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Neuroanatomical asymmetry patterns in individuals with schizophrenia and their non-psychotic siblings

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Abstract

Neuroanatomical endophenotypes may reveal insights into the processes by which genetic factors increase the risk of developing schizophrenia. To determine whether patterns of neuroanatomical asymmetries may be useful as schizophrenia-related endophenotypes, we compared patterns of structural asymmetries in patients with schizophrenia, healthy controls, and their respective siblings. The surfaces of the left and right amygdala, hippocampus, thalamus, caudate nucleus, putamen, globus pallidus, and nucleus accumbens were assessed in 40 pairs of healthy comparison controls (CON) and their siblings (CON-SIB) and 25 pairs of patients with schizophrenia (SCZ) and their siblings (SCZ-SIB) in magnetic resonance (MR) images using large deformation diffeomorphic metric mapping (LDDMM) and parallel transport techniques. The within-subject asymmetry deformation of each structure was first measured via LDDMM, and then translated to a global template via parallel transport for evaluation of the patterns of asymmetry both within and across siblings. Our results revealed that asymmetries observed in CON subjects occurred in the amygdala and the anterior segment of the hippocampus with more pronounced expansion deformation in the right-sided structures (R>L asymmetry) but not in the basal ganglia and thalamus. Disturbance in this pattern of asymmetries was observed in both SCZ and SCZ-SIB subjects. More specifically, exaggerations and reductions in the normative pattern of asymmetries were observed in the amygdala–hippocampus formation, basal ganglia, and thalamus. These altered patterns of asymmetries are present in subjects with schizophrenia and their siblings, and therefore may represent a schizophrenia-related endophenotype.

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Keywords

Shape asymmetry; Siblings; Subcortical structures; Schizophrenia; Large deformation diffeomorphic metric; mapping; Parallel transport; Magnetic resonance imaging

Introduction

The normal brain is asymmetric between hemispheres. For example, there is cerebral torque in most people, i.e. the right frontal lobe is larger than the left and the left occipital lobe is larger than the right (Chapple et al., 2004; LeMay, 1976; Sharma et al., 1999; Weinberger et al., 1982). Given that the brain's asymmetry is the result of neurodevelopmental processes and schizophrenia is hypothesized to have a neurodevelopmental component (Klar, 1999), disturbances in the development of neuroanatomical asymmetry in cortical and subcortical structures have long been hypothesized to be involved in the pathogenesis of schizophrenia (Klar, 1999). Alternatively, fluctuating asymmetry may be a secondary consequence of an impairment of buffering mechanisms during development, having no etiological role in the disease.

Magnetic resonance (MR)-based volumetric analysis has revealed evidence of a disturbance of cerebral torque (Chance et al., 2005; Falkai et al., 1995; Sommer et al., 2001) as well as a reduction or exaggeration of the normative asymmetries of cortical and subcortical structures in schizophrenia (Barta et al., 1995, 1997; Csernansky et al., 2004; Shenton et al., 1987, 1992, 2001; Sommer et al., 2001). In several papers, Crow et al. (Crow, 1999, 2007; Crow et al., 1989a) put forward an influential hypothesis suggesting that schizophrenia might arise because of an abnormality in the genetic control of asymmetry development. Some MR-based volumetric studies have provided support for the hypothesis that neuroanatomical asymmetries are a marker for the genetic liability for schizophrenia (Sharma et al., 1999), while others have failed to support this hypothesis (Chapple et al., 2004). These discrepant results may be due to methodological differences in neuroanatomical definitions and delineation, or differences in the populations studied, the latter of which could reflect the underlying biological heterogeneity of schizophrenia.

Newly developed techniques for brain mapping can provide the precise location of structural deviation across clinical populations by carrying an individual anatomy through mathematical transformation onto another brain or onto a population template (Toga and Thompson, 2003). Thus, these techniques can provide highly detailed information about the regional specificity of neuroanatomical descriptors. Using such brain mapping techniques, researchers have found evidence of disturbances in the normative patterns of asymmetry of the Sylvian fissure and cortical shape as well as the hippocampus and thalamus in schizophrenia (Csernansky et al., 2002, 2004; Hoff et al., 1992; Kim et al., 2005; Narr et al., 2001, 2004, 2007; Wang et al., 2001). Our groups have previously revealed an exaggeration of the normal asymmetry pattern in the hippocampus and thalamus in schizophrenia patients aged around 40 using large-deformation high-dimensional brain mapping (HDBM-LD) (Csernansky et al., 2002, 2004; Wang et al., 2001). However, the application of such techniques to populations of relatives that are at increased risk of developing schizophrenia because of their genetic and shared environmental relationship to someone with the illness has not yet been reported. Studies of neuroanatomical asymmetries in the relatives of patients with schizophrenia would provide critical information about whether genetic influences are a likely contributor to asymmetry disturbances in schizophrenia.

In-vivo brain mapping studies tend to group brain structures into two broad categories: (1) cortical mantle and (2) deep nuclei or structures represented by a surface with globular shape

at a level of MRI analysis. Previous volumetric studies have revealed volume reduction in the cortical area, especially the temporal lobe (Honea et al., 2005; Lui et al., 2009a). The present study sought to investigate whether asymmetry abnormalities of the structures in the second category, including the amygdala, hippocampus, thalamus, caudate nucleus, putamen, globus pallidus, and nucleus accumbens, are an important part of the pathogenesis of schizophrenia in individuals with schizophrenia and their non-psychotic siblings at age of 20. Unlike our previous HDBM-LD shape analysis (Csernansky et al., 1998, 2002, 2004; Harms et al., 2007; Mamah et al., 2007, 2008; Wang et al., 2001), our new diffeomorphic shape analysis framework in this study (Fig. 1) assessed within-subject asymmetry deformation via large deformation diffeomorphic metric mapping (LDDMM) surface mapping (Vaillant and Glaunes, 2005; Vaillant et al., 2007) and then translated it to a global template without changing its metric (its inner product) via parallel transport for group comparison (Qiu et al., 2008b; Younes, 2007; Younes et al., 2008). Moreover, our statistical analysis modeled the covariance of shape variations in the seven structures for detecting asymmetry abnormalities within and across siblings. This is superior to most of brain mapping analysis on a single structure using the same dataset as that in this paper (Harms et al., 2007; Mamah et al., 2008) as well as using different datasets in previous studies (Csernansky et al., 2002, 2004; Hoff et al., 1992; Kim et al., 2005; Mamah et al., 2007; Narr et al., 2001, 2004, 2007; Wang et al., 2001) in the sense that influence of shape deformation from adjacent structures is also taken into account into the statistical model. In keeping with Crow's hypothesis that abnormalities of cerebral asymmetry are an important part of the pathogenesis of schizophrenia (Crow et al., 1989a, b), we predicted that abnormal asymmetry patterns of the seven structures would be observed in both the individuals with schizophrenia and their siblings as compared to healthy comparison subjects and their siblings.

Methods

Subjects

The subjects for this study were recruited through the Conte Center for the Neuroscience of Mental Disorders (CCNMD) at Washington University in St. Louis and included: (1) individuals with DSM-IV schizophrenia [SCZ]; (2) siblings of individuals with schizophrenia [SCZ-SIB]; (3) healthy controls [CON]; and (4) siblings of healthy controls [CON-SIB]. All siblings were full siblings, based on self-report. The subjects used in this study were identical to those used in our recent studies of the thalamus (Harms et al., 2007) and basal ganglia (Mamah et al., 2008). The study was approved by the Washington University St. Louis Institutional Review Board, and all subjects gave their written informed consent following a complete description of the study. Demographic information for the four groups of subjects is contained in Table 1.

All subjects were diagnosed using DSM-IV criteria on the basis of a consensus between a research psychiatrist who conducted a semi-structured interview and a trained research assistant who used the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P) (First et al., 2001). Participants from any of the four groups were excluded if they: (a) met DSM-IV criteria for current substance abuse or dependence (i.e., during the month preceding the assessment); (b) had a clinically unstable or severe medical disorder, or a medical disorder that confounded the assessment of psychiatric diagnosis or rendered research participation dangerous; (c) had a head injury (past or present) with documented neurological sequelae or loss of consciousness; or (d) met DSM-IV criteria for mental retardation (mild or greater in severity).

SCZ participants were recruited from local inpatient and outpatient treatment facilities, and were stabilized on antipsychotic medication for at least 2 weeks before participating in the study (reported antipsychotic medication during the 4 weeks before clinical assessment was

one of the following: atypical antipsychotics, *n*=20; typical, *n*=1; combination of atypical and typical, *n*=2; unknown because of participation in a blinded medical trial, *n*=2). CON participants were required to have no lifetime history of Axis I psychotic or major mood disorders (e.g. major depressive disorder and bipolar disorder) and no first-degree relatives with a psychotic disorder. Potential SCZ-SIB subjects were excluded if they had a lifetime history of any DSM-IV Axis I psychotic disorder, but not other DSM-IV Axis I disorders. Therefore, to control for possible effects arising from psychiatric disorders other than schizophrenia, the siblings of healthy comparison subjects were included as an additional comparison group. The CON-SIB subjects were enrolled in an identical manner to the SCZ-SIB subjects, and met the same general and specific inclusion and exclusion criteria.

Image acquisition

Magnetic resonance (MR) scans of the whole brain were collected using a Siemens Magnetom Vision 1.5 T imaging system using a standard head coil and a 3D FLASH sequence (TR/TE=20/5.4 ms, flip angle=30°, number of acquisitions=1, voxel size=1×1×1 mm^3, scanning time=13.5 min). Signal intensity differences across subjects were normalized by linear rescaling, using the intensity of the corpus callosum and the lateral ventricle as reference structures (Wang et al., 2007).

Structure delineation

The surfaces of the selected structures (hippocampus, amygdala, thalamus, caudate nucleus, globus pallidus, putamen, and nucleus accumbens) were delineated from MRI scans using a large deformation high-dimensional brain mapping (HDBM-LD) based on a global template (Csernansky et al., 2004; Haller et al., 1997; Harms et al., 2007; Mamah et al., 2007; Wang et al., 2006). The template was constructed using an MRI scan collected from a healthy comparison subject not otherwise included in the study. Each MRI scan in our study was landmarked at defined positions with basal ganglia–thalamus complex and hippocampal–amygdala formation that corresponded to landmarks placed in the template scan. The template image was then deformed onto the subject MR scans first through affine transformation by using the landmarks then a large deformation transformation found by HDBM-LD (Haller et al., 1997). The surface representation of each subject's structures was generated by superimposing the deformed template surface. The reliability and validity of the delineation approach against manual outlining has been previously demonstrated in Haller et al. (1997) and Wang et al. (2007). It has been successfully used in other studies (Csernansky et al., 2004; Haller et al., 1997; Harms et al., 2007; Mamah et al., 2007; Wang et al., 2006).

Shape analysis

We applied the two-level analysis (see Fig. 1) in order to quantify anatomical variations of within-subject structural asymmetries (i.e., left versus right) in a common coordinate system.

Within-subject asymmetry shape (first level)

Large deformation diffeomorphic metric surface mapping (LDDMM-surface) (Vaillant and Glaunes, 2005; Vaillant et al., 2007) was applied to seeking optimal initial momentum that encodes within-subject shape deformation from the right side to the left side.

Parallel translation of within-subject asymmetry deformation to a global template (second level)

Since the within-subject asymmetry deformation found in the first level of the analysis is in the right structure coordinates of each subject, our second level of analysis translated this within-subject deformation to a global template along the geodesic connecting the subject's right structure to the global template via a parallel transport technique in diffeomorphisms.

Parallel translation is taken from Riemannian geometry, which displaces vectors along a curve without changing properties such as the dot-products of the initial momentum. In the Euclidean space, the operation of transferring vector fields is the standard translation of vectors. In a space with anatomical shapes, however, parallel translation is nonlinear, and can be computed by solving perturbations of geodesics in the shape space (Qiu et al., 2008b; Younes, 2007; Younes et al., 2008). We particularly computed the perturbations of geodesics through studying the variation of the geodesic shooting equation (Miller et al., 2006) when the initial momentum encoding within-subject asymmetry deformation is given as a small variation (Qiu et al., 2008b; Younes, 2007; Younes et al., 2008). The detailed theoretical derivation of the parallel transport is discussed elsewhere (Qiu et al., 2008b; Younes, 2007; Younes et al., 2008). The advantage of using parallel transport to transfer within-subject asymmetry deformation to the global template is that the deformation information (e.g. the initial momentum) is transferred so that the metric (inner products on the initial momentum) is maintained.

The log-Jacobian determinant of the within-subject right-to-left deformation was computed at each location (i.e., surface node) of the global template for each individual structure and subject, as a localized measure of the volume ratio of the left structure to the right structure. Its value of zero indicates no shape difference between the right and left structures, whereas a value greater or less than zero indicates that the left structure is expanded or compressed at this location relative to the right structure, respectively. The log-Jacobian determinant indexed over the global template is referred to as the *asymmetry deformation map* throughout the paper.

Statistical analysis

We assumed that the asymmetry deformation maps were derived from random processes. Its covariance can be constructed based on a complete set of the Laplace–Beltrami bases (LB-bases) on structure M^i and thus the asymmetry deformation map of M^i ($\mu^i(\mathcal{X})$) can be characterized by a linear combination of these LB-basis functions, ψ_k^i, and their associated coefficients (LB coefficients), F_k^i, in the form of

$$\mu^i(x)=\sum_{k=1}^{N_i} F_k^i \psi_k^i(x),\ x \in M^i. \tag{1}$$

k indexes the kth LB-basis function. i indexes the subcortical structure, $i \in$ {hippocampus, amygdala, thalamus, caudate, putamen, globus pallidus, nucleus accumbens}. The construction of the LB-basis functions indexed over the surface of structure i, M^i, was previously described elsewhere (Qiu et al., 2006; Qiu et al., 2008a). $\psi_k^i(x)$ is deterministic for a specific structure and only dependent on the geometry of M^i (Qiu et al., 2006, 2008a). A finite number of random variables, F_k^i, k=1,2,⋯, N_i, are thus used to characterize the asymmetry deformation map, μ^i ($\mathcal{X}$), on which statistical inferences were examined. N_i is determined by the goodness-of-fit at a discrepancy level of 0.05 such that $\frac{\left|\mu^i(x)-\sum_{k=1}^{N_i} F_k^i \psi_k^i(x)\right|^2}{\left|\mu^i(x)\right|^2}=0.05$.

Normative asymmetry pattern in each individual structure

To quantify the normative asymmetry pattern in the CON group, two-tailed Wilcoxon signed-rank tests on each of the LB coefficients, F_k^i, k=1,2,⋯, N_i, for every i, were used to test the null hypothesis that the mean of the LB coefficient is zero. The Bonferroni correction was used to

keep the total chance of erroneously reporting a difference across all structures below a significance level of 0.05.

Group comparisons in asymmetry

A statistical analysis was conducted to compare the asymmetry patterns of the surfaces of the seven structures across subject groups (Qiu and Miller, 2008). The asymmetry deformation map of each structure was first decomposed into a linear combination of the LB-basis functions according to Eq. (1). The covariance pattern of the asymmetry deformation maps across all structures was studied via principal component analysis (PCA) on the LB coefficients (Qiu and Miller, 2008). A finite number of the principal components (PCs) were selected to account for 85% variance among the LB coefficients of the seven structures. We modeled each PC score using mixed model analysis with group information as the independent variable while controlling for gender. The sibling information was modeled as a random effect so that the error term in the model was split into errors between and within siblings. Contrasts were made for pairwise group comparisons.

Permutation testing was used to provide correct results to evaluate the significance of the PC scores for group comparisons of interest (Nichols and Holmes, 2002). In 10,000 randomized analyses, CON and SCZ subjects were mixed and randomly assigned into two groups. The sibling pair information remained the same. In each randomized analysis, the mixed model analysis was performed on each PC score, and the *t*-value for the pairwise group contrast of interest was obtained. Then the highest *t*-value across PC scores was used to construct the empirical distribution of *t*-statistics, so that the resulting permutation-based threshold controlled for false positives across the entire set of PC scores. This “PC-wise” threshold was set at a significance level of 0.0083 (we used 0.05/6=0.0083 as significance level because of six pairwise group comparisons that were performed). The PCs with *t*-statistics above the threshold were selected to characterize the asymmetry pattern differences between groups.

Results

Fig. 2 illustrates the asymmetry deformation maps averaged over each of the subject groups. Based on the color scale, these illustrations suggest that the surface of the amygdala–hippocampus complex shows the most pronounced R>L deformation in all four groups. Mild R>L or L>R asymmetries are revealed in local regions of the surfaces of other structures, including the thalamus and basal ganglia.

Asymmetry pattern in healthy individuals

To quantify the pattern of normative structural asymmetry in the group of CON subjects, we performed a statistical analysis of the asymmetry deformation map for each structure. The second column on Table 2 lists the number of the LB coefdicients used in the statistical testing for each individual structure (total of 121 for the seven structures). The Wilcoxon signed-rank revealed a list of LB coefficients with *p*-value less than 0.0004 (the third column of Table 2) after Bonferroni correction for the multiple comparisons (α=0.05/121≈0.0004). For the purpose of visualization, the LB-bases associated with these coefficients were back projected onto the template surface coordinates for illustrating the statistical results of normative asymmetry patterns (Fig. 3). This figure suggests that substantial R>L asymmetry occurs in the anterior segment of the hippocampus, and relatively mild R>L asymmetry is also observed in the posterior segment of the hippocampus but not the posterior-lateral aspect of the hippocampus. In the amygdala, R>L asymmetry is present through its entire body with relatively equivalent strength, which is consistent with the observed major contribution of the first LB-basis (constant everywhere). Very mild asymmetry is also evident in the globus pallidus. However, there was little normative asymmetry in the thalamus and other basal ganglia structures.

Abnormalities of asymmetry patterns in SCZ and SCZ-SIB

As mentioned in the previous section, the total 121 LB coefficients characterized asymmetry deformation maps of the seven structures. In group comparisons, these LB coefficients were projected to 24 PCs via PCA, and mixed model analysis of these PCs was performed to test for significant effects of group within and across the sibling pairs.

The mixed model analysis and subsequent permutation testing indicated that no PC differed significantly between CON and CON-SIB (controlling for false positives across the entire set of PC scores as part of the permutation testing, and using Bonferroni correction to account for multiple group comparisons; see Methods), even though the visual comparison of the asymmetry patterns between CON and CON-SIB (top two rows of Fig. 2) shows their subtle difference. Perhaps, the difference in the magnitude of the asymmetry deformity between CON and CON-SIB is not substantial enough to achieve statistical significance. Similarly, no group differences in the PCs were found in the comparison of SCZ with SCZ-SIB.

The mixed model analysis revealed that the 13th PC score for the SCZ-SIB was significantly different from both CON and CON-SIB (p=0.0040 and 0.0022, respectively). For the visualization purpose, the 13th PC score was back projected to the LB-coefficient space by multiplying the 13th PC basis with the difference in the 13th PC score between SCZ-SIB and CON or between SCZ-SIB and CON-SIB. The LB coefficients were then back projected to the template coordinates by multiplying the LB-basis functions with their associated LB coefficients. The left and right columns in Fig. 4 respectively illustrate the resulting differences in asymmetry patterns. Fig. 4 suggests that there are two groupings of anatomical regions respectively represented by patterns of exaggerated and diminished R>L asymmetry in SCZ-SIB relative to the normative asymmetry pattern in CON and CON-SIB subjects. The grouping reflected by the exaggerated R>L asymmetry in SCZ-SIB (warm color) when compared with CON and CON-SIB involved the medial aspect of the hippocampus, the medial aspect of the caudate head, nucleus accumbens, posterior-lateral putamen, and posterior thalamus. In turn, the grouping associated with the diminished R>L asymmetry in SCZ-SIB (cool color) involved the anterior-lateral aspect of the hippocampus, the amygdala, the ventral aspect of the putamen, posterior pallidus, and anterior–ventral thalamus.

The mixed model analysis on these PCs also revealed that the 12th PC showed a significant group difference between SCZ and CON or CON-SIB subjects (p=0.0060 and 0.0038, respectively). The left and right columns in Fig. 5 respectively illustrate the differences in asymmetry patterns between SCZ and CON or CON-SIB subjects. Fig. 5 again suggests that there are two groupings of anatomical regions represented by patterns of exaggerated and diminished R>L asymmetry in SCZ relative to the normative asymmetry pattern in CON and CON-SIB subjects. Regions with the exaggerated R>L asymmetry in SCZ (warm color) included the anterior-medial aspect of the hippocampal head, the middle hippocampal body, the lateral aspect of the amygdala, the lateral tail of the caudate body, the lateral head of putamen, and medial aspect of thalamic body, lateral head of the thalamus, and the thalamic tail. In turn, the grouping associated with diminished R>L asymmetry in SCZ involved the lateral aspect of the hippocampal head and tail, medial aspect of the amygdala, posterior-lateral aspect of the putamen, posterior-lateral aspect of the thalamus.

Discussion

In this study, we evaluated the normative asymmetry pattern of the deep nuclei and hippocampus–amygdala formation in healthy control subjects, and then explored the potential influences of the disease, as well as the interaction of shared environmental and genetic factors, on this pattern in subjects with schizophrenia and their non-psychotic siblings. Using the LDDMM and parallel transport techniques, we demonstrated a normative pattern of R>L

asymmetry, which was most evident in the anterior and posterior medial segments of the hippocampus and in the amygdala, but not in the other structures. By referencing the normative asymmetry deformation of the seven structures of interest, the asymmetry shape abnormalities in subjects with schizophrenia and their siblings are at least partially contributed by genetic factors.

Our findings suggest that a reduction or exaggeration in the normative pattern of asymmetry in the selected seven structures may represent an endophenotype related to the genetic liability for schizophrenia. While the presence of an abnormality in the normative pattern of structural asymmetry in the siblings of schizophrenia patients may be due to either genetic or shared environmental factors, prior twin and adoption studies of subjects with schizophrenia have indicated that shared environmental factors have a negligible contribution to overall etiology of schizophrenia (Cannon et al., 1998; Cardno et al., 1999; Kendler et al., 1994). Our findings related to the comparisons of asymmetry patterns within and across CON and SCZ pairs (no asymmetry difference within CON or SCZ pair and significant difference across CON and SCZ pairs) support this interpretation as well. Additional studies of subjects with schizophrenia and their siblings are necessary to quantify the relative contributions of genetic and environmental factors to the development of abnormal neuroanatomical asymmetries in schizophrenia.

Visualization of the normative asymmetry pattern of the seven structures (Fig. 3) revealed the detailed locations where R>L or L>R asymmetry occurred, and shed light on some of the prior conflicting results of amygdala volumetric studies (Pedraza et al., 2004;Pruessner et al., 2000). In this study, our normative asymmetry pattern in the hippocampus significantly overlapped with previous findings (Csernansky et al., 2002;Wang et al., 2001) that the surfaces of the left hippocampus appeared to be compressed inward compared with the right hippocampus along its superior-lateral and inferior-medial segments. But our hippocampal findings more emphasize the normative R >L asymmetry in the anterior segment but less pronounced in the posterior segment. Perhaps, this may be due to the difference in age between this study (subjects with age around 20) and our previous studies (subjects with age around 40) (Csernansky et al., 2002;Wang et al., 2001). We also found that the surface of the left amygdala was deformed inward relative to the right side. In contrast, relatively few asymmetries were found in the surfaces of the thalamus, which is consistent with the findings in Harms et al. (2007) using the same dataset. The integration of these findings with volumetric assessments of normal cerebral asymmetry in earlier studies (Sharma et al., 1999) suggests that normative R>L asymmetries may develop in more anterior regions and normative L>R asymmetries may develop in more posterior regions, not only in the cortical mantle, but also in the hippocampus and amygdala. Genetic influences have been suggested as one of the mechanisms whereby the normative patterns of brain asymmetries develop (Geschwind and Galaburda, 1987); however, the specific genes involved in such mechanisms are not well understood.

Our results add to the knowledge derived from prior MRI volumetric studies of subjects with schizophrenia and their relatives to test Crow's hypothesis that schizophrenia may arise because of a genetically determined maldevelopment of brain asymmetries (DeLisi et al., 1997; Fan et al., 2008; Hulshoff Pol et al., 2006; Prasad and Keshavan 2008; Sharma et al., 1999). Our study also adds new information to the prior results of volumetric studies in that we were able to show specific patterns of disturbances in the normative asymmetry patterns in both patients with schizophrenia and their non-psychotic siblings. Even through two different PCs (the 12th and 13th) were used to characterize the abnormal asymmetry patterns of the structures in the SCZ and SCZ-SIB subjects, the asymmetry patterns of these two groups appeared similar in our visualizations (Figs. 4 and 5) when compared to the CON and CON-SIB subjects. Two groupings of anatomical regions were identified based on overall evidence of an exaggeration or reduction in the normative pattern of R>L asymmetry. The regions where

we found evidence of a more pronounced of R>L asymmetry in SCZ and SCZ-SIB subjects were: 1) the medial aspect of the hippocampus (subiculum, dentate, and CA3), which is connected with the entorhinal cortex and 2) the centromedial aspect of the thalamus, which is connected with the parietal and temporal lobes. Notably, these are subregions within the hippocampus and thalamic complex that are closely related to cortical regions that support memory, language, and sensory control circuits in the temporal and parietal lobes, and where others have found evidence of similarly altered cortical asymmetries. In particular, prior studies in schizophrenia subjects have suggested the presence of a loss of normal asymmetry (L>R) in brain structures such as the planum temporale and sensory cortex (Barta et al., 1997; Sharma et al., 1999). In contrast, regions showing an exaggerated L>R asymmetry in both SCZ and SCZ-SIB were: 1) the lateral aspect of the hippocampus (CA1), which is connected with CA3 and subiculum, and 2) the amygdala, which is connected with the hippocampus, cingulate and prefrontal cortex, and 3) the ventral lateral aspect of the thalamus, which is connected with the basal ganglia, cerebellum and motor cortex. Again, these are subregions of the hippocampus, amygdala, and thalamic complex that support memory, executive, and motor control circuits, and where others have found evidence of similarly altered cortical asymmetries in the prefrontal and motor cortex (Sharma et al., 1999). In summary, our results suggest that there may be more than one way in which normative patterns of brain asymmetry are altered by the disease state of schizophrenia and the genetic risk of developing it. Moreover, multiple cortical–subcortical networks of structures are likely to be involved in the development of such asymmetries in the context of the pathogenesis of schizophrenia.

Some changes in the patterns of the asymmetries in these structures had a different appearance in SCZ and SCZ-SIB subjects relative to CON subjects. These differences were most evident in the basal ganglia and the medial body, ventral posterior lateral of the thalamus (see Figs. 4 and 5). Based on the color scale in Figs. 4 and 5, the asymmetry abnormalities in these regions are mild, which suggests that the influence of the disease state of schizophrenia may be small relative to the influence of genetic or shared environmental factors related to the risk of developing the disease. This is also supported by no asymmetry difference between SCZ and SCZ-SIB. Beyond the abnormalities in the anatomical asymmetry, a large number of twin and familiar studies have suggested that the brain morphometric alternations, such as the frontotemporal abnormalities and increased prefrontal gyrification, probably lie in the pathophysiological pathway that leads to the development of clinical manifestation and also probabilistically increase the risk for the future development of schizophrenia (Fan et al., 2008;Harris et al., 2007;Hulshoff Pol et al., 2006;Job et al., 2005;Pantelis et al., 2003). Overall, much remains to be learned regarding the relative contributions of genetic risk factors, shared environmental risk factors, and disease-related factors to the development of abnormalities of neuroanatomical abnormalities. Moreover, further study is needed to examine how specific genes and their interactions with the environment may produce alterations in brain structure and function that accompany schizophrenia. Thus, such studies may ultimately shed light on the underlying molecular mechanisms related to both normal and abnormal brain morphometry.

The brain mapping techniques used in this study offer a new approach to the quantification of neuroanatomical asymmetries in both health and disease. Even though age and illness duration of the subjects in this study were less than those in previous studies (Csernansky et al., 2002, 2004; Wang et al., 2001), our asymmetry shape analysis in Fig. 1 well characterized within-subject asymmetry deformation in the global template. It together with the statistical analysis on multiple structures was sensitive to identify patterns of neuroanatomical asymmetries that may be useful as schizophrenia-related endophenotypes in young individuals with schizophrenia and their non-psychotic siblings.

The study has limitations that should be noted. The samples were not matched for potential differences such as gender, especially in the group of schizophrenia. Since there are not enough female SCZ subjects to look for the interaction of gender and diagnosis, our mixed model analysis controlled for gender. Perhaps, it could reduce potential influences due to gender. Impractically small sample sizes prohibited the examination of gender differences separately in biological risk groups in existing twin studies as well (Hulshoff Pol et al., 2006; Narr et al., 2002). Influences of gender and genetic interactions on neuroanatomical asymmetries are needed to be investigated when large samples are available. In addition, all patients with schizophrenia in this study were stabilized 2 weeks before their participation. The medication could affect the morphometry of subcortical structures, especially in the caudate (Davis et al., 2005). However, recent studies with drug-naïve patients with schizophrenia found abnormalities in volumes of the basal ganglia and thalamus (Lawrie et al., 2001; Shenton et al., 2001) and revealed the association between volume reduction in thalamus and genetic (Lawrie et al., 2001; Lui et al., 2009b). A future study on medication effects on the pattern of subcortical shape asymmetry is needed to be conducted.

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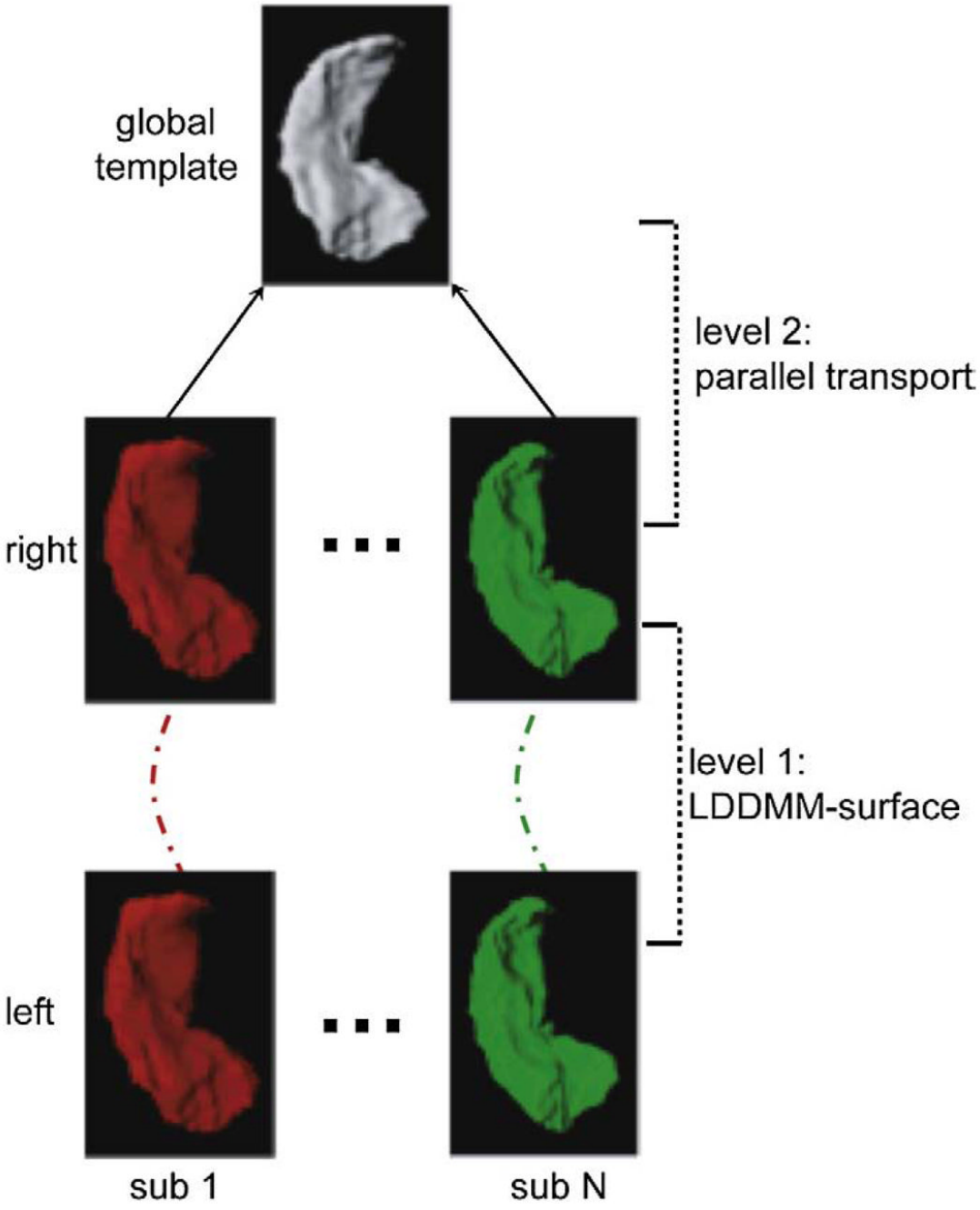

Fig. 1.

A schematic for asymmetry shape assessments. In the first level of analysis, large deformation diffeomorphic metric surface mapping (LDDMM-surface) deforms the right structure to the left structure of each subject so that within-subject shape asymmetry is encoded in the diffeomorphic transformation. In the second level of analysis, within-subject asymmetry deformation is translated along the geodesic connecting the subject's right structure and a global template via parallel transport without incorporating across-subject shape deformation for group comparison in a global template.

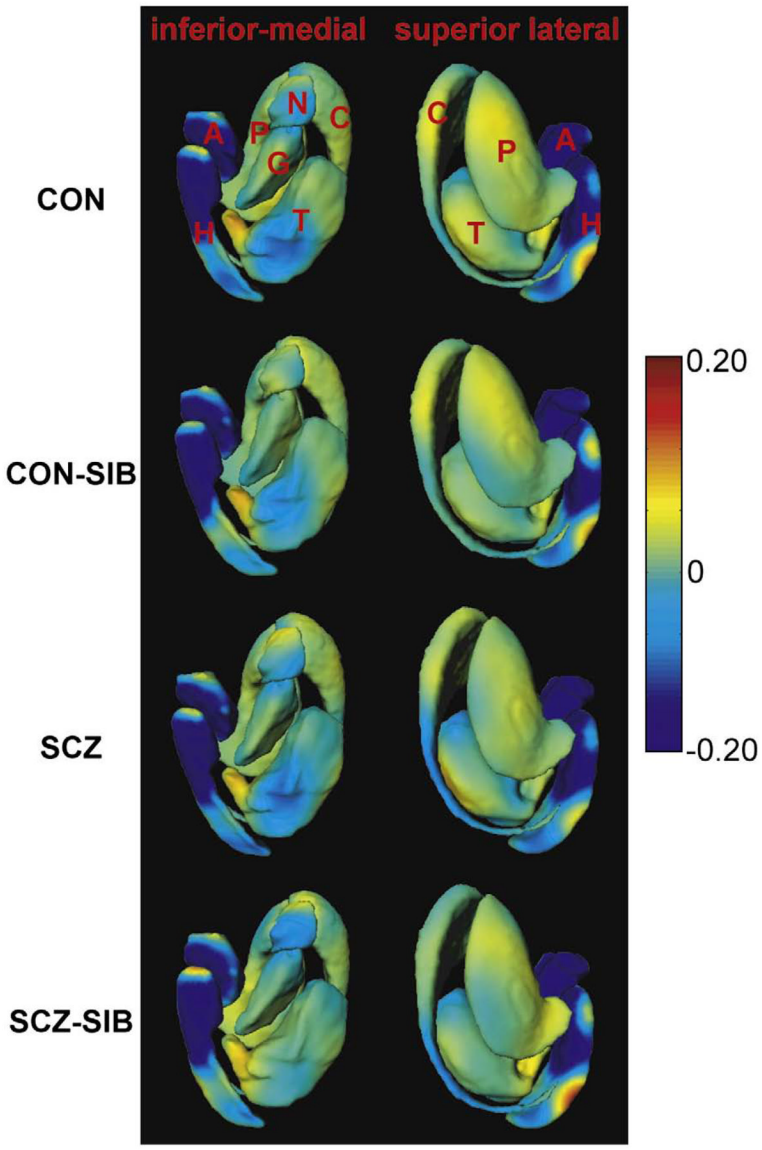

Fig. 2.

Figure shows average asymmetry map within each group in two views (left column: inferior-medial view; right column: superior-lateral view). Panels from the top to the bottom respectively illustrate the average asymmetry map in the control (CON), control sibling (CON-SIB), schizophrenia (SCZ), and schizophrenia sibling (SCZ-SIB) groups. The color scale represents the logarithm of the Jacobian determinant of the within-subject right-to-left deformation averaged within each group. Cool color represents the region where the structure of the right side is expanded compared to the one of the left side, whereas warm color denotes the region where the structure of the right side is compressed compared to the one of the left side. Key: A — amygdala, H — hippocampus, T — thalamus, C — caudate, P — putamen, G — globus pallidus, N — nucleus accumbens.

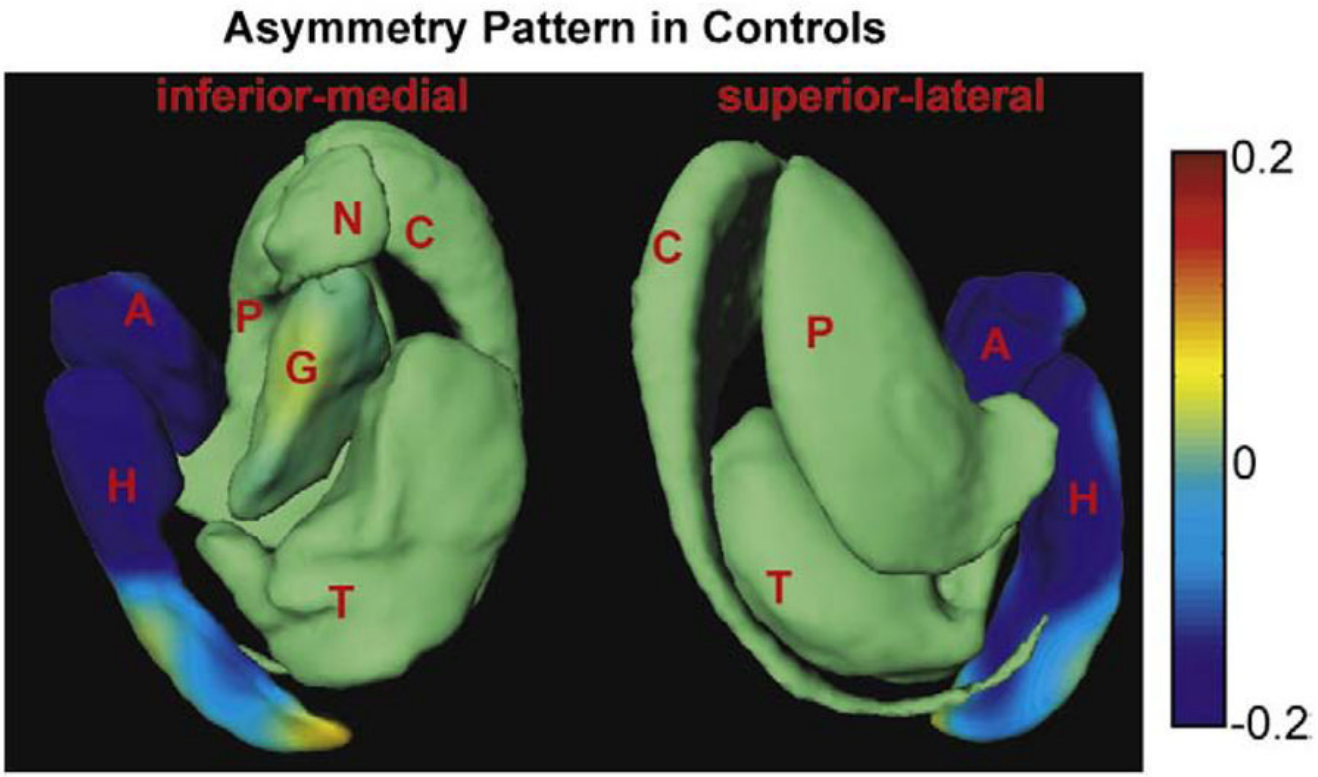

Fig. 3.

A statistically significant representation of the asymmetry pattern in healthy controls was obtained by back-projecting the statistically significant LB coefficients (third column of Table 2) onto the template surface coordinates (left column: inferior-medial view; right column: superior-lateral view). Cool color denotes the region with R>L asymmetry, whereas warm color denotes the region with R<L asymmetry. Color scale is the same as in Fig. 2.

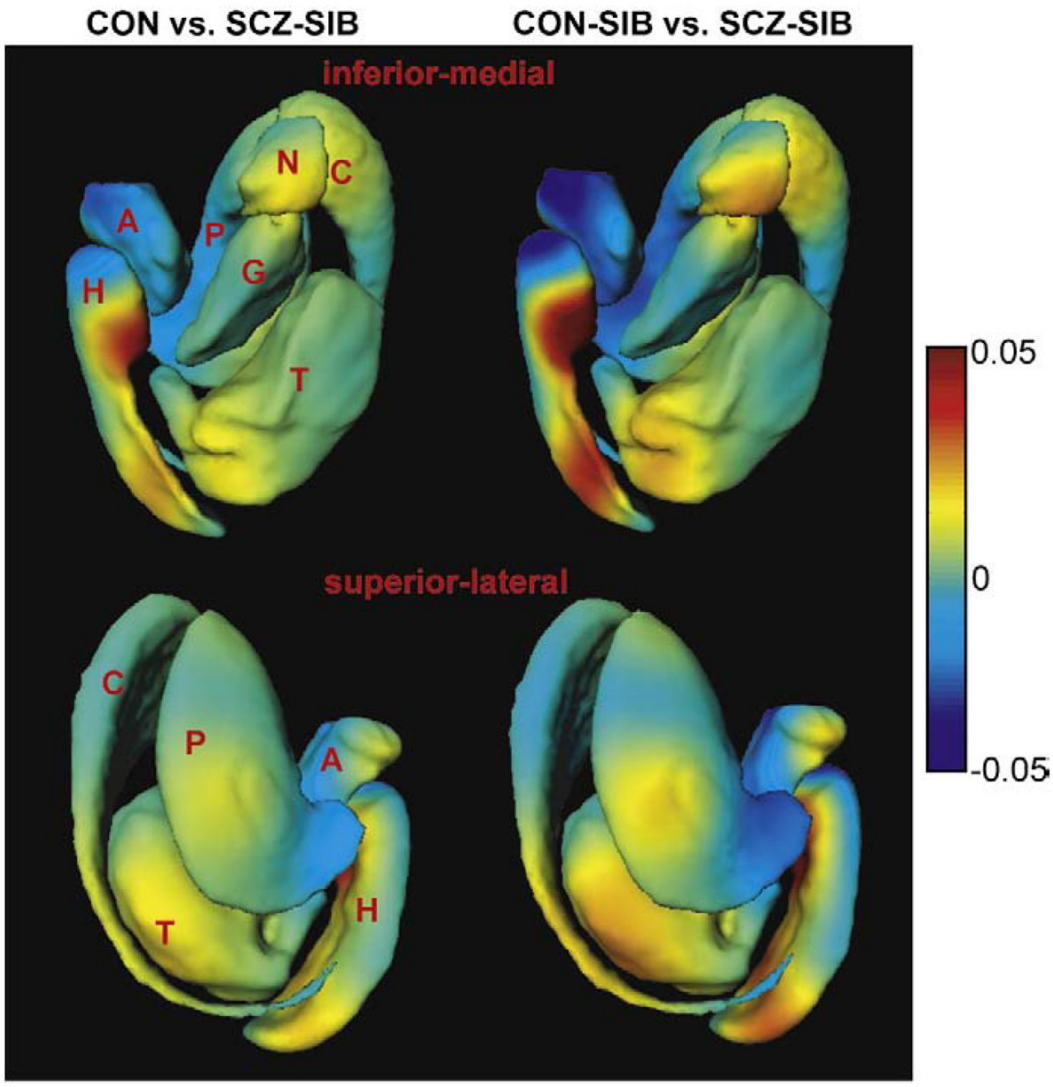

Fig. 4.

Difference of the surface asymmetry patterns between CON (CON-SIB) and SCZ-SIB was expressed in the 13th PC. This was first back projected to the LB-coefficient space and then back projected to the template coordinates by multiplying the resulting LB coefficients with their corresponding LB-basis functions. Figure shows the group difference in asymmetric surface deformation between the control (CON) and schizophrenia sibling (SCZ-SIB) groups (left column) and between the groups of the control siblings (CON-SIB) and schizophrenia siblings (right column). Top and bottom rows respectively show the inferior-medial and superior-lateral views of all structures. Color scale represents ratio of the log-Jacobian determinant in CON (CON-SIB) to that in SCZ-SIB. Warm color denotes regions with exaggerated R>L asymmetry in SCZ-SIB when compared to CON or CON-SIB. Cool color denotes regions with diminished R>L asymmetry in SCZ-SIB.

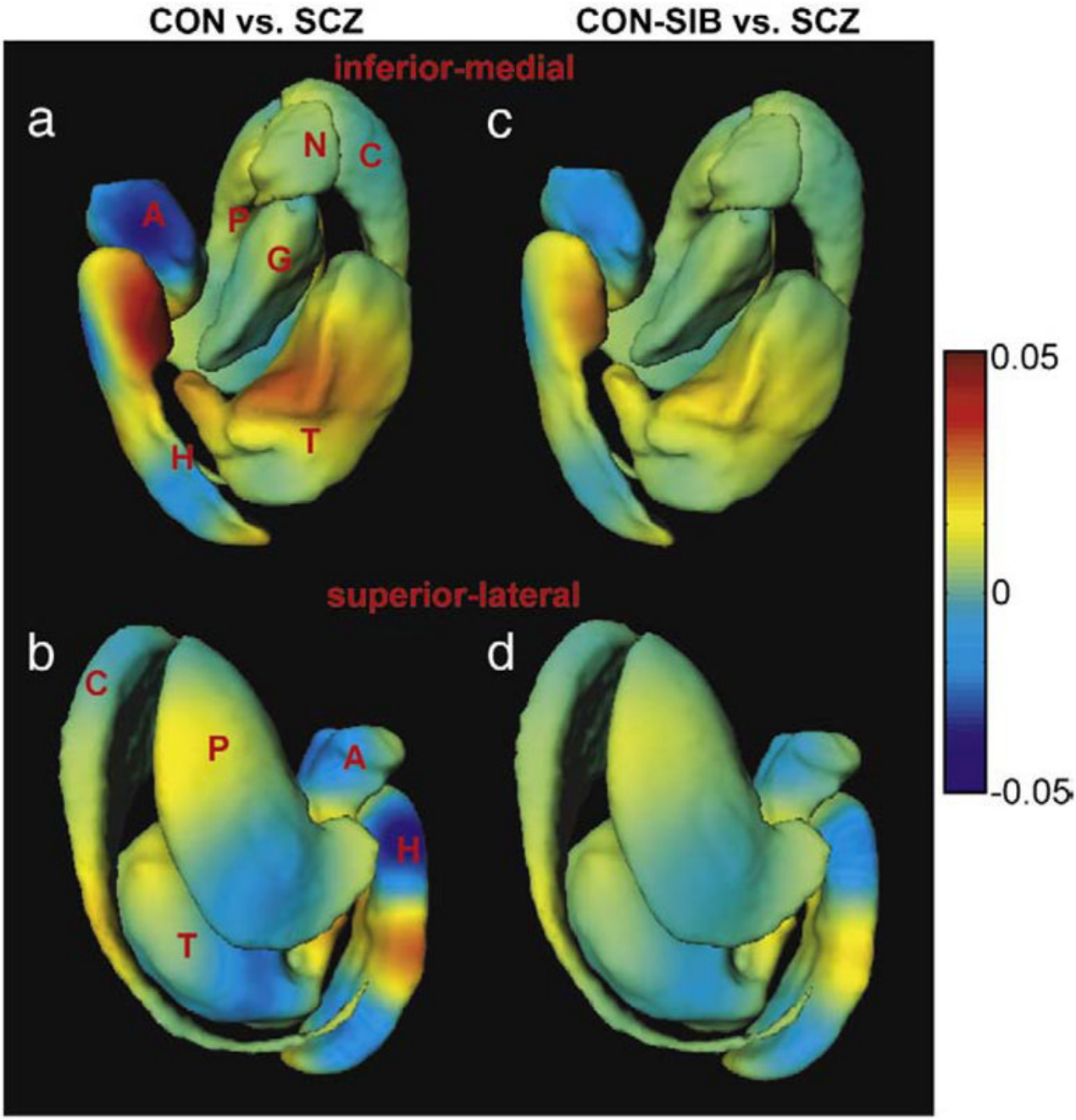

Fig. 5.

Difference of the surface asymmetry patterns between CON (CON-SIB) and SCZ expressed in the 12th PC score. Warm color denotes regions with exaggerated R>L asymmetry in SCZ when compared to CON or CON-SIB. Cool color denotes regions with diminished R>L asymmetry in SCZ. See Fig. 3 caption for further details.

Table 1

Demographic information of the subjects.

Subject group	*N*	Mean illness durat. (SD)	Mean age (SD)	Gender		Handedness		Parental SES mean (SD)
				F	M	R	L	
Schizophrenia	25	4.6 years (4.4)	22.6 (3.2)	5	20	21	4	2.9 (1.2)
Non-psychotic schizophrenia siblings	25	–	22.3 (3.5)	15	10	23	2	2.9 (1.0)
Control	40	–	21.2 (3.6)	18	22	35	5	2.9 (1.0)
Control siblings	40	–	20.0 (3.5)	29	11	37	3	3.1 (0.9)

The groups differed in their gender distribution (Fisher's exact test, $p<0.001$) but not in handedness (defined as the hand used for writing, $p=0.72$), or parental socioeconomic status (SES) ($F(3,126)=0.4$, $p=0.8$). The group differences in age were statistically significant ($F(3,126)=3.7$, $p=0.01$), but the actual differences in mean age were less than 3 years across the groups.

Table 2

The number of the Laplace–Beltrami (LB) coefficients used to characterize the asymmetry deformation map of each individual structure is listed in the second column.

	N	Indexes
Amygdala	8	1,4,8
Hippocampus	19	1,2,5,9,13,14,17,18
Thalamus	26	
Caudate	22	
Globus pallidus	13	11,12
Putamen	27	
Nucleus accumbens	6	

The third column lists the indexes of the LB coefficients that contribute the structure asymmetry at a Bonferroni-corrected level of significance of $p<0.0004$ in two-tailed Wilcoxon sign-ranked tests.