

An introduction to the putamen in schizophrenia.

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ABSTRACT

Historically the putamen has been known to have a key role in regulating motor function. However in recent years the importance of this nucleus in cognitive functions has become more understood, with a rough dorso-ventral distribution of function being described by several studies. Additionally the importance of the putamen as a key site of anti-psychotic action, inhibiting the uptake of dopamine from the nigrostriatal tract, has been emphasized with recent studies. This has led to renewed focus on this structure in the cognitive symptoms of schizophrenia.

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ARTICLE

The putamen is one of the basal ganglia nuclei and part of the striatum. It is a large structure clearly visible in coronal section through the striatum (see Figure 1). Historically it has been associated with motor function. Parkinson's'-induced putamen lesions can cause involuntary muscle tremors or movements, and putamen atrophy in Huntingdon's can result in jerky and unpredictable movements. In recent years increased research into this region has suggested a far broader range of functions for the putamen, including a critical role in schizophrenia and psychosis.

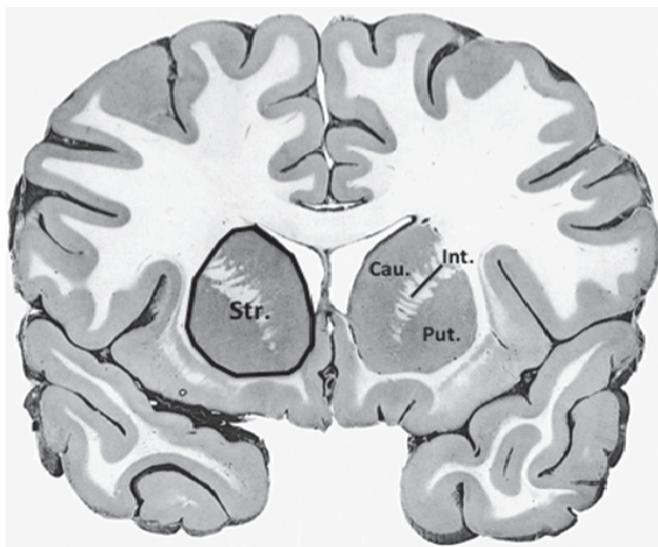


Figure 1. Coronal section at the level of the human striatum. The striatum (Str.) is composed of the Caudate (Cau.) and Putamen (Put.) either side of the Internal Capsule (Int.), the primary white matter structure of the striatum. Adapted from Hanaway & Kent (1987)

The putamen, along with the adjacent caudate, is composed predominantly of medium spiny neurons.

There is a complex mixture of cell types by chemistry with GABA-ergic cells making up around 95% of striatal neurons, with adenosinergic, dopaminergic, glutamatergic and substance-P containing neurons all present in smaller numbers within the putamen and striatum as a whole. These spiny neurons are densely packed and have many connections with each other, making pathways within the putamen extremely difficult to elucidate.

By far the largest input to the striatum is from the cortex, with all regions of the cortex represented, known as the corticostriatal pathway. The corticostriatal pathway does not equally split between the caudate and putamen, reflecting functional differences between these nuclei. The putamen receives input from the somatic sensory cortex in the parietal lobe, the extrastriate visual cortex and the auditory association region of the temporal lobes. The caudate nucleus mainly receives cortical projections from multiple association cortices. Frontal lobe input to the striatum is functionally from motor systems for both nuclei. Within these inputs there is structural organization, as visual and somatic sensory cortical projections are topographically mapped within different regions of the putamen.

The main output structure for medium spiny neuron axons is the thalamus, although major pathways also project from the striatum to the globus pallidus and the nucleus accumbens, as well as reciprocal projections back to the dopaminergic regions of the ventral tegmentum area and substantia nigra (reviewed in Purves *et al.* 2001; Shepherd, 2013). There is also functional separation within the striatum, with dorsal medium spiny neurons mainly involved in motor regulation, controlling limb, body and eye movement. In contrast ventral medium spiny neurons are linked to behavior, regulating reinforcement, aversion, reward and motivation systems (Ferre *et al.*, 2010; Yager *et al.*, 2015).

When examining basal ganglia involvement in schizophrenia, historically the key findings are to do with the dopamine system and the site of antipsychotic drug

action. The dopaminergic projection from the substantia nigra to the striatum is known as the nigrostriatal pathway and is the most well-characterised long dopaminergic pathway in the brain. The nigrostriatal pathway is formed from axons projecting from the large dopamine-producing neurons in the substantia nigra and rises dorsally to terminate in the dorsal striatum, including areas of the caudate and putamen. Immunohistochemical studies show the presence of intrinsic dopaminergic neurons which are not normally abundant in the striatum. The density of these neurons increases after lesioning of the nigrostriatal pathway, suggesting that they might serve as a compensatory mechanism for the lack of striatal dopamine (Betarbet *et al.*, 1997). They display a very particular pattern of striatal distribution, being especially abundant in the anterior-dorsal part of the caudate and putamen. Imaging and neuropathological investigation of striatal dopamine has 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, and is linked to symptom severity in patients (Howes *et al.*, 2013).

In the human brain the highest concentration of dopamine receptors are in the substantia nigra and basal ganglia, with D1 and D2 receptors showing the greatest density in the striatum (Hall *et al.* 1994; Hurd *et al.* 2001; Meador-Woodruff *et al.* 1996). Whilst D1 receptors are found in high concentrations in the corpus of the caudate, the medial putamen and the nucleus accumbens, the highest are found in the lateral putamen (De Keyser *et al.*, 1988; Cortés 1989; Hall *et al.* 1994; Meador-Woodruff *et al.* 1996). The D2 receptor has a similar distribution with high concentrations observed in the corpus of the caudate, the lateral and medial putamen and the nucleus accumbens (Camps *et al.* 1989; Khan *et al.* 1998; Murray 1994).

Despite the co-localisation of the D1 and D2 receptors in the striatum being somewhat similar the location of the dopamine receptors on striatal cells the projections are quite different (Kreitzer, 2009). D1 receptors are found exclusively post-synaptically on GABAergic striatonigral cells, which predominantly project ventrally to the substantia nigra (Gerfen *et al.* 1990). In contrast D2 receptors have a predominantly presynaptic location and are found on GABAergic striatopallidal cells, the projections of which head out of the striatum into the globus pallidus, another of the basal ganglia structures (Civelli *et al.* 1991; Gerfen *et al.* 1990).

Changes in the shape and size of the putamen in schizophrenia have been attributed to the consequences of antipsychotic and neuroleptic treatments, supported by animal studies and human MRI scans (Andersson *et al.*, 2002; Dazzan *et al.*, 2005; Mamah *et al.*, 2007). However ultra-structural examination of the spiny neurons of the striatum show changes in spine shape and axon density in the adjacent caudate, not the putamen, arguing against drug treatments as a cause (Kung *et al.*, 1998), and larger putamen sizes have been reported increased in schizotypal disorder without anti-psychotic treatment (Chemerinski *et al.*, 2013). A case where a 38-year old man with no relevant family history experienced a

lacunar infarct of the putamen region in the left basal ganglia and developed persecutory delusions and delusional memory, worsening over time until referral to a psychiatric unit suggests a functional link to psychosis (Farid & Mahadun, 2009).

Such is the relationship between putamen size and cognitive and mood function that some studies have suggested a correlation between them. Patients with good outcome schizophrenia have larger relative mean putamen, but not caudate, size than poor outcome patients or controls. A lateralised effect was observed too, with this enlargement more prominent for the dorsal putamen and right hemisphere. Striatal size was not related to whether patients were currently being treated with atypical or typical neuroleptics or whether they had been predominantly treated with typical or atypical neuroleptics over the past 3 years. This suggests the possibility that the expansion of putamen size may be a physiological correlate of neuroleptic responsiveness or that small putamen size at disease onset may be a predictor of outcome (Buchsbaum *et al.*, 2003). Stereological examination of the putamen in schizophrenia confirmed the imaging finding of decreased volume and showed a decrease on total neuron number (Kreczmanski *et al.*, 2007). Repeated amphetamine treatment, known to stimulate striatal dopamine, has been shown to increase dendritic spine density on putamen medium spiny neurons (Li *et al.*, 2003), suggesting that the number of cells and overall size are not the only factors in the interaction between schizophrenia, drug treatment and patient outcome. The putamen specifically and striatal structure in general has not been well researched in mental illness and changes to this system are not well understood, but is clearly of critical importance in the symptomatology of schizophrenia.

The evidence suggests that the dopaminergic activity from the nigrostriatal pathway provides direct or indirect trophic and functional support to the putamen. Whether this is done by known mechanisms, such as growth factors or direct stimulation of neurons by connecting synapses, or by some other mechanism is not clear.

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