

# Magnetic Resonance Imaging of the Thalamus and Adhesio Interthalamica in Twins With Schizophrenia

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**Context:** Abnormalities of the thalamus are thought to be central to the pathophysiology of schizophrenia. These abnormalities include altered structure and shape of the thalamus itself and possibly changes to the adhesio interthalamica (or massa intermedia), the gray matter bridge connecting the 2 thalamic lobes. However, it is not clear to what extent these abnormalities are determined by the genetic liability for schizophrenia.

**Objective:** To investigate thalamic volume and the presence of the adhesio interthalamica in monozygotic (MZ) twins concordant or discordant for schizophrenia.

**Design:** Study of MZ twins.

**Setting:** Patients were drawn from inpatient and outpatient clinics. Twin controls were recruited from a volunteer twin register and through media advertisements.

**Participants:** A total of 123 twins participated: 19 MZ twin pairs concordant for schizophrenia, 15 MZ schizophrenic twins and 16 MZ nonschizophrenic twins drawn from 17 pairs discordant for schizophrenia, and 27 MZ twin pairs without schizophrenia. Groups were matched for age, sex, handedness, level of education, parental socioeconomic status, and ethnicity.

**Main Outcome Measures:** The volume of the thalamus (including right and left hemispheres) was measured (in cubic centimeters) and the presence of the adhesio interthalamica was ascertained from structural magnetic resonance images.

**Results:** Concordant twin pairs displayed significantly reduced thalamic volume compared with control twins, even when covarying for effects of whole-brain volume, age, and sex. There was a significant linear decrease in thalamic volume (control greater than discordant nonschizophrenic greater than discordant schizophrenic greater than concordant). In all groups, right thalamus was larger than left thalamus. There was no difference across groups in the frequency of the adhesio interthalamica.

**Conclusions:** Volumetric thalamic abnormalities in schizophrenia occur in twin pairs concordant for schizophrenia. These abnormalities may mark the substantial genetic contribution to the illness seen in concordant twin pairs, whereas the adhesio interthalamica is unlikely to be affected in schizophrenia.

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SCHIZOPHRENIA IS KNOWN TO be associated with subtle changes in brain anatomy.<sup>1</sup> Postmortem studies as well as in vivo neuroimaging investigations suggest slightly reduced whole-brain volume and ventricular enlargement, in particular of the lateral ventricles.<sup>2</sup> Specific gray matter volume reductions have been observed in medial temporal lobe structures, the frontal lobe, the cerebellum, and the thalamus.<sup>2</sup> Twin and family studies suggest that some of these abnormalities may be in part genetically mediated.<sup>3-8</sup>

The thalamus is thought to play an important role in the pathophysiology of schizophrenia in part owing to its unique

location and connectivity. The thalamus acts as a central relay station, transferring peripheral sensory inputs to the cortex and mediating corticocortical connections between areas particularly implicated in schizophrenia, such as frontal and temporal cortices. A number of theoretical accounts of schizophrenia have placed the thalamus in the center of dysfunctional neural connectivity.<sup>9-11</sup>

Structural neuroimaging studies of the thalamus have provided evidence of planimetric, volumetric, or morphologic abnormalities in people with schizophrenia,<sup>12-17</sup> although some studies have failed to find evidence of volume or area reductions<sup>18-21</sup> (for review see Sim et al<sup>22</sup>). More recent neuroimaging studies point to se-

lective reduction of anterior and mediodorsal thalamic subnuclei.<sup>14,23</sup> Postmortem studies have observed reductions in volume and neuron number in the thalamus in schizophrenia, particularly in the mediodorsal nucleus.<sup>24-28</sup> However, not all postmortem studies have found mediodorsal abnormalities.<sup>29</sup> Given the prominent interconnections between the mediodorsal thalamic nucleus and the prefrontal cortex, it is possible that the genetic contribution to frontal lobe abnormalities in schizophrenia<sup>4</sup> may be reflected in the structure of the thalamus.

Evidence of a possible genetic contribution to thalamic abnormalities in schizophrenia comes from a study of family members of schizophrenic patients in which increasing genetic risk for schizophrenia (but not bipolar disorder) was associated with more severe volume reductions in the thalamus.<sup>30</sup> Studying twins concordant and discordant for schizophrenia affords the unique opportunity to further test hypotheses concerning genetic or environmental contributions to neuroanatomy.<sup>4</sup> To date there has been only 1 study of thalamic volume in twins discordant for schizophrenia, to our knowledge.<sup>31</sup> This study did not observe volume reductions in discordant twin pairs compared with controls. However, the small sample size of that study (8 discordant pairs, 5 control pairs) compromised the strength of these findings.

In addition, studying monozygotic (MZ) twins concordant for schizophrenia would significantly enhance the explanatory power of the twin design. It has been argued that twins concordant for schizophrenia, ie, pairs where both members carry a diagnosis of schizophrenia, are subject to greater genetic liability than discordant pairs.<sup>3,6,32</sup> Evidence of this proposition comes from studies demonstrating that known nongenetic risk factors for schizophrenia, such as complications of labor,<sup>33</sup> are more common among discordant than concordant twin pairs.<sup>34</sup> Therefore, if a particular neuroanatomic abnormality is due to genetic liability for schizophrenia, it should be observed at greater frequency or intensity in concordant twins but to a lesser extent in discordant twins.

One aspect of thalamic anatomy that has received relatively little research attention in the field of schizophrenia concerns the adhesio interthalamica. Thalamic growth during embryonic development may result in a connection of the medial surfaces of the 2 thalamic lobes, known as *adhesio interthalamica* (or *massa intermedia*). Postmortem and in vivo neuroimaging examinations have shown that this "bridge" is absent in approximately 20% of the human population.<sup>35</sup>

Few studies have examined the presence of the adhesio interthalamica in schizophrenia; the results of these studies are inconsistent. While 2 neuroimaging investigations have suggested that this structure may be more frequently absent in patients than in controls,<sup>36,37</sup> others failed to make this observation<sup>38,39</sup> or observed reduced frequency only in female patients.<sup>40</sup> In addition, a postmortem study found no significant difference between patients and controls.<sup>36</sup> No study of the adhesio interthalamica in schizophrenic twins has been reported to date, to our knowledge.

The present study aimed to investigate the volume of the thalamus and the presence of the adhesio interthal-

amica in MZ twins with or without schizophrenia by means of magnetic resonance (MR) imaging. Given the previously observed influence of genetic liability to schizophrenia on thalamic volume<sup>30</sup> and the assumption that twins concordant for schizophrenia possess greater genetic contribution to the illness,<sup>3,6,32,34</sup> it was expected that concordant twins would show greater thalamic abnormalities relative to nonschizophrenic control twins than discordant pairs would.

## METHODS

### PARTICIPANTS

Probands were referred from across the United Kingdom by their treating psychiatrists. Control twins were recruited from the Institute of Psychiatry Volunteer Twin Register and by national media advertisements. Exclusion criteria for all participants were a history of neurologic illness or of systemic illness with known neurologic complication, history of head injury with loss of consciousness of more than 1 minute, and current substance misuse or dependence. Participants provided written informed consent. The study had ethical permission (South East Multi-Centre Research Ethics Committee).

Clinical diagnoses were confirmed by structured clinical interviews performed by 2 trained psychiatrists using the Schedule for Affective Disorders and Schizophrenia—Lifetime Version<sup>41</sup> augmented with further clinical information to make DSM-IV diagnoses.<sup>42</sup> Current psychotic symptoms in the probands were assessed with the Scales for the Assessment of Positive (SAPS) and Negative (SANS) Symptoms.<sup>43,44</sup> Handedness was determined with the Annett scale.<sup>45</sup> Parental socioeconomic status was determined by means of a national standardized scale.<sup>46</sup> The number of years spent in full-time education was obtained. Monozygosity was confirmed with 12 highly polymorphic microsatellite markers and twin likeness questionnaires. The probands' medication status was recorded at assessment, and their age at first contact with psychiatric services was established as a proxy measure of age at illness onset.

In concordant pairs, both members met DSM-IV criteria for schizophrenia or schizoaffective disorder. In discordant pairs, 1 member (the proband) met DSM-IV criteria for schizophrenia or schizoaffective disorder while the co-twin was free of any psychotic illness. Controls were required to be free of personal or family history (to second-degree relatives) of psychosis or any schizophrenia spectrum disorder. The probability that any of the discordant pairs would become concordant for schizophrenia in the future was low given that a mean of 11.9 years (SD, 11.2 years) had elapsed since the onset of the illness in the probands.<sup>47</sup> All probands were clinically stable at the time of assessment, with no changes in their medications in the preceding 6 months. Chlorpromazine (CPZ) equivalents were calculated for probands to allow an investigation of treatment correlates of thalamic volume.

### MR IMAGING

Participants underwent MR imaging (Signa Advantage scanner; General Electric Co, Milwaukee, Wis) at 1.5 T. A 3-dimensional T1-weighted coronal spoiled gradient image of the whole head was obtained. The sequence used an echo time of 5 milliseconds, a repetition time of 35 milliseconds, a flip angle of 30°, number of excitations of 1, and a field of view of 200 × 200 mm, yielding 124 contiguous sections of 1.5-mm thickness. The voxel dimensions were 1 × 1 × 1.5 mm. Imaging took place on identical imagers with identical protocols at either of 2 sites

(St Georges Hospital, London, or The Maudsley Hospital, London). In all twin pairs, both members were imaged at the same site. Data from both sites were combined on the basis of these methodologic precautions, and as comparable numbers of twins from each group were imaged at each site ( $\chi^2=1.56$ ;  $P=.67$ ) and there was no effect of site or site  $\times$  group interaction on thalamic volume, with or without whole-brain volume as covariate (all  $P>.26$ ).

Image analysis was undertaken on the basis of stereologic principles implemented in PC-based software (MEASURE)<sup>48</sup> at 1 site, without knowledge of participant group status. MEASURE superimposes a grid on the image and allows the user to view voxels in 3 mutually orthogonal planes. Grid points falling within a region of interest are manually marked by a rater. Head tilt was corrected in all brains before measurements to align images along the anterior commissure–posterior commissure (AC-PC) line and the interhemispheric fissure. The coefficient of error for the structures rated was less than 5% according to the Gundersen and Jensen formula.<sup>49</sup> For the thalamus, a grid setting of  $3 \times 3 \times 2$  was used, with 1 grid point equaling 1 voxel. The thalamus could typically be seen on approximately 9 to 10 consecutive frontal images, 15 to 17 sagittal images, and 6 to 7 horizontal images (**Figure 1**).

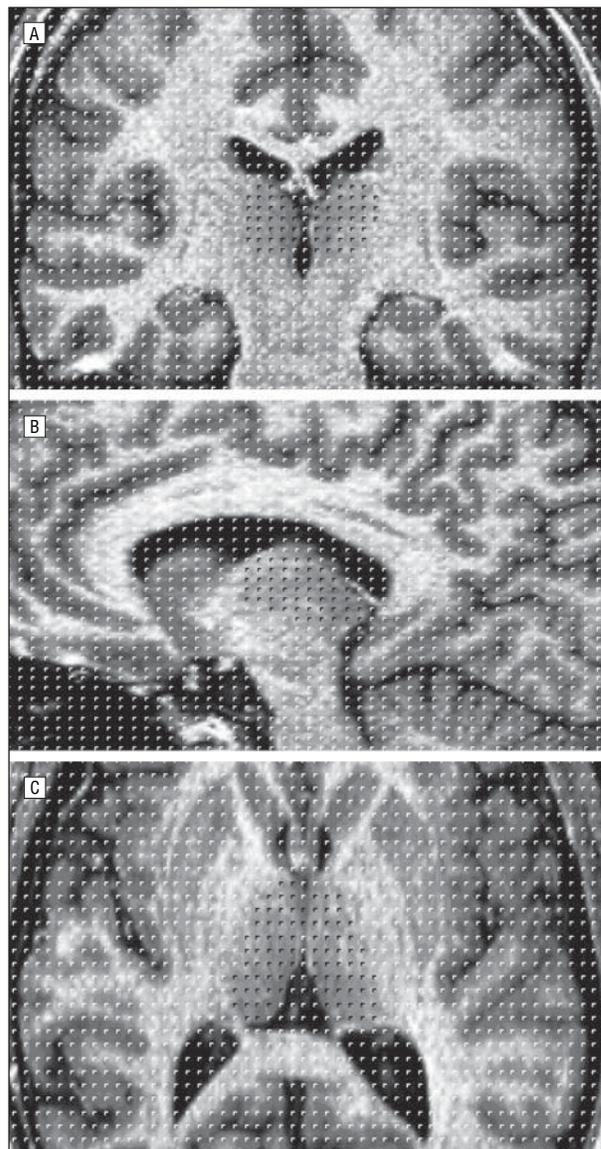
The anatomic boundaries of the thalamus were determined in accordance with a previously described protocol<sup>50</sup> and using an additional neuroanatomy atlas.<sup>51</sup> The anterior boundary of the thalamus is formed by the fornix and the genu of the internal capsule. The posterior end of the thalamus merges with the crus fornix and borders the third ventricle. The thalamus is bordered laterally by the internal capsule and medially by the third ventricle. The inferior boundary is where the most inferior aspect of thalamic gray matter reaches the brainstem, which can be distinguished in the present images from the thalamus in gray-scale intensity. The superior boundary is where the roof of the thalamus protrudes into the main body of lateral ventricles. While the adhesio interthalamica was marked as being within the thalamic boundaries, the habenula, a small nucleus of the thalamic complex adjacent to the posterior end of the roof of the third ventricle, was excluded.<sup>21</sup> Volumes were calculated separately for left and right thalamus by splitting the image midsagittally. If midsagittal grid points occurred that could not be clearly attributed to right or left thalamus, they were excluded in their calculation. Intrarater (rater U.E.;  $n=10$ ; intraclass correlation coefficient [ICC], 0.96) and interrater (raters U.E. and N.M.;  $n=10$ ; ICC, 0.95) reliabilities for total thalamic volume were high.

The presence or absence of the adhesio interthalamica was established from coronal, axial, and sagittal images simultaneously displayed in MEASURE. If no connection between the thalamic lobes could be seen on any image, the adhesio interthalamica was judged as absent. Intrarater (rater U.E.;  $n=12$ ;  $\kappa=0.88$ ) and interrater (raters U.E. and N.M.;  $n=12$ ;  $\kappa=0.88$ ) agreement was high.

The definition of whole-brain volume followed our previous work<sup>6,52,53</sup> and included all voxels falling within cortical and subcortical gray matter, white matter, and the brainstem superior to the foramen magnum. Cerebellum, cerebrospinal fluid, optic chiasm, pineal and pituitary glands, dura mater, and superior sagittal, straight, and transverse sinuses were excluded. A MEASURE grid setting of  $5 \times 5 \times 5$  was used. Intrarater ( $n=10$ ; ICC,  $>0.97$ ) and interrater ( $n=10$ ; ICC,  $>0.98$ ) reliabilities were high (raters N.M., U.E., N.E.v.H., and K.M.).

## STATISTICAL ANALYSIS

The genetic relatedness of twin pairs and the resulting within-family correlations violate the assumption of independent ob-



**Figure 1.** Magnetic resonance images of the thalamus representing 3 orthogonal orientations displayed with MEASURE software. A, Coronal plane; B, sagittal plane; and C, horizontal plane. Grid points falling within the anatomic boundaries of the thalamus are black instead of white.

servations made in analysis of variance. Therefore, differences between groups (concordant, discordant schizophrenic, discordant nonschizophrenic, and control) were analyzed with regression models that allowed for correlations within twin clusters and departures from normality by using the robust sandwich estimator to estimate standard errors implemented in Stata 8.2 statistical software (StataCorp, College Station, Tex). The significance level was set at  $P \leq .05$ .

Initial analyses were carried out to compare demographic variables between groups. Group differences in age, years of education, and parental socioeconomic status were examined by means of linear regression models with robust standard errors. Group differences in sex, ethnicity, and handedness were examined by logistic regressions with robust standard errors of the respective binary dependent variables (sex, male-female; ethnicity, white–Afro-Caribbean; handedness: right-handed–left-handed). To examine differences in clinical data, the 2 proband groups (concordant, discordant) were compared on SAPS, SANS, age at first contact, and CPZ equiva-

**Table 1. Demographic Variables by Group\***

Variable	Group				Group Comparison Test
	Concordant (n = 38)	Discordant Affected (n = 15)	Discordant Unaffected (n = 16)	Control (n = 54)	
Age, y	35.53 (9.05)	32.20 (12.68)	31.62 (11.95)	35.73 (10.12)	$F_{3,61} = 1.56, P = .21$
Sex, No. M/F twins	30/8	10/5	9/7	34/20	$\chi^2_3 = 4.72, P = .19$
Handedness, No. (%) right-handed twins	30 (79)	11 (73)	14 (88)	45 (83)	$\chi^2_3 = 1.43, P = .70$
Years of education	12.95 (2.81)	12.00 (3.16)	12.56 (2.42)	13.94 (2.60)	$F_{3,62} = 1.61, P = .20$
Parental socioeconomic status	2.61 (0.90)	2.47 (1.06)	2.44 (1.03)	2.71 (0.91)	$F_{3,60} = 0.26, P = .86$
Ethnicity, No. (%) white twins	34 (89)	13 (87)	15 (94)	54 (100)	$\chi^2_2 = 1.86, P = .39$

\*Data reflect mean (SD) unless otherwise stated.

lents by means of regression models with robust standard errors, and on type of antipsychotic medication (typical or atypical) by means of logistic regression with robust standard errors.

For group comparisons on thalamic volume, effects of side (right or left) and side  $\times$  group interactions were first evaluated. In the absence of any statistical evidence of a dependency of the group difference on side, hemispheres were combined and group comparisons of total thalamic volume were carried out. If these were then statistically significant at the .05 level, they were followed by 6 pairwise post hoc group comparisons using the Bonferroni adjustment. An additional post hoc test was carried out to investigate whether there was a linear trend for thalamic reduction following the hypothesized pattern of control greater than discordant nonschizophrenic greater than discordant schizophrenic greater than concordant. Therefore, the adjusted significance level for post hoc tests was  $.05/7 = .007$ . Sex and age were included in the regression models as covariates to adjust for possible effects of these variables on brain structure. Analyses of group differences in thalamic volume were repeated with whole-brain volume used as an additional covariate, to examine whether possible thalamic volume differences may be accounted for by overall effects of brain volume.<sup>54</sup> Between-group differences in whole-brain volume were investigated with age and sex used as covariates.

To provide a heritability index of total thalamic volume, ICCs were calculated for each twin category (concordant, discordant, and control) from a model that included sex, age, and whole-brain volume as covariates. These ICCs measure the degree of (positive) correlation between the scores of the members of each twin pair after controlling for effects of predictor variables other than affected status. A bootstrapping approach was used to compare the ICCs between twin categories. The bootstrap algorithm resampled twin pairs within each twin category to generate percentile confidence intervals for mean ICCs and tests for zero differences between twin categories. The Bonferroni correction was used to adjust the ICC tests for 3 pairwise comparisons (adjusted significance level,  $.05/3 = .017$ ).

Clinical correlates of thalamic volume were investigated separately in the concordant and discordant proband groups since effects may differ between groups. This was done by means of a regression model with robust standard errors predicting thalamic volume in separate analyses from SAPS, SANS, age at first contact with psychiatric services, and CPZ equivalents, with age and sex as covariates. Effects of treatment status on thalamic volume were investigated in each group by comparing patients taking typical antipsychotics with patients taking atypical antipsychotics, with age and sex used as covariates. When a significant effect was found, the analysis was repeated with whole-brain volume as additional covariate to determine the anatomic specificity of the finding.

Finally, group differences regarding the presence or absence of the adhesio interthalamica were examined by logistic regression with robust standard errors, using group (concordant, discordant affected, discordant unaffected, and control) as the explanatory variable and adhesio (present or absent) as the dependent variable. Age and sex were used as covariates and the analyses were repeated with whole-brain volume used as an additional covariate, as before. Clinical correlates of adhesio interthalamica presence or absence and group  $\times$  adhesio effects on thalamic volume could not be evaluated because of the very small number of twins in the concordant and discordant groups without adhesio interthalamica (5.3% and 6.7%, respectively).

## RESULTS

### DEMOGRAPHIC AND CLINICAL VARIABLES

The final sample comprised 123 MZ twins. There were 38 members from 19 concordant twin pairs, 31 members from 17 discordant twin pairs (15 probands, 16 co-twins), and 54 members from 27 control twin pairs. Data were excluded for 2 probands and 1 nonschizophrenic co-twin from 3 discordant pairs because of movement artifact. Demographic variables are summarized in **Table 1**. All participants were of either white or Afro-Caribbean ethnicity. There were no significant effects of group on age, sex, ethnicity, handedness, parental socioeconomic status, or years of education.

Among the nonschizophrenic members of the discordant pairs, 10 met criteria for a previous *DSM-IV* Axis I diagnosis: depression (n=3); depression and alcohol abuse (n=1); depression and simple phobia (n=1); obsessive-compulsive disorder, depression, and drug and alcohol abuse (n=1); panic disorder, mania, and depression (n=1); simple phobia (n=1); simple phobia, panic disorder, and depression (n=1); and generalized anxiety disorder, panic disorder, and depression (n=1). The frequency of psychiatric diagnoses was significantly higher in this group than in the healthy controls ( $\chi^2_1 = 9.65, P = .002$ ), of whom 8 met criteria for a previous *DSM-IV* Axis I diagnosis: depression (n=3); mania (n=1); depression and drug and alcohol abuse (n=2); drug abuse (n=1); and specific phobia, agoraphobia, and drug abuse (n=1). None of the control twins or unaffected members of discordant pairs was unwell at the time of assessment or taking any psychotropic medication.

**Table 2. Clinical Variables by Proband Group\***

	Group		Group Comparison Test
	Concordant (n = 38)	Discordant Affected (n = 15)	
SAPS	6.76 (4.41)	7.25 (4.63)	$F_{1,30} = 0.01, P = .75$
SANS	10.69 (4.37)	9.75 (6.47)	$F_{1,30} = 0.22, P = .64$
Age at first contact, y	21.11 (4.86)	21.62 (5.90)	$F_{1,31} = 0.07, P = .79$
Type of medication, No. typical/atypical	14/16 (8 NA)	7/3 (5 NA)	$\chi^2 = 1.31, P = .25$
CPZ equivalents	580.97 (421.38)	500.00 (371.12)	$F_{1,29} = 0.32, P = .58$

Abbreviations: CPZ, chlorpromazine; NA, not available; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

\*Data reflect mean (SD) unless otherwise stated.

**Table 3. Neuroanatomic Variables by Group\***

	Group			
	Concordant (n = 38)	Discordant Affected (n = 15)	Discordant Unaffected (n = 16)	Control (n = 54)
Total thalamus, cm <sup>3</sup>	9.78 (1.18)	10.22 (2.45)	10.26 (1.11)	10.88 (1.18)
Right thalamus, cm <sup>3</sup>	5.04 (0.62)	5.14 (1.25)	5.21 (0.56)	5.51 (0.66)
Left thalamus, cm <sup>3</sup>	4.68 (0.70)	5.03 (1.26)	4.99 (0.69)	5.33 (0.57)
Whole brain, cm <sup>3</sup>	983.82 (83.75)	972.54 (159.01)	990.29 (160.22)	1040.20 (100.69)
Adhesio interthalamica, No. (%) absent	2 (5)	1 (7)	2 (12)	8 (15)

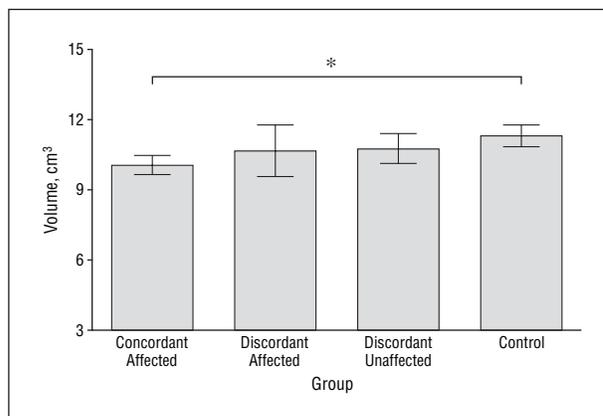
\*Data reflect mean (SD) unless otherwise stated. The sum of right and left thalamus is less than the total thalamus because of the exclusion of midsagittal image sections from this calculation.

Clinical variables of probands from the concordant and discordant groups are summarized in **Table 2**. The 2 groups did not differ significantly in type (typical or atypical) or dose (CPZ equivalents) of antipsychotic treatment, age at first contact with psychiatric services, or positive (SAPS) and negative (SANS) schizophrenic symptom scores at the time of assessment.

### THALAMIC VOLUME

Thalamic volumes are summarized by group in **Table 3** and **Figure 2**. Using left and right thalamic volumes as dependent variables and covarying for age and sex, there was no significant side  $\times$  group interaction ( $F_{3,61} = 1.35, P = .27$ ) but a significant effect of side ( $F_{1,61} = 24.57, P < .001$ ), indicating larger right than left thalamus across groups (see Table 3). Further analyses were thus carried out with total thalamic volume collapsed across hemisphere.<sup>5</sup>

With total thalamic volume as dependent variable and covarying for age and sex, an overall effect of group was observed ( $F_{3,61} = 6.66, P < .001$ ). Post hoc comparisons showed that the concordant group had significantly smaller thalamic volumes than did the control group ( $t_{61} = 4.45, P < .001$ ), while all other pairwise comparisons were nonsignificant after Bonferroni adjustment (all  $P > .03$ ). These results remained essentially unchanged when covarying for whole-brain volume (overall group effect:  $F_{3,61} = 3.54, P = .02$ ; pairwise comparison between concordant and control groups:  $t_{61} = 3.17, P = .002$ ; all other comparisons:  $P > .09$ ).



**Figure 2.** Thalamic volume by group. Bars and limit lines represent age- and sex-adjusted means and 95% confidence intervals, respectively. \* $P < .001$ .

For completeness, group differences were evaluated separately for left and right thalamus. For left thalamus, there was an overall group effect (without whole-brain volume as covariate:  $F_{3,61} = 7.04, P < .001$ ; with whole-brain volume as covariate:  $F_{3,61} = 4.13, P = .01$ ) and a significant pairwise comparison between concordant and control groups (without whole-brain volume:  $t = 4.59, P < .001$ ; all other comparisons,  $P > .05$ ; with whole-brain volume:  $t = 3.49, P = .001$ ; all other comparisons,  $P > .10$ ). For right thalamus, there was an overall group effect (without whole-brain volume as covariate:  $F_{3,61} = 5.25, P = .003$ ; with whole-brain volume as covar-

**Table 4. Intraclass Correlations by Twin Category**

Twin Category	Estimated ICC	95% CI for ICC*
Concordant (19 twin pairs)	0.17	0.00 to 0.80
Discordant (14 twin pairs)	0.00	0.00 to 0.65
Control (27 twin pairs)	0.69	0.66 to 0.95

Twin Category Comparison	Estimated ICC Difference	95% CI for Difference*
Concordant-discordant	0.17 ( <i>P</i> = .56)	-0.45 to 0.65
Concordant-control	-0.52 ( <i>P</i> = .02)	-0.87 to -0.02
Discordant-control	-0.69 ( <i>P</i> = .004)	-0.91 to -0.17

Abbreviations: CI, confidence interval; ICC, intraclass correlation.  
\*Based on 2000 bootstrap simulations.

iate this was reduced to trend level:  $F_{3,61}=2.42$ ,  $P=.08$ ) and a significant pairwise comparison between concordant and control groups (without whole-brain volume:  $t=3.93$ ,  $P<.001$ ; all other comparisons,  $P>.05$ ; with whole-brain volume:  $F_{3,61}=2.59$ ,  $P=.01$ ; all other comparisons,  $P>.16$ ). These results, therefore, replicate the main finding for total thalamus.

Figure 2 suggests the expected linear decrease in thalamic volume from control via discordant to concordant twins. Post hoc analysis showed that this trend was significant ( $t_{61}=3.69$ ,  $P<.001$ ; with whole-brain volume as covariate:  $t_{61}=2.74$ ,  $P=.008$ ).

The groups differed significantly on whole-brain volume when covarying for age and sex ( $F_{3,61}=3.91$ ,  $P=.01$ ). Post hoc analysis showed that concordant twins had significantly smaller volumes than controls ( $t_{61}=3.27$ ,  $P=.002$ ), while all other pairwise comparisons were non-significant after Bonferroni adjustment (all  $P>.04$ ).

#### ICCS OF THALAMIC VOLUME

The ICCs for the concordant, discordant, and control twin categories are shown in **Table 4**. The ICCs were adjusted for age, sex, and whole-brain volume; thus, twin correlations reflect only between-subject differences not due to these variables. The observed ICC twin category differences indicated that controls showed a moderate to large ICC (0.69), concordant pairs showed a small ICC (0.17), and discordant pairs did not exhibit any twin correlation (ICC, 0.00). While the control ICC was statistically different from the discordant pairs' ICC even after adjusting for 3 comparisons, the difference between controls and concordant pairs was reduced to a trend after Bonferroni adjustment. The difference between concordant and discordant pairs was not statistically significant even before adjustment.

#### CLINICAL CORRELATES OF THALAMIC VOLUME

In the concordant group, there were no significant correlations between thalamic volume and SAPS, SANS, or age at first contact with psychiatric service (all  $P>.12$ ), but there was a trend toward a positive relationship with CPZ equivalents ( $P=.06$ ). This trend became clearly non-

significant when whole-brain volume was included as covariate ( $P=.21$ ). There was no difference in thalamic volume between typically and atypically treated concordant probands, with ( $F_{1,16}=0.20$ ,  $P=.66$ ) or without ( $F_{1,16}=0.00$ ,  $P=.97$ ) whole-brain volume as additional covariate.

In the discordant proband group, there were no significant correlations between thalamic volume and SAPS, age at first contact with psychiatric service, or CPZ equivalents (all  $P>.13$ ), but there was a trend for a negative correlation between thalamic volume and SANS ( $P=.05$ ). This correlation became nonsignificant when whole-brain volume was added as covariate ( $P=.54$ ). There was no difference in thalamic volume between typically and atypically treated discordant probands, with ( $F_{1,9}=0.29$ ,  $P=.61$ ) or without ( $F_{1,9}=0.33$ ,  $P=.58$ ) whole-brain volume as covariate.

#### ADHESIO INTERTHALAMICA

There was no significant effect of group on the frequency of the adhesio interthalamica with age and sex used as covariates ( $\chi^2_3=1.35$ ,  $P=.72$ ). When whole-brain volume was included as additional covariate, this result remained essentially unchanged ( $\chi^2_3=1.20$ ,  $P=.75$ ).

#### COMMENT

The key finding from this study is the reduction of thalamic volume in MZ twins concordant for schizophrenia compared with healthy control twins. The differences in thalamus across group were seen in both right and left thalamus, and right thalamus was larger than left thalamus across groups. Right greater than left laterality effects have been reported in previous volumetric MR imaging studies of the human thalamus.<sup>18,21,23,54-58</sup>

The thalamus is an important subcortical structure integrating sensory, motor, and cognitive processes. Reports of hypofunction<sup>59</sup> and abnormal structure or shape<sup>12-15</sup> point to an involvement of this structure in the pathophysiology of schizophrenia.<sup>9,10</sup> Evidence of thalamic volume reductions in recent-onset or drug-naïve schizophrenia patients<sup>13,15</sup> as well as in individuals at high risk for psychosis<sup>60</sup> suggests that these effects are seen before the possible operation of any putative neurodegenerative or illness chronicity-related processes.

These findings suggest that thalamic abnormalities in schizophrenia might be the result of genetic or early environmental factors. Supporting the role of genetic (or familial) factors in thalamic volume reductions, a small number of studies have shown this abnormality in non-schizophrenic family members of people with schizophrenia.<sup>58,60,61</sup> In addition, a recent MR imaging study of families multiply affected with schizophrenia<sup>30</sup> showed that greater genetic risk for schizophrenia was associated with greater thalamic volume reductions.<sup>30</sup>

The present finding of reduced thalamic volume in MZ concordant rather than discordant twins can be integrated with these results. Monozygotic concordant twin pairs are thought to experience greater genetic loading for schizophrenia than either discordant pairs or singletons.<sup>3,6,32</sup> This increased genetic loading may manifest it-

self in thalamic volume reductions that are observed in the MZ concordant group but are not significant in the discordant group. The unaffected co-twins of schizophrenic patients in the MZ discordant group had thalamic volumes intermediate between those of the patients and the controls. The increased variance in the discordant schizophrenic group combined with the relatively small sample size of the 2 discordant groups might have been a reason why these differences did not reach formal levels of statistical significance. However, a post hoc test showed that there was an overall linear trend in thalamic volumes following the pattern of control > discordant nonschizophrenic > discordant schizophrenic > concordant, supporting the model outlined herein.

The thalamic volume reduction in the concordant group showed neuroanatomic specificity, given that the group differences were maintained when whole-brain volume was used as a covariate. This important finding demonstrates that thalamic volume reductions occurred over and above possible effects of generalized brain atrophy and implicates the thalamus as a specific region in the pathophysiology of schizophrenia.

Research into cortical structure and function in twins with schizophrenia has shown that the prefrontal cortex (and its behavioral correlates, eg, working memory) is likely to be under substantial genetic control.<sup>4,62</sup> Although specific behavioral tests of thalamic function are not available, the intense connections between the thalamus and the prefrontal cortex support the role of the thalamus in genetically mediated corticosubcortical circuitry impairments in schizophrenia. The subnucleus of the thalamus that may experience the most significant volume reduction, ie, the mediodorsal nucleus,<sup>23,56,59</sup> is known to have substantial connections with the prefrontal cortex.

It is instructive to compare the present pattern of findings with findings in other brain structures that have been investigated in schizophrenic patients and their relatives. For example, medial temporal lobe structures do not appear to consistently show evidence of strong genetic influences in schizophrenia.<sup>5,6,52</sup> A recent study<sup>7</sup> of MZ and dizygotic twins discordant for schizophrenia showed that the nonschizophrenic members of these 2 types of twin pairs did not differ from each other. This suggests that the increased genetic vulnerability in the MZ co-twins compared with dizygotic co-twins did not significantly affect hippocampal volume. Instead, environmental risk factors such as fetal hypoxia may be of importance,<sup>63</sup> and illness-related changes during the prodromal phase appear to be most pronounced in temporal lobe structures.<sup>64</sup> In contrast, the shape of the lateral ventricle, an area bordering the superior aspect of the thalamus, appears to be under substantial genetic control in healthy and discordant twins.<sup>65</sup>

Intraclass correlations showed significant twin correlations only in the control group, compatible with the known heritability of human brain anatomy.<sup>66-68</sup> The ICCs were significantly stronger in controls than discordant pairs, who did not show significant twin correlations in thalamic volume. It is possible that the expression of the schizophrenic pathology in one member of these twin pairs but not in the other member may have caused the erosion of twin pair similarity in thalamic volume.<sup>5,69</sup> Con-

cordant twins' ICC fell between the control and discordant ICCs but was not significantly different from zero. This finding suggests the operation of additional nongenetic or illness-related factors in this group. However, samples of dizygotic twins are needed to address this question more comprehensively.

The groups did not differ with regard to the presence of the adhesio interthalamica. Previous studies have remained equivocal concerning possible anatomic abnormalities of this structure in schizophrenia.<sup>36-40</sup> Our data suggest that the absence of the adhesio interthalamica is unlikely to be a crucial factor in the pathophysiology of schizophrenia. This conclusion is strengthened by the observation of a significant effect for thalamic volume (including the adhesio interthalamica) in the concordant group.

Several limitations of this study should be noted. First, we did not investigate thalamic subnuclei. Given the anatomic and functional heterogeneity of the thalamus, further investigation of subnuclei is called for. Second, most patients in this study were pharmacologically treated at the time of assessment. This fact represents a limitation of this and many MR imaging studies in schizophrenia given the possible operation of antipsychotic treatment effects on gray matter volumes (for review see Scherk and Falkai<sup>70</sup>). However, in this context it is important to remember that the 2 patient samples in this study (concordant and discordant affected twins) did not differ in terms of medication type or CPZ equivalents. Third, the patients in this study had all been ill for a number of years, introducing possible effects of illness chronicity on brain structure (however, see Weinberger and McClure<sup>71</sup>). Finally, 2 MR scanners were used in this study, introducing possible confounds. However, the 2 scanners were identical and used identical scan protocols. Furthermore, comparable numbers of participants from each twin category were imaged at each site and there were no differences in thalamic volume between participants imaged at the 2 sites or interactions between group and site.

To conclude, thalamic abnormalities are likely to play a role in the pathophysiology of schizophrenia<sup>10</sup>; this study suggests that these abnormalities are to a significant extent genetically mediated. Given the role of the thalamus as a primary relay station within the brain, abnormalities in this structure could be causally related to the manifold sensory, cognitive, and emotional changes seen in people with schizophrenia. Further work is needed to address the precise neuropathological and molecular genetic substrates of the macroscopic structural abnormalities seen in schizophrenia.

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