A REVIEW OF CAUDATE NUCLEUS VOLUME IN FIRST EPISODE PSYCHOSIS

Heather Taylor, Angelo Ricciardi, Paola Dazzan

Abstract

Object: The object of this review was to identify and critically review studies that investigated caudate volume in first episode psychosis patients, with a further interest into the possible effects of antipsychotic medication.

Method: We searched the Medline and Pubmed databases using the medical subject heading (MESH) terms: ‘schizophrenia’ and ‘caudate volume’ and ‘MRI’. The electronic search was then repeated using the terms ‘psychosis’ and ‘caudate volume’. Studies published up to the 31st December 2007 as an article, rather than a letter or abstract, were included.

Results: A total of 11 cross sectional studies and 6 longitudinal studies included patients with a first psychotic episode in comparison to healthy controls. These studies suggest that at the time of the first psychotic episode, before treatment is started, patients have a smaller caudate volume than healthy individuals; once treatment has begun, the caudate becomes similar in volume in first episode psychosis patients and in healthy controls. Longitudinal studies suggest that treatment with antipsychotic drugs, particularly typical antipsychotics, may cause an increase in caudate volume over time.

Conclusions: Differences in findings on caudate volume in first episode psychosis may be explained by both the pathophysiology of psychosis and the use of antipsychotic medications. To further understand the role of these changes, studies would benefit from evaluating larger samples of antipsychotic naïve individuals at illness onset.

Key Words: Caudate volume – MRI – First-Episode Psychosis – Antipsychotic Medication – Basal Ganglia

Declaration of interest: None

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Background

Schizophrenia is a disorder in which thought processes and perception are severely impaired. A person experiencing schizophrenia may experience positive symptoms such as delusions or hallucinations, and may also experience negative symptoms such as avolition or amotivation. Social withdrawal, lack of insight and reduced cognition could also be considered part of the clinical picture of schizophrenia.

Magnetic Resonance Imaging (MRI) has been applied to the study of many aspects of mental illness, and has enabled a better understanding of the neurobiology of mental disorders, and of the pathophysiology of schizophrenia. Many studies have investigated brain morphology in patients affected by schizophrenia, and a number of brain regions have been consistently identified as abnormal in patients with schizophrenia. A meta-analysis conducted by Wright et al. (Wright et al. 2000) examined a number of brain regions, and found that ventricles tend to be larger in patients, whereas structures within the subcortical regions, such as the hippocampus and amygdala, seem to be smaller in patients with schizophrenia. Furthermore, a more recent meta-analysis by Vita et al. (Vita et al. 2006) supported these findings of an increased ventricular volume and reduction of the hippocampus, but did not confirm a reduction of the amygdala. Vita et al. (2006) performed the meta-analysis only on studies that evaluated patients with first episode schizophrenia. This may suggest that brain morphology may change over the course of the illness.

A large number of MRI studies have also specifically investigated the volume of the caudate nucleus (Corson et al. 1999a, Chakos et al. 1995, Bilder et al. 1993, Mamah et al. 2007). It is particularly interesting to investigate the caudate structure and volume in patients with psychosis as this structure may have an intrinsic link with the pathophysiology of psychosis in general, and of schizophrenia in particular. The caudate is a major target area for the subcortical dopamine projections, and along with other basal ganglia structures it regulates the organisation and information flow between the frontal lobes and the rest of the brain (Middleton & Strick 2000). The caudate is particularly involved in movement control, and has

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<td>First Episode Psychosis vs Healthy Controls</td>
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<td>All Naive, 1.5T, 1.5mm</td>
<td>ROI, Nucleus Accumbens included</td>
<td>No differences between FEP and HC.</td>
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Legend: FEP = First Episode Psychosis, HC = Healthy Control, ROI = Region of Interest, VBM = Voxel-Based Morphometry
importance in learning and memory. In fact, disruptions in this system have been associated with behavioural problems and poorer cognitive functioning similar to that observed in psychosis (Heckers 1997).

Within the studies which have investigated caudate volume in the schizophrenic population there is little agreement in relation to volumetric changes. A number of studies suggest that this structure is reduced in volume in this disorder, while others suggest that caudate volume is increased or unchanged in individuals with schizophrenia (Chakos et al. 1994). It has been suggested that these inconsistencies could result, at least in part, from an effect of antipsychotic drugs on caudate. This is suggested by studies that have reported an increase in caudate volumes after treatment with typical antipsychotics (Chakos et al. 1994, Keshavan et al. 1994b, Corson et al. 1999a, Corson et al. 1999b, Lang et al. 2001, Scheepers et al. 2001). Since the caudate has a high density of dopamine receptors, and the major pharmacologic action of antipsychotic medications is the dopaminergic system, this structure may be particularly susceptible to the effects of antipsychotics. Therefore, when evaluating caudate morphology in psychosis it is essential to investigate the effect of medications on its volume. This would help establishing whether antipsychotics are responsible for caudate volume changes, or if these are directly related to the disease, or whether they result from an interaction of both factors. Therefore, it is paramount to investigate the morphology of a structure like the caudate in patients who are experiencing their first episode of psychosis, as these patients will have been exposed to antipsychotics only for a relatively short period of time. Furthermore, studying patients at their first psychotic episode would identify changes which would be unlikely due to degenerative processes.

In this paper we review studies that specifically investigated caudate volume in first episode psychosis patients, and further explore the potential effects of antipsychotic medications on caudate volume.

Method

Data Sources

Medline and Pubmed databases were searched using the medical subject heading (MESH) terms: ‘schizophrenia’ and ‘caudate volume’ and ‘MRI’. The electronic search was then repeated using the terms ‘psychosis’ and ‘caudate volume’. The search included studies published up to the 31st December 2007. Studies were then cross-referenced to search for studies which were previously not identified within the electronic searches.

Study Selection

Studies were selected by the first author (HT) and checked by the last author (PD). We included structural Magnetic Resonance Imaging studies reporting directly on caudate nucleus volume in subjects at the first episode of any psychosis. All diagnoses of first episode psychosis were included in this review, as a clear diagnosis within the psychoses spectrum is often not certain at the time of first contact. Both longitudinal and follow up studies were included if the differences between first episode patients and healthy controls were commented upon and reported. Studies that evaluated the caudate with other neuroimaging methods such as Positron Emission Tomography, Single Photon Emission Computed Tomography, and functional Magnetic Resonance Imaging were not included in this review. A number of studies included the nucleus accumbens in the measurement of the caudate volume, and this was noted for the individual studies to improve comparability.

Data Extraction

For each identified study, we recorded (Table 1): [a] year of publication; [b] study design; [c] patient and control sample characteristics; [d] breakdown of diagnosis; [e] type of antipsychotic medication; [f] MRI and slice thickness; [g] method for estimating caudate volume (region of interest, automated analysis and voxel-based analysis; inclusion or exclusion of nuclear accumbens; any covariate included in the statistical analyses); [h] main findings on caudate volume at baseline and follow up (where appropriate).

As the type of antipsychotic treatment has been shown to affect subcortical structures (Dazzan et al. 2005), we also recorded treatment type (treatment with atypical or typical antipsychotics, or both; antipsychotic-naïve status) and length.

Results

We identified 17 papers that investigated caudate volume in first episode psychosis patients. Of these, 11 papers used a cross-sectional design, comparing first episode psychosis patients with healthy controls at a single time point (DeLisi et al. 1991, Keshavan et al. 1998, Gur et al. 1998, Corson et al. 1999a, Gunduz et al. 2002, Cahn et al. 2002, Epping et al. 2004, Jayakumar et al. 2005, Tauscher-Wisniewski et al. 2005, Chua et al. 2007, Crespo-Facorro et al. 2007). One paper also included chronic patients in their investigations, but the data on the chronically ill individuals have not been included in this review.


Cross-sectional studies comparing first episode psychosis patients and healthy controls

A total of 11 cross sectional studies compared caudate volume of first episode psychosis patients with that of healthy controls. Within these studies it is important to attempt to identify the potential effects of antipsychotic use. Therefore, we will report separately
on studies that have investigated caudate volume in antipsychotic naïve patients and those that have evaluated patients treated with antipsychotics.

**Studies investigating antipsychotic naïve patients**

Seven studies within this review were available on patients who were drug-naïve at the time of MRI (Keshavan et al. 1998, Corson et al. 1999a, Cahn et al. 2002, Jayakumar et al. 2005, Chua et al. 2007, Gunduz et al. 2002, Tauscher-Wisniewski et al. 2005). These studies are extremely valuable when investigating brain morphology as they offer an insight into brain volumes related to the pathophysiology of the illness, before factors such as medications can have an affect.

Keshavan et al. (1998) investigated treatment naïve and newly diagnosed patients with schizophrenic and non-schizophrenic psychoses. They observed that both groups had a caudate volume reduced bilaterally, in comparison to healthy controls. In fact, after co-varying for intracranial volume, there was a difference of approximately 14% in caudate volume between patients and healthy controls. The authors concluded that the smaller caudate volume in newly diagnosed psychotic patients could be due to the primary pathophysiology of psychosis, and that the larger caudate volume demonstrated in previous studies could be due to the effect of antipsychotic medication.

These findings are supported by evidence from Corson et al. (1999), who examined 36 first episode psychosis patients and found a 5% reduction in caudate volume in this group in comparison to healthy controls. Further support comes from the study of Jayakumar et al. (2005), which reported a significantly smaller caudate volume in first episode psychosis patients in comparison to healthy individuals. Finally, Chua et al. (2006) have recently reported an 11% bilateral reduction in caudate nucleus volume in first episode patients in comparison with controls.

This decrease in caudate volume has not been reported by all the studies on antipsychotic-naïve patients reviewed here. Both Gunduz et al. (2002) and Cahn et al. (2002) reported no significant difference between first episode psychosis patients and healthy subjects, findings which were later also supported by Tauscher-Wisniewski et al. (2005), Gunduz et al. (2002) and Tauscher-Wisniewski et al. (2005) also explored the relationship between caudate volume and length of untreated psychosis, and found no correlation between these two variables.

In a number of the studies identified, the effect of age on caudate volume was also commented upon. Of the studies that analysed the effect of age on caudate volume (Lieberman et al. 2001, Gunduz et al. 2002, Tauscher-Wisniewski et al. 2002, Chua et al. 2007, Tauscher-Wisniewski et al. 2005), three studies found a negative correlation between age and caudate volume (Lieberman et al. 2001, Gunduz et al. 2002, and Tauscher-Wisniewski et al. 2005). Both Lieberman et al. (2001) and Tauscher-Wisniewski et al. (2005) found that this was the case in both patients and healthy controls, while Gunduz et al. (2002) found this correlation only across the control group. Finally, Chua et al. (2007) found no correlation between age and caudate volume.

The discrepancies in findings across these studies on antipsychotic naïve individuals may be due to methodological differences. For example, differently from most of the other studies, the study by Tauscher-Wisniewski et al. (2005) included the nucleus accumbens in the caudate measurement, and the study by Gunduz et al. (2002) used a slice thickness larger than that of other studies.

**Studies investigating patients receiving antipsychotic medications**

The studies reviewed here have investigated caudate volume in individuals treated with typical or atypical antipsychotics (or both) for a maximum of 12 weeks, with the exception of one study that did not report any information on length of treatment (Ettinger et al. 2004). These studies consistently show that caudate volume in first episode psychosis patients is not significantly different from that of healthy individuals (DeLisi et al. 1991, Gur et al. 1998, Ettinger et al. 2004, Crespo-Facorro et al. 2007). Interestingly, DeLisi et al. (1991) investigated caudate volume in both first episode and chronic patients, in comparison to healthy controls. Although the difference was not significant, the caudate volume was smaller in first episode patients than in either the chronic or the healthy individuals. Unfortunately, most of the studies identified did not provide enough information on treatment to explore whether there was an effect of type or dose of antipsychotic. However, Gur et al. (1998) investigated 96 patients with schizophrenia, 75 of which had been previously treated (mostly with typical antipsychotics) and 21 of which were antipsychotic-naïve. Although no significant differences were found across medication groups, a higher dose of typical antipsychotics was associated with a significantly larger caudate volume.

Some studies have also explored the relationship between caudate volume and symptomatology. In the study by Gur et al. (1998) a larger caudate volume was associated with greater positive symptoms, specifically hallucinations, in antipsychotic naïve patients, and with negative symptoms in those patients who had been previously treated. This may suggest that positive symptom severity is associated with an increase in the caudate volume initially, but it is the negative symptoms which may sustain this increase. However, it is also possible that the antipsychotics used to treat the positive symptoms are sustaining the increase in caudate volume and are more effective at treating the positive symptoms than the negative symptoms. These findings are in conflict with evidence from Crespo Facorro and colleagues (2007), who found that an increased severity of initial positive symptoms was associated with a smaller (rather than a larger) caudate volume. This inconsistency may be due to the fact that the majority of patients in this study (Crespo-Facorro et al. 2007) were treated with atypical antipsychotics, while the majority of patients in Gur and colleagues (1998) study, were on treatment with typical antipsychotics, which have been reported to increase caudate volume.
Two studies explored the relationship between caudate volume and cognitive functioning (Crespo-Facorro et al. 2007, DeLisi et al. 1991). Both studies found no significant correlation between brain morphological measurements and cognitive functioning. Finally, Ettinger et al. (2004) explored the effect of age on caudate volume and found a negative correlation in both the patient and healthy control groups.

In summary, cross-sectional studies suggest that at the time of the first psychotic episode, before treatment with antipsychotic commences, caudate volume may be smaller than that of healthy individuals. However, these studies also suggest that once treatment is started, the volume becomes similar to that of non-psychotic individuals, possibly because of the effect of antipsychotics on caudate.

Longitudinal Studies on first episode psychosis patients and healthy controls.

Six longitudinal studies compared first episode psychosis patients and healthy controls, at multiple time points. These studies mostly report on subjects treated at baseline with a mixture of both typical and atypical antipsychotic (Chakos et al. 1994, Tauscher-Wisniewski et al. 2002, Lieberman et al. 2005, Glenthøj et al. 2007), without differentiating caudate volume according to treatment. Therefore, in the next section, we will consider all longitudinal studies together.

Five of the longitudinal studies reported on a direct caudate volume comparison between first episode patients and healthy controls at multiple time points (Chakos et al. 1994, Lieberman et al. 2001, Lang et al. 2001, Tauscher-Wisniewski et al. 2002, Glenthøj et al. 2007), while one reported on longitudinal changes in volume only within group (Lieberman et al. 2005). These studies consistently reported no differences in caudate volume between first episode patients and healthy controls, independently from baseline treatment status. Even in the study by Lieberman et al. (2005), although there was no direct comparison of baseline volumes between the first episode patient group and the controls, the mean values reported in the paper do suggest no difference in caudate volume between the two groups.

The seminal longitudinal study by Chakos et al. (1994) investigated a group of 29 first episode psychosis patients, who had no prior exposure to antipsychotic medication, or had minimal prior exposure but had undergone a two-week wash-out period before being scanned. Although no significant difference was found between the patient group and the controls at baseline, after a treatment interval of 18 months with standardised antipsychotic regimes, an increase of 5.7% in caudate volume was found in the patient group, whereas the control group exhibited a decrease of 1.6% in volume within the same period.

In a subsequent study, Lieberman et al. (2001) investigated 107 first episode psychosis patients who were medication naïve and 20 healthy controls. This study also found that over a follow up period of 12 months, in which patients were treated with typical antipsychotics, patients had a significant increase in caudate volume, while controls did not. Interestingly, caudate volume changes were observed again in a more recent study by Lieberman et al. (2005). Here, the authors were able to investigate changes in caudate volume separately in patients taking haloperidol (a typical antipsychotic) and in those taking olanzapine (an atypical antipsychotic). The authors found that caudate volume increased significantly in the haloperidol treated patients compared with patients treated with olanzapine, at various time points (weeks 24, 52 and 104). Unfortunately, a direct comparison of caudate volume between patients and healthy controls was not performed, either at baseline or at follow up.

Further to these studies, Glenthøj et al. (2006) conducted a study to examine basal ganglia volume in drug-naïve first episode patients, before and after treatment with either an atypical (risperidone) or a typical (zuclopenthixol) antipsychotic drug. MRI scans were obtained before and after treatment to investigate the specific effect of these drugs on basal ganglia volumes. After 12 weeks of treatment, absolute volumes of the basal ganglia were found to have increased in patients. However, this volume increase was only observed for the putamen in the risperidone group, and not for the caudate and nucleus accumbens. It is important to note that at baseline patients had a smaller (albeit not significantly) caudate volume than the controls. Therefore, it is possible that treatment did have an effect on caudate in the patient group, making it more similar in size to that of the controls.

In contrast with these data, Lang et al. (2001) found no change in caudate volume over 12 months. Also differently from the other findings reviewed earlier, Tauscher-Wisniewski et al. (2002) found a 9% decrease in caudate volume over 5 years in a small group of 15 patients, 8 of which were drug naïve at baseline. Again, these conflicting findings may be due to different methodologies (the slice thickness in the Lang and colleagues (2001) study was 4 mm with 1 mm gap), or the smaller sample sizes investigated.

Only 2 longitudinal studies (Lang et al. 2001, Tauscher-Wisniewski et al. 2002) investigated the effect of age on caudate volume, and neither found any correlation between age and caudate volume.

Discussion

This review identified 17 studies which explored caudate volume in first episode psychosis patients using structural MRI. The studies reviewed suggest that at the time of the first psychotic episode, before treatment is started, patients have a smaller caudate volume than healthy individuals; while once treatment has begun the caudate becomes similar in volume in first episode psychosis patients and in healthy controls. Longitudinal studies suggest that treatment with antipsychotic drugs may cause an increase in caudate volume over time, and that this increase may be different in relation to typical or atypical antipsychotic use.

The caudate has an intrinsic link to the pathophysiology of schizophrenia and its neuroanatomical alterations may reflect a neurodevelopmental aberration.
within patients affected by this illness. The smaller caudate volumes in patients who are antipsychotic naïve may be part of a disruption within the cortical-striatal neural networks, which has been implicated in the pathogenesis of schizophrenia (Keshavan et al. 1998). The specific substrate of this caudate volume decrement remains unclear, and possible mechanisms may include toxin-induced neuronal destruction (Mattson et al. 1996), or an exaggeration of periadolescent synaptic pruning, possibly in glutamatergic corticotubercular nuclei (Keshavan et al. 1994a).

In contrast, initiation of treatment may bring to an increase in size. Furthermore, a specific effect of antipsychotic drugs is supported by evidence that this volume increase can be reverted by suspension of the drug or switching to clozapine, an atypical antipsychotic (Keshavan et al. 1994b, Chakos et al. 1994). However, it remains unclear what mechanisms underlie this basal ganglia increase, and what is detected as a change in volume could be for example the consequence of changes in tissue perfusion, fat, or water content associated with antipsychotic use (Weinberger & McClure 2002). Several mechanisms have been put forward to explain the increase in basal ganglia volume in association with typical antipsychotics use, and particularly with use of different types of antipsychotics.

For example, typical antipsychotics have an antagonistic effect on D2 receptors that could explain changes in structures rich in these receptors, such as the caudate. The chronic block of D2 may lead to a proliferation of D2 receptors, and the resulting increased metabolism and blood flow may lead to an increase in size of the ganglia (Miller et al. 1997). It is also possible that this D2 proliferation induces changes in the dendritic tree that then lead to an increase in volume (Miller et al. 1997).

This review highlights that several variables can potentially affect caudate nucleus volume. These include the use of antipsychotic medication, age, and symptom severity. Therefore, not only can the treatment have an effect on the volume of the caudate, but the characteristics of the illness itself are potentially associated with differences in caudate morphology. In contrast, there seem to be no association between caudate volume and cognitive function. This is somewhat unexpected, since dopamine activity in the caudate is associated with aspects of cognitive functioning such as memory. A disruption of dopaminergic activity could potentially cause deficits in these functions, but this was not observed in the studies reviewed.

This review also demonstrates the diverse outcomes across studies, even within those studies which examined first episode psychosis patients who were antipsychotic medication naïve. This highlights the possible limitations which seem implicit in all MRI studies, which include different image acquisition parameters and analysis techniques, used along with a variety of sample sizes. In addition, matching the patient sample with the controls in areas such as age, gender and education does not always occur, and these factors can have a potential confounding effect on the result. Although these factors can reduce comparability of findings, the studies reviewed concur to suggest that changes in caudate volume may be part of the pathophysiology of psychosis, and that if more is to be understood about the role of these changes, studies would benefit from evaluating larger samples of antipsychotic naïve individuals with a longitudinal design.

References


ganglia volumes in first-episode schizophrenia and healthy comparison subjects. *Biological Psychiatry* 51, 801-808.


