An introduction to the caudate in schizophrenia.

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A B S T R A C T

Introduction

The caudate forms the medial part of the striatum and has clear involvement with both cognitive and motor functions. Damage to this structure has been reported to produce a 'schizophrenia-like' state, and so has been the subject of some investigation. As with the adjacent putamen, the caudate receives dopaminergic input from the nigrostriatal tract, with recent imaging studies suggesting a pronounced effect of anti-psychotic medication on the size of this structure.

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The caudate is a dense subcortical nucleus composed of spiny neurons and forms the dorsal striatum along with the putamen. It forms the medial part of the striatum, with the putamen forming the more lateral area. They are often considered a single functional unit separated by the striatal white matter tract known as the internal capsule (shown in figure 1). It has much in common with the putamen, receiving dopaminergic inputs from the nigrostriatal pathway, specifically originating from the midbrain reticular formation (A8 dopamine cells) and the substantia nigra pars compacta (A9 dopamine cells) (Fallon and Moore, 1978). The caudate also receives projections all the way from the dorsolateral prefrontal cortex and the premotor cortex, and in turn sends projections to the globus pallidus and reciprocal projections to the substantia nigra. There are also complex and reciprocal connections between several thalamic nuclei and the caudate, reviewed in (Haber and Calzavara, 2009, Smith et al., 2004).

The functional connections clearly show why the caudate is thought to play an important role in cognition and movement, whilst damage to this structure has been observed to result in schizophrenia-like behavioural change, suggesting a possible role for the caudate in this illness (Heckers, 1997, Middleton and Strick, 1994). Functionally the caudate is part of the cortico-basal ganglia-thalamic loop, suggested to be the key network regulating motivation, planning and cognition for the development and expression of goal-directed behaviours (Yager et al., 2015, Haber and Calzavara, 2009).

The primary focus of investigation of the basal ganglia in schizophrenia has to do with the dopamine system and the various sites of antipsychotic drug action in the striatum. The dopaminergic projection from the substantia nigra to the striatum is known as the nigrostriatal pathway and is the most well characterised long dopamine pathway in the brain. The nigrostriatal pathway is formed from axons projecting from the large dopamine-producing neurons in the substantia nigra, identified above as A8 and A9 cells, and rises dorsally to terminate in the superior part of the striatum across areas of the caudate and putamen. Imaging and neuropathological investigation of striatal dopamine have found elevated dopamine synthesis capacity is seen in the origin of dopamine neurons in the substantia nigra as well as their striatal terminals in schizophrenia, linked to severity of psychosis in patients. The increased nigrostriatal dopmaine is likely to be a result of excess production in dopmine-positive nigral oval cells (Howes et al., 2013) (Davis et al., 1991).

The caudate is reported to show a decrease in total volume in schizophrenia, contrary to the effect described in the adjacent putamen, although some authors have suggested this is the result of medication rather than fundamental biology (Mamah et al., 2007, Buchsbaum et al., 2003). However imaging studies have shown that the decrease of caudate volume is also found in antipsychotic-naïve first episode patients (Ebdrup et al., 2010), and ultrastructural examination of the spiny neurons of the striatum show changes in spine shape and axon density in the caudate. Spine pruning, as the process of losing neuronal spine is known, has been shown to be correlated strongly with long-term antipsychotic medication use. This has specifically been implicated in models of circuit control of striatal dopamine, progressive spine pruning strongly effecting elevated frontal cortical excitation of pyramidal neurons as a result of striatal hyperdopaminergia (Kim et al., 2015, Ho et al., 2011). However the findings are not totally consistent, with conflicting results suggesting increased caudate volume in first episode schizophrenia, with volume increase proportional to greater amounts of antipsychotic medication and younger age at the time of

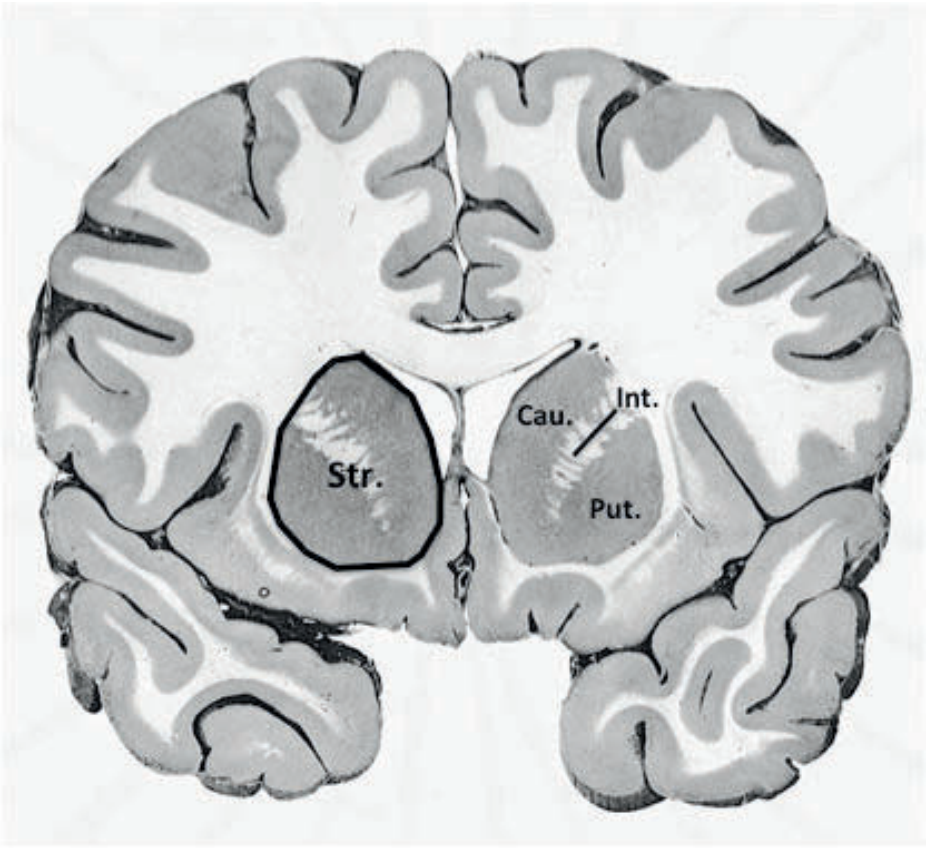

Figure 1.

Coronal section at the level of the human striatum. The striatum (Str.) is composed of the Caudate (Cau.) and Putamen (Put.) either side of the Internal Capsule (Int.), the primary white matter structure of the striatum. Adapted from Hanaway & Kent (1987)

the first scan (Chakos et al., 1994, Hokama et al., 1995), possibly arguing against drug treatments being the cause of caudate changes (Kung et al., 1998a, Kung et al., 1998b).

Volumetric MRI studies show decreases of 8-9% in caudate volume in the offspring of patients with schizophrenia (Rajarethinam et al., 2007), although other investigations have not reported similar changes in first-degree relatives (Lawrie et al., 2001). If these alterations are borne out but further research we must accept that not all of these offspring would develop schizophrenia and so any neuroanatomical alterations are more likely to reflect a measure of susceptibility, the causation of which could be due to excessive synaptic pruning or some problem in normal development (Keshavan et al., 2005).

However meta-analysis of the caudate in schizophrenia have tended to show a volumetric change, with suggesting decreasing caudate size more common (Glahn et al., 2008). Caudate volume is often reported reduced in first episode schizophrenia, with progressive decreases reported over time in a dose-dependent manner with medication (Ebdrup et al., 2010, Ebdrup et al., 2011, Glenthoj et al., 2007). This is consistent with meta-analyses suggesting increased loss of basal ganglia grey matter over time in chronic schizophrenia compared to first episode, the complexity of reported findings specifically in the caudate over time show this requires more detailed investigation (Ellison-Wright et al., 2008).

Stereological studies have, somewhat typically, produced conflicting findings. Initial findings suggested that the caudate has higher neuron counts in schizophrenia (Beckmann and Lauer, 1997), but more recent studies have concluded the caudate has shown similar neuropathological changes to the putamen, with a decreased total number of neurons in schizophrenia (Kreczmanski et al., 2007). The possible causes of such directly conflicting results may well be down to the stereological methods, a controversial subject that has been discussed elsewhere (von Bartheld, 2002, Gaebel, 2011). Ultrastructural morphometric study of myelinated fibres in the caudate in schizophrenia demonstrated atrophy of axon due to the alteration of myelin sheath (Uranova et al., 2013), possibly indicating disruption of signal transmission in the caudate-related networks described previously.

Whilst a reported change in caudate volume in first episode schizophrenia and the offspring of schizophrenia patients suggests a more fundamental biological alteration of the caudate in this illness, the interaction of antipsychotic drug treatments and cortical volume suggest a more complex situation. Changes in ultrastructural factors show that caudate size is only a small part of the issue, with changes in spine density and myelination likely having significant effects on neuron-neuron communication and hence network function. Further work, is required to elucidate the role the caudate plays in schizophrenia and

other disorders, particularly in functional network roles and changes in specific cell types in this structure. We are only at the start of detailed examination of the caudate in schizophrenia, with likely relationships to genetics, development, age of onset and drug treatments.

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