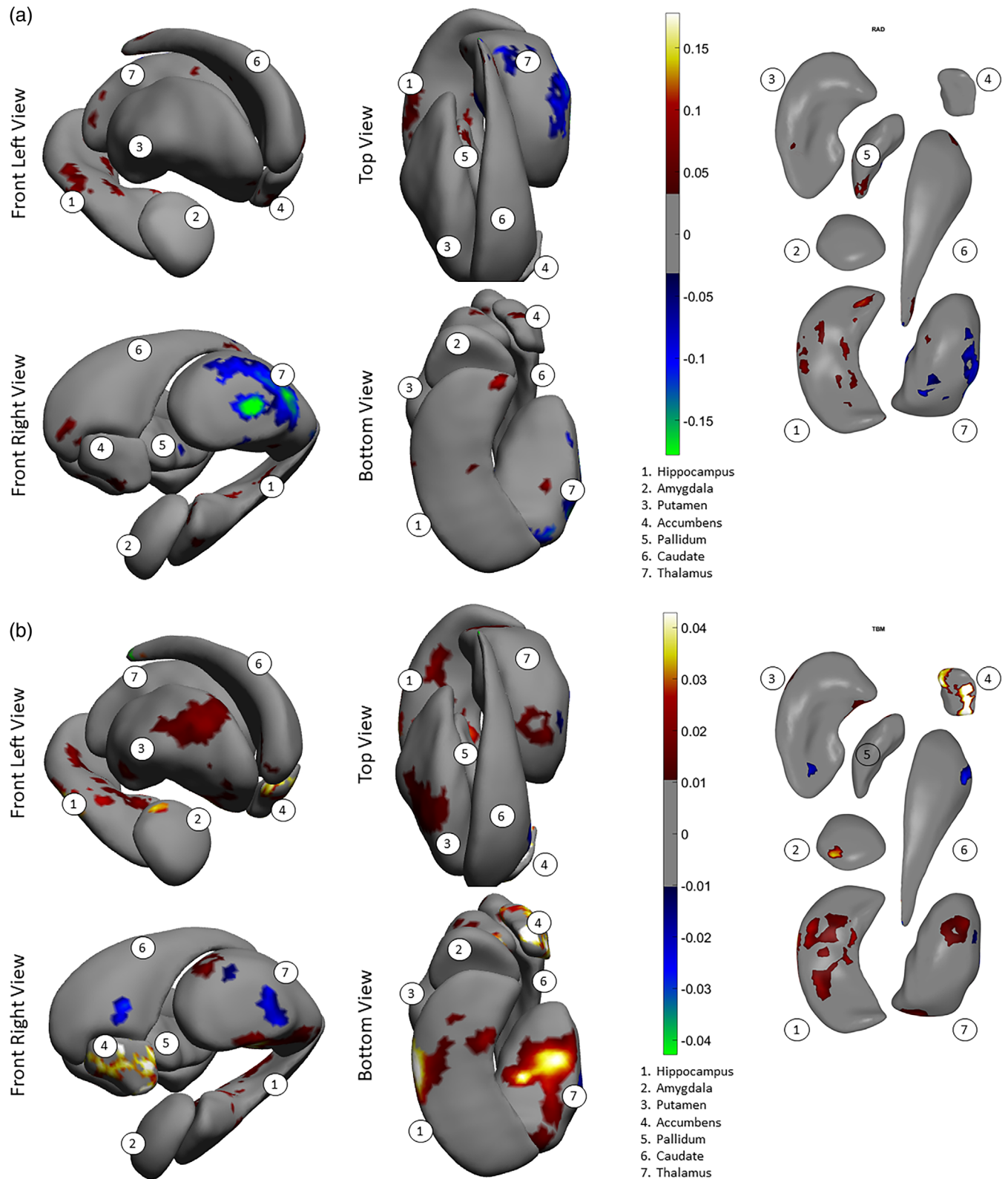

FIGURE 3 Legend on next page.

3.3 | Clinical correlates

In a prior study of structural volumes, we did not detect any significant correlations between chlorpromazine dose equivalents or psychopathology measures and volume differences in a large subset of the patients from 15 of 21 samples analyzed here (van Erp et al., 2016). However, in the present study, using our shape meta-analysis, we found small but statistically significant relationships between higher chlorpromazine dose equivalents and shape-derived thinning (Cohen's $d = -.00008$ to $-.00014$, Figure 4a) and surface contraction (Cohen's $d = -.00005$ to $-.00004$, Figure 4b) in the hippocampus and amygdala, and also in the caudate, accumbens, and thalamus. In addition, we found small but statistically significant relationships between elevated positive symptom (SAPS total) scores and thinning (Cohen's $d = -.00002.5$ to $-.00005$, Figure 5a) and contraction (Cohen's $d = -.00005$ to $-.00014$, Figure 5b) in the hippocampus, amygdala, caudate, and thalamus.

4 | DISCUSSION

In this meta-analysis of subcortical shape variations in schizophrenia, we found a predominance of concave, disease-related, shape differences in the bilateral amygdala, hippocampus, accumbens, and thalamus. As there was a concordance of thinning and surface contraction, these surface changes may reflect losses of subvolumes relatively near the structural surfaces. In turn, we found a predominance of convex, disease-related, shape differences in the bilateral putamen and the pallidum. Notably, the caudate showed a mix of both concave and convex shape differences. In the majority of these instances, differences in thinning/thickening and contraction/expansion were concordant (i.e., overlapping), which suggested to us that these changes more likely reflected variable subvolume changes relatively close to the structural surfaces.

The ranking of effect sizes (i.e., Cohen's d) corroborated the shape observations, and were consistent with prior volume-based meta-analyses (Haijma et al., 2013; van Erp et al., 2016). In a meta-analysis of overlapping subjects, the volumes of the hippocampus, amygdala, accumbens, and the thalamus were reported to be smaller in individuals with schizophrenia compared to healthy control participants, while the volumes of the putamen and the pallidum were larger, and the volume of the caudate did not differ (van Erp et al., 2016). In a

meta-analysis of over 18,000 subjects, Haijma et al. also reported volume reductions in the hippocampus, amygdala, accumbens, and the thalamus for individuals with schizophrenia compared with healthy control participants, with no volumetric differences in the caudate and putamen, and enlargement in the pallidum (Haijma et al., 2013). Our meta-analysis also revealed patterns of shape differences that were contiguous across neighboring structures (Figures S9–S11). For example, concave shape differences extended across the amygdala, hippocampus, accumbens, and thalamus, with larger differences crossing between the amygdala and hippocampus, between the hippocampus and thalamus, and between the caudate and accumbens (Figures S9 and S11). These shape differences confirmed findings previously reported by multiple individual shape studies; that is, in the anteriolateral (CA1) and subicular portions of the hippocampus (Csernansky et al., 2002; Lee et al., 2004; McClure et al., 2013), and anterior and pulvinar portions of the thalamus (Csernansky, Schindler, et al., 2004); see supplemental materials for a more in-depth summary of literature findings.

Previous work has observed that when compared with healthy control participants, individuals with schizophrenia show smaller neuron sizes in the CA1 and subiculum subfields of the hippocampus (Arnold et al., 1995), reduced total number of neurons in the lateral nucleus of amygdala (Kreczmanski et al., 2007), and in the anteroventral, anteromedial, and mediodorsal nuclei and pulvinar of the thalamus (Dorph-Petersen & Lewis, 2017; Young, Manaye, Liang, Hicks, & German, 2000). Microscopic reductions in neuron size or total number of neurons may manifest in macroscopical reductions in gray matter volume measured in MRI. Smaller neuronal size may reflect structural and/or metabolic compromise in the soma, or reduction in the synapses and dendrites that are metabolically supported (Arnold et al., 1995). Furthermore, post mortem studies of individuals with schizophrenia show reduced pre- and postsynaptic markers in hippocampal pyramidal neurons (Glantz & Lewis, 1997; Harrison, 1999b; Harrison & Eastwood, 1998), as well as shorter length, number, and complexity of dendritic processes (Garey et al., 1998; Rosoklija et al., 2000).

Regarding the caudate and putamen, *postmortem* studies have reported both larger (Beckmann & Lauer, 1997) as well as smaller disease-related changes in total neuron number (Kreczmanski et al., 2007). Consistent with this mix of findings, we observed both convex and concave shape differences in these structures (Figure S11). In addition, the regions where convex or concave

FIGURE 3 Effects of diagnosis (i.e., schizophrenia vs. control) for (a) asymmetry index of thickness, (b) asymmetry index of surface dilation/contraction (log Jacobian determinant). Vertex-wise asymmetry indices for thickness and surface dilation/contraction were calculated as the absolute values of left-versus-right differences. The effects are tested in models that included diagnosis sex, age, age x sex, age², age² x sex, and ICV. Effect sizes (Cohen's d, see text) are visualized on subcortical surfaces. In the left two columns, the subcortical structures—1. hippocampus, 2. amygdala, 3. putamen, 4. accumbens, 5. pallidum, 6. caudate, and 7. thalamus—are shown as a group situated in template space, from front left, front right, top and bottom viewpoints of the brain. L = left hemisphere. R = right hemisphere. In the right column, the subcortical structures are positioned generally from a bottom viewpoint, with some slightly rotated about their own principal axis to be oblique, for better exposure: caudate—pi/7 or about 25°, accumbens—pi/10 or 18°, pallidum—pi/3 or 60°. Color scale indicates intensity of effect sizes. Cooler colors (i.e., negative effect sizes) indicate reduced asymmetry for schizophrenia as compared with controls, and warmer colors (i.e., positive effect sizes) indicate exaggerated asymmetry. Gray color indicates nonsignificant surface vertices after multiple comparison correction
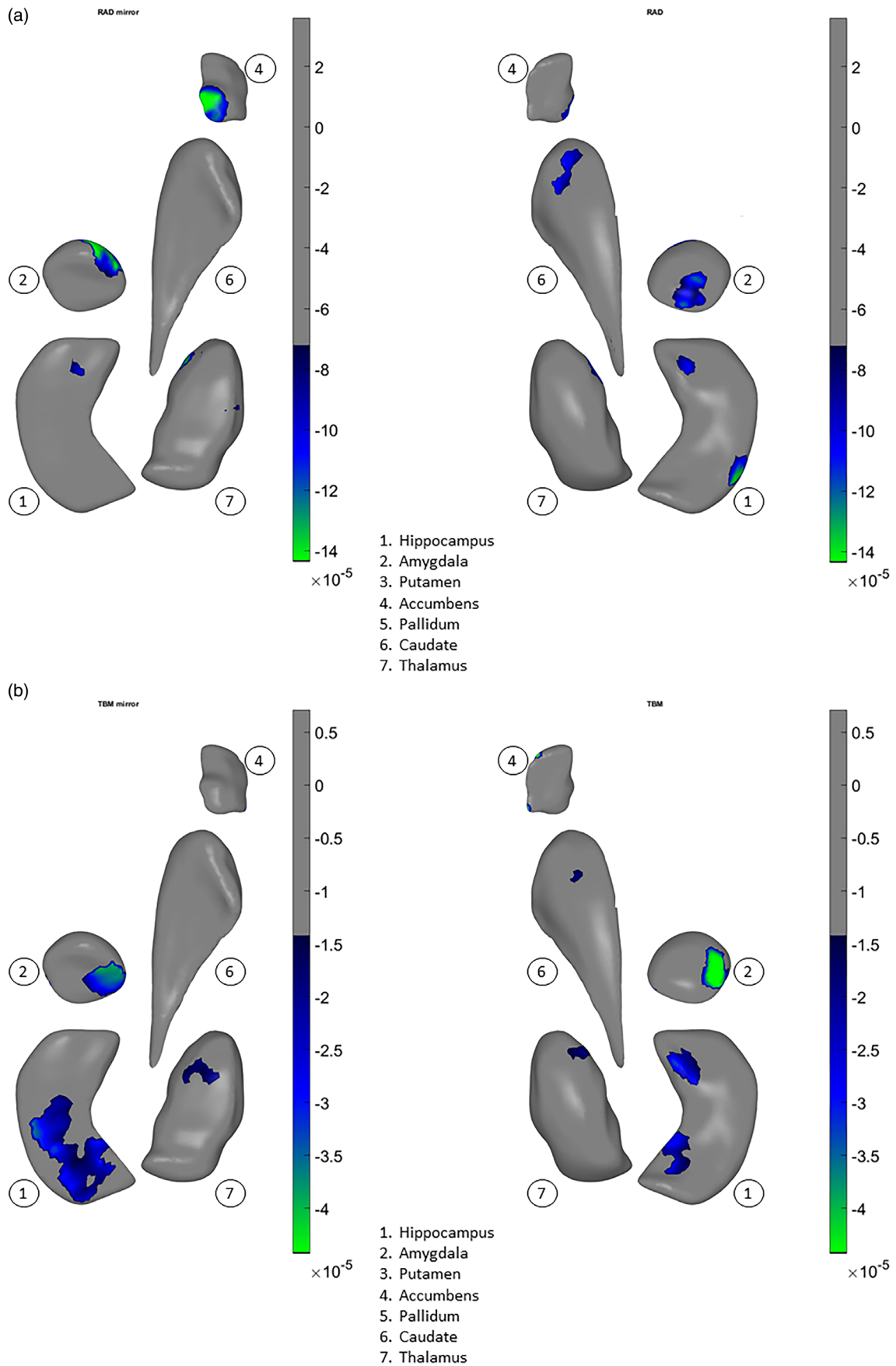
FIGURE 4   Legend on next page.

differences were found tended to be contiguous with the loss and expansion patterns observed in neighboring structures. For example, convex shape differences extended across the caudate and putamen, and adjoining regions, whereas the dorsal concave shape differences in the caudate extended across to the neighboring thalamus. Our observed shape differences are consistent with these patterns of neuronal deficits reported in *postmortem* studies of individuals with schizophrenia, suggesting that common or similar disease mechanisms may contribute to gray matter volume reduction across multiple subcortical regions.

With regard to shape asymmetry, we also observed patterns that extended across multiple, neighboring structures. One predominantly exaggerated asymmetry pattern was observed across the hippocampus, amygdala, and thalamus in individuals with schizophrenia compared to control participants, while a pattern of *diminished* asymmetry in individuals with schizophrenia encompassed the ventral striatum and ventral and dorsal thalamus. Exaggerated asymmetry patterns in schizophrenia across multiple structures have not been reported by previous, volume-based meta-analyses, perhaps due to their subtlety. In the aforementioned meta-analysis of over 18,000 subjects, Haijma et al. reported no statistically significant differences in global left-versus-right subcortical volume effect sizes between individuals with schizophrenia and healthy control participants (Haijma et al., 2013), though left-sided decreases in hippocampus and amygdala volumes were greater than the right-sided decreases. In a meta-analysis comparing 884 individuals with schizophrenia and 1,680 healthy control participants, Okada et al. also reported increased leftward asymmetry only for the pallidum volume in schizophrenia, but not for other subcortical structures (Okada et al., 2016). Our observed exaggerated asymmetry across the multiple subcortical structures, that is, the hippocampus, amygdala, and thalamus, may be partially attributable to a genetic mechanism that controls the development of cerebral asymmetry in schizophrenia (Brun et al., 2008; Crow et al., 1989; Satizabal et al., 2019; Thompson et al., 2001; van der Meulen et al., 2020). Diminished asymmetry such as the effects we observed in the ventral striatum and ventral and dorsal thalamus might be a result of epigenetic dysregulation (Abdolmaleky et al., 2019). Environmental insults during neurodevelopment could also lead to disturbed brain asymmetry observed later in life (Algan & Rakic, 1997; Schindler et al., 2002). In addition, abnormal developments in neuroanatomical asymmetry may underlie the disturbed asymmetry patterns in brain network connectivity in individuals with schizophrenia (Gomez-Gastiasoro

et al., 2019; Guo, Han, Li, & Reddick, 2019; McKenna, Babb, Miles, Goff, & Lazar, 2020; Wang et al., 2019). Ongoing studies of populations of subjects at genetic risk for developing schizophrenia, such as relatives of patients with schizophrenia (de Zwarte et al., 2019; Harms et al., 2007; Mamah et al., 2008; Zhu et al., 2018), may help elucidate the specific roles of genetic influence and environmental factors that contribute to the development of schizophrenia.

The brain's deeper structures are integral components of distributed functional network circuitry. In particular, the thalamus and striatum have direct, excitatory connections with the cortex, while the pallidum receives inhibitory signals from the striatum and limbic structures, and in turn, passes inhibitory signals to the thalamus. Information from different cortical areas, including the prefrontal, frontal, motor, and sensory areas, is received by the striatum via excitatory projections, and then passed on to the thalamus via inhibitory projections from the pallidum. The thalamus projects to the cortex, completing a cortico-basal ganglia-thalamo-cortical loop (Kandel, Schwartz, & Jessell, 1991). The hippocampus and amygdala also have reciprocal excitatory connections with the medial prefrontal cortex (Barbas & Blatt, 1995; Carmichael & Price, 1995), and project to the anterior nucleus of the thalamus as part of Papez' circuit (Jankowski et al., 2013). Structural neuroimaging studies have demonstrated that schizophrenia is associated with widespread gray matter reduction in the brain, predominantly in medial temporal, frontal, and parietal cortical regions, as well in the midline limbic structures and the deep thalamic and striatal nuclei (Bora et al., 2011; Fornito, Yucel, Patti, Wood, & Pantelis, 2009; Honea, Crow, Passingham, & Mackay, 2005; Keshavan, Prasad, & Pearlson, 2007; Lawrie & Abukmeil, 1998; Levitt et al., 2010; McCarley et al., 1999; Palaniyappan, Balain, & Liddle, 2012; Pantelis et al., 2009; Pearlson & Calhoun, 2007; Pearlson & Marsh, 1999; Schmitt, Hasan, Gruber, & Falkai, 2011; Shenton, Dickey, Frumin, & McCarley, 2001; Shenton, Whitford, & Kubicki, 2010). These multifocal brain abnormalities are hypothesized to reflect a "fragmentation of brain pathologies" that ultimately leads to breakdowns in network organization (Shenton et al., 2001; van den Berg, Gong, Breakspear, & van Leeuwen, 2012). Advances in structural and functional neuroimaging studies continue to provide evidence that schizophrenia is a disorder with subtle, multifocal abnormalities involving distributed changes in brain network architecture (Wang & Csernansky, 2014). Our shape meta-analysis findings help us understand this network disorganization in schizophrenia by isolating the specific locations of structural subvolume abnormalities

FIGURE 4 Overall and vertex-wise effects of chlorpromazine dose equivalents across both hemispheres for (a) thickness, (b) surface dilation/contraction (log Jacobian determinant). The effects are tested in models that included diagnosis sex, age, age x sex, age^2, age^2 x sex, and ICV. Small but statistically significant relationships are found between higher chlorpromazine dose equivalents and locally reduced thickness (a) and surface contraction (b) in the hippocampus, amygdala, caudate, accumbens, and thalamus. In the left column, the subcortical structures—1. hippocampus, 2. amygdala, 4. accumbens, 6. caudate, and 7. thalamus—are positioned generally from a bottom viewpoint, with some slightly rotated about their own principal axis to be oblique, for better exposure: caudate—pi/7 or about 25°, accumbens—pi/10 or 18°. In the right column, the subcortical structures are positioned generally from a top viewpoint with the same rotations. Color scale indicates intensity of effect sizes. Cooler colors indicate negative associations, that is, higher chlorpromazine dose equivalents are associated with reduced surface measures. Gray color indicates nonsignificant surface vertices after multiple comparison correction. Putamen and pallidum are not shown as no effects were found for these subcortical structures
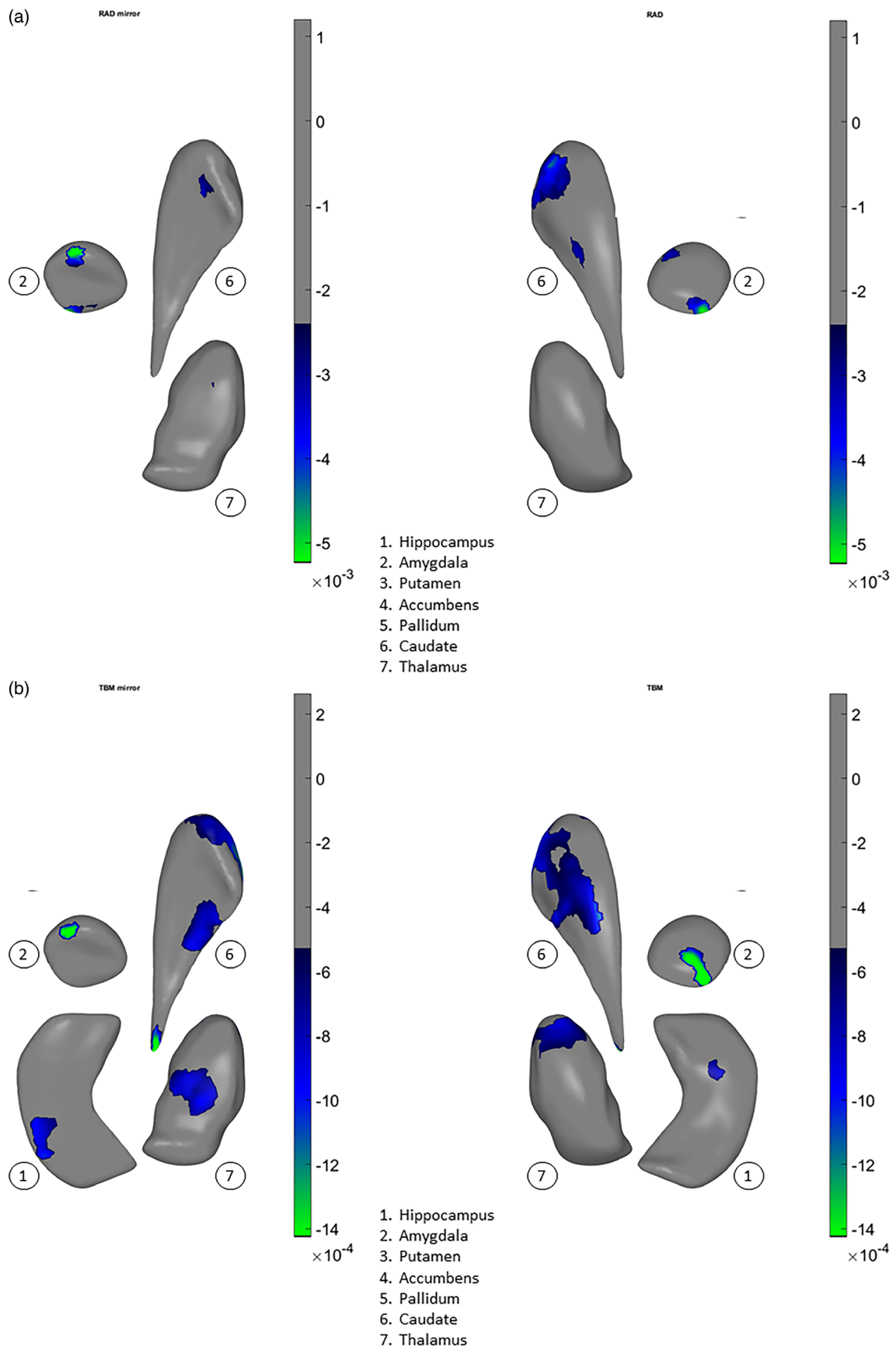
(a)

RAD mirror

RAD

1. Hippocampus
2. Amygdala
3. Putamen
4. Accumbens
5. Pallidum
6. Caudate
7. Thalamus

(b)

TBM mirror

TBM

1. Hippocampus
2. Amygdala
3. Putamen
4. Accumbens
5. Pallidum
6. Caudate
7. Thalamus

FIGURE 5   Legend on next page.

on the surface of deep-brain structures to identify which afferent and efferent connections are affected (Bullmore, Frangou, & Murray, 1997; Friston & Frith, 1995; Meyer-Lindenberg et al., 2001; Volkow et al., 1988; Weinberger, Berman, Suddath, & Torrey, 1992).

Focal subcortical shape deformities in individuals with schizophrenia, such as the anterior-lateral, posterior-lateral aspects of the hippocampus, are known to correlate with focal thinning of cortical regions involved in both dorsal and ventral visual processes (Qiu et al., 2010), as well as lower white matter integrity as measured by fractional anisotropy (Qiu et al., 2010). These findings are consistent with cellular studies showing that the number of neurons expressing NADPH-d enzyme is lower in the hippocampus (Akbarian et al., 1993) as well as in the dorsolateral prefrontal cortex (Akbarian et al., 1993), of subjects with schizophrenia, suggesting the presence of a common pathological process that has interrupted normal neurodevelopment (Akbarian, Vinuela, et al., 1993). Cobia et al. (2017) showed that inward deformity of thalamic shape in the pulvinar region correlated with reduced thickness of the frontal, temporal and parietal cortices, and longitudinal changes in these thalamic and cortical subregions were similarly correlated. The thalamic surface zones reported by Cobia et al. (2017) strongly overlapped with thalamic regions that were the thinnest in our meta-analysis. The pulvinar of the thalamus has broad distributions of connections across the association cortex (Sherman & Guillery, 2011), and its abnormalities were found to be related to cortical abnormalities in individuals with schizophrenia (Sherman & Guillery, 2011). Therefore, our shape findings provide further structural evidence that the development of multiple brain structures are affected in schizophrenia, which support changes in functional brain networks.

Our shape meta-analysis found that higher chlorpromazine dose equivalents were related to concave shape differences primarily in the hippocampus and amygdala, but also in the caudate, accumbens, and thalamus. The literature on the association between subcortical structure and second-generation antipsychotic treatment reflects conflicting findings. In van Erp et al., where an overlapping sample was analyzed for subcortical volumes (van Erp et al., 2016), no relationship was found between chlorpromazine dose equivalents and differences in subcortical volumes. However, the volumetric meta-analysis by Haijma et al. (2013) found that a higher dose of atypical antipsychotics was associated with larger caudate volumes. While some studies have found that antipsychotics were related to increases in gray matter volume or attenuated volume reduction in subcortical

structures (see Konradi & Heckers, 2001; Roiz-Santianez et al., 2015 for reviews), others have reported that volume reductions in the hippocampus (Li et al., 2018) and caudate (Roiz-Santianez et al., 2014) were associated with antipsychotic drug treatment (Dorph-Petersen et al., 2005; Ho et al., 2011; Roiz-Santianez et al., 2015). In a shape analysis by Mamah et al. (2012), schizophrenia patients who were taking olanzapine showed inward shape changes in the hippocampus as compared with healthy controls, but changes that were relatively smaller than inward shape observed in patients taking first-generation antipsychotics. In a meta-analysis of 778 schizophrenia patients, a longer duration of illness was correlated with increased globus pallidus volumes (Hashimoto et al., 2018). In rodent studies, antipsychotic drugs have been shown to affect synaptic ultrastructure, but not neuronal number or size. Atypical antipsychotics tended to upregulate dendritic spine formation and synaptogenesis, whereas typical antipsychotic drugs tended to downregulate them or have no significant effect (Critchlow, Maycox, Skepper, & Krylova, 2006; Delotterie et al., 2010). Following atypical antipsychotic treatment, increased synapses have been observed in the striatum (see Harrison, 1999a for a review) and the hippocampus (Park et al., 2013), whereas typical antipsychotics were not associated with similar changes (Critchlow et al., 2006). Further examination of the mechanisms of antipsychotic drugs' effects on brain structures may help explain the findings of relationships between drug classes and brain changes (i.e., concave shape differences or volume reductions associated with higher doses of first- or second- generation drugs) (Li et al., 2018).

Our shape meta-analysis showed that higher positive symptom severity (SAPS total) scores were associated with concave shape differences in the hippocampus, amygdala, caudate, and thalamus. In the abovementioned volumetric meta-analysis in an overlapping sample (van Erp et al., 2016), no relationships between subcortical volumes and severity of positive or negative symptoms were found. Moreover, in the literature, the association between subcortical structure and psychopathological symptoms has been largely absent (Gong, Lui, & Sweeney, 2016; Haukvik, Hartberg, & Agartz, 2013; Levitt et al., 2010; Li et al., 2018). While the inconsistent relationship in the literature suggests that subcortical structures may not reflect the intensity of psychopathology (Gong et al., 2016), our findings are consistent with the few studies that have shown a relationship between increased positive symptom severity and reduced accumbens volume (Mamah et al., 2007), longitudinal thalamic shape deformation (Wang et al., 2008), and reductions in cortical gray matter measures (Chen et al., 2014).

FIGURE 5   Overall and vertex-wise effects of SAPS total scores across both hemispheres for (a) thickness, (b) surface dilation/contraction (log Jacobian determinant). The effects are tested in models that included diagnosis sex, age, age x sex, age^2, age^2 x sex, and ICV. Small but statistically significant relationships are found between higher SAPS total scores and locally reduced thickness in the amygdala, caudate, and thalamus (a), and surface contraction (b) in the hippocampus, amygdala, caudate, and thalamus. In the left column, the subcortical structures—1. hippocampus (panel b, surface contraction only), 2. amygdala, 6. caudate, and 7. thalamus—are positioned generally from a bottom viewpoint, with some slightly rotated about their own principal axis to be oblique, for better exposure: caudate—pi/7 or about 25°, accumbens—pi/10 or 18°. In the right column, the subcortical structures are positioned generally from a top viewpoint with the same rotations. Color scale indicates the intensity of effect sizes. Cooler colors indicate negative associations, that is, higher chlorpromazine dose equivalents are associated with reduced surface measures. Gray color indicates nonsignificant surface vertices after multiple comparison correction. Accumbens, putamen, and pallidum are not shown as no effects were found for these subcortical structures

Future studies in structural shape should consider the following limitations with respect to our particular analytic tools: In the hippocampus, we found concave changes more prominently in the lateral (proximal to the CA1 hippocampal subfield) and medial regions (proximal to the subiculum). These patterns were more posterior than the more anterior shape deformities reported by groups using diffeomorphic surface mapping methods (Csernansky et al., 2002; Qiu et al., 2010). One explanation may be that the FreeSurfer software, used by every site in our meta-analysis, generates subcortical gray matter boundaries that are sometimes noisy (Wang et al., 2009). While this noise may not affect whole-structure volume measurements (see volume meta-analysis paper by van Erp et al. (2016), it may influence shape measurements such as ours, based on vertex-wise information. The nature of the meta-analysis in this study did not permit the implementation of methodologies that could have generated smooth subcortical surfaces. In addition, harmonization of heterogeneous clinical variables (such as medication, psychopathological symptoms) is challenging, given the differences in outcome measures/ variables used.

There is a growing literature of subtypes of schizophrenia. Using MRI, EEG, ocular motor, and cognition measures, the B-SNIP consortium reported three biotypes that differed on social-relational negative symptoms (Clementz et al., 2020). We and others have reported subtypes as defined by the degree of neuropsychological impairment who differed also in their cortical neuroanatomy (Cobia, Csernansky, & Wang, 2011). McCutcheon, Abi-Dargham, and Howes (2019), however, reported no evidence of subtypes based on treatment responses in a meta-analysis. The ENIGMA consortium provides an ideal setting for future, prospective meta-analytical studies to define and validate subtypes of schizophrenia based on genetics, cognition and other biomarker measures (Smeland et al., 2017; T. Wang et al., 2017). Using polygenic risk scores (PGRS), a recent review of associations between functional MRI activity and polygenic risk for schizophrenia reports that although genetic modulation on brain function for schizophrenia occurs predominantly in frontal areas, it also impacts the task-dependent recruitment across multiple brain regions (Purcell et al., 2009). The ENIGMA consortium is therefore also ideal for meta-analytic studies that can provide anatomical and connectomic mechanisms for the widespread cognitive deficits observed in schizophrenia (Smeland et al., 2017). Further, while antipsychotic drugs and behavioral treatments have not been effective in relieving negative symptoms and cognitive impairment in schizophrenia (Green, Kern, & Heaton, 2004; Nuechterlein et al., 2011), cognitive behavior therapy could lead to increased activation in the thalamus (Kumari et al., 2010) (see Howells, Baldwin, and Kingdon (2016) for a review). Treatment modalities such as aerobic exercise have been shown to improve positive and negative symptoms and quality of life (Dauwan, Begemann, Heringa, & Sommer, 2016; Firth, Cotter, Elliott, French, & Yung, 2015; Vancampfort, Rosenbaum, Ward, & Stubbs, 2015). Aerobic exercise has been demonstrated to improve a range of cognitive functions such as working memory and verbal learning (Vakhrusheva, Marino, Stroup, & Kimhy, 2016) and brain structure (Kandola, Hendrikse, Lucassen, & Yucel, 2016; Malchow et al., 2016; Pajonk et al., 2010)

among individuals with schizophrenia. The mechanism by which aerobic exercise renders these beneficial effects are not established but is reportedly related to improvement in neurogenesis and neuroplasticity processes, particularly in the hippocampus (Falkai et al., 2013; Vakhrusheva et al., 2016). Therefore, future studies may provide further mechanistic basis and targets for potential interventions.

Finally, as data were merged from multiple sites, we chose a statistical design based on meta-analysis to generate consensus maps from the various data sets analyzed. Other approaches are possible, and in Radua et al. (2020) we compared meta-analysis with mega-analysis, in which individual level data from all sites are centralized, and site-level effects are be modeled as random effects. In a meta-analysis, which we used here, it is not assumed that the data from each site have the same mean and variance, as models are fitted locally and effect sizes are combined, with a site-dependent weight. Although we did not do this here, additional adjustments can be made to the data from each site to further harmonize it, including ComBat and its variants (Fortin et al., 2018; Pomponio et al., 2020), hierarchical Bayes models (Kia et al., 2020), and generative adversarial networks (Liu et al., 2021). It is still an open question how to adjust site-level data to increase the distributional overlap across sites, especially when inclusion criteria differ somewhat and latent confounds at each site can lead to under- or overadjustment of data (Kia et al., 2020). As such we used a meta-analysis, which gives comparable results to other methods in recent comparisons (Radua et al., 2020).

In conclusion, our meta-analysis of subcortical shapes revealed strong patterns of shape differences and shape asymmetry differences that provide finer-scale information than prior studies of structural volumes, and spanned multiple neighboring subcortical structures. Findings from our shape meta-analysis suggest that common mechanisms may contribute to gray matter reduction across multiple subcortical regions, which may enhance our understanding of the nature of network disorganization in schizophrenia.

5 | COLLABORATORS

Clinical Neuroscience, Karolinska Institutet, & Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden; Pauliina Victorsson, Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, & Stockholm Health Care Services, Stockholm County Council, Stockholm, Sweden; Göran Engberg, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; Sophie Erhardt, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; Lilly Schwieler, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; Anna Malmqvist, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; Mikael Hedberg, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; Funda Orhan, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; Carl M Sellgren, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; Fredrik Piehl, Neuroimmunology Unit, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; Ingrid Agartz, NORMENT, Division of Mental Health and Addiction, Oslo University Hospital & Institute of Clinical Medicine, University of Oslo.

ACKNOWLEDGMENTS

CONFLICT OF INTERESTS

One of the authors (TGMvE) has had a research contract with Otsuka Pharmaceutical. One of the authors (AP) has served as a consultant for Boehringer Ingelheim. One of the authors (DJS) has received research grants and/or honoraria from Lundbeck and Sun. One of the authors (DHM) has served as a consultant for Boehringer Ingelheim, Aptinyx, and Greenwich Biosciences. One of the authors (SC) has received grant support from AstraZeneca as co-investigator, and has served as a speaker for Otsuka Pharmaceuticals. Authors PMT, CRKC, and NJ received a research grant from Biogen, Inc. (Boston) for research unrelated to this manuscript. The remaining authors declare no potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Christopher R. K. Ching https://orcid.org/0000-0003-2921-3408

David C. Glahn https://orcid.org/0000-0002-4749-6977

Li Shen https://orcid.org/0000-0002-5443-0503

Shan Cong https://orcid.org/0000-0002-5981-7678

Lars T. Westlye https://orcid.org/0000-0001-8644-956X

Theodore D. Satterthwaite https://orcid.org/0000-0001-7072-9399

Fabrizio Piras https://orcid.org/0000-0003-3566-5494

Gianfranco Spalletta https://orcid.org/0000-0002-7432-4249

Raymond Salvador https://orcid.org/0000-0001-5557-1562

Lei Wang https://orcid.org/0000-0003-3870-3388

REFERENCES

Abdolmaleky, H. M., Gower, A. C., Wong, C. K., Cox, J. W., Zhang, X., Thiagalingam, A., ... Thiagalingam, S. (2019). Aberrant transcriptomes and DNA methylomes define pathways that drive pathogenesis and loss of brain laterality/asymmetry in schizophrenia and bipolar disorder. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 180(2), 138–149. https://doi.org/10.1002/ajmg.b.32691

Akbarian, S., Bunney, W. E., Jr., Potkin, S. G., Wigal, S. B., Hagman, J. O., Sandman, C. A., & Jones, E. G. (1993). Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. *Archives of General Psychiatry*, 50(3), 169–177.

Akbarian, S., Vinuela, A., Kim, J. J., Potkin, S. G., Bunney, W. E., Jr., & Jones, E. G. (1993). Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. *Archives of General Psychiatry*, 50(3), 178–187.

Algan, O., & Rakic, P. (1997). Radiation-induced, lamina-specific deletion of neurons in the primate visual cortex. *The Journal of Comparative Neurology*, 381(3), 335–352. https://doi.org/10.1002/(sici)1096-9861(19970512)381:3<335::aid-cne6>3.0.co;2-3

Arnold, S. E., Franz, B. R., Gur, R. C., Gur, R. E., Shapiro, R. M., Moberg, P. J., & Trojanowski, J. Q. (1995). Smaller neuron size in schizophrenia in hippocampal subfields that mediate cortical-hippocampal interactions. *The American Journal of Psychiatry*, 152(5), 738–748. https://doi.org/10.1176/ajp.152.5.738

Barbas, H., & Blatt, G. J. (1995). Topographically specific hippocampal projections target functionally distinct prefrontal areas in the rhesus monkey. *Hippocampus*, 5(6), 511–533. https://doi.org/10.1002/hipo.450050604

Beckmann, H., & Lauer, M. (1997). The human striatum in schizophrenia. II. Increased number of striatal neurons in schizophrenics. *Psychiatry Research*, 68(2–3), 99–109.

Berman, N. G., & Parker, R. A. (2002). Meta-analysis: Neither quick nor easy. *BMC Medical Research Methodology*, 2, 10. https://doi.org/10.1186/1471-2288-2-10

Bonelli, R. M., & Cummings, J. L. (2007). Frontal-subcortical circuitry and behavior. *Dialogues in Clinical Neuroscience*, 9(2), 141–151.

Bora, E., Fornito, A., Radua, J., Walterfang, M., Seal, M., Wood, S. J., ... Pantelis, C. (2011). Neuroanatomical abnormalities in schizophrenia: A multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophrenia Research*, 127(1–3), 46–57.

Brun, C., Lepore, N., Pennec, X., Chou, Y. Y., Lee, A. D., Barysheva, M., ... Thompson, P. M. (2008). A tensor-based morphometry study of genetic influences on brain structure using a new fluid registration method. *Medical Image Computing and Computer-Assisted Intervention*, 11(Pt 2), 914–921. https://doi.org/10.1007/978-3-540-85990-1_110

Bullmore, E. T., Frangou, S., & Murray, R. M. (1997). The dysplastic net hypothesis: An integration of developmental and dysconnectivity theories of schizophrenia. *Schizophrenia Research*, 28(2–3), 143–156.

Carmichael, S. T., & Price, J. L. (1995). Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *The Journal of Comparative Neurology*, 363(4), 615–641. https://doi.org/10.1002/cne.903630408

Chakravarty, M. M., Rapoport, J. L., Giedd, J. N., Raznahan, A., Shaw, P., Collins, D. L., ... Gogtay, N. (2015). Striatal shape abnormalities as novel neurodevelopmental endophenotypes in schizophrenia: A longitudinal study. *Human Brain Mapping*, 36(4), 1458–1469. https://doi.org/10.1002/hbm.22715

Chakravarty, M. M., Steadman, P., van Eede, M. C., Calcott, R. D., Gu, V., Shaw, P., ... Lerch, J. P. (2013). Performing label-fusion-based segmentation using multiple automatically generated templates. *Human Brain Mapping*, 34(10), 2635–2654. https://doi.org/10.1002/hbm.22092

Chen, Z., Deng, W., Gong, Q., Huang, C., Jiang, L., Li, M., ... Li, T. (2014). Extensive brain structural network abnormality in first-episode treatment-naive patients with schizophrenia: Morphometrical and covariation study. *Psychological Medicine*, 44(12), 2489–2501. https://doi.org/10.1017/S003329171300319X

Ching, C. R. K., Gutman, B. A., Sun, D., Villalon Reina, J., Ragothaman, A., Isaev, D., ... Bearden, C. E. (2020). Mapping subcortical brain alterations in 22q11.2 deletion syndrome: Effects of deletion size and convergence with idiopathic neuropsychiatric illness. *The American Journal of Psychiatry*, 177(7), 589–600. https://doi.org/10.1176/appi.ajp.2019.19060583

Chye, Y., Mackey, S., Gutman, B. A., Ching, C. R. K., Batalla, A., Blaine, S., ... Garavan, H. (2020). Subcortical surface morphometry in substance dependence: An ENIGMA addiction working group study. *Addiction Biology*, 25(6), e12830. https://doi.org/10.1111/adb.12830

Clementz, B. A., Trotti, R. L., Pearlson, G. D., Keshavan, M. S., Gershon, E. S., Keedy, S. K., ... Tamminga, C. A. (2020). Testing psychosis phenotypes from bipolar-schizophrenia network for intermediate phenotypes for clinical application: Biotype characteristics and targets. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 5(8), 808–818. https://doi.org/10.1016/j.bpsc.2020.03.011

Cobia, D. J., Csernansky, J. G., & Wang, L. (2011). Cortical thickness in neuropsychologically near-normal schizophrenia. *Schizophrenia Research*, 133(1–3), 68–76. https://doi.org/10.1016/j.schres.2011.08.017

Cobia, D. J., Smith, M. J., Salinas, I., Ng, C., Gado, M., Csernansky, J. G., & Wang, L. (2017). Progressive deterioration of thalamic nuclei relates to cortical network decline in schizophrenia. *Schizophrenia Research*, 180, 21–27. https://doi.org/10.1016/j.schres.2016.08.003

Cohen, J. (1992). A power primer. *Psychological Bulletin*, 112(1), 155–159. https://doi.org/10.1037//0033-2909.112.1.155

Coscia, D. M., Narr, K. L., Robinson, D. G., Hamilton, L. S., Sevy, S., Burdick, K. E., ... Szeszko, P. R. (2009). Volumetric and shape analysis of the thalamus in first-episode schizophrenia. *Human Brain Mapping*, 30(4), 1236–1245. https://doi.org/10.1002/hbm.20595

Critchlow, H. M., Maycox, P. R., Skepper, J. N., & Krylova, O. (2006). Clozapine and haloperidol differentially regulate dendritic spine formation and synaptogenesis in rat hippocampal neurons. *Molecular and Cellular Neurosciences*, 32(4), 356–365. https://doi.org/10.1016/j.mcn.2006.05.007

Crow, T. J., Ball, J., Bloom, S. R., Brown, R., Bruton, C. J., Colter, N., ... Roberts, G. W. (1989). Schizophrenia as an anomaly of development of cerebral asymmetry. A postmortem study and a proposal concerning the genetic basis of the disease. *Archives of General Psychiatry*, 46(12), 1145–1150. https://doi.org/10.1001/archpsyc.1989.01810120087013

Csernansky, J. G., Joshi, S., Wang, L., Haller, J. W., Gado, M., Miller, J. P., ... Miller, M. I. (1998). Hippocampal morphometry in schizophrenia by high dimensional brain mapping. *Proceedings of the National Academy of Sciences of the United States of America*, 95(19), 11406–11411.

Csernansky, J. G., Schindler, M. K., Splinter, N. R., Wang, L., Gado, M., Selemon, L. D., ... Miller, M. I. (2004). Abnormalities of thalamic volume and shape in schizophrenia. *The American Journal of Psychiatry*, 161(5), 896–902. https://doi.org/10.1176/appi.ajp.161.5.896

Csernansky, J. G., Wang, L., Jones, D., Rastogi-Cruz, D., Posener, J. A., Heydebrand, G., ... Miller, M. I. (2002). Hippocampal deformities in schizophrenia characterized by high dimensional brain mapping. *The American Journal of Psychiatry*, 159(12), 2000–2006.

Csernansky, J. G., Wang, L., Joshi, S. C., Ratnanather, J. T., & Miller, M. I. (2004). Computational anatomy and neuropsychiatric disease: Probabilistic assessment of variation and statistical inference of group

difference, hemispheric asymmetry, and time-dependent change. *NeuroImage*, 23(Suppl 1), S56–S68.

Danivas, V., Kalmady, S. V., Venkatasubramanian, G., & Gangadhar, B. N. (2013). Thalamic shape abnormalities in antipsychotic naive schizophrenia. *Indian Journal of Psychological Medicine*, 35(1), 34–38. https://doi.org/10.4103/0253-7176.112198

Dauwan, M., Begemann, M. J., Heringa, S. M., & Sommer, I. E. (2016). Exercise improves clinical symptoms, quality of life, global functioning, and depression in schizophrenia: A systematic review and meta-analysis. *Schizophrenia Bulletin*, 42(3), 588–599. https://doi.org/10.1093/schbul/sbv164

de Zwarte, S. M. C., Brouwer, R. M., Agartz, I., Alda, M., Aleman, A., Alpert, K. I., ... van Haren, N. E. M. (2019). The association between familial risk and brain abnormalities is disease specific: An ENIGMA-relatives study of schizophrenia and bipolar disorder. *Biological Psychiatry*, 86(7), 545–556. https://doi.org/10.1016/j.biopsych.2019.03.985

Delotterie, D., Ruiz, G., Brocard, J., Schweitzer, A., Roucard, C., Roche, Y., ... Andrieux, A. (2010). Chronic administration of atypical antipsychotics improves behavioral and synaptic defects of STOP null mice. *Psychopharmacology*, 208(1), 131–141. https://doi.org/10.1007/s00213-009-1712-3

Dorph-Petersen, K. A., & Lewis, D. A. (2017). Postmortem structural studies of the thalamus in schizophrenia. *Schizophrenia Research*, 180, 28–35. https://doi.org/10.1016/j.schres.2016.08.007

Dorph-Petersen, K. A., Pierri, J. N., Perel, J. M., Sun, Z., Sampson, A. R., & Lewis, D. A. (2005). The influence of chronic exposure to antipsychotic medications on brain size before and after tissue fixation: A comparison of haloperidol and olanzapine in macaque monkeys. *Neuropsychopharmacology*, 30(9), 1649–1661. https://doi.org/10.1038/sj.npp.1300710

Falkai, P., Malchow, B., Wobrock, T., Gruber, O., Schmitt, A., Honer, W. G., ... Cannon, T. D. (2013). The effect of aerobic exercise on cortical architecture in patients with chronic schizophrenia: A randomized controlled MRI study. *European Archives of Psychiatry and Clinical Neuroscience*, 263(6), 469–473. https://doi.org/10.1007/s00406-012-0383-y

Firth, J., Cotter, J., Elliott, R., French, P., & Yung, A. R. (2015). A systematic review and meta-analysis of exercise interventions in schizophrenia patients. *Psychological Medicine*, 45(7), 1343–1361. https://doi.org/10.1017/S0033291714003110

Fornito, A., Yucel, M., Patti, J., Wood, S. J., & Pantelis, C. (2009). Mapping grey matter reductions in schizophrenia: An anatomical likelihood estimation analysis of voxel-based morphometry studies. *Schizophrenia Research*, 108(1–3), 104–113.

Fortin, J. P., Cullen, N., Sheline, Y. I., Taylor, W. D., Aselcioglu, I., Cook, P. A., ... Shinohara, R. T. (2018). Harmonization of cortical thickness measurements across scanners and sites. *NeuroImage*, 167, 104–120. https://doi.org/10.1016/j.neuroimage.2017.11.024

Friston, K. J., & Frith, C. D. (1995). Schizophrenia: A disconnection syndrome? *Clinical Neuroscience*, 3(2), 89–97.

Garey, L. J., Ong, W. Y., Patel, T. S., Kanani, M., Davis, A., Mortimer, A. M., ... Hirsch, S. R. (1998). Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. *Journal of Neurology, Neurosurgery, and Psychiatry*, 65(4), 446–453. https://doi.org/10.1136/jnnp.65.4.446

Glantz, L. A., & Lewis, D. A. (1997). Reduction of synaptophysin immunoreactivity in the prefrontal cortex of subjects with schizophrenia. Regional and diagnostic specificity. *Archives of General Psychiatry*, 54(10), 943–952. https://doi.org/10.1001/archpsyc.1997.01830220065010

Gomez-Gastiasoro, A., Zubiaurre-Elorza, L., Pena, J., Ibarretxe-Bilbao, N., Rilo, O., Schretlen, D. J., & Ojeda, N. (2019). Altered frontal white matter asymmetry and its implications for cognition in schizophrenia: A tractography study. *NeuroImage: Clinical*, 22, 101781. https://doi.org/10.1016/j.nicl.2019.101781

Gong, Q., Lui, S., & Sweeney, J. A. (2016). A selective review of cerebral abnormalities in patients with first-episode schizophrenia before and

after treatment. *The American Journal of Psychiatry*, *173*(3), 232–243. https://doi.org/10.1176/appi.ajp.2015.15050641

Green, M. F., Kern, R. S., & Heaton, R. K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: Implications for MATRICS. *Schizophrenia Research*, *72*(1), 41–51. https://doi.org/10.1016/j.schres.2004.09.009

Guo, J., Han, Y., Li, Y., & Reddick, W. E. (2019). Reduced brain microstructural asymmetry in patients with childhood leukemia treated with chemotherapy compared with healthy controls. *PLoS One*, *14*(5), e0216554. https://doi.org/10.1371/journal.pone.0216554

Gutman, B. A., Jahanshad, N., Ching, C. R., Wang, Y., Kochunov, P. V., Nichols, T. E., & Thompson, P. M. (2015). Medial demons registration localizes the degree of genetic influence over subcortical shape variability: An N= 1480 meta-analysis. *The IEEE International Symposium on Biomedical Imaging*, *2015*, 1402–1406. https://doi.org/10.1109/ISBI.2015.7164138

Gutman, B. A., Wang, Y., Rajagopalan, P., Toga, A. W., & Thompson, P. M. (2012). *Shape matching with medial curves and 1-D group-wise registration*. Paper presented at the 2012 9th IEEE International Symposium on Biomedical Imaging (ISBI), 2-5 May 2012.

Haijma, S. V., Van Haren, N., Cahn, W., Koolschijn, P. C., Hulshoff Pol, H. E., & Kahn, R. S. (2013). Brain volumes in schizophrenia: A meta-analysis in over 18 000 subjects. *Schizophrenia Bulletin*, *39*(5), 1129–1138. https://doi.org/10.1093/schbul/sbs118

Harms, M. P., Wang, L., Mamah, D., Barch, D. M., Thompson, P. A., & Csernansky, J. G. (2007). Thalamic shape abnormalities in individuals with schizophrenia and their nonpsychotic siblings. *The Journal of Neuroscience*, *27*(50), 13835–13842.

Harrison, P. J. (1999a). The neuropathological effects of antipsychotic drugs. *Schizophrenia Research*, *40*(2), 87–99. https://doi.org/10.1016/s0920-9964(99)00065-1

Harrison, P. J. (1999b). The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain*, *122*(Pt 4), 593–624. https://doi.org/10.1093/brain/122.4.593

Harrison, P. J., & Eastwood, S. L. (1998). Preferential involvement of excitatory neurons in medial temporal lobe in schizophrenia. *Lancet*, *352*(9141), 1669–1673. https://doi.org/10.1016/S0140-6736(98)03341-8

Hashimoto, N., Ito, Y. M., Okada, N., Yamamori, H., Yasuda, Y., Fujimoto, M., ... Cocoro. (2018). The effect of duration of illness and antipsychotics on subcortical volumes in schizophrenia: Analysis of 778 subjects. *NeuroImage: Clinical*, *17*, 563–569. https://doi.org/10.1016/j.nicl.2017.11.004

Haukvik, U. K., Hartberg, C. B., & Agartz, I. (2013). Schizophrenia – What does structural MRI show? *Tidsskrift for Den Norske Legeforening*, *133*, 850–853.

Ho, B. C., Andreasen, N. C., Ziebell, S., Pierson, R., & Magnotta, V. (2011). Long-term antipsychotic treatment and brain volumes: A longitudinal study of first-episode schizophrenia. *Archives of General Psychiatry*, *68*(2), 128–137.

Ho, T. C., Gutman, B., Pozzi, E., Grabe, H. J., Hosten, N., Wittfeld, K., ... Schmaal, L. (2020). Subcortical shape alterations in major depressive disorder: Findings from the ENIGMA major depressive disorder working group. *Human Brain Mapping*. https://doi.org/10.1002/hbm.24988

Hochberg, Y., & Benjamini, Y. (1990). More powerful procedures for multiple significance testing. *Statistics in Medicine*, *9*(7), 811–818.

Honea, R., Crow, T. J., Passingham, D., & Mackay, C. E. (2005). Regional deficits in brain volume in schizophrenia: A meta-analysis of voxel-based morphometry studies. *The American Journal of Psychiatry*, *162*(12), 2233–2245.

Howells, F. M., Baldwin, D. S., & Kingdon, D. G. (2016). Can cognitive behaviour therapy beneficially influence arousal mechanisms in psychosis? *Human Psychopharmacology*, *31*(1), 64–69. https://doi.org/10.1002/hup.2499

Jahanshad, N., & Thompson, P. M. (2017). Multimodal neuroimaging of male and female brain structure in health and disease across the life span. *Journal of Neuroscience Research*, *95*(1–2), 371–379. https://doi.org/10.1002/jnr.23919

Jankowski, M. M., Ronnqvist, K. C., Tsanov, M., Vann, S. D., Wright, N. F., Erichsen, J. T., ... O'Mara, S. M. (2013). The anterior thalamus provides a subcortical circuit supporting memory and spatial navigation. *Frontiers in Systems Neuroscience*, *7*, 45. https://doi.org/10.3389/fnsys.2013.00045

Kandel, E., Schwartz, J., & Jessell, T. (Eds.). (1991). *Principles of neural science*. Norwald: Connecticut: Appleton & Lange.

Kandola, A., Hendrikse, J., Lucassen, P. J., & Yucel, M. (2016). Aerobic exercise as a tool to improve hippocampal plasticity and function in humans: Practical implications for mental health treatment. *Frontiers in Human Neuroscience*, *10*, 373. https://doi.org/10.3389/fnhum.2016.00373

Keshavan, M. S., Prasad, K. M., & Pearlson, G. (2007). Are brain structural abnormalities useful as endophenotypes in schizophrenia? *International Review of Psychiatry*, *19*(4), 397–406.

Khan, A. R., Wang, L., & Beg, M. F. (2008). FreeSurfer-initiated fully-automated subcortical brain segmentation in MRI using large deformation diffeomorphic metric mapping. *NeuroImage*, *41*(3), 735–746. https://doi.org/10.1016/j.neuroimage.2008.03.024

Kia, S. M., Huijsdens, H., Dinga, R., Wolfers, T., Mennes, M., Andreassen, O. A., . . . Marquand, A. F. (2020). Hierarchical bayesian regression for multi-site normative modeling of neuroimaging data. *arXiv*:2005.12055

Konradi, C., & Heckers, S. (2001). Antipsychotic drugs and neuroplasticity: Insights into the treatment and neurobiology of schizophrenia. *Biological Psychiatry*, *50*(10), 729–742.

Kreczmanski, P., Heinsen, H., Mantua, V., Woltersdorf, F., Masson, T., Ulfig, N., ... Schmitz, C. (2007). Volume, neuron density and total neuron number in five subcortical regions in schizophrenia. *Brain*, *130*(Pt 3), 678–692. https://doi.org/10.1093/brain/awl386

Kriegeskorte, N., Goebel, R., & Bandettini, P. (2006). Information-based functional brain mapping. *Proceedings of the National Academy of Sciences of the United States of America*, *103*(10), 3863–3868. https://doi.org/10.1073/pnas.0600244103

Kumari, V., Antonova, E., Fannon, D., Peters, E. R., Ffytche, D. H., Premkumar, P., ... Kuipers, E. (2010). Beyond dopamine: Functional MRI predictors of responsiveness to cognitive behaviour therapy for psychosis. *Frontiers in Behavioral Neuroscience*, *4*, 4. https://doi.org/10.3389/neuro.08.004.2010

Langers, D. R., Jansen, J. F., & Backes, W. H. (2007). Enhanced signal detection in neuroimaging by means of regional control of the global false discovery rate. *NeuroImage*, *38*(1), 43–56. https://doi.org/10.1016/j.neuroimage.2007.07.031

Lawrie, S. M., & Abukmeil, S. S. (1998). Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. *The British Journal of Psychiatry*, *172*, 110–120.

Lee, J. M., Kim, S. H., Jang, D. P., Ha, T. H., Kim, J. J., Kim, I. Y., ... Kim, S. I. (2004). Deformable model with surface registration for hippocampal shape deformity analysis in schizophrenia. *NeuroImage*, *22*(2), 831–840. https://doi.org/10.1016/j.neuroimage.2004.02.004

Lerch, J. P., Carroll, J. B., Spring, S., Bertram, L. N., Schwab, C., Hayden, M. R., & Henkelman, R. M. (2008). Automated deformation analysis in the YAC128 Huntington disease mouse model. *NeuroImage*, *39*(1), 32–39. https://doi.org/10.1016/j.neuroimage.2007.08.033

Levitt, J. J., Bobrow, L., Lucia, D., & Srinivasan, P. (2010). A selective review of volumetric and morphometric imaging in schizophrenia. *Current Topics in Behavioral Neurosciences*, *4*, 243–281.

Li, W., Li, K., Guan, P., Chen, Y., Xiao, Y., Lui, S., ... Gong, Q. (2018). Volume alteration of hippocampal subfields in first-episode antipsychotic-naive schizophrenia patients before and after acute antipsychotic treatment. *NeuroImage: Clinical*, *20*, 169–176.

Li, X., Black, M., Xia, S., Zhan, C., Bertisch, H. C., Branch, C. A., & DeLisi, L. E. (2015). Subcortical structure alterations impact language

processing in individuals with schizophrenia and those at high genetic risk. *Schizophrenia Research*, *169*(1–3), 76–82. https://doi.org/10.1016/j.schres.2015.08.001

Liu, M., Maiti, P., Thomopoulos, S., Zhu, A., Chai, Y., Kim, H., & Jahanshad, N. (2021). Style transfer using generative adversarial networks for multi-site MRI harmonization. *bioRxiv*, 2021.2003.2017.435892. https://doi.org/10.1101/2021.03.17.435892

Malchow, B., Keeser, D., Keller, K., Hasan, A., Rauchmann, B. S., Kimura, H., ... Falkai, P. (2016). Effects of endurance training on brain structures in chronic schizophrenia patients and healthy controls. *Schizophrenia Research*, *173*(3), 182–191. https://doi.org/10.1016/j.schres.2015.01.005

Mamah, D., Alpert, K. I., Barch, D. M., Csernansky, J. G., & Wang, L. (2016). Subcortical neuromorphometry in schizophrenia spectrum and bipolar disorders. *NeuroImage: Clinical*, *11*, 276–286. https://doi.org/10.1016/j.nicl.2016.02.011

Mamah, D., Harms, M. P., Barch, D., Styner, M., Lieberman, J. A., & Wang, L. (2012). Hippocampal shape and volume changes with antipsychotics in early stage psychotic illness. *Frontiers in Psychiatry*, *3*, 96. https://doi.org/10.3389/fpsyt.2012.00096

Mamah, D., Harms, M. P., Wang, L., Barch, D., Thompson, P., Kim, J., ... Csernansky, J. G. (2008). Basal ganglia shape abnormalities in the unaffected siblings of schizophrenia patients. *Biological Psychiatry*, *64*(2), 111–120.

Mamah, D., Wang, L., Barch, D., de Erausquin, G. A., Gado, M., & Csernansky, J. G. (2007). Structural analysis of the basal ganglia in schizophrenia. *Schizophrenia Research*, *89*(1–3), 59–71. https://doi.org/10.1016/j.schres.2006.08.031

McCarley, R. W., Wible, C. G., Frumin, M., Hirayasu, Y., Levitt, J. J., Fischer, I. A., & Shenton, M. E. (1999). MRI anatomy of schizophrenia. *Biological Psychiatry*, *45*(9), 1099–1119 doi:S0006-3223(99)00018-9 [pii].

McClure, R. K., Styner, M., Maltbie, E., Lieberman, J. A., Gouttard, S., Gerig, G., ... Zhu, H. (2013). Localized differences in caudate and hippocampal shape are associated with schizophrenia but not antipsychotic type. *Psychiatry Research*, *211*(1), 1–10. https://doi.org/10.1016/j.pscychresns.2012.07.001

McCutcheon, R. A., Abi-Dargham, A., & Howes, O. D. (2019). Schizophrenia, dopamine and the striatum: From biology to symptoms. *Trends in Neurosciences*, *42*(3), 205–220. https://doi.org/10.1016/j.tins.2018.12.004

McKenna, F., Babb, J., Miles, L., Goff, D., & Lazar, M. (2020). Reduced microstructural lateralization in males with chronic schizophrenia: A diffusional kurtosis imaging study. *Cerebral Cortex*, *30*(4), 2281–2294. https://doi.org/10.1093/cercor/bhz239

Meyer-Lindenberg, A., Poline, J. B., Kohn, P. D., Holt, J. L., Egan, M. F., Weinberger, D. R., & Berman, K. F. (2001). Evidence for abnormal cortical functional connectivity during working memory in schizophrenia. *The American Journal of Psychiatry*, *158*(11), 1809–1817.

Narr, K. L., Thompson, P. M., Sharma, T., Moussai, J., Blanton, R., Anvar, B., ... Toga, A. W. (2001). Three-dimensional mapping of temporo-limbic regions and the lateral ventricles in schizophrenia: Gender effects. *Biological Psychiatry*, *50*(2), 84–97.

Nuechterlein, K. H., Subotnik, K. L., Green, M. F., Ventura, J., Asarnow, R. F., Gitlin, M. J., ... Mintz, J. (2011). Neurocognitive predictors of work outcome in recent-onset schizophrenia. *Schizophrenia Bulletin*, *37*(Suppl 2), S33–S40. https://doi.org/10.1093/schbul/sbr084

Okada, N., Fukunaga, M., Yamashita, F., Koshiyama, D., Yamamori, H., Ohi, K., ... Hashimoto, R. (2016). Abnormal asymmetries in subcortical brain volume in schizophrenia. *Molecular Psychiatry*, *21*(10), 1460–1466. https://doi.org/10.1038/mp.2015.209

Pajonk, F. G., Wobrock, T., Gruber, O., Scherk, H., Berner, D., Kaizl, I., ... Falkai, P. (2010). Hippocampal plasticity in response to exercise in schizophrenia. *Archives of General Psychiatry*, *67*(2), 133–143. https://doi.org/10.1001/archgenpsychiatry.2009.193

Palaniyappan, L., Balain, V., & Liddle, P. F. (2012). The neuroanatomy of psychotic diathesis: A meta-analytic review. *Journal of Psychiatric Research*, *46*(10), 1249–1256.

Pantelis, C., Yucel, M., Bora, E., Fornito, A., Testa, R., Brewer, W. J., ... Wood, S. J. (2009). Neurobiological markers of illness onset in psychosis and schizophrenia: The search for a moving target. *Neuropsychology Review*, *19*(3), 385–398. https://doi.org/10.1007/s11065-009-9114-1

Park, S. W., Lee, C. H., Cho, H. Y., Seo, M. K., Lee, J. G., Lee, B. J., ... Kim, Y. H. (2013). Effects of antipsychotic drugs on the expression of synaptic proteins and dendritic outgrowth in hippocampal neuronal cultures. *Synapse*, *67*(5), 224–234. https://doi.org/10.1002/syn.21634

Pearlson, G. D., & Calhoun, V. (2007). Structural and functional magnetic resonance imaging in psychiatric disorders. *Canadian Journal of Psychiatry*, *52*(3), 158–166.

Pearlson, G. D., & Marsh, L. (1999). Structural brain imaging in schizophrenia: A selective review. *Biological Psychiatry*, *46*(5), 627–649.

Pomponio, R., Erus, G., Habes, M., Doshi, J., Srinivasan, D., Mamourian, E., ... Davatzikos, C. (2020). Harmonization of large MRI datasets for the analysis of brain imaging patterns throughout the lifespan. *NeuroImage*, *208*, 116450. https://doi.org/10.1016/j.neuroimage.2019.116450

Purcell, S. M., Wray, N. R., Stone, J. L., Visscher, P. M., O'Donovan, M. C., Sullivan, P. F., ... International Schizophrenia, C. (2009). Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature*, *460*(7256), 748–752. https://doi.org/10.1038/nature08185

Qiu, A., Gan, S. C., Wang, Y., & Sim, K. (2013). Amygdala-hippocampal shape and cortical thickness abnormalities in first-episode schizophrenia and mania. *Psychological Medicine*, *43*(7), 1353–1363. https://doi.org/10.1017/S0033291712002218

Qiu, A., & Miller, M. I. (2008). Multi-structure network shape analysis via normal surface momentum maps. *NeuroImage*, *42*(4), 1430–1438. https://doi.org/10.1016/j.neuroimage.2008.04.257

Qiu, A., Tuan, T. A., Woon, P. S., Abdul-Rahman, M. F., Graham, S., & Sim, K. (2010). Hippocampal-cortical structural connectivity disruptions in schizophrenia: An integrated perspective from hippocampal shape, cortical thickness, and integrity of white matter bundles. *NeuroImage*, *52*(4), 1181–1189. https://doi.org/10.1016/j.neuroimage.2010.05.046

Radua, J., Vieta, E., Shinohara, R., Kochunov, P., Quide, Y., Green, M. J., ... Collaborators, E. C. (2020). Increased power by harmonizing structural MRI site differences with the ComBat batch adjustment method in ENIGMA. *NeuroImage*, *218*, 116956. https://doi.org/10.1016/j.neuroimage.2020.116956

Renteria, M. E., Hansell, N. K., Strike, L. T., McMahon, K. L., de Zubicaray, G. I., Hickie, I. B., ... Wright, M. J. (2014). Genetic architecture of subcortical brain regions: Common and region-specific genetic contributions. *Genes, Brain, and Behavior*, *13*(8), 821–830. https://doi.org/10.1111/gbb.12177

Roalf, D. R., Vandekar, S. N., Almasy, L., Ruparel, K., Satterthwaite, T. D., Elliott, M. A., ... Gur, R. E. (2015). Heritability of subcortical and limbic brain volume and shape in multiplex-multigenerational families with schizophrenia. *Biological Psychiatry*, *77*(2), 137–146. https://doi.org/10.1016/j.biopsych.2014.05.009

Roiz-Santianez, R., Ayesa-Arriola, R., Tordesillas-Gutierrez, D., Ortiz-Garcia de la Foz, V., Perez-Iglesias, R., Pazos, A., ... Crespo-Facorro, B. (2014). Three-year longitudinal population-based volumetric MRI study in first-episode schizophrenia spectrum patients. *Psychological Medicine*, *44*(8), 1591–1604. https://doi.org/10.1017/S0033291713002365

Roiz-Santianez, R., Suarez-Pinilla, P., & Crespo-Facorro, B. (2015). Brain structural effects of antipsychotic treatment in schizophrenia: A systematic review. *Current Neuropharmacology*, *13*(4), 422–434.

Roshchupkin, G. V., Gutman, B. A., Vernooij, M. W., Jahanshad, N., Martin, N. G., Hofman, A., ... Adams, H. H. H. (2016). Heritability of the shape of subcortical brain structures in the general population. *Nature Communications*, *7*, 13738. https://doi.org/10.1038/ncomms13738

Rosoklija, G., Toomayan, G., Ellis, S. P., Keilp, J., Mann, J. J., Latov, N., … Dwork, A. J. (2000). Structural abnormalities of subicular dendrites in subjects with schizophrenia and mood disorders: Preliminary findings. *Archives of General Psychiatry*, 57(4), 349–356. https://doi.org/10.1001/archpsyc.57.4.349

Satizabal, C. L., Adams, H. H. H., Hibar, D. P., White, C. C., Knol, M. J., Stein, J. L., … Ikram, M. A. (2019). Genetic architecture of subcortical brain structures in 38,851 individuals. *Nature Genetics*, 51(11), 1624–1636. https://doi.org/10.1038/s41588-019-0511-y

Schindler, M. K., Wang, L., Selemon, L. D., Goldman-Rakic, P. S., Rakic, P., & Csernansky, J. G. (2002). Abnormalities of thalamic volume and shape detected in fetally irradiated rhesus monkeys with high dimensional brain mapping. *Biological Psychiatry*, 51(10), 827–837. https://doi.org/10.1016/s0006-3223(01)01341-5

Schmitt, A., Hasan, A., Gruber, O., & Falkai, P. (2011). Schizophrenia as a disorder of disconnectivity. *European Archives of Psychiatry and Clinical Neuroscience*, 261(Suppl 2), S150–S154. https://doi.org/10.1007/s00406-011-0242-2

Shenton, M. E., Dickey, C. C., Frumin, M., & McCarley, R. W. (2001). A review of MRI findings in schizophrenia. *Schizophrenia Research*, 49(1–2), 1–52.

Shenton, M. E., Whitford, T. J., & Kubicki, M. (2010). Structural neuroimaging in schizophrenia: From methods to insights to treatments. *Dialogues in Clinical Neuroscience*, 12(3), 317–332.

Sherman, S. M., & Guillery, R. W. (2011). Distinct functions for direct and transthalamic corticocortical connections. *Journal of Neurophysiology*, 106(3), 1068–1077.

Smeland, O. B., Frei, O., Kauppi, K., Hill, W. D., Li, W., Wang, Y., … Neuro, C. C. W. G. (2017). Identification of genetic loci jointly influencing schizophrenia risk and the cognitive traits of verbal-numerical reasoning, reaction time, and general cognitive function. *JAMA Psychiatry*, 74(10), 1065–1075. https://doi.org/10.1001/jamapsychiatry.2017.1986

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E., Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, 23(Suppl 1), S208–S219. https://doi.org/10.1016/j.neuroimage.2004.07.051

Thompson, P. M., Cannon, T. D., Narr, K. L., van Erp, T., Poutanen, V. P., Huttunen, M., … Toga, A. W. (2001). Genetic influences on brain structure. *Nature Neuroscience*, 4(12), 1253–1258. https://doi.org/10.1038/nn758

Thompson, P. M., Hayashi, K. M., de Zubicaray, G., Janke, A. L., Rose, S. E., Semple, J., … Toga, A. W. (2003). Dynamics of gray matter loss in Alzheimer's disease. *The Journal of Neuroscience*, 23(3), 994–1005.

Thompson, P. M., Jahanshad, N., Ching, C. R. K., Salminen, L. E., Thomopoulos, S. I., Bright, J., … Consortium, E. (2020). ENIGMA and global neuroscience: A decade of large-scale studies of the brain in health and disease across more than 40 countries. *Translational Psychiatry*, 10(1), 100. https://doi.org/10.1038/s41398-020-0705-1

Thompson, P. M., Stein, J. L., Medland, S. E., Hibar, D. P., Vasquez, A. A., Renteria, M. E., … Alzheimer's Disease Neuroimaging Initiative, E. C. I. C. S. Y. S. G. (2014). The ENIGMA Consortium: Large-scale collaborative analyses of neuroimaging and genetic data. *Brain Imaging and Behavior*, 8(2), 153–182. https://doi.org/10.1007/s11682-013-9269-5

Vaillant, M., Qiu, A., Glaunes, J., & Miller, M. I. (2007). Diffeomorphic metric surface mapping in subregion of the superior temporal gyrus. *NeuroImage*, 34(3), 1149–1159.

Vakhrusheva, J., Marino, B., Stroup, T. S., & Kimhy, D. (2016). Aerobic exercise in people with schizophrenia: Neural and neurocognitive benefits. *Current Behavioral Neuroscience Reports*, 3(2), 165–175. https://doi.org/10.1007/s40473-016-0077-2

van den Berg, D., Gong, P., Breakspear, M., & van Leeuwen, C. (2012). Fragmentation: Loss of global coherence or breakdown of modularity in functional brain architecture? *Frontiers in Systems Neuroscience*, 6, 20. https://doi.org/10.3389/fnsys.2012.00020

van der Meulen, M., Wierenga, L. M., Achterberg, M., Drenth, N., Van, I. M. H., & Crone, E. A. (2020). Genetic and environmental influences on structure of the social brain in childhood. *Developmental Cognitive Neuroscience*, 44, 100782. https://doi.org/10.1016/j.dcn.2020.100782

van Erp, T. G., Hibar, D. P., Rasmussen, J. M., Glahn, D. C., Pearlson, G. D., Andreassen, O. A., … Turner, J. A. (2016). Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular Psychiatry*, 21(4), 585. https://doi.org/10.1038/mp.2015.118

Vancampfort, D., Rosenbaum, S., Ward, P. B., & Stubbs, B. (2015). Exercise improves cardiorespiratory fitness in people with schizophrenia: A systematic review and meta-analysis. *Schizophrenia Research*, 169(1–3), 453–457. https://doi.org/10.1016/j.schres.2015.09.029

Volkow, N. D., Wolf, A. P., Brodie, J. D., Cancro, R., Overall, J. E., Rhoades, H., & Van Gelder, P. (1988). Brain interactions in chronic schizophrenics under resting and activation conditions. *Schizophrenia Research*, 1(1), 47–53.

Wang, L., & Csernansky, J. G. (2014). Recent advances in neuroimaging biomarkers of schizophrenia. In P. G. Janicak, S. R. Marder, R. Tandon, & M. Goldman (Eds.), *Schizophrenia* (pp. 71–103). New York: Springer.

Wang, L., Joshi, S. C., Miller, M. I., & Csernansky, J. G. (2001). Statistical analysis of hippocampal asymmetry in schizophrenia. *NeuroImage*, 14(3), 531–545.

Wang, L., Khan, A., Csernansky, J. G., Fischl, B., Miller, M. I., Morris, J. C., & Beg, M. F. (2009). Fully-automated, multi-stage hippocampus mapping in very mild Alzheimer disease. *Hippocampus*, 19(6), 541–548.

Wang, L., Mamah, D., Harms, M. P., Karnik, M., Price, J. L., Gado, M. H., … Csernansky, J. G. (2008). Progressive deformation of deep brain nuclei and hippocampal-amygdala formation in schizophrenia. *Biological Psychiatry*, 64(12), 1060–1068. https://doi.org/10.1016/j.biopsych.2008.08.007

Wang, Q., Zhang, J., Liu, Z., Crow, T. J., Zhang, K., Palaniyappan, L., … Li, T. (2019). "brain connectivity deviates by sex and hemisphere in the first episode of schizophrenia"-A route to the genetic basis of language and psychosis? *Schizophrenia Bulletin*, 45(2), 484–494. https://doi.org/10.1093/schbul/sby061

Wang, T., Zhang, X., Li, A., Zhu, M., Liu, S., Qin, W., … Liu, B. (2017). Polygenic risk for five psychiatric disorders and cross-disorder and disorder-specific neural connectivity in two independent populations. *NeuroImage: Clinical*, 14, 441–449. https://doi.org/10.1016/j.nicl.2017.02.011

Wang, Y., Song, Y., Rajagopalan, P., An, T., Liu, K., Chou, Y. Y., … Alzheimer's Disease Neuroimaging, I. (2011). Surface-based TBM boosts power to detect disease effects on the brain: An N=804 ADNI study. *NeuroImage*, 56(4), 1993–2010. https://doi.org/10.1016/j.neuroimage.2011.03.040

Weinberger, D. R., Berman, K. F., Suddath, R., & Torrey, E. F. (1992). Evidence of dysfunction of a prefrontal-limbic network in schizophrenia: A magnetic resonance imaging and regional cerebral blood flow study of discordant monozygotic twins. *The American Journal of Psychiatry*, 149(7), 890–897.

Womer, F. Y., Wang, L., Alpert, K. I., Smith, M. J., Csernansky, J. G., Barch, D. M., & Mamah, D. (2014). Basal ganglia and thalamic morphology in schizophrenia and bipolar disorder. *Psychiatry Research*, 223(2), 75–83. https://doi.org/10.1016/j.pscychresns.2014.05.017

Woods, S. W. (2003). Chlorpromazine equivalent doses for the newer atypical antipsychotics. *The Journal of Clinical Psychiatry*, 64(6), 663–667.

Yang, Y., Nuechterlein, K. H., Phillips, O. R., Gutman, B., Kurth, F., Dinov, I., … Narr, K. L. (2012). Disease and genetic contributions toward local tissue volume disturbances in schizophrenia: A tensor-based morphometry study. *Human Brain Mapping*, 33(9), 2081–2091.

Young, K. A., Manaye, K. F., Liang, C., Hicks, P. B., & German, D. C. (2000). Reduced number of mediodorsal and anterior thalamic neurons in schizophrenia. *Biological Psychiatry*, *47*(11), 944–953.

Zhu, F., Liu, F., Guo, W., Chen, J., Su, Q., Zhang, Z., ... Zhao, J. (2018). Disrupted asymmetry of inter- and intra-hemispheric functional connectivity in patients with drug-naive, first-episode schizophrenia and their unaffected siblings. *eBioMedicine*, *36*, 429–435. https://doi.org/10.1016/j.ebiom.2018.09.012

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.