Caudate volume in offspring of patients with schizophrenia

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Summary Caudate nuclei are smaller in drug-naive people with schizophrenia but larger in antipsychotic-treated patients. In this magnetic resonance imaging study we found volume reduction of right and left caudate by 8.9 and 8.1% respectively in 50 offspring without psychosis of patients with schizophrenia compared with 53 age- and gender-matched controls, providing new evidence that caudate volume reduction may be a trait-related abnormality in schizophrenia.

Declaration of interest None.

The caudate nucleus is a major target area for the subcortical dopamine projection system, which is implicated in the patho-physiology of schizophrenia. Caudate and other basal ganglia nuclei help regulate and organise the information flow between frontal lobes and the rest of the brain and play a major part in higher cognitive functions and movement (Middleton & Strick, 1994). Disruptions in this system or lesions of the basal ganglia result in movement disorders and behavioural problems similar to schizophrenia (Heckers, 1997).

Previous studies have shown enlarged caudate in patients treated with dopamine-blocking antipsychotics (Jernigan et al, 1991); however, a reduction has been reported among drug-naive patients (e.g. Keshavan et al, 1998) but it is not known whether this reduction precedes the illness. At-risk studies have shown brain abnormalities and behavioural deviances supporting neurodevelopmental pathology prior to psychosis (Lawrie et al, 2001; Rajarethinam et al, 2004; Job et al, 2005; Keshavan et al, 2005). We predicted that individuals at risk would have a smaller caudate nucleus than those with no family history of mental illness.

METHOD

Fifty young people (22 males and 28 females, mean age 15.4 years, s.d.=3.6) with at least one parent with schizophrenia and 53 healthy comparison participants (27 males and 28 females, mean age 16.5 years, s.d.=4.4) with no family history of mental illness participated from an ongoing study at the University of Pittsburgh. Other findings from this study have been reported elsewhere (Rajarethinam et al, 2004; Keshavan et al, 2005). The parental diagnosis in the high-risk group was ascertained with the Structured Clinical Interview for DSM–IV (SCID; Spitzer et al, 1992) and consensus clinical diagnosis. Comparison participants were similar in age, gender and socio-economic and geographical background but with no family history of mental illness. In the high-risk group 26 (57%) had Axis I psychopathology and IQ was lower (control group, mean IQ 115, s.d.=12; high-risk group, mean IQ 103, s.d.=13; F=7.184, $P < 0.011$). None of the participants had psychosis. Seven participants were being treated with stimulants and four with antidepressants, but none with antipsychotics. The University of Pittsburgh institutional review board approved the study. All participants provided written consent; those under 18 years provided informed assent also. Participants aged 15 years or younger were evaluated with the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K–SADS–PL version; Kaufman et al, 1999) and those over 15 were evaluated using the SCID. Anyone with a lifetime history of psychosis, significant neurological or medical illness, current substance use disorder, or any contraindication for magnetic resonance imaging (MRI) was excluded from participating in either group.

For MRI, 124 T_1-weighted 1.5 mm coronal slices, without interslice gap, were obtained using a 1.5 T GE scanner (General Electric, Milwaukee, Wisconsin, USA) with three-dimensional spoiled gradient recall acquisition, matrix $256 \times 256 \times 192$, field of view 24 cm, repetition time 25 ms, and time to echo 5 ms. Scans were reviewed to exclude structural abnormalities. The total brain volume was measured by a semi-automatic method using BRAINS2 software (Magnotta et al, 2002) and manually edited for accuracy. The interrater reliability between the four raters ranged from 0.98 to 0.99.

Caudate volumes were measured using the artificial neural network application, a semi-automated tracing method in BRAINS2, with manual editing for accuracy by two trained raters (P.T. and M.U.). Measurement included the head and body of the caudate but not the tail. The test–retest reliability for each rater was established using a set of three scans: (P.T.) right caudate r=0.98, left caudate r=0.99; (M.U.) right caudate r=0.99, left caudate r=0.95. The interrater reliability (intraclass r=0.94 for both right and left caudate) was established using a set of nine scans. Differences in age and intracranial volume were examined by two-tailed un-paired t-tests. Multivariate analysis based on the general linear model was conducted with group status (at-risk v. control) and intracranial volume as predictor variables and caudate volumes as dependent variables.

RESULTS

Age and gender distribution were not significantly different between the groups. The mean total brain volume of the high-risk group (1311.25 cm^3, s.d.=130.7) was significantly smaller than that of the comparison group (1391.21 cm^3, s.d.=136.3, F=9.223, $P > 0.003$). Analysis of co-variance using brain volume as a covariate revealed that the right caudate was significantly smaller in the high-risk group (F=4.014, $P < 0.05$) and the left caudate showed a trend for reduction (F= 2.92, P=0.091) (Fig. 1). The right and left caudate nuclei were smaller in the high-risk group by 8.9 and 8.1% respectively (right caudate: control mean volume 3.58 cm^3, s.d.=0.51; high-risk mean volume 3.26 cm^3, s.d.=0.45; left caudate: control mean volume 3.57 cm^3, s.d.=0.51, high-risk mean volume 3.28 cm^3, s.d.=0.49). Psychopathology or medication status did not have any significant effect on caudate volumes.

DISCUSSION

Our findings indicate that abnormalities in the caudate nucleus may be seen in young relatives of patients with schizophrenia. Individuals at risk for schizophrenia exhibit

behavioural problems and brain abnormalities, suggesting that some form of the pathological process may begin before the onset of symptoms (Keshavan *et al*, 2005). However, not all of these at-risk individuals would develop schizophrenia; therefore, the observed neuroanatomical alterations may reflect a measure of familial risk or susceptibility. The conversion to psychosis may result from an interaction between such susceptibility factors and unknown environmental influences or developmental/maturational changes that may involve this system.

Our observations are consistent with studies of basal ganglia function in individuals at risk for schizophrenia. Adult first-degree relatives of schizophrenia patients made more errors on an antisaccade task than a comparison group, suggesting a dysfunction of dorsolateral prefrontal cortex, caudate nucleus, or both (Clementz *et al*, 1994). Similarly, functional MRI studies have shown decreased activation of the caudate with antisaccade tasks in unaffected relatives (Raemaekers *et al*, 2006). These findings suggest that an alteration of the structural and functional integrity of corticostriatal neural networks may represent familial or premorbid risk of schizophrenia. It is conceivable that this network may have a role in other neuro-cognitive deficits such as attentional impairments found in at-risk individuals (Keshavan *et al*, 2005). In addition, in the context of conflicting research regarding the increase and decrease in caudate volume in relation to treatment or drug-naive status, our data clearly support the hypothesis that volume reduction rather than enlargement of the caudate nucleus is associated with the pathophysiology of schizophrenia. In contrast, Lawrie *et al* (2001) reported no difference in the caudate volumes in at-risk relatives (not
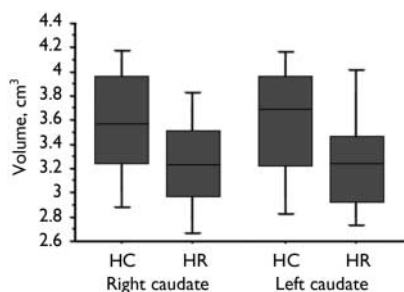

Fig. 1 Covarying for the total intracranial volume, the right caudate volume was significantly smaller in the high-risk group (HR) than in the healthy control group (HC) ($F=4.014$, $P<0.05$), and the left caudate showed a trend for reduction ($F=2.92$, $P=0.091$).

offspring), some of whom were symptomatic.

To our knowledge, few studies have examined basal ganglia in asymptomatic, untreated, adolescent offspring who are at genetic risk of schizophrenia. High-risk studies enable investigation of neuropathology without the confounds of state-related illness manifestations and medication effects. The neuroanatomical specificity of the observed findings is unclear, but caudate volume reductions might be part of an abnormal corticostriatal network; we and others have found prefrontal and temporal cortical volume deficits in this population (Rajarethinam *et al*, 2004; Job *et al*, 2005). The precise mechanisms underlying caudate volume reduction are unclear, and may involve either a failure of normal development or an excessive pruning (Keshavan *et al*, 2005).

These findings are intriguing, but must be considered preliminary, need replication and may not be generalisable to non-familial forms of schizophrenia. Although the difference was modest, type I errors are unlikely as the sample was large. Our findings support the notion that smaller caudate is a marker of genetic susceptibility, but it is not known whether this abnormality is present at birth or becomes evident during childhood and adolescence. Prospective studies in high-risk individuals suggest that about 10–15% develop schizophrenia, although up to 40% develop schizophrenia-spectrum psychopathology (Erlenmeyer-Kimling *et al*, 1997). Follow-up of these individuals will help elucidate the role of the caudate in premorbid vulnerability to and later progression into schizophrenia.

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