Volumetric and Shape Analysis of the Thalamus in First-Episode Schizophrenia

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Abstract: Thalamic abnormalities have been implicated in the pathogenesis of schizophrenia, although the majority of studies used chronic samples treated extensively with antipsychotics. Moreover, the clinical and neuropsychological correlates of these abnormalities remain largely unknown. Using high-resolution MR imaging and novel methods for shape analysis, we investigated thalamic subregions in 35 (25 M/10 F) first-episode schizophrenia patients compared with 33 (23 M/10 F) healthy volunteers. The right and left thalami were traced bilaterally on coronal brain slices and volumes were compared between groups. In addition, regional abnormalities were identified by comparing distances, measured from homologous thalamic surface points to the central core of each individual's surface model, between groups in 3D space. Patients had significantly less total thalamic volume compared with healthy volunteers. Statistical mapping demonstrated most pronounced shape abnormalities in the pulvinar; however, estimated false discovery rates in these regions were sizable. Smaller thalamus volume was significantly correlated with worse overall neuropsychological functioning and specific deficits were observed in the language, motor, and executive domains. There were no significant associations between thalamus volume and positive or negative symptoms. Our findings suggest that thalamic abnormalities are evident at the onset of a first episode of schizophrenia prior to extensive pharmacologic intervention and that these abnormalities have neuropsychological correlates. *Hum Brain Mapp* 30:1236–1245, 2009. © 2008 Wiley-Liss, Inc.

Key words: thalamus; schizophrenia; neuropsychology; MRI; shape analysis

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INTRODUCTION

Abnormalities in the thalamus have been hypothesized to play an important role in the pathophysiology of schizophrenia. Andreasen et al. [1998, 1999] have proposed that a disruption in prefrontal-thalamic-cerebellar circuitry may contribute to the cognitive disturbances that are characteristic of the disease. Other neural models of schizophrenia implicating the thalamus have focused on impaired sensory gating [Carlsson and Carlsson, 1990; Jones, 1997] and abnormalities in the mediodorsal nucleus (MDN) [Fuster, 1997; Popken et al., 2000]. Moreover, the parvocellular

portion of the MDN has reciprocal connections with the dorsolateral prefrontal cortex, which is important for the mediation of executive functions [Mega and Cummings, 1994] that are central to neuropsychological models of schizophrenia [e.g., Bilder et al., 2000].

Several postmortem studies investigating the thalamus in schizophrenia have reported reduced volume in nuclei that have extensive reciprocal connections with cortical regions implicated in schizophrenia. For example, several studies reported abnormalities in the pulvinar [Byne et al., 2002; Danos et al., 2003], which has connections with the parieto-occipital association cortices [Romanski et al., 1997], the prefrontal cortex [Romanski et al., 1997], and the entorhinal cortex [Insausti et al., 1987]. Abnormalities in the medial dorsal nucleus have also been reported [Danos et al., 2003, 2005], which has dense reciprocal connections with the prefrontal cortex [Giguere and Goldman-Rakic, 1988]. Further cytoarchitectural abnormalities have been reported with reductions in thalamic neuronal size [Byne et al., 2002], density [Byne et al., 2002; Pakkenberg, 1990, 1992], and total volume [Danos et al., 2003] in postmortem brains of patients with schizophrenia. Although such studies have provided important neurohistological findings, potential limitations of such studies include chronicity of illness, cause of death, and extensive prior pharmacologic intervention, which has been linked to changes in brain morphology [e.g., Dorph-Petersen et al., 2005].

In vivo magnetic resonance (MR) imaging volumetric studies have provided further evidence that patients with schizophrenia have thalamic abnormalities compared with healthy volunteers [Andreassen et al., 1994, 1990; Byne et al., 2001; Csernansky et al., 2004; Flaum et al., 1995; Gur et al., 1998; Staal et al., 2001], although several studies have yielded negative findings [Arciniegas et al., 1999; Hazlett et al., 1999; Portas et al., 1998]. In addition, thalamic changes in never-medicated schizophrenia [Buchsbaum et al., 1996; Gur et al., 1998] and neuroleptic naïve first-episode schizophrenia patients [Gilbert et al., 2001] have also been reported.

The failure to find consistent differences in thalamic volume in schizophrenia may be related to the possibility that abnormalities are localized to specific subregions. Although several studies have investigated this possibility, findings have not always been consistent. For example, Gilbert et al. [2001] reported significantly reduced volume in thalamic subdivisions associated with the dorsomedial nucleus and the pulvinar when comparing first-episode patients with healthy volunteers. Buchsbaum et al. [1996] and Hazlett et al. [1999] reported that the left anterior thalamic region was smaller in patients compared with healthy volunteers. More recently, Csernansky et al. [2004] utilized high-dimensional brain mapping to compare shape, symmetry, and volume of the thalamus in schizophrenia patients relative to healthy subjects. Results indicated smaller thalamic volume in schizophrenia patients accompanied by deformities of thalamic shape in the extreme regions of the anterior and posterior regions of the thalamus, suggesting changes specific to the anterior and dorsomedial nuclei.

In this study, we used volumetry and shape analysis to investigate the regional specificity of thalamic abnormalities in patients with schizophrenia compared with healthy volunteers. Patients were studied at the onset of their first-episode of illness to minimize possible confounds associated with long-term exposure to antipsychotic medications and potential neurodegenerative effects of chronic disease. Using shape analysis we tested the hypothesis that patients would have less thalamic volume compared with healthy volunteers and that patients would demonstrate regional abnormalities in the pulvinar and dorsomedial nucleus of the thalamus as assessed via shape analysis. We further tested the hypothesis that reduced thalamic volume and shape abnormalities would be associated with greater severity of clinical and neuropsychological deficits among patients.

MATERIALS AND METHODS

Subjects

This study included 35 patients with first-episode schizophrenia participating in a clinical treatment trial comparing the efficacy of olanzapine versus risperidone being conducted at the Zucker Hillside Hospital in Glen Oaks, NY. Further details regarding ascertainment and clinical characterization of the total sample are available elsewhere [Robinson et al., 2006]. All patients had fewer than 12 weeks (lifetime) antipsychotic treatment, and no history of serious neurologic or endocrine disorder. Thirty patients were antipsychotic drug-naïve at the time of the scan and five were treated previously (median = 3 days, range = 1–14 days). The medication and length of treatment for the five previously treated patients is as follows: risperidone, 7 days; haldol, 3 days; risperidone, 14 days; fluphenazine, 1 day; olanzapine and haldol, 2 days. Patient diagnoses and duration of pretreatment psychosis were based on SCID interview [First et al., 1998] and supplemented by information from family members when available. Diagnoses were confirmed in a consensus conference consisting of senior researchers and clinicians. Diagnoses for patients included schizophrenia ($N = 29$), schizophreniform disorder ($N = 3$), and schizoaffective disorder ($N = 3$). Mean age at first psychotic symptoms was 24.1 (SD = 4.1) years. In addition, 33 healthy volunteers participated in the study and were matched to the patient group on distributions of sex, race, age, handedness, and parental social class. Demographics among healthy volunteers did not differ significantly from the subgroup of 30 antipsychotic drug naïve patients. Healthy volunteers were recruited from the general population with flyers and advertisements and were free from any Axis I disorder as determined by the nonpatient version of the SCID [First et al., 1998]. In addition, none of the healthy volunteers reported having a first-degree relative with an Axis I disorder. This study was approved by the North Shore – Long Island Jewish Medical Center Institutional Review Board and written informed consent was obtained from all study participants.

MR Imaging Procedures

MR exams were conducted at the Long Island Jewish Medical Center. Images were acquired in the coronal plane using a three-dimensional fast spoiled gradient recall (SPGR) acquisition with inversion recovery Prep on a 1.5-T whole body superconducting imaging system (General Electric Medical System, Milwaukee, WI). The SPGR images were obtained with the following parameters: repetition time = 10–14.7 s; echo time = 4.3–5.5 ms; field of view = 22 cm. This sequence produced 124 contiguous images (slice thickness = 1.5 mm) through the whole head with in-plane resolution of 0.86×0.86 mm in a 256×256 matrix. All scans were reviewed by a neuroradiologist and a member of the research team, and any scan with significant artifacts was repeated.

Delineation Criteria

The neuroanatomic criteria for thalamic delineation were adapted from Portas et al. [1998] and based on atlases of thalamic anatomy [Duvernoy and Bourgoin, 1991; Roberts and Hanaway, 1971]. One rater (D.C.) blind to group status traced the right and left thalamus in the coronal plane from anterior to posterior. Images were first imported into MEDx [Sensor Systems, 2004] where an equalization algorithm was used to enhance the contrast of the thalamus with the surrounding structures. MultiTracer [Woods, 2003] was then used to facilitate the accurate identification of neuroanatomic boundaries by allowing the operator to view the cursor position and the delineated boundaries in all three orthogonal planes simultaneously. Contours were drawn on magnified images to permit the tracking of small-scale neuroanatomical features.

Manual segmentation of the thalamus was made on 20 or 21 consecutive slices. The most anterior boundary of the thalamus was defined as the point at which the tail of the caudate nucleus was no longer visible. The medial border of both the genu and the posterior limb of the internal capsule served as the lateral border to the thalamus, separating it from the adjacent lentiform nucleus. The midpoint of the third ventricle served as the medial border. The thalamus is bound superiorly by the lateral ventricles. When moving from anterior to posterior, the height of the structure decreases in the coronal view allowing the fornix to serve as the superior boundary in the more posterior slices. Finally, the midpoint of the third ventricle served as the inferior boundary and the posterior boundary was defined when the thalamus merged under the crux fornix. Intraclass correlation coefficients (ICCs) between two operators on nine randomly selected cases were 0.91 for the right thalamus and 0.94 for the left thalamus.

Surface-Based Methods

We used surface-based anatomical mesh modeling methods that allow the matching of homologous thalamic sur-

face points among individuals to identify regional changes in thalamic morphology [Thompson et al., 1996, 1997] between diagnostic groups. The purpose of examining thalamic surface deformations/expansions was to determine whether overall volume differences are attributable to local or global changes in morphology.

For surface mapping procedures, the manually derived contours were first made spatially uniform across the thalamic surface. That is, the spatial frequency of digitized points making up the thalamic surface traces were equalized within and across brain slices. Each thalamic surface thus formed a regular parametric grid with the same origin allowing spatially homologous grid points from the thalamic surfaces to be matched among subjects at high spatial resolution. The origins of the surface contours were first defined manually and corrected using automated methods on a slice-by-slice basis to ensure that the start of each contour reflected the same coordinate locations (the most medial superior point of the thalamic surface trace). The surface-based matching procedures thus allow the averaging of thalamic surface morphology across groups, the quantification of the 3D variation among homologous surface points to the group averages and for surface features of the thalamus to be compared statistically in 3D.

To identify the regional changes in thalamic shape/surface deformation that indicate the regional specificity of thalamic volume changes in patients compared with healthy volunteers, the 3D parametric surface models of all thalami were skeletonized [Thompson et al., 2003]. Specifically, for each thalamic surface model, a 3D medial curve along the anterior-posterior axis of the thalamus was derived. The distance from each spatially uniform thalamic surface point to this central curve was measured. Each thalamic surface point was thus assigned a distance measure from the central core of the thalamus to the thalamus surface boundary (Fig. 1). Because the derived medial curve represents the center of mass, if one side of the thalamus is deformed inward, the medial axis shifts slightly to accommodate this surface depression. Therefore, radial distance measures reflect changes on all sides of the thalamus with the depressed region showing the greatest changes. Because radial distances from the medial core to the surface boundary are measured at thousands of points along the surface, the resulting radial distance maps detect nonuniform changes in surface structure on a very local scale. Distance fields that index local expansions or contractions/depression in thalamic surface morphology are then compared statistically between groups at equivalent thalamic surface points in 3D as described in our prior work [Narr et al., 2004].

Brain Size Measurements

Total brain volume was measured after manually removing nonbrain tissue (skull, scalp and meninges, extracortical CSF) and the cerebellum from each brain volume. ICCs for scalp-editing procedures were >0.99. Total

Figure 1.

Regional differences in thalamic volume are estimated by measuring the distances from homologous thalamic surface points (blue) to the central core (medial axis) of the individual's thalamic surface model (purple). Each surface point on the thalamus is thus assigned a radial distance measure to allow statistical comparisons of local surface contractions and expansions at equivalent surface locations between groups.

brain volume estimates were retained for use as a covariate in subsequent statistical analyses of thalamic volume and shape.

Neurocognitive Assessments

Neuropsychological tests were administered at baseline during a session that typically lasted 90 min. The baseline battery included 18 tests from which variables were selected to characterize several neuropsychological domains. Based on previous work [Bilder et al., 2000], the following domains were represented: language, memory, executive, motor, and speed of processing. A global neuropsychological scale representing the mean of these five scales was computed. Scores for each scale were computed by averaging z scores on contributing variables using healthy controls as a reference group with a mean of 0 and $SD = 1$. All scales were computed so that higher values were indicative of better performance.

Additional scaling procedures were applied to improve the psychometric properties. Each test variable was exam-

ined for extreme values, and in several instances these deviant scores were replaced by scores within the tails of their underlying distributions. The distributions were examined both within and between groups and variance-stabilizing algorithms were used to optimize homogeneity of variance between groups. Chronbach's alpha was computed for each domain to determine the internal consistency of items. Domains and coefficient alpha (in parentheses) included: (1) Language (0.86) comprising Verbal Fluency, Controlled Word Association Test and Animal Naming; (2) Motor (0.70) comprising Finger Tapping and Grooved Pegboard Test; (3) Speed of Processing (0.82) comprising Cancellation Test, Digit Symbol, Trail Making Test, part A and Trail Making Test, part B; (4) Executive Function (0.90) comprising Wisconsin Sorting Test Categories, and Wisconsin Sorting Test Perseverative Errors; and (5) Memory (0.86) comprising Wechsler Memory Scale, Logical Memory—Immediate and Delayed Recall, and Visual Memory Immediate and Delayed Recall and WAIS-R Digit Span.

Clinical Assessments

We computed two symptom cluster scores based on items from the Hillside Clinical Trials Version [Robinson et al., 2000] of the Scale for the Assessment of Negative Symptoms (SANS) [Andreasen et al., 1982], and Schedule for Affective Disorders and Schizophrenia-Change Version [Spitzer and Endicott, 1978] with psychosis and disorganization items (SADS-C + PD). The positive symptom cluster score was computed as the average of the severity of delusions and severity of hallucinations items from the SADS-C + PD. The negative symptom cluster score was computed as the average of the global ratings of affective flattening, alogia, avolition-apathy, and asociality from the SANS.

Figure 2.

Correlations between thalamic volume and neuropsychological performance in patients with schizophrenia.

TABLE I. Sample characteristics

	First-episode patients (<i>N</i> = 35)	Healthy volunteers (<i>N</i> = 33)	Statistic	df	<i>P</i>
Age (years)	25.3 ± 5.8	24.1 ± 4.1	<i>t</i> = −0.97	66	NS
Sex	25 M/10 F	23 M/10 F	χ^2 = 0.03	1	NS
Race ^a	11, 16, 2, 4, 2	15, 10, 4, 4, 0	χ^2 = 4.6	4	NS
Handedness	0.69 (6)	0.72 (5)	<i>t</i> = 0.25	62	NS
Parental SES ^b	3, 9, 17, 3, 3	6, 7, 13, 1, 1	χ^2 = 3.04	4	NS
Education ^c	12.4 (1.6)	14.7 (2.2)	<i>t</i> = 4.8	62	<0.001

^a Categories for frequencies of ethnic/racial composition included: Caucasian, African-American, Hispanic, Asian, other.

^b Data missing for 5 controls to comment. Hollingshead-Redlich System.

^c Hollingshead-Redlich Scale, where 1 = postgraduate and 6 = junior high school.

Handedness

Hand preference was assessed using a modified 20-item Edinburgh Inventory. The total number of tasks for which the subject used their left or right hand items was scored, and the laterality quotient was computed as (total right − total left)/(total right + total left). Thus laterality quotients could range from 1.00 (all tasks with right) to −1.00 (all tasks with left). Subjects with a laterality quotient greater than 0.70 were classified as dextral; the rest were classified as nondextral.

Statistical Analyses

Group differences in demographic variables were examined using independent groups *t* tests. Chi-square tests were used to examine differences in joint classifications of discrete variables. To confirm the hypothesis of global thalamic volume reductions in schizophrenia, we used repeated measures ANCOVA. Group (patient versus healthy volunteer) and sex served as between subjects factors. Hemisphere served as the repeated measures factor. Age and total brain volume were used as statistical covariates. For volumetric analyses the distribution of the dependent measures was inspected to ensure they did not deviate from normality. Pearson product moment correlations were used to examine the relationship between thalamic volume and neuropsychological and clinical measures. We used the method described by Meng et al. [1992] to compare the magnitude of correlation coefficients and to test for specificity of structure–function relations. This method tests the differences between the magnitudes of two correlations regardless of whether they are statistically significant.

To evaluate regional differences in thalamic volume as indexed by measures of thalamic radial distance, the same statistical model used to determine the presence of overall volumetric differences was employed, although shape analyses were performed for each hemisphere separately. Specifically, ANCOVAs using diagnostic group and sex as independent variables and age and total brain volume as covariates were performed at equivalent thalamic surface locations in 3D using the statistical program R (www.

r-project.org). Uncorrected two-tailed probability values from these analyses were mapped onto the averaged thalamic surface models of the entire group and displayed in 3D space. For tests of overall volume differences and for statistical mapping of surface-based measures, a two-tailed alpha level of *P* < 0.05 was used as the threshold for statistical significance. Because statistical comparisons were performed at hundreds of thalamic surface locations, false discovery rate (FDR) methods were used to confirm analyses involving thalamic radial distances. FDR estimates the proportion of false positive results or Type I errors among all positive statistical tests performed for thalamic surface points. Under conditions that are generally accepted as appropriate for imaging data, FDR estimates are valid even when the statistical tests are not independent due to spatial correlations in the data [Genovese et al., 2002; Storey et al., 2004].

RESULTS

Sample characteristics for the schizophrenia patients and healthy comparison subjects are provided in Table I. Patients did not differ significantly from healthy volunteers in distributions of sex, age, handedness, parental social class, and racial/ethnic composition. However, as expected, schizophrenia patients had significantly less education compared with healthy volunteers. Unadjusted mean thalamic volumes for the right and left hemisphere are presented by sex for patients and healthy volunteers in Table II. Adjusted (for age and total brain volume) mean

TABLE II. Unadjusted mean thalamic volumes in patients and healthy volunteers (mm³)

	Patients		Healthy volunteers	
	M (<i>n</i> = 25)	F (<i>n</i> = 10)	M (<i>n</i> = 23)	F (<i>n</i> = 10)
Right	5,563 (645)	5,223 (686)	5,891 (674)	5,837 (426)
Left	5,223 (686)	4,883 (574)	5,657 (575)	5,905 (527)

Standard deviations are given in parentheses.

thalamic volumes are as follows: male patients (mean = 5,273 mm³, SE = 93.5), female patients (mean = 5,480 mm³, SE = 169.2), male controls (mean = 5,640 mm³, SE = 100.24), and female controls (mean = 6,056 mm³, SE = 146.04).

ANCOVA revealed a significant main effect of group such that patients had less total thalamic volume compared with healthy volunteers ($F = 13.77$, $df = 1, 62$, $P < .001$; partial η^2 squared = 0.182). There was a significant main effect of sex such that female subjects had larger thalamic volumes than males ($F = 4.77$, $df = 1, 62$, $P = 0.039$; $\eta^2 = 0.067$). The sex by hemisphere interaction was significant ($F = 5.86$, $df = 1, 62$, $P = 0.018$; $\eta^2 = 0.086$) such that males had greater right compared with left hemisphere thalamic volume in contrast to females who did not demonstrate this effect. Neither the group-by-sex nor group-by-hemisphere interactions were statistically significant. Total thalamus volume was significantly correlated with age at first psychotic symptoms ($r = -0.38$, $df = 35$, $P = 0.026$), but not with duration of untreated psychosis when examined as a continuous variable. Similarly, there were no significant group differences in thalamus volume when patients were categorized as having less than 1 year or greater than 1 year of untreated psychosis. Total thalamic volume correlated significantly with age in patients ($r = -0.41$, $df = 35$, $P = 0.015$), but not in healthy volunteers ($r = -0.16$, $df = 33$, $P = 0.37$).

Correlations of total thalamic volume with the neuropsychological domains are provided in Figure 2. These analyses revealed that total thalamic volume was significantly and positively correlated with global neuropsychological functioning among patients ($r = 0.43$, $df = 31$, $P = 0.017$). Investigation of the individual neuropsychological domains included in the global domain revealed that thalamic volume correlated significantly with language ($r = 0.38$, $df = 33$, $P = 0.028$), motor ($r = 0.45$, $df = 35$, $P = 0.006$), and executive ($r = 0.50$, $df = 35$, $P = 0.002$) functioning.

Testing the specificity of structure–function relations revealed that total thalamus volume correlated significantly more strongly with language [$z(\text{diff}) = 2.44$, $df = 33$, $P = 0.007$], motor [$z(\text{diff}) = 2.45$, $df = 34$, $P = 0.007$], and executive [$z(\text{diff}) = 2.45$, $df = 33$, $P = 0.007$] functioning compared with memory functioning. In addition, total thalamus volume correlated significantly more strongly with language [$z(\text{diff}) = 2.34$, $df = 33$, $P = 0.01$], motor [$z(\text{diff}) = 2.50$, $df = 34$, $P = 0.006$], and executive [$z(\text{diff}) = 2.15$, $df = 34$, $P = 0.02$] functioning compared with speed of processing. There were no significant correlations between thalamic volume and severity of positive or negative symptoms. None of these findings changed substantially when we examined the subgroup of antipsychotic drug-naïve patients compared with healthy volunteers or examined structure–function relations in this subgroup alone.

Shape differences between the diagnostic groups and for sex are illustrated in Figure 3. Significant reductions in ra-

dial distances used to index thalamic volume reductions are referenced by the color bar showing two-tailed probability values obtained from each thalamic surface location. These statistical maps show pronounced asymmetric surface deformations in the right posterior (pulvinar) thalamic region in first-episode patients compared with healthy volunteers. After FDR correction [Storey, 2002; Storey et al., 2004], however, the estimated FDR for regions showing significant group differences at $P < 0.05$ was 26%. For regional sex effects, the estimated FDR for uncorrected P -values of 0.05 was 10%. Uncorrected regional results for the group-by-sex interaction were largely negative. Significant correlations between thalamic surface deformations and the neuropsychological domains are provided in Figure 4. These findings indicate that global functioning is associated with relatively widespread thalamic structural alterations, although findings did appear more pronounced caudally. None of the shape analysis structure–function relations was significant following FDR correction (estimated FDR rate $> 99\%$).

DISCUSSION

Although postmortem and in vivo neuroimaging studies in schizophrenia have reported thalamic volumetric alterations and abnormalities within discrete nuclei, findings have been largely inconsistent. Moreover, little research has been directed at understanding the functional correlates of thalamic structural pathology in schizophrenia. The main finding of our study is that patients experiencing a first episode of schizophrenia have reduced total thalamic volume compared with healthy volunteers while controlling for the effects of age and total brain volume. Investigation of structure–function relations revealed that lower thalamic volume was significantly correlated with worse performance in language, motor, and executive domains, but not with memory or speed of processing. Shape analysis revealed that although abnormalities were most pronounced in the pulvinar region among patients, regional effects were not of large magnitude.

Our findings provide additional evidence for reduced thalamic volume in schizophrenia, which is consistent with prior work in first-episode [Crespo-Facorro et al., 2007; Ettinger et al., 2001; Gilbert et al., 2001; Lang et al., 2006; Salgado-Pineda et al., 2003] and chronic [Andreasen et al., 1994; Csernansky et al., 2004; Staal et al., 2001] patients. Moreover, the lack of a significant group by hemisphere interaction is consistent with prior work [Csernansky et al., 2004; Hazlett et al., 1999]. There is little consensus, however, regarding which specific regions of the thalamus may be abnormal in schizophrenia. Several studies reported shape differences in the anterior thalamus, thus implicating the dorsomedial nucleus [Buchsbaum et al., 1996; Csernansky, 2004; Hazlett et al., 1999]. In contrast, other studies reported abnormalities in the pulvinar region [Csernansky et al., 2004; Gilbert et al., 2001].

Figure 3.

Statistical maps showing significant differences in radial distances for main effects of diagnosis (top), sex (middle), and diagnostic group-by-sex interactions (bottom) after correcting for age and brain size.

The pulvinar may be of particular relevance to schizophrenia given that it occupies nearly one-quarter of the total thalamic volume [Romanski et al., 1997] and has reciprocal connections with other cortical regions implicated in the disorder such as the prefrontal cortex [Romanski et al., 1997], parieto-occipital association cortices [Romanski et al., 1997], and the entorhinal cortex [Insausti et al., 1987]. Moreover, reduced pulvinar volume has been identified in postmortem samples [Byne et al., 2002]. FDR corrections of our thalamus data, however, indicated that the expected percentage of false positives was 26% or that 74% of the observed uncorrected results reflect true positives. Thus, our findings, while implicating overall differences of thalamic shape between groups, do not warrant firm conclusions regarding the regional specificity of thalamic abnormalities and suggest that the pattern of structural alterations may be more global.

Little research has been directed at understanding the neuropsychological correlates of thalamic structural alterations in schizophrenia. Several studies indicated significant associations between less thalamic volume and worse performance on measures of attention [Salgado-Pineda et al., 2003] and visual memory [Csernansky et al., 2004]. In con-

trast, a recent study [Crespo-Facorro et al., 2007] reported a significant association between more thalamic volume and neuropsychological functioning including Trail Making, parts A and B, Cancellation Test, WAIS-R Digit Symbol-Coding, and WAIS-R Digit Span—Backward. In this study, thalamic volume was significantly and positively correlated with language, motor, and executive functioning among patients. Moreover, less thalamic volume was significantly more strongly correlated with deficits in language, motor, and executive functioning than with memory and speed of processing, suggesting specificity to these functional domains. Our findings converge with fMRI studies reporting abnormal thalamic activity in patients with schizophrenia compared with healthy volunteers while performing executive [Camchong et al., 2006] and motor [Rubia et al., 2001] tasks and during language processing [Koeda et al., 2006]. In this study, we did not find any evidence that specific parts of the thalamus were selectively correlated with neuropsychological deficits suggesting that the observed neuropsychological deficits reflect relatively widespread thalamic structural alterations.

We also observed significant asymmetry ($R > L$) in the thalamus among men compared with women, which con-

Figure 4.

Surface deformation probability maps of structure–function relations in schizophrenia.

verges with a volumetric MR imaging study reporting greater right compared with left thalamus volume in male schizophrenia patients [Deicken et al., 2002]. Similarly, our results are consistent with a recent study [Kovalev et al., 2003] investigating sex effects on brain asymmetry in a cohort of 380 healthy adults. Specifically, in that study, male brains were found to be more asymmetric than females with significant effects observed in the thalamus. Interestingly, we also observed a significant main effect of sex such that females had more thalamic volume compared with males even after controlling for the effects of total brain volume. In a study evaluating the effect of handedness and sex on the volumes of selected subcortical structures and cerebellar hemispheres in healthy humans, women had significantly larger subcortical structures than men after accounting for differences in brain size [Szabo et al., 2003]. Although the functional implications of larger relative thalamus volume in women are unclear, some research has implicated sex differences in thalamic brain activity in association with processing unpleasant linguistic stimuli related to interpersonal conflicts [Shirao et al., 2005] and neural responses to happy or sad emotions presented in the form of facial expressions, scenes, and words [Lee et al., 2005].

We found no evidence that thalamic volume was associated with either positive or negative symptoms. Similarly, several prior studies [Csernansky et al., 2004; Ettinger et al., 2001; Portas et al., 1998] reported no significant association between thalamic volume and/or shape and negative symptoms in schizophrenia, although a recent study by Crespo-Facorro et al. [2007] reported that increased thalamic volume was associated with greater negative symptom severity in a cohort of first-episode nonaffective psychotic patients. Another study investigating the relationship between thalamic shape and positive symptoms was not significant [Csernansky et al., 2004]. In contrast, Portas et al. [1998] reported significant correlations between less thalamus volume and greater bizarre behavior, hallucinations, and thought disorder in a sample of more chronic patients. Subjects in this study were most similar to the cohort studied by Crespo-Facorro et al. [2007]. As acknowledged by Crespo-Facorro et al. [2007], however, antipsychotic medications may have led to thalamic volume changes in their cohort and influenced structure–function relations despite their sample having been treated for a very short time (mean = 4.75 weeks) prior to scanning. Differences in illness duration, antipsychotic medication exposure, as well as degree of positive and negative symptoms at the time of the scan could account for discrepant findings among studies investigating the clinical and neuropsychological correlates of thalamic structural pathology in schizophrenia.

We also found that total thalamus volume was significantly correlated with age at first psychotic symptoms similar to the study by Crespo-Facorro et al. [2007]. As noted by Crespo-Facorro et al. [2007], one possibility that might account for the association of larger thalamus volume and

earlier age of onset could be related to a compensatory reaction of the thalamus to abnormalities elsewhere in the brain [e.g., Hazlett et al., 2004; Mitelman et al., 2006]. Alternatively, larger thalamus volume could reflect an abnormality in programmed synaptic elimination [Feinberg, 1982]. MR imaging studies report an inverted U-shaped trajectory of age with cortical and subcortical gray matter [Giedd et al., 1997; Lenroot et al., 2007], and computer simulations suggest that aberrant synaptic pruning could account for the development of schizophrenia [Hoffman and Dobscha, 1989] as well as hallucinations [Hoffman and McGlashan, 1999]. In addition, the finding that age correlated significantly and negatively with thalamus volume in patients, but not healthy volunteers supports the possibility that a neurodevelopmental disturbance affecting neuronal pruning within the thalamus could play a role in the observed findings.

There were several limitations to this study that preclude firm conclusions. First, it should be acknowledged that the shape analysis measures are sensitive to points only on the thalamic surface, and thus, it is not possible to detect regional changes that are specific to the medial thalamus. Second, we did not have information regarding functional brain activity in the thalamus and it is conceivable that specificity of thalamic abnormalities might be observed using fMRI or PET in contrast to regional volumetry, which was the focus of the present investigation. Third, it is possible that we did not detect significant associations with positive or negative symptoms because we had limited power to detect correlations. Fourth, the relationship between thalamic deformations and the cortical surface was not investigated, but would be a worthwhile goal of future research as it may clarify specific patterns of abnormalities within cortico-thalamic networks. Lastly, given the novel method used in this study and the limitations of standard high-resolution structural imaging protocols to identify the cytoarchitectural boundaries of the thalamic subnuclei, it may be premature to make any strong conclusions regarding the diffuse or focal nature of thalamic abnormalities in the pathogenesis of schizophrenia.

In conclusion, we report evidence for structural alterations involving the thalamus in patients experiencing a first episode of schizophrenia prior to extensive antipsychotic treatment and that these structural alterations have neuropsychological correlates.

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