Regional specificity of thalamic volume deficits in male adolescents with early-onset psychosis

Joost Janssen, Yasser Aleman-Gomez, Santiago Reig, Hugo G. Schnack, Mara Parellada, Montserrat Graell, Carmen Moreno, Dolores Moreno, J. M. Mateos-Perez, J. M. Udias, Celso Arango and Manuel Desco

Background
Thalamic volume deficits are associated with psychosis but it is unclear whether the volume reduction is uniformly distributed or whether it is more severe in particular thalamic regions.

Aims
To quantify whole and regional thalamic volume in males with early-onset psychosis and healthy male controls.

Method
Brain scans were obtained for 80 adolescents: 46 individuals with early-onset psychosis with a duration of positive symptoms less than 6 months and 34 healthy controls. All participants were younger than 19 years. Total thalamic volumes were assessed using FreeSurfer and FSL-FIRST.

Results
Total thalamic volume was smaller in participants with early-onset psychosis relative to controls. Regional thalamic volume reduction was most significant in the right anterior mediodorsal area and pulvinar.

Conclusions
In males with minimally treated early-onset psychosis, thalamic volume deficits may be more pronounced in the anterior mediodorsal and posterior pulvinar regions, adding strength to findings from post-mortem studies in adults with psychosis.

Declaration of interest
None.

Participants
The participants were 80 males: 46 with first-episode psychosis (psychosis group) and 34 healthy controls (control group). The psychosis group were recruited from the two child and adolescent psychiatry in-patient units in Madrid (Hospital General Universitario Gregorio Marañon and Hospital Universitario Infantil Niño Jesús). These two units serve a population of approximately five million people. All males consecutively seen at these facilities between April 2002 and November 2005 who fulfilled the inclusion criteria described below were invited to participate in the study. At baseline, 58 individuals were eligible for the study. Seven of these refused the magnetic resonance imaging (MRI) scan because of fear. Furthermore, two individuals were excluded because of insufficient image quality for neuroimaging analyses. At follow-up, three participants were excluded because they no longer fulfilled diagnostic inclusion criteria for psychosis (see Clinical assessment), thus leaving a sample of 46 individuals. The inclusion criteria for the psychosis group were: male, presence of positive psychotic symptoms within a DSM-IV13 psychotic disorder (including schizophrenia, bipolar I disorder, schizoaffective disorder, schizophreniform disorder, delusional disorder, shared psychotic disorder, brief psychotic disorder, psychotic disorder not otherwise specified (NOS), major depression with psychotic features) before the age of 18 years and a maximum 6-month history of positive symptomatology at the time of enrolment. Exclusion criteria were: presence of other concomitant Axis I disorder at the time of evaluation that might account for the psychotic symptoms (such as autism-spectrum disorders, post-traumatic stress disorder or acute stress disorder), mental retardation per the DSM-IV criteria, including not only an IQ score below 70 but also impaired functioning, neurological

Chronic adult-onset schizophrenia is associated with smaller whole thalamic volume1 and post-mortem findings point to selective thalamic deficits in the anterior and mediodorsal nuclei and the pulvinar.2 The thalamus is a relay station that contains abundant efferent and afferent connections to the cortex. Therefore, structural alterations to the thalamus can cause a disruption in the thalamic–cortical–thalamic circuitry, leading to the typical psychosis-like cognitive and clinical symptoms.3 A recent meta-analysis concluded that few studies investigated thalamic deficits in individuals with first-episode psychosis.1 Given that antipsychotic medication may alter thalamic volume4 it makes sense to measure thalamic volume in individuals with first-episode psychosis, particularly in adolescents with a short duration of illness and low doses of antipsychotic medication. Furthermore, studying these early-onset groups provides information about whether the thalamic abnormalities seen in adolescents are consistent with or different from the ‘adult’ expression of these disorders.5 Early-onset psychosis will convert into different diagnostic categories, such as adolescent-onset schizophrenia and early-onset bipolar I disorder, over time. These diagnoses may share some degree of underlying pathology as evidenced by common volume deficits in cortical structures such as the insular, anterior cingulate and orbitofrontal cortex6 and subcortical structures such as the hippocampus.7 A smaller thalamic volume has been found in early-onset schizophrenia8 although the results for early-onset bipolar disorder are inconsistent.9,10 In adolescents with psychosis it is unclear whether volumetric thalamic abnormalities are specific to particular thalamic nuclei as opposed to affecting the entire thalamus uniformly. In this study we examined total and regional thalamus volume between male adolescents (younger than 18 years of age) with early-onset first-episode psychosis (duration of positive symptoms less than 6 months) and healthy male controls. This study sample eliminates the potentially confounding effects of gender.
disorders, and a history of head trauma with loss of consciousness. We excluded individuals that fulfilled criteria for presence of substance misuse or dependence at baseline. All potential participants had a careful assessment of drug-use history and drug urine analysis at baseline. If the assessment was positive individuals were included in the study only if positive symptoms persisted 14 days after a negative urine analysis. Six individuals had a history of cannabis use at baseline, but the distribution of their thalamic volumes within the psychosis group was even (not biased to smaller or larger values). Urine test analyses were repeated at various time points during a 2-year clinical follow-up. All participants in the psychosis group had a thorough medical examination as part of our standard clinical guidelines protocol.

The control group consisted of 34 healthy males recruited from the same schools and residential areas as the psychosis group. The inclusion criteria for controls were similar age and coming from the same geographical areas as those in the psychosis group, no current and previous psychiatric disorder as measured by the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL), and no neurological disorders, or head trauma or mental retardation (per the DSM-IV criteria). Further information regarding the inclusion and exclusion criteria can be found in Castro-Fornieles et al.15

The study was approved by the institutional review boards of both participating clinical centres. After the study was thoroughly explained to the participants, written informed consent was obtained from both the legal representatives and the individuals. All of the participants met MRI safety criteria.

Clinical assessment

Diagnosis was made according to the DSM-IV criteria using the K-SADS-PL. Clinical diagnostic interviews were performed during the initial hospitalisation by four experienced psychiatrists trained in this interview. Diagnostic consensus was reached in cases where presence or absence of psychiatric diagnoses was in doubt. Psychotic symptoms were assessed using the validated Spanish version of the Positive and Negative Syndrome Scale (PANSS).16 Four psychiatrists participated in the PANSS rating. Single-rater intraclass correlation coefficients for the PANSS ratings were calculated separately for the fixed set of four psychiatrists by comparing each psychiatrist with a gold standard on a randomly selected sample of ten participants.17 Intraclass correlation coefficients ranged from 0.72 to 0.96. Given that among early-onset first-episode psychoses most diagnostic changes occur during the first year after onset of positive symptoms, we used a 2-year follow-up diagnosis to ensure diagnostic reliability.18 At baseline, 9 participants had schizophrenia, 11 had bipolar I disorder, and 29 had another psychotic disorder. At the 2-year follow-up, 13 participants had schizophrenia, 17 had bipolar I disorder and 16 had another psychotic disorder (5 individuals with schizoaffective disorder, 2 with schizophreniaiform disorder, 1 with major depression with psychotic features, 6 with psychotic disorder NOS and 2 with brief psychotic disorder). Three participants were excluded from the study because they did not fulfill K-SADS-PL criteria for psychosis at the 2-year follow-up, leaving a total sample size of 46 individuals in the psychosis group. The parental socioeconomic status was measured using the Hollingshead−Redlich scale.19 Assessment of handedness was performed as described in Castro-Fornieles.15

The age at onset of psychosis was defined as the age at which the participant experienced positive psychotic symptoms for the first time (delusions or hallucinations of any kind that qualify for a DSM-IV diagnosis). Information about age at onset was assessed using the K-SADS-PL interview by asking the individual and their parents/legal guardians retrospectively about the first appearance of delusions and/or hallucinations. The individual and parents/legal guardians were interviewed separately. If possible, other relatives that were not present at the interview were consulted for confirmation of the gathered information about age at onset. Duration of psychosis was defined as the time difference between age at onset of psychosis and scan acquisition. Duration of treatment was defined as the time between initiation of antipsychotic treatment and scan acquisition.

Medication

At the time of the baseline assessment, all of those in the psychosis group were on antipsychotic medication. In total 80% (n = 39) of the sample (n = 49) were receiving only one antipsychotic, and the remaining 20% (n = 10) were receiving two antipsychotics simultaneously. With the exception of two individuals, the group were receiving a second-generation antipsychotic. Distribution of the antipsychotic treatment was as follows: 51% (n = 25) risperidone, 33% (n = 16) quetiapine, 29% (n = 14) olanzapine, 4% (n = 2) ziprasidone, and 4% (n = 2) haloperidol. The chlorpromazine equivalent dose was calculated from the dose of antipsychotics received (Table 1).20 The mean daily antipsychotic dose in chlorpromazine equivalents was 282.4 mg (s.d. = 194.7).

MRI Acquisition

All participants were scanned on the same 1.5 T Philips MRI scanner (Philips Gyroscan; Philips Medical Systems, Best, The Netherlands). Two magnetic resonance sequences were applied to all the participants: a T1-weighted, three-dimensional, gradient echo scan with 1.5 mm slice thickness (echo time (TE) = 4.6 ms, repetition time (TR) = 9.3 ms, flip angle 30°, field of view (FOV) = 256 mm, and in-plane voxel size 0.98 × 0.98 mm²) and a T2-weighted turbo spin echo scan with 3.5 mm slice thickness (turbo factor 15, TE = 120 ms, TR = 5809 ms, FOV = 256 mm, and in-plane voxel size 0.98 × 0.98 mm²). Both T1- and T2-weighted images were used for clinical neurodiagnostic evaluation by an independent neuroradiologist. No participants showed clinically significant brain pathology.

Image analysis

Intracranial volume assessment

The assessment of intracranial volume has been described before.6 Brain-extracted images were obtained using the Fmrib Software Library (FSL)-Brain Extraction Tool (version 2) algorithm,21 and then manually edited to remove remaining non-intracranial tissue voxels using in-house Unix software.22

Whole thalamic volume assessment

Assessment of thalamic volume was performed by using the FreeSurfer (v4.4.0, http://surfer.nmr.mgh.harvard.edu) package.23 To confirm that our volume findings were independent of the preprocessing method, automated assessment of thalamus volume was also performed using the FSL-FIRST (v4.1.4) package.24 In the current study we focus on the volumes obtained simultaneously. With the exception of two individuals, the group were receiving a second-generation antipsychotic. Distribution of the antipsychotic treatment was as follows: 51% (n = 25) risperidone, 33% (n = 16) quetiapine, 29% (n = 14) olanzapine, 4% (n = 2) ziprasidone, and 4% (n = 2) haloperidol. The chlorpromazine equivalent dose was calculated from the dose of antipsychotics received (Table 1).20 The mean daily antipsychotic dose in chlorpromazine equivalents was 282.4 mg (s.d. = 194.7).

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validated through comparison with manual tracing and has been used before in studies assessing thalamic volume.\textsuperscript{23} Automatic segmentation by FreeSurfer is done by automatic labelling of subcortical tissue classes using an atlas-based Bayesian segmentation procedure. FreeSurfer comes with a participant-independent probabilistic atlas in Talairach space that was pre-computed from a training set of individuals whose brains were manually labelled. FreeSurfer image preprocessing steps included an affine registration with Talairach space, intensity normalisation, skull strip and a high dimensional non-linear volumetric alignment to the probabilistic atlas in Talairach space. Importantly, as normalisation into Talairach space is an internal component of the FreeSurfer pipeline, the thalamic segmentations are returned in the native space of the individual. FreeSurfer calculated the probability of a class at each voxel location as the probability that the given class appeared at that location in the training set times the likelihood of getting the participant-specific intensity value from that class. An initial segmentation was generated by assigning each point to the class for which the above probability was greatest. The neighbourhood function was then used to recalculate the class probabilities and re-segment the data using the new class probabilities. This procedure was repeated until the result converged.\textsuperscript{23} FreeSurfer assessment of thalamus volume follows neuroanatomical criteria described in Frazier et al.\textsuperscript{7} Briefly, the criteria state that assessment includes all thalamic nuclei except for lateral and medial geniculate bodies. The medial border is the third ventricle, cerebrospinal fluid (CSF) or the cerebral exterior midline. The lateral border is the internal capsule. The anterior border is the interventricular foramen (foramen of Monro), and posteriorly the thalamus overlaps the midbrain and is bordered by CSF. The inferior border is the hypothalamic fissure, or the hippocampus in the most posterior extent. Superiorly the thalamus assessment is bordered by the transverse cerebral fissure, lateral ventricle, white matter, or in the anterior portion, the caudate. All segmentations were found accurate after visual inspection.

Regional thalamic volume assessment

Regional thalamic volume was assessed by generating thalamic surfaces based on Spherical Harmonics Decomposition Point Distribution Models (SPHARM-PDM)\textsuperscript{(v1.8, www.nitrc.org/projects/\textbackslash spharm-pdm).\textsuperscript{25,26} This method has been used before in studies investigating regional subcortical volume deficits in people with late-life depression, Alzheimer's disease, schizophrenia and individuals at increased genetic risk for schizophrenia.\textsuperscript{27-30} The purposes of SPHARM-PDM are: to establish a correspondence between the thalamic surfaces of individuals in an unbiased way, i.e. without using a template (other than for alignment and flipping); to provide a uniform sampling across the surfaces, such that subsequent statistical tests are valid; and to smooth the surfaces by removing high-frequency contributions. Using the method, three parameters are defined by the user: a voxel resolution, SPHARM degree and subdivision level. For the current study an isotropic voxel resolution of 0.5 mm, a SPHARM-PDM degree of 15, and a subdivision level of 10 was chosen. To ensure that our choice for the three parameters was adequate we investigated the effect of modifications of these three parameters on the SPHARM-PDM-based thalamus surface; this is detailed in online supplement 2.

The inputs for the method were the thalamus segmentations generated by FreeSurfer. The pipeline consisted of the following steps: first, the three-dimensional thalamus masks were resampled to an isotropic voxel resolution and processed to fill any isolated empty voxels inside the mask. These masks were then converted to boundary surface meshes, and a spherical parameterisation was computed from the mesh using an area-preserving, distortion-minimising spherical mapping.\textsuperscript{25} Second, the surfaces of the masks were represented on the sphere in terms of SPHARM-based shape descriptions.\textsuperscript{26} These shape descriptions characterise the surfaces by sets of coefficients weighting the SPHARM basis functions, i.e. the SPHARM coefficients, up to a certain SPHARM degree. Using the first-order ellipsoid from the SPHARM coefficients, the spherical parameterisations of all participants were aligned to establish correspondence across the surfaces. This alignment was achieved by rotation of the parameterisation, such that the spherical equator, 0\degree and 90\degree longitudes coincide with those of the first-order ellipsoid. However, the first-order ellipsoid can be flipped along any of its axes with the same result. We therefore used a 'flip' template (the first surface of our sample, described by SPHARM coefficients) to test all possible flips along the first-order ellipsoid axis and select the one whose reconstruction had minimal distance to the 'flip' template. Third, the SPHARM-based surfaces of all participants were subdivided into an equal number of surface points (SPHARM-PDM) via an icosahedron subdivision level. Although each surface point has a one-to-one correspondence across participants, the surfaces are in the native image space. Therefore, the surfaces must all be aligned to a common space prior to investigating any group differences. To achieve this, a mean thalamus surface computed over all participant's first-order ellipsoid-aligned thalamus surfaces was calculated. Thereafter the first-order ellipsoid-aligned SPHARM-PDM-based thalamus surfaces were aligned to the mean surface using Procrustes alignment (translation and rotation to minimise least-square residuals of corresponding three-dimensional points in the image).\textsuperscript{31} Finally, for the statistical analysis a mean SPHARM-PDM-based thalamic surface was estimated from the Procrustes aligned surfaces for each group separately.

Statistical analyses

Statistical analyses examined whether (a) demographic data, (b) intracranial volume, (c) total thalamus volume and (d) distances between the average thalamic surfaces were different between the psychosis group and the control group. Comparison four was performed on a point-by-point basis across the entire thalamic surface to address the specificity of regional thalamic volume changes in early-onset psychosis.

Demographic and clinical data

To test for group differences in demographic data, the Student's t-test was used for the continuous variables and chi-square for discrete categorical variables.

Group-wise analysis of whole thalamic volume

To test whether whole thalamic volume reductions were associated with early-onset psychosis, we used the general linear model with diagnostic group (psychosis group, control group) as the independent variable. To test whether whole thalamic volume reductions were associated with schizophrenia or bipolar disorder, we used the general linear model with diagnostic group (schizophrenia, bipolar disorder) as the independent variable. Left and right thalamic volumes were included as repeated measures to evaluate possible interactions between diagnosis and hemisphere. Intracranial volume and age were included as covariates in the analyses as they are known to be related to structural brain measures. Chlorpromazine equivalent dose was examined as a potential covariate but not included because of a lack of significance, i.e. it did not correlate with whole or regional
Intracranial volumes for each group are shown in Table 2. The analyses involved MANCOVA outputs two results that are corrected for multiple comparisons, false discovery rate (FDR with 

correction for multiple comparisons was necessary. Shape-

Intracranial volume and total left and right thalamic volumes of the adolescent males with early-onset psychosis and controls

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Psychosis group (n = 46)</th>
<th>Control group (n = 34)</th>
<th>t-test</th>
<th>x²</th>
<th>P</th>
</tr>
</thead>
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<tr>
<td>Age, years: mean (s.d.) range</td>
<td>15.8 (1.5) 12–18</td>
<td>15.1 (1.7) 12–17</td>
<td>–2.00</td>
<td>1.77</td>
<td>0.05</td>
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<td>Handedness (right/left/ambidexter): n</td>
<td>40/4/0</td>
<td>26/4/1</td>
<td></td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>Level of education, years</td>
<td>8.5</td>
<td>8.5</td>
<td>–0.60</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Parental socioeconomic status: mean score</td>
<td>2.7</td>
<td>2.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of psychosis: years: mean (s.d.) range</td>
<td>15.5 (1.5) 10–17</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of psychosis: weeks: mean (s.d.) range</td>
<td>12.9 (10.4) 0–24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of treatment: weeks: mean (s.d.) range</td>
<td>2.2 (2.0) 0–11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine equivalents, mg: mean (s.d.)</td>
<td>282.4 (194.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive and Negative Syndrome Scale, mean (s.d.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>25.7 (5.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>22.7 (6.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General psychopathology</td>
<td>48.7 (9.9)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

a. Missing data for five participants.
b. Parental socioeconomic status was measured using the Hollingshead–Redlich scale.
c. Age at onset of psychosis was defined as the age at which positive symptoms appeared for the first time.
d. The duration of psychosis was defined as the time between first appearance of positive symptoms and scan acquisition. Missing data for one participant.
e. The duration of treatment was defined as the time between start of antipsychotic treatment and scan acquisition.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Psychosis group (n = 46)</th>
<th>Control group (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial volume, cc</td>
<td>1517.7 (112.2)</td>
<td>1511.8 (115.0)</td>
</tr>
<tr>
<td>Thalamic volume, cc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>8.5 (0.8)</td>
<td>8.7 (0.8)</td>
</tr>
<tr>
<td>Right</td>
<td>8.0 (0.7)</td>
<td>8.3 (0.8)</td>
</tr>
</tbody>
</table>

Thalamic deficits and early-onset psychosis

Group-wise analysis of regional thalamus volume

To test for regional thalamic volume differences, shapeAnalysisMANCOVA (version 1.0) (http://www.nitrc.org/projects/shape_mancova) was used. ShapeAnalysisMANCOVA uses a permutation-based approach to compute the local significance values. At each permutation a general linear model-based MANCOVA metric (the Hotelling trace coefficient) is computed for every surface (x,y,z) coordinate, which constitutes the local statistic value of the group difference. The distributions sampled via the permutation approach yield the local P-values. This non-parametric approach allows testing for significance even if the surface coordinates are not normally distributed. Intracranial volume and age were included as covariates in the tests. There were 1002 surface points. Owing to the 1002 comparisons, a correction for multiple comparisons was necessary. ShapeAnalysisMANCOVA outputs two results that are corrected for multiple comparisons, false discovery rate (FDR with q = 0.05) corrected results, and Bonferroni corrected results. The magnitude in millimetres and direction (i.e. surface inflation or deflation) of the distances before and after correction for multiple comparisons were mapped onto the averaged left and right thalamic surface models of the entire group. To assess whether thalamic measures were related to clinical variables, correlation coefficients were computed.

Results

Demographic and clinical data

There were no significant group differences in handedness, years of education, and parental socioeconomic status (Table 1). Age was slightly older in the psychosis group. Intracranial volumes were not significantly different in the psychosis group compared with the control group (t = –0.56 (d.f. = 81), P = 0.58). Mean intracranial volumes for each group are shown in Table 2.

Whole thalamic volume

A main effect of diagnosis was observed for overall thalamic volumes after covarying for intracranial volume and age (F(1,76) = 5.68, P = 0.02, d = –0.35). No significant interactions with hemisphere were observed. That is, the psychosis group showed significant thalamic volume reductions in both the left and right hemispheres after correction for age and intracranial volume (left: F(1,76) = 3.78, P = 0.05, d = –0.29, right: F(1,76) = 6.57, P = 0.01, d = –0.41) (Fig. 1).

Comparing the schizophrenia and bipolar subgroups for overall thalamic volumes while covarying for intracranial volume and age gave no main effect of diagnosis (F(1,26) = 0.64, P = 0.43, d = –0.20) (Fig. 2).

Regional thalamic volume

Before correction for multiple comparisons, widespread bilateral regional thalamic volume differences were observed (online Fig. D54). Only right-sided regional differences survived correction for multiple comparisons (online Fig. D55). Three clusters comprising a total of 24 surface points showed a significant surface deflation in the psychosis group that ranged from 0.39 to 1.05 mm after FDR correction. Mean surface deflation over the three clusters was 0.66 mm (s.d. = 0.20). Comparing the schizophrenia and bipolar subgroups revealed no significant differences in regional thalamic volumes after correction for multiple comparisons.

Correlation with clinical variables

Within the psychosis group, both total and regional thalamic measures were not significantly related to age at onset of psychosis and years of education, and parental socioeconomic status (Table 1).
psychosis, duration of psychosis, duration of treatment and PANSS scores.

**Discussion**

The main findings of this study were, first, that male adolescents with early-onset first-episode psychosis showed a bilateral whole thalamus volumetric deficit. Second, the psychosis group demonstrated statistically significant right-sided regional thalamic volume differences in areas corresponding to the anterior mediodorsal and pulvinar nuclei when compared with the control group.

**Whole thalamus volume**

Our findings are congruent with previous MRI reports of smaller total thalamus volume in adolescents with early-onset schizophrenia.5,8,9,36 For early-onset bipolar disorder prior findings are inconsistent.5,9,37 The present study contrasts with previous early-onset bipolar disorder reports in that those studies examined mixed diagnostic samples including individuals with non-psychotic bipolar disorder and individuals with a longer duration of illness and extensive medicinal treatment, including lithium. These differences, in particular the prolonged use of medication, may explain the discrepancy in results because exposure to typical and atypical antipsychotics was shown to have rapid opposite effects on thalamic volume in adults with first-episode psychosis and schizophrenia and cerebral biochemical changes were found after treatment with lithium and risperidone in early-onset bipolar disorder.10,38 These results indicate that prolonged medication use can change cerebral structure. The current results denote that volumetric thalamic deficits are present shortly after symptom onset in minimally treated adolescents with psychosis who go on to develop schizophrenia and bipolar I disorder.

Although there was no interaction between diagnosis and hemisphere, the effect size of the left side was lower compared with the right side. The effect of limited sample sizes on detection of subtle thalamic volume differences has been noted and may also be a plausible explanation for the difference in effect sizes.2 A role for brain asymmetry in the aetiology of psychosis has been suggested but larger left than right thalamus volumes and the reverse have been reported, making it difficult to conclude whether lateralised thalamus volume deficits have any role in this pathology.4,39,40

**Regional thalamus volume**

The surface-based analysis showed statistically significant regional volume differences in the anterior mediodorsal and pulvinar regions between those in the psychosis group and the control group. The psychosis group showed surface deflation relative to the control group in these areas, which indicates a smaller volume. Structural abnormalities in these regions, including reduced volume, have been reported in post-mortem and in vivo MRI studies in medicated and medication-naïve adults with first-episode psychosis and schizophrenia.41,42 As can be seen in online Fig. DS1, the statistically uncorrected maps indicated widespread bilateral differences between the psychosis group and the control group, including anterior and pulvinar regions. These results must, however, be interpreted with caution as they are not appropriately corrected for multiple comparisons.

**Anterior mediodorsal thalamic region and pulvinar**

The thalamus is an important hub in the communication network between distinct associative cortical areas. With regard to psychosis, the anterior mediodorsal and pulvinar regions combined occupy approximately one-third of the total thalamus...
volume and both anterior and posterior thalamic regions have abundant reciprocal connections with the prefrontal, temporal, parieto-occipital and the entorhinal cortex. Functional and structural prefrontal impairments are hallmark deficits of psychosis. These deficits may be associated with the regional structural thalamic impairments seen in the current study. In an explorative analysis we found significantly smaller prefrontal cortex volume in individuals with early-onset psychosis when compared with controls, although prefrontal cortex volume and thalamus volume were not correlated (results not shown). A relationship between prefrontal structural impairment and thalamic impairment thus remains speculative but evidence in favour of such a relationship is coming from studies measuring the integrity of prefrontothalamic white matter connections using diffusion tensor imaging. These studies show that smaller volume of prefrontal grey matter structures is associated with deficits of the adjoining corticothalamic white matter tracts in adolescents with first-episode schizophrenia. Furthermore, changes in prefrontal dopaminergic neurotransmission are marked in individuals with psychosis and recent studies in humans and non-human primates have shown that the anterior mediodorsal area is a thalamic region with a particularly high level of dopaminergic innervation. Dopaminergic projections to the thalamus and prefrontal cortex have the same origin and the thalamic and prefrontal regions that receive these projections are highly reciprocally connected. Speculatively, alterations in prefrontal dopaminergic neurotransmission may thus influence dopaminergic receptivity in the thalamic anterior mediodorsal region that could lead to impairment of corticothalamic circuits in individuals with psychosis. Thalamic structural abnormalities in adolescents with early-onset psychosis, together with findings of smaller thalamic volume in young individuals with an increased genetic risk for psychosis, suggest that thalamic volumetric deficits are a vulnerability marker for the disease. This interpretation is supported by longitudinal studies that have reported baseline thalamic volume deficits to be non-progressive, although others have not replicated this. In the current study, the reported effect sizes for whole thalamic volume reduction are small to moderate (Cohen’s d = 0.3 to −0.4). These effect sizes are comparable with previous meta-analytically estimated effect sizes for reduction of thalamus and hippocampal volume but considerably lower than effect sizes of increased lateral ventricle volume (d = 0.7) in adults with first-episode and chronic schizophrenia. The cross-sectional design of the current study impedes an interpretation as to whether thalamic volume deficits represent increased sensitivity for psychosis or whether the deficits are a consequence of psychosis or related variables.

Regarding the effect of patient subgroups, we know of only two prior studies that compared volume of subcortical brain structures between youths with early-onset bipolar disorder, schizophrenia and healthy controls. Frazier et al. reported a smaller right-sided thalamic volume in the schizophrenia group whereas the other study did not find a group difference in thalamic volume. In the current study no group differences were found between the bipolar and schizophrenia subgroups. Recent and older meta-analyses indicate a modest effect size (Cohen’s d = 0.4) for thalamic volume reduction in schizophrenia. Therefore the reduced sample size when comparing patients only is too small to detect differences of d = 0.4 with high statistical power.

Limitations
There are several limitations to this study. First, we did not have manual tracings of the thalamus to use as a gold standard in order to estimate the accuracy of the automated segmentations. However, volume differences between groups were confirmed by two different automated methods, thus strengthening the reliability of our findings. Second, the patient subgroups comparison suffers from insufficient statistical power because of the small sample sizes. Third, post-mortem studies are necessary in relating markers to the underlying disease process and the ultimate proof can only be provided by pathological validation of these markers.

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References


**Thalamic volume assessment and results using FSL-FIRST**

Whole thalamus volume assessment

Automated assessment of total thalamus volume was performed twice; once using FreeSurfer and once using the FSL-FIRST (v4.1.4) package. Thalamus segmentation using FreeSurfer and FSL-FIRST has been validated through comparison with manual tracing. Automatic segmentation by FreeSurfer is done by automatic labelling of subcortical tissue classes using an atlas-based Bayesian segmentation procedure. FreeSurfer comes with a subject-independent probabilistic atlas in Talairach space that was pre-computed from a training set of individuals whose brains were manually labelled. FreeSurfer image preprocessing steps included an affine registration with Talairach space, intensity normalisation, skull strip and a high dimensional non-linear volumetric alignment to the probabilistic atlas in Talairach space. FreeSurfer calculated the probability of a class at each voxel location as the probability that the given class appeared at that location in the training set and the likelihood of getting the subject-specific intensity value from that class. An initial segmentation was generated by assigning each point to the class for which the above probability was greatest. The neighbourhood function was then used to recalculate the class probabilities and resegment the data using the new class probabilities. This procedure was repeated until the result converged.\(^{53}\) The FSL-FIRST method is a probabilistic adaptation of the active appearance model.\(^ {54}\) The method is informed by the shape and intensity variations of a structure from a training set for the purpose of automatically segmenting the structure. A multivariate Gaussian model of vertex location and intensity variation is used, and is based on having point correspondence across individuals (same number and labelling of vertices across individuals). The necessary correspondence is imposed during the parameterisation of the labelled images with a deformable model. The model is fit to new images by maximising the posterior probability of shape given the observed intensities. All segmentations were found to be accurate after visual inspection.

**Whole thalamus volume analysis from FSL-FIRST**

A main effect of diagnosis was observed for overall thalamic volumes after covarying for intracranial volume and age \(F(1,76) = 5.32, P = 0.02, d = 0.35\). No significant interactions with hemisphere were observed. That is, after correction for intracranial volume and age, individuals in the psychosis group showed a trend-level thalamic volume reduction in the left and a significant reduction in the right hemisphere (left: \(F(1,76) = 3.32, P = 0.07, d = 0.29\), right: \(F(1,76) = 7.43, P = 0.008, d = 0.46\)). See Figs DS1 and DS2.

**Additional references**


Online supplement 2

**Determination of an adequate combination of parameters for generating spherical harmonics (SPHARM)-based thalamic surfaces**

The goal was to find an adequate combination of the three parameters that are chosen by the user (voxel resolution, SPHARM degree and subdivision level) for calculating the SPHARM-based thalamic surfaces.

The SPHARM degree determines the number of spherical basis functions that are needed to express the initial (not SPHARM-based) boundary surface meshes. If the SPHARM degree is increased, a higher number of basis functions will be used and the surface representation will be sharper. If the SPHARM degree decreases, a smoother surface representation will be obtained. The subdivision level represents the number of points of the spherical grid for the surface spherical mapping. If the subdivision level is increased, the SPHARM-based surface will have a higher number of points allowing for a better spatial representation of the initial boundary surface. In case of the thalamus, which has a smooth surface, a high subdivision level is not mandatory.

Previous studies using SPHARM to assess the shape of subcortical structures have suggested a SPHARM degree ranging from 12 to 15 and a subdivision level ranging from 10 to 20 as adequate. To find an adequate combination of the three parameters for the current study, SPHARM-based surfaces were created using different parameter combinations within the proposed ranges. FreeSurfer assessments of the thalamus were resampled to three voxel resolutions (0.5, 0.75 and 1 mm). Five SPHARM degrees (7, 12, 13, 14, 15) and three subdivision levels (10, 15, 20) were combined with the three-voxel resolution parameters. The SPHARM-based surfaces were generated in native space for each possible combination of the voxel resolution, SPHARM degree and subdivision-level parameters. For every parameter combination, the absolute distance in millimetres between the SPHARM-based surface and the initial (not SPHARM) surface was computed for each surface element. The distance was calculated as the length of the normal vector at each surface element from the SPHARM-based surface until its corresponding intersection point with the initial (not SPHARM) surface. A shorter distance reflects a good approximation of the initial (not SPHARM) surface by the SPHARM-based surface. For each parameter combination, the distance was averaged over all surface elements and over all 80 participants. This mean distance was then outlined against all combinations of the parameters (Fig. DS3).

**Additional references**


Fig. DS3  Graphs (with error bars indicating the standard deviation) showing that increasing the SPHARM degree from 7 to 12 demonstrably shortens the mean distance, suggesting that increasing the number of SPHARM basis functions will result in a better approximation of the initial (not SPHARM) surface. As can be seen, changing the voxel resolution and the subdivision level did not strongly affect the mean distance. Based on these findings, a voxel resolution of 0.5 \times 0.5 \times 0.5 \text{ mm}, SPHARM degree of 15, and a subdivision level of 10 was found to be an adequate combination of parameters for generating the SPHARM-based surfaces.
Fig. DS4  Left and right thalamus regional volumetric differences before correction for multiple comparisons between 34 adolescent male controls and 46 adolescent males with early-onset psychosis.

(a) the left superior and frontal view of the average thalamus surface of all controls and individuals in the psychosis group with a superimposed distance map. The colour bars show the magnitude and direction of the differences (distance in mm) between the average surfaces of each group obtained by SPHARM-PDM. A positive distance means that the average surface of the individuals in the early-onset psychosis group represents contraction with respect to the average surface of the controls (i.e. surface deflation of those in psychosis group) and vice versa. (b) as for (a) but for the right thalamus surface. RAW denotes uncorrected.

Fig. DS5  Right-sided thalamus regional volumetric differences after correction for multiple comparisons between 34 adolescent male controls and 46 adolescent males with early-onset psychosis.

(a) the right superior and frontal view of the average thalamus surface of all those in the control and psychosis groups with a superimposed distance map, after false discovery rate (5%) correction for multiple comparisons. The colour bars show the magnitude and direction of the differences (distance in mm) between the average surfaces of each group obtained by SPHARM-PDM. Anterior mediodorsal and posterior pulvinar regions showed surface deflation in the psychosis group, meaning that in this region the surface of those with psychosis showed contraction. (b) as for (a) but after Bonferroni correction for multiple comparisons.
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Joost Janssen, Yasser Alemán-Gómez, Santiago Reig, Hugo G. Schnack, Mara Parellada, Montserrat Graell, Carmen Moreno, Dolores Moreno, J. M. Mateos-Pérez, J. M. Udias, Celso Arango and Manuel Desco

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