Reduced anterior internal capsule and thalamic volumes in first-episode psychosis

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Received 11 August 2005; received in revised form 25 April 2006; accepted 1 May 2006
Available online 21 June 2006

Abstract

Background: The thalamus is the gateway for sensory and motor information en route to the cortex. Information is processed via thalamocortical and corticothalamic pathways coursing through the internal capsules. In this study, we investigated the relationship between the anterior limb of the internal capsule, posterior limb of the internal capsule, and thalamus in first-episode psychosis (FEP).

Methods: Twenty-nine FEP subjects (26 DSM-IV schizophrenia, 2 schizoaffective disorder, 1 psychosis not otherwise specified) and 22 healthy volunteers participated in this study. Anterior limb of the internal capsule (AIC), posterior limb of the internal capsule (PIC), and the thalamus volumes were manually determined from MRI scans.

Results: FEP subjects had reduced AIC volumes \(F(1,45)=6.18, p=0.017\) and thalamic volumes \(F(1,45)=8.00, p=0.007\) compared to healthy volunteers. PIC volumes did not differ. Significant correlations between AIC volumes and thalamic volumes were observed in subjects with FEP, but not in healthy volunteers. Negative relationships between thalamic volumes and symptom severity were also observed.

Conclusions: The AIC and thalamic volumes were reduced in subjects with FEP compared to healthy volunteers. Abnormalities in thalamocortical and orticothalamic pathways may contribute to functional disruption of neural circuits in psychosis.

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Keywords: Schizophrenia; Psychosis; Internal capsule; Thalamus; Cortico-thalamic circuitry; MRI

1. Introduction

The presence of subtle to moderate abnormalities of brain anatomy, biochemistry and metabolism in schizophrenia are now well established given the advent of multiple modalities of structural and functional brain imaging. The most consistent structural findings include overall reduction in total brain volumes (van Haren et al., 2004), dilation or enlargement of the ventricles (Nakamura et al., 2004; Shenton et al., 2001), volume reductions in frontal grey matter (James et al., 2004; Gaser et al., 2004a), bilateral reductions in hippocampal volume (Seidman et al., 2003), and reduction in volumes of midline structures in nonmedicated subjects...
(basal ganglia, thalamus) (Csernansky et al., 2004; Gaser et al., 2004b). Previous studies have shown that exposure to traditional antipsychotics can induce striatal enlargement, however, it is not clear if other medial structures, particularly the thalamic nuclei, are also affected in the same manner (Chakos et al., 1994, 1995; Lang et al., 2004, 2001).

While none of the previously reported structural abnormalities are individually unique to, or sufficient to explain the diversity of neuropsychiatric and neurocognitive symptoms in schizophrenia, in tandem they may form a basis for a more general functional disconnectivity. Functional circuits connecting frontal areas to the basal ganglia and thalami are of particular interest in schizophrenia. These circuits subserve sensory processing, sensory gating and cognitive processes such as memory, attention and psychomotor control (Benedict et al., 2004; Schuler et al., 2003; Coull et al., 2004). The thalami are composed of various subnuclei that can be anatomically divided into the medial dorsal nucleus, the anterior nucleus and the lateral dorsal nucleus (Taber et al., 2004). The medial dorsal nucleus and the anterior nucleus have garnered more attention in schizophrenia research as these regions have multiple projections via the internal capsules to and from regions in the frontal cortex involved in memory, emotion, motivation and directed attention (Taber et al., 2004; Tekin and Cummings, 2002; Herrero et al., 2002). Interruptions in these pathways may lead to increased vulnerability to schizophrenia and provide a basis for explaining the multiplicity of symptoms (James et al., 2004). Various structural MRI alterations are supported by data from functional studies that have reported abnormal pallidal and thalamic glucose metabolism in schizophrenia patients (Yasuno et al., 2004; Galeno et al., 2004; Hazlett et al., 2004; Talvik et al., 2003). Moreover, thalamic activity levels appear to be increased by antipsychotic treatment in schizophrenia, suggesting that the thalamus is an important target for antipsychotic agents (Muller et al., 2003). Reduced levels of metabolic activity in the thalamus as measured by positron emission tomography and single-photon emission computed tomography of cerebral perfusion have been linked to cognitive deficits and increased severity of both positive and negative symptoms (Lehrer et al., 2005; Min et al., 1999).

Concomitant observations of structural abnormalities of the thalamus in patient populations with schizophrenia have been inconsistent. Some studies have reported reductions in thalamic volumes (Gaser et al., 2004b; Brickman et al., 2004; Gur et al., 1998), while others have found no differences between schizophrenia subjects and healthy volunteers (Pruess et al., 2005; Cahn et al., 2002). Inconsistencies in the findings may be the result of variability in the selected subjects and the measurement protocols across studies. Additionally, antipsychotic medication effects could contribute to the variability in findings. In this regard, exposure to antipsychotic medications may induce thalamic hypertrophy in some subjects and this could be related to changes in psychotic symptoms (Strungas et al., 2003). However, more stringent studies suggest that thalamic volumes in antipsychotic-naive schizophrenia patients are either unchanged or reduced at baseline and increase in response to exposure to high-dose atypical antipsychotics after a year or more of treatment (Gur et al., 1998; Cahn et al., 2002). Strungas et al. (2003) observed that bilateral reductions of thalamic nuclei were related to poor response to risperidone treatment, whereas increased thalamic volumes after exposure to risperidone were related to decreased positive symptom severity. In contrast, Gur et al. (1998) observed a relationship between higher thalamic volumes and more severe positive symptoms. In a recent study, Pruess et al. (2005) also found a relationship between increased thalamic volume and more severe symptoms.

The nature of the relationship between thalamic volume, effects of antipsychotic medications and symptom severity in schizophrenia remains unclear and requires further investigation. Because the thalamus is so highly interconnected with multiple regions of the brain, persistent dysfunction of the cortico-thalamic circuits rather than thalamic abnormalities alone may be a core contributor to the observed cognitive deficits and symptoms in schizophrenia (Mendrek et al., 2004, 2005). Recent evidence for corticosubcorticothalamic disconnectivity in schizophrenia has also emerged from diffusion tensor imaging studies describing reduced fractional anisotropy, a measure of the directionality and structural organization of white matter, in multiple white matter regions (Burns et al., 2003; Kubicki et al., 2002; Lim et al., 1999). Changes or abnormalities in white matter tracts may be an important factor in detecting how and where functional circuits are derailed in schizophrenia. Both a loss of integrity and decreased cohesiveness of white matter tracts may contribute to circuit dysfunction in schizophrenia (Flynn et al., 2003; Kubicki et al., 2004). Indeed, recent structural investigations have described reduced volumes of the anterior limb of the internal capsule in both schizotypal and chronic schizophrenia patients (Zhou et al., 2003; Suzuki et al., 2004). These observations are of interest, as white matter fibers traversing the anterior and posterior limbs of the internal capsule contain numerous afferent and efferent connections between the frontal and medial...
temporal lobes and the thalamus (Axer and Keyserlingk, 2000; Basser et al., 2002; Velakoulis et al., 2002). Moreover, reductions in internal capsule volumes may be related to increased severity of negative symptoms in these patients (Pailhère-Martinet et al., 2001). Given the functional significance of the numerous thalamic pathways that course through the internal capsule to multiple cortical regions, any abnormalities of the internal capsule could lead to a diversity of symptoms in schizophrenia and related psychotic disorders. Conversely, abnormalities of the thalamic nuclei might be paralleled by deficits of structure or volume in the internal capsules that would underlie the mechanism for cortico-thalamic circuit dysfunction in schizophrenia.

While DTI studies of specific white matter tracts interconnecting fronto-medial and fronto-temporal regions have reported reduced fractional anisotropy in these regions (Lim et al., 1999; Kumra et al., 2004), findings have been inconsistent (Steel et al., 2001). Differences in patient cohort samples and imaging acquisition parameters may contribute to the between-study inconsistencies. To investigate the relationship between internal capsule anatomy and the thalamus in schizophrenia, the current study assessed bilateral thalamic and internal capsule volumes in a cohort of first-episode psychosis (FEP) subjects. It was expected that these patients would have reductions in both internal capsule and thalamic volumes and that these reductions would be inter-related. Potential relationships between thalamic volume and symptom severity were examined with exploratory correlational analyses. It was expected that reduced thalamic volumes would be associated with greater symptom severity.

2. Subjects

Subjects for this study were recruited as part of a longitudinal study of early psychosis through the Nova Scotia Early Psychosis Program in Halifax and from the local Halifax community. Subjects were a subpopulation of a large naturalistic clinical protocol that initially involved over 50 subjects. Only those that met criteria for analyses for this study were included. A final total of 29 first-episode psychosis subjects and 22 healthy age and gender-matched volunteers were included in this study (demographic information provided in Table 1). Approval for this study was granted by the Dalhousie University Ethics Committee. Informed written consent was obtained for all subjects. Subjects under the age of legal consent in Canada (below age 16) also had prior parental assent to enter into the study. Subjects under 16 included 1 FEP subject (age 13.7) and 1 healthy volunteer (age 12.8). Exclusion criteria were a significant history of head injury or loss of consciousness exceeding 5 min, a history of facial or nasal trauma, a history of DSM-IV substance abuse, a current diagnosis of substance abuse during treatment or at follow-up, a history of seizure disorder or a family history of psychotic disorders for healthy volunteers. At baseline some subjects were antipsychotic-naive \((N=4)\); however a number had been briefly prescribed risperidone \((N=24)\) or olanzapine \((N=1)\) as the only antipsychotic (see Table 1). Total lifetime exposure to antipsychotics was limited to a maximum of 12 weeks for this study. In addition, five subjects were receiving adjunct medications (see Table 1). This window of antipsychotic exposure was selected as previously published data suggested that brief exposure is insufficient to induce volumetric increases to other subcortical regions (Lang et al., 2001).

3. Methods

3.1. Scan acquisition

Details on the scan acquisition for this study have been described elsewhere (Lang et al., 2004, 2001). Briefly, scans were acquired with a Siemens Magneton 1.5T scanner. A coronal inversion recovery sequence \((\text{TR/TE}=2000/20\ \text{ms},\ \text{FOV}=200\ \text{cm},\ \text{slice thickness}=4\ \text{mm},\ \text{inter-slice gap}=1\ \text{mm},\ \text{matrix size}=168\times256,\ \text{pixel size}=1.04\times0.78\ \text{mm},\ 18\ \text{slices total})\) was obtained to facilitate the volumetric assessment of the anterior limb of the internal capsule (AIC), the posterior limb of the internal capsule (PIC), and thalamic nuclei (Fig. 1). An inversion recovery (IR) sequence was performed for this study as it provided optimal resolution of the greywhite tissue boundaries. In comparison to 3D spoiled-gradient recall (SPGR) collected on the same scanner, the white-grey pixel intensity for the IR sequence was 1.42 versus 0.89 for the SPGR sequence. An additional T2-weighted axial sequence was obtained to facilitate the assessment of total intracranial brain volumes.

3.2. ROI acquisition

A single rater (B.K.), blind to diagnosis and gender performed volumetric measures. The AIC, located bilaterally, is a large bundle of fibers found anterior to the anterior commissure and is bound laterally by the putamen-globus pallidus complex (also known as the lenticular nucleus) and superio-medially by the caudate in the coronal view. The AIC measures began three
slices prior to and ended when the anterior commissure was visualized. The PIC, also located bilaterally, is a large bundle of fibers found posterior to the anterior commissure and is laterally bound by the posterior lenticular nucleus, superio-medially bound by the caudate and inferiomedially bound by the thalamus. The PIC measures began one slice posterior to the anterior commissure and included a total of three slices (see Fig. 1). The thalamus is bound superiorly by the 3rd ventricle, laterally by the lateral ventricles and inferiorly by the red nuclei and crus cerebri. Measurement of the thalamus began two slices posterior to the anterior commissure and included a total of four slices. On posterior slices where both thalamus and PIC were visible, the regions were subdivided manually (see Fig. 1). All regions of interest were manually traced with reference to neuroanatomical atlases (Haines, 1995; Duvernay, 1991). Final area measurements were the mean of four independent trials. The sum of the areas of each side was multiplied by 5 mm (4 mm slice thickness plus 1 mm inter-slice gap) to obtain volumes for all regions of interest. The reliability of all MRI volumes were established with inter-rater reliability tests to determine interclass coefficients (ICC). ICC values were as follows: Total intracranial volume (DL, BK, VG): 0.997, total left and right thalamus volumes (BK, VG): 0.960, total left and right AIC volumes (DL, BK): 0.823, total left and right PIC volumes (DL, BK): 0.858.

3.3. Statistical analyses

Demographic variables (age, education) and total intracranial volumes were compared with independent t-tests. Parental SES was examined with a Chi-squared analysis. Between group differences of bilateral anterior internal capsule volumes, posterior internal capsule

<table>
<thead>
<tr>
<th>Variable</th>
<th>First-Episode Psychosis Subjects (N=29)</th>
<th>Healthy Volunteers (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parental socio-economic statusa</td>
<td>High: N=10 Moderate: N=15 Low: N=4</td>
<td>High: N=11 Moderate: N=9 Low: N=0</td>
</tr>
<tr>
<td>Mean Years Education</td>
<td>10.9 (2.0) (7.0–14.0)b</td>
<td>13.6 (2.6) (7.0–16.0)c</td>
</tr>
<tr>
<td>Gender</td>
<td>21 M, 8 F</td>
<td>12 M, 10 F</td>
</tr>
<tr>
<td>Mean age yrs (Range)</td>
<td>22.0 (5.1) (13.7–33.2)</td>
<td>24.7 (6.4) (12.8–33.1)</td>
</tr>
<tr>
<td>Mean PANSS score (Range)</td>
<td>78.7 (26.1) (33.0–123.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean Positive Subscale score (Range)</td>
<td>17.6 (8.1) (7.0–38.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean Negative Subscale score (Range)</td>
<td>20.6 (8.1) (7.0–35.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean Psychopathology score (Range)</td>
<td>40.4 (12.7) (19.0–60.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean dose antipsychotics (mg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>risperidone (N=24)</td>
<td>2.6 (1.1) (1.0–6.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>olanzapine (N=1)</td>
<td>15.0 (N/A)</td>
<td>N/A</td>
</tr>
<tr>
<td>drug-naive (N=4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean weeks antipsychotics (Range)</td>
<td>5.3 (3.8) (0.0–12.0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Adjunct medications-mg/day (Range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lorazepam</td>
<td>3.0 (–) N=1</td>
<td></td>
</tr>
<tr>
<td>paroxetine</td>
<td>20.0 (–) N=1</td>
<td>N/A</td>
</tr>
<tr>
<td>clonazepam</td>
<td>2.0 (–) N=1</td>
<td></td>
</tr>
<tr>
<td>fluoxetine</td>
<td>40.0 (–) N=2</td>
<td></td>
</tr>
<tr>
<td>Anterior limb internal capsule (mm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Left (SD)</td>
<td>1421d (276)</td>
<td>1581 (225)</td>
</tr>
<tr>
<td>Mean Right (SD)</td>
<td>1515d (304)</td>
<td>1738 (235)</td>
</tr>
<tr>
<td>Posterior limb internal capsule (mm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Left (SD)</td>
<td>2096 (248)</td>
<td>2075 (222)</td>
</tr>
<tr>
<td>Mean Right (SD)</td>
<td>2170 (245)</td>
<td>2154 (224)</td>
</tr>
<tr>
<td>Thalamus (mm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Left (SD)</td>
<td>4078d (411)</td>
<td>4253 (325)</td>
</tr>
<tr>
<td>Mean Right (SD)</td>
<td>4215d (443)</td>
<td>4512 (356)</td>
</tr>
<tr>
<td>Total intracranial volume (cm³) (SD)</td>
<td>1461.0 (169.6)</td>
<td>1479 (108)</td>
</tr>
</tbody>
</table>

a Parental socio-economic status based on classifications given by the Canadian Occupational Classification Index (HRDC, 1993). Parental occupation data were not available for 2 healthy volunteers.
b Education information was not available for 1 subject with psychosis.
c Education information was not available for 1 healthy volunteer.
d Statistically different at the 0.05 level.
volumes and thalamic volumes were investigated with repeated-measures ANCOVAs, with group and gender entered as main effects, age and total intracranial volumes entered as covariates and side entered as a repeated measure. Investigation of the relationships between these volumes in healthy volunteers and patients were performed using Pearson’s correlations. Post-hoc analyses (Fisher’s LSD/Student’s t-tests) were applied. Exploratory correlational analyses between antipsychotic dose, thalamic volume and symptom severity were performed. Symptoms were assessed with the Positive and Negative Syndrome Scale, a 30-item 7-point rating scale standardized for typological and dimensional assessment of schizophrenic phenomena (Kay et al., 1987). Symptom severity was based on both total PANSS score and PANSS subscale scores for Positive, Negative and General Psychopathology symptoms.

4. Results

4.1. Part 1: Demographic data

Overall, healthy volunteers had significantly higher levels of educational attainment compared to subjects with first-episode psychosis ($t(47) = -4.04, p = 0.0002$). However, there were no differences in parental socio-economic status (SES) between healthy volunteers and subjects with psychosis ($X^2(2) = 4.03, p > 0.13$). Healthy volunteers and first-episode psychosis subjects were of similar age ($t(49) = -1.83, p = 0.07$). There were no between-group differences in total intracranial volumes ($t(55), p = 0.66$); however, gender differences in total intracranial volumes were observed ($F(1, 47) = 20.73, p < 0.0001$). Subsequent ANCOVAs included intracranial volume, gender and age as covariates as there was a trend towards an age effect.

4.2. Part 2: Subregional volumetric comparisons of anterior and posterior internal capsules and thalamic nuclei

Left and right volumes of the internal capsule limbs and the thalamic nuclei are shown in Fig. 2. Anterior internal capsule (AIC) volumes were significantly smaller bilaterally in subjects with psychosis compared to healthy volunteers ($F(1, 45) = 6.18, p = 0.017$; Fisher’s LSD $p = 0.01$). There were significant interactions of diagnosis $\times$ side ($F(1, 45) = 6.00, p = 0.018$) and
gender × side \( (F(1,45) = 6.08, p = 0.018) \), with male FEP subjects having significantly smaller right Anterior internal capsule volumes compared to healthy volunteers \( (t(31) = -2.97, p = 0.006) \). Over all, first-episode psychosis subjects had left anterior internal capsule volumes that were 10.2% smaller and right anterior capsule volumes that were 12.9% smaller than healthy volunteers based on their mean volumes. In contrast, no between-group differences were observed in posterior internal capsule volumes \( (F(1,45) = 0.06, p = 0.81) \), nor were any left–right differences seen \( (F(1,45) = 2.07, p = 0.16) \). Neither diagnosis × side \( (F(1,45) = 0.47, p = 0.50) \) nor gender × side \( (F(1,45) = 19, p = 0.67) \) interactions were observed. As with AIC volumes, thalamic volumes were significantly smaller in subjects with psychosis compared to healthy volunteers \( (F(1,45) = 8.00, p = 0.007) \). A significant effect of side was observed \( (F(1,45) = 5.73, p = 0.021) \) and a significant interaction of diagnosis × side was observed \( (F(1,45) = 5.49, p = 0.023) \), with FEP subjects having greater reductions on the right side. No gender × side interaction was observed \( (F(1,45) = 1.91, p = 0.17) \). Consistent with the pattern of AIC results, first-episode psychosis subjects had mean left thalamic volumes that were 3.8% smaller and right thalamic volumes that were 6.2% smaller compared to healthy volunteers.

### 4.3. Part 3: Correlational analyses of relationships between thalamic and internal capsule volumes

Bivariate scattergrams of left and right internal capsule volumes versus thalamic volumes in FEP subjects and healthy volunteers are shown in Fig. 3. Right AIC and right thalamic volumes were positively correlated to each other \( (r = 0.51, p = 0.005) \) in subjects with psychosis, however, this correlation was not observed in the healthy volunteers \( (r = 0.22, p = 0.32) \). Similarly, a positive correlation between left AIC and left thalamus volume was seen in subjects with psychosis \( (r = 0.40, p = 0.03) \), but not in healthy volunteers \( (r = 0.19, p = 0.39) \). Correlations between AIC volumes and thalamic volumes in subjects with psychosis remained significant after Bonferroni correction only for right AIC and right thalamus (threshold for significance set at \( p \leq 0.0125 \)). No significant correlations between either left or right PIC and ipsilateral thalamic volumes were observed in either group (all \( p \)-values > 0.30).

### 4.4. Part 4: Correlational analyses of relationships between thalamic volume and antipsychotic treatment in subjects with psychosis

At the time of scan, 24 of 29 FEP subjects were treated with risperidone (range 1.0–6.0 mg/day) and 4 of 29 FEP subjects were antipsychotic naive for this study. For the following exploratory analyses, the subject treated with olanzapine was excluded. Exploratory correlations between dose of antipsychotic and thalamic volume revealed no significant relationships between dose and right or left thalamic volume in subjects with psychosis (Right: \( r = 0.09 p = 0.69 \), Left: \( r = 0.12, p = 0.57 \)). However, exploratory analyses did reveal a trend for a negative correlation between left thalamus volume and total PANSS score \( (r = -0.39, p = 0.06) \), and left thalamus volume and General...
Psychopathology subscale score ($r = -0.43$, $p = 0.04$). No correlations of symptom severity and thalamic volume were observed for the right side.

5. Discussion

As hypothesized, in this study we observed bilateral reductions in anterior internal capsule volumes in subjects who are in the early phases of psychosis compared to healthy volunteers. This finding was more pronounced on the right side. In contrast, no volume reductions were observed in the posterior internal capsules in subjects with psychosis, nor were left–right differences observed. These observations are congruent with reports from diffusion tensor imaging and structural magnetic resonance imaging of abnormal fractional anisotropy of the anterior limbs of the internal capsules and reduced internal capsule density in subjects with schizophrenia (Park et al., 2004; Hulshoff Pol et al., 2004). The anterior limb of the internal capsule includes fibers comprising the anterior thalamic peduncle, which connects the medial and anterior thalamic nuclei with the prefrontal cortex and the cingulate gyrus (Fitzgerald, 1992). Abnormalities of the prefrontal cortex and cingulate gyrus have been implicated in schizophrenia and may be responsible for deficits in attention, insight and working memory (Delamilliere et al., 2004; Shad et al., 2004; Perlstein et al., 2003; Quintana et al., 2004). The current data indicates that loss of connectivity between frontal areas via the internal capsules and the thalamus may be contributing to observed cognitive deficits in early phase psychotic illness.

Similar to the anterior internal capsules, bilateral reductions in thalamic volumes were observed in schizophrenia patients compared to healthy volunteers. The results from our study parallel those of Gur et al. (1998), who also reported a reduction in thalamic volume in a cohort of drug-naive schizophrenia patients.

Fig. 3. Relationships of raw anterior internal capsule volumes to thalamic volumes in first-episode psychosis subjects and healthy volunteers. Significant correlations of right AIC and right thalamic volumes ($p = 0.005$) and left AIC and left thalamic volumes ($p = 0.03$) were observed in FEP subjects, but not in healthy volunteers.
Interestingly, Gur et al. (1998) reported a finding of increased thalamic volumes in schizophrenia patients treated with either higher dose typical or higher dose atypical antipsychotics. Our sample of first-episode psychosis subjects at the time of their scan had received modest doses of mostly atypical antipsychotic medications (a mean of 2.6 mg of risperidone per day for 12 weeks or less, which is equivalent to 94.5 chlorpromazine units per day). In contrast, the medicated schizophrenia subjects in the Gur study (Gur et al., 1998) had received a mean of 433.5 chlorpromazine units per day for a mean of 107.9 weeks. The current data do not support a relationship between antipsychotic exposure and thalamic volume; however, this may be related to the short exposure period of the current group. Exposure to either typical or atypical antipsychotics was associated with increased thalamic volume in the Gur study (Gur et al., 1998), indicating that the thalamus may indeed be altered by antipsychotic treatment. Whether these increases would be permanent is unclear. Data from basal ganglia volume studies in schizophrenia in which switching from typical to atypical antipsychotics or to no medication led to decreases in volumes, suggesting that a decrease in thalamic volumes would be expected if subjects were to cease antipsychotic medications (Lang et al., 2004; Corson et al., 1999; Khorram et al., in press).

In the current study, right anterior internal capsule and right thalamic volume were positively correlated in subjects with psychosis. Exploratory analyses in the current sample suggest that reductions in the thalamus were related to the severity of general psychopathology as measured by the PANSS, as predicted. This contradicts the findings of Gur et al. (1998) as well as Pruess et al. (2005), who observed greater severity of positive symptoms in schizophrenia subjects with larger thalamic volumes. The study by Pruess et al. (2005), which included a cohort of nonmedicated and chronically treated patients, reported a positive association between symptom severity and thalamic only in the chronically treated cohort. Some controversy exists regarding these findings, as other groups have observed a negative relationship between severity of negative symptoms and thalamic volume (Portas et al., 1998). Differences in the assessment tools employed to measure symptom severity and the phase of illness at time of assessment may have contributed to the variability across the different studies.

5.1. Caveats

In the present study one subject of 13.7 years of age was included in the FEP cohort. While it has been suggested that early-onset or childhood onset of schizophrenia represents an extreme presentation of the schizophrenia syndrome, this classification is typically used for onset at or below 11 years of age (Rapoport et al., 1997). As this individual was more appropriately designated as an adolescent and as regresional analyses did not show that this subject was an outlier for any volumetric or clinical measures, the data were preserved for statistical analyses.

5.2. Conclusions

Bilateral reductions of anterior limb and thalamic volumes were observed in a cohort of drug-naive or minimally treated first-episode psychosis subjects, suggesting that abnormalities of volume are present very early in the course of illness. Additionally, abnormalities of left thalamic volumes may be particularly associated with severity of clinical symptoms. The thalamus is a central hub for multiple cortico-subcortical pathways involved in higher order planning, learning and attention, which are all affected in psychosis. Atypical antipsychotics may preferentially target dopamine receptors in the thalamus, suggesting that they could exert similar volumetric changes on the thalamus as those observed in the basal ganglia after sufficient exposure (Bressan et al., 2003). Whether abnormalities of anterior limb and thalamic volume predate the acute onset of psychosis remains to be determined.

Acknowledgements

The authors gratefully acknowledge Ms. Melissa M. Butler RTNM CCRC, Mr. Jason O. Brown BSc RTNM, Ms. Diana L Sonnichsen BSc RTNM, Ms. Charlene A. Day RN MN, Ms. Janet L. Gallant RN BSc CN, Dr. Heather M. Miliken MD FRCP and Dr. David Whitehorn PhD MScN for their invaluable assistance and technical expertise.

Dr. Honer is supported by the Canadian Institutes of Health Research (Grant: NET54013) and the Michael Smith Foundation for Health Research. Other grant support has been provided by the Stanley Medical Research Institute, the Dr. Norma Calder Foundation for Schizophrenia Research, and NARSAD.

Dr. Kopala is supported by a Dalhousie University Clinical Scientist Award and investigator initiated grants from Janssen-Ortho Canada and Eli-Lilly Canada. Additional funding for scans was provided by the Queen Elizabeth II Hospital Health Science Research Foundation and the Department of Psychiatry, Dalhousie University.
References


with reduced volume in right medial temporal/anterior cingulate grey matter in patients with chronic schizophrenia. Schizophrenia Research 57 (1), 43–49.
