

An introduction to the Internal Capsule in schizophrenia

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A B S T R A C T

The internal capsule is a significant white matter tract observed within the basal ganglia. It contains the majority of the cortico-spinal fibres and acts as the major relay for multiple cortico-subcortical networks and inputs to the thalamus from the body, as well as connecting to the corona radiata on the superior surface and the cerebral peduncle and spinal neurones on the inferior aspect. Decreased fractional anisotropy of the internal capsule has been reported by multiple studies in schizophrenia, although the details of the effects and precise regions of the internal capsule affected are complex. Structural MRI has shown that white matter density in this structure is decreased, irrespective of volume change. Changes in oligodendrocyte- and astrocyte-related gene expression have also been shown. Overall the internal capsule is a complex connective part of the brain that has significant disruption in schizophrenia, although detailed studies on cell, axon and molecular causes of this have not been performed.

Key words: Basal Ganglia, White Matter, Internal Capsule, Schizophrenia

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To anyone familiar with the basal ganglia during dissection, its distinct structure is characterised by large nuclei with a substantial white matter tract running through from the superior to the inferior surfaces (Shown in coronal section in Fig. 1.) Whilst it may be typical to focus on the subcortical grey matter in the nearby basal ganglia and thalamus, the internal capsule is a complicated structure in its own right, made up of multiple substantial white matter tracts with roles in several key pathways.

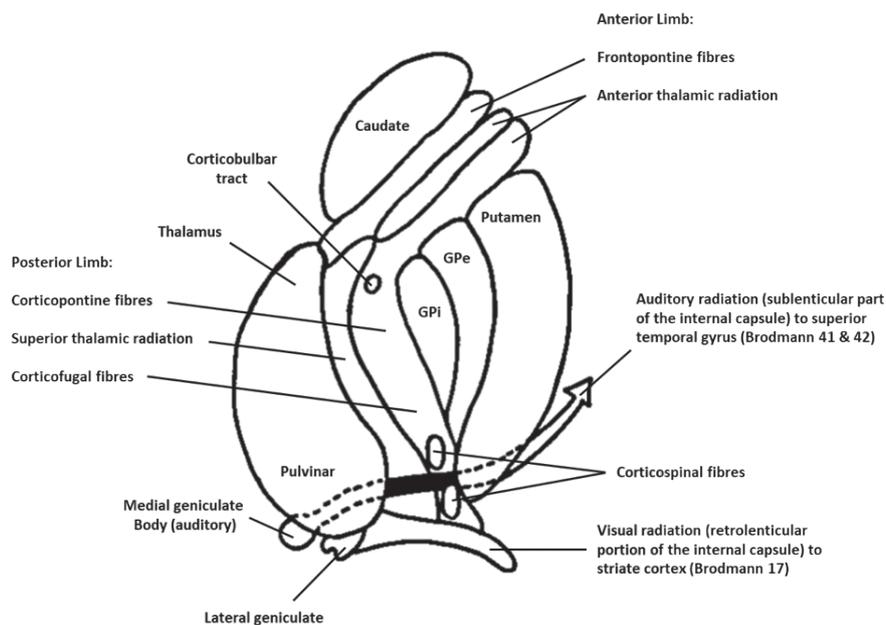
Fig 1. Coronal cut of human brain at through the anterior striatum. Str – Striatum, Cau – Caudate, Int – Internal Capsule, Put – Putamen.



The internal capsule is a substantial white matter structure lying between the caudate and putamen in the anterior basal ganglia and between the caudate head, putamen and thalamus more caudally. It has a key role in whole brain function, with almost all neural connections to and from the cerebral cortex running through it, as well as being the primary route of thalamic fibre tracts. As shown in Fig. 2, there are smaller fibre tracts within the internal capsule. The corticobulbar tracts relays signals from the motor cortex to the motor nuclei of the cranial nerves and other brainstem targets, whilst the corticopontine tract

has descending fibres from the cerebral cortex through internal capsule, then the cerebral peduncle the pontine nuclei. Also, there are descending fibre tracts known as the corticospinal fibres, which run from the cerebral cortex through the internal capsule to the spinal neurons and interneurons. The superior thalamic radiation has multiple fibres rising from the body and leaving the medial surface of the posterior limb of the internal capsule towards the thalamus, before being redirected to the parietal lobe for general sensation.

Fig 2. Schematic of coronal cut of stratum showing the anterior and posterior limbs and genu of the internal capsule. GPI – Globus Pallidus internal, GPe - Globus Pallidus external. Medial surface to left.



Other fibres project from the cerebral cortex to basal ganglia structures, such as the putamen and caudate, as well as disparate subcortical structures. These fibres fan out above the internal capsule to connect to the whole cerebral cortex in a fan-like structure called the corona radiata, where they merge and entwine with cerebral-cerebral connections in the centrum semiovale of each hemisphere.

Anatomically the internal capsule is a continuous sheet which forms the medial boundary of the lenticular nucleus (the putamen and globus pallidus) and continues round to partially enclose the lenticular nucleus caudally and inferiorly. The inferior region is where the fibres descending to the cerebral peduncle are funneled, whereas the superior surface is the direction of fibres destined to move into the corona radiata.

The internal capsule in schizophrenia has been examined using imaging methods by several studies. These fall in to two main methodological groups.

The first is the use of Diffusion Tensor Imaging to measure fractional anisotropy (FA). Many studies have consistently shown that, compared with controls, patients with schizophrenia displayed significantly lower FA of the internal capsule (Grazioplene et al., 2018). Whilst this finding has been repeatedly demonstrated, further details have shown the typical confusion that schizophrenia research is known for. Some of these studies have suggested that the decreased FA is present in the posterior limb (Holleran et al., 2014, Ublinskii et al., 2015, Ho et al., 2017, Meng et al., 2018), whilst others on the anterior limb (Levitt et al., 2010). Whilst most studies have shown a lateralised FA change, they often disagree on whether it is in the left or right hemisphere (Ellison-Wright et al., 2014, Holleran et al., 2014, Ho et al., 2017, Meng et al., 2018). More recent, and perhaps more sensitive examinations, have shown FA decrease in schizophrenia in the cerebral peduncle (Ho et al., 2017) and the corona radiata (Meng et al., 2018), suggesting this may be a functional change in axon alignment and function rather than a specifically structural one.

Interestingly, FA changes in the internal capsule have been reported to be linked to cognitive performance in the disorder. Anterior limb FA correlated positively with performance on measures of spatial and verbal declarative/episodic memory in schizophrenia (Levitt et al., 2010), and reductions in internal capsule anisotropy have been linked with poor outcomes in schizophrenia, with right hemispheric changes more significantly associated with positive symptomatology (Mitelman et al., 2007a, Mitelman et al., 2007b).

As internal capsule FA changes have been reported in first episode schizophrenia cases it may be that FA in this structure predate the onset of illness, suggesting a possible method of diagnosis prior to first episode (Ublinski et al., 2015).

The second method is structural MRI, where studies have suggested significant volume reduction in the bilateral anterior limbs of the internal capsule (Suzuki et al., 2002), although more recent examination has shown a significant increase in volume in the anterior limbs (Goghari et al., 2011). However, multiple examinations have shown white matter density is decreased in internal capsule independent of volume (Hulshoff Pol et al., 2004, Suzuki et al., 2004, Lang et al., 2006).

Similar to the implications of decreased FA, volumetric internal capsule changes have been associated with symptomatology. Patients with poor-outcome had significantly smaller dorsal areas than healthy comparison subjects, but good-outcome patients did not differ from healthy comparison subjects. Larger relative volumes of the caudate, putamen, and thalamus are reported to be associated with larger volumes of the internal capsule in healthy comparison subjects and good-outcome patients, consistent with frontal-striatal-thalamic pathways. Larger ventricles were associated with smaller internal capsules, particularly in healthy comparison subjects. These findings are consistent with the FA data, suggesting disruption of internal capsule fibers in poor-outcome schizophrenia patients. (Brickman et al., 2006)

Myelin-related genes have been examined in the internal capsule in schizophrenia due to the internal capsule's role in the cortico-striato-thalamic circuits (Mega and Cummings, 1994). The results are complex, but the authors show decreased mRNA in CNP, GALC, MOG and MAG expression in schizophrenia. Interestingly they also show increased ALDH1L1 and GFAP mRNA in schizophrenia (Barley et al., 2009), suggesting a possible change in astrocyte function, as well as the myelin-related roles. Whilst only a single study, this suggests possible routes for further molecular and neuropathological roles of glia in the internal capsules white matter disruption.

Overall there is considerable evidence for significant disruption of white matter tracts within the internal

capsule, although narrowing down the precise causes and effects has proved elusive. As Holleran et al (2014) state, "These deficits can be driven by a number of factors that are indistinguishable using in vivo diffusion-weighted imaging, but may be related to reduced axonal number or packing density, abnormal glial cell arrangement or function, and reduced myelin." To establish the extent of internal disruption in schizophrenia, and possible causes of the findings described above, we require experiments to examine the axonal arrangement and glial cell biology of this structure, and the genetic and molecular factors that may underlie the local regulation of white matter to elucidate the causes of the observed changes.

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