The Basal Ganglia

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9.1 The Basal Ganglia

The basal ganglia refer to a variety of subcortical neuronal structures with roles such as motor learning, executive functions and behaviour and emotions. Basal ganglia refers to nuclei embedded deep in the brain hemispheres such as the striatum or caudate-putamen and globus pallidus (GP), although typically includes structures located in the diencephalon such as the subthalamic nucleus (STN) and mesencephalon such as the substantia nigra (SN). It was clinical observed that during the twentieth century which showed that lesions of the lenticular nucleus, the grouping of the putamen and globus pallidus (GP), and the subthalamic nucleus (STN) was associated with Parkinsonism, dystonia and hemiballismus [1, 2].

The basal ganglia can be roughly categorised into input nuclei, output nuclei and intrinsic nuclei. Input nuclei are those structures receiving incoming information from different sources such as the cortex, nigra of thalamus. The caudate, putamen and the nucleus accumbens (NAcc) are input nuclei. The output nuclei are those structures that project from the basal ganglia to the thalamus and consist of the internal part of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). The intrinsic nuclei such as the external segment of the globus pallidus (GPe), the STN and the substantia nigra pars compacta (SNc) are located between the input and output nuclei in the information pathway. Cortical and thalamic efferent information enters the striatum where it is processed within the basal ganglia system, output nuclei (GPi and SNr) project mainly to the thalamic VNG, themselves relaying projections to the frontal cortex [3].

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9.2 Caudate

The caudate is a dense subcortical nucleus composed of spiny neurons and forms the striatum along with the putamen. The caudate 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 (IC) (Fig. 9.1). 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 SNc (A9 dopamine

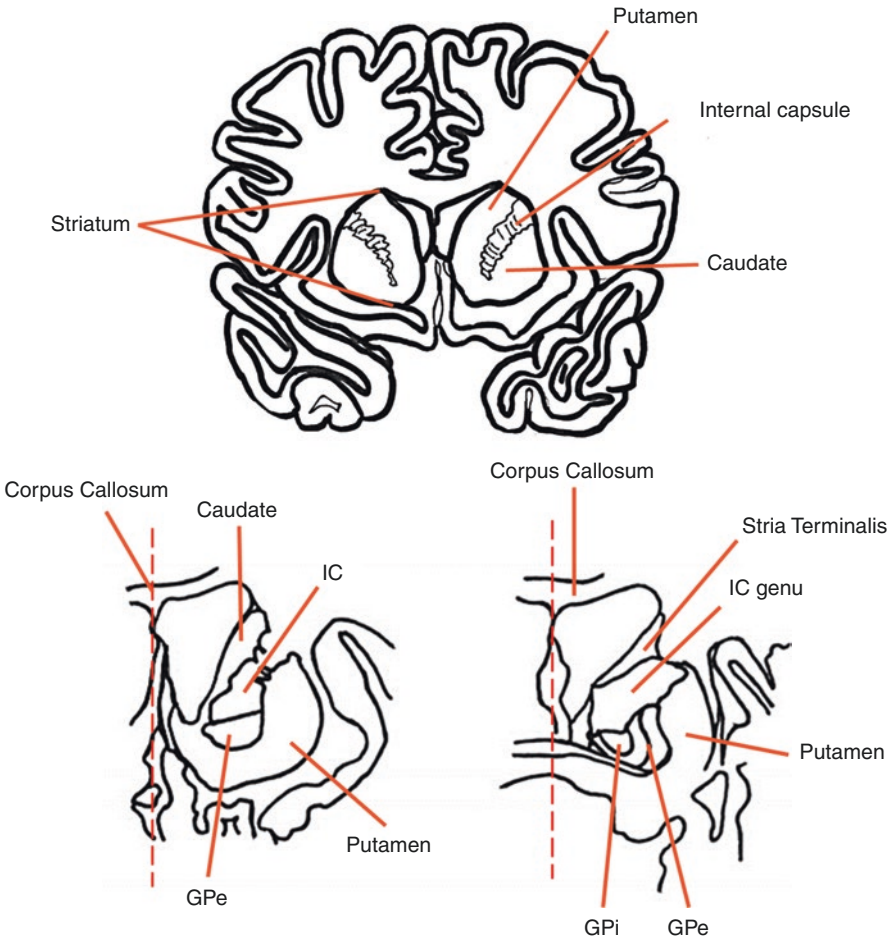

Fig. 9.1 Coronal view of the striatum. The striatum is composed of the caudate and putamen on either side of the internal capsule (IC), the primary white matter structure of the basal ganglia. Lower images show schematics of the striatum at its anterior end (lower left) and more posteriorly (lower right). Dotted red line represents the midline of the brain. *IC* internal capsule, *GPi* globus pallidus internal part, *GPe* globus pallidus external part

cells) [4, 5]. The caudate also receives projections from the dlPFC and the premotor cortex and in turn sends projections to the GP as well as reciprocal projections to the SN. There are also complex and reciprocal connections between several thalamic nuclei and the caudate, (reviewed in [6, 7]). 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 [8, 9]. 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 [6, 10].

The primary focus of investigation of the basal ganglia in schizophrenia has to do with the DA system and the various sites of antipsychotic drug action in the striatum. The DA-projection from the SN to the striatum is known as the nigrostriatal pathway and is the most well-characterised long DA-pathway in the brain. The nigrostriatal pathway is formed from axons projecting from the large DA-producing neurons in the SN, 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 DA have found that elevated DA-synthesis capacity is seen in the origin of DA neurons in the SN as well as their striatal terminals in schizophrenia, linked to severity of psychosis in patients. The increased nigrostriatal DA is likely to be a result of excess production in DA-positive nigral oval cells [11–13].

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 the fundamental biology of the illness [14, 15]. However, imaging studies have shown that the decrease of caudate volume is also found in antipsychotic-naïve first-episode patients [16], and ultrastructural examination of the spiny neurons of the striatum show changes in spine shape and axon density in the caudate. Spine pruning, the process of losing neuronal spines, 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 DA, and progressive spine pruning strongly effecting elevated frontal cortical excitation of pyramidal neurons as a result of striatal hyperdopaminergia [17, 18]. But these 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 the first scan [19, 20], possibly arguing against drug treatments being the cause of caudate changes [21, 22].

Volumetric MRI studies show decreases of 8–9% in caudate volume in the offspring of patients with schizophrenia [23], although other investigations have not reported similar changes in first-degree relatives [24]. If these alterations are borne out by further research we must accept that not all of these offspring would develop schizophrenia. Therfore 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 [25]. Meta-analysis of the caudate

in schizophrenia has tended to show a volumetric change, suggesting decreasing caudate size more common [26]. Caudate volume is often reported to be reduced in first-episode schizophrenia, with progressive decreases reported over time in a dose-dependent manner with medication [16, 27, 28]. This is consistent with meta-analyses suggesting increased loss of basal ganglia grey matter over time in chronic schizophrenia compared to the first episode, and the complexity of reported findings specifically in the caudate over time shows this requires more detailed investigation [29].

Stereological studies have, somewhat typically, produced conflicting findings. Initial findings suggested that the caudate has higher neuron counts in schizophrenia [30], but more recent studies have concluded that the caudate has shown similar neuropathological changes to the putamen, with a decreased total number of neurons in schizophrenia [31]. The possible causes of such directly conflicting results may well be down to the stereological methods, a controversial subject that has been discussed elsewhere [32, 33]. Ultrastructural morphometric study of myelinated fibres in the caudate in schizophrenia demonstrated atrophy of axon due to the alteration of myelin sheath [34], possibly indicating disruption of signal transmission in the caudate-related networks described previously. Treatment-responsive schizophrenia subjects had about a 40% decrease in the number of mitochondria per synapse in the caudate nucleus and putamen, whilst treatment-resistant cases had normal values. A decrease in mitochondrial density in the neuropil distinguishes paranoid from undifferentiated schizophrenia.

Mitochondrial hyperplasia occurs within axon terminals that synapse onto dopamine neurons, but mitochondria in dopamine neuronal somata are similar in size and number. In schizophrenia, mitochondria are differentially affected depending on the brain region, cell type, subcellular location, treatment status, treatment response and symptoms [35].

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 suggests 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.

9.3 Putamen

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 Fig. 9.1). Historically, it has been associated with motor function as 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.

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 organisation, 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 GP and NAcc, as well as reciprocal projections back to the DA regions of the VTA and SN [36, 37]. There is also functional separation within the striatum, with dorsal medium spiny neurons mainly involved in motor regulation, controlling limb, body and eye movement, whilst in contrast ventral medium spiny neurons are linked to behaviour, regulating reinforcement, aversion, reward and motivation systems [10, 38].

When examining basal ganglia involvement in schizophrenia, the key findings are to do with the DA-system and the site of antipsychotic drug action. Immunohistochemical studies show the presence of intrinsic DA 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 DA [39]. They display a very particular pattern of striatal distribution being especially abundant in the anterior-dorsal part of the striatum. In the human brain, the highest concentration of DA receptors is in the basal ganglia, with D_1 and D_2 receptors showing the greatest density in the striatum [40–42]. Whilst D_1 receptors are found in high concentrations in the corpus of the caudate, the medial putamen and the NAcc, the highest are found in the lateral putamen [40, 42, 43]. The D_2 receptor has a similar distribution with high concentrations observed in the corpus of the caudate, the lateral and medial putamen and the NAcc [45–47]. Despite the co-localisation of the D1 and D2 receptors in the striatum being somewhat similar to the location of the dopamine receptors on striatal cells, the projections are quite different [48]. D_1 receptors are found exclusively post-synaptically on GABA-ergic striatonigral cells, which predominantly project

ventrally to the SN [49]. In contrast, D_2 receptors have a predominantly presynaptic location and are found on GAB-ergic striatopallidal cells, the projections of which head out of the striatum into the GP, another of the basal ganglia structures [49, 50].

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 [15, 51, 52]. However, ultra-structural examination of the spiny neurons of the striatum shows changes in spine shape and axon density in the adjacent caudate, not the putamen, arguing against drug treatments as a cause [21, 22], and larger putamen sizes have been reported to be increased in schizotypal disorder without anti-psychotic treatment [53]. 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 [54].

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 [14]. Stereological examination of the putamen in schizophrenia confirmed the imaging finding of decreased volume and showed a decrease on total neuron number [31]. Repeated amphetamine treatment, known to stimulate striatal DA, has been shown to increase dendritic spine density on putamen medium spiny neurons [55], 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 have 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 DA 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.

9.4 Internal Capsule

To anyone familiar with the basal ganglia during dissection, the distinct structure of the IC substantial as a large white matter tract running through from the superior to the inferior surfaces of the striatum is well known (shown in coronal section in

Figs. 9.1 and 9.2) 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.

The IC is the large 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. 9.2, there are smaller fibre tracts within the IC. 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, through the cerebral peduncle to the pontine nuclei. Also, there are descending fibre tracts known as the corticospinal fibres which run from the cerebral cortex through the IC 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 processing of general sensation information. Other fibres projects from the cerebral cortex to basal ganglia structures, such as the putamen

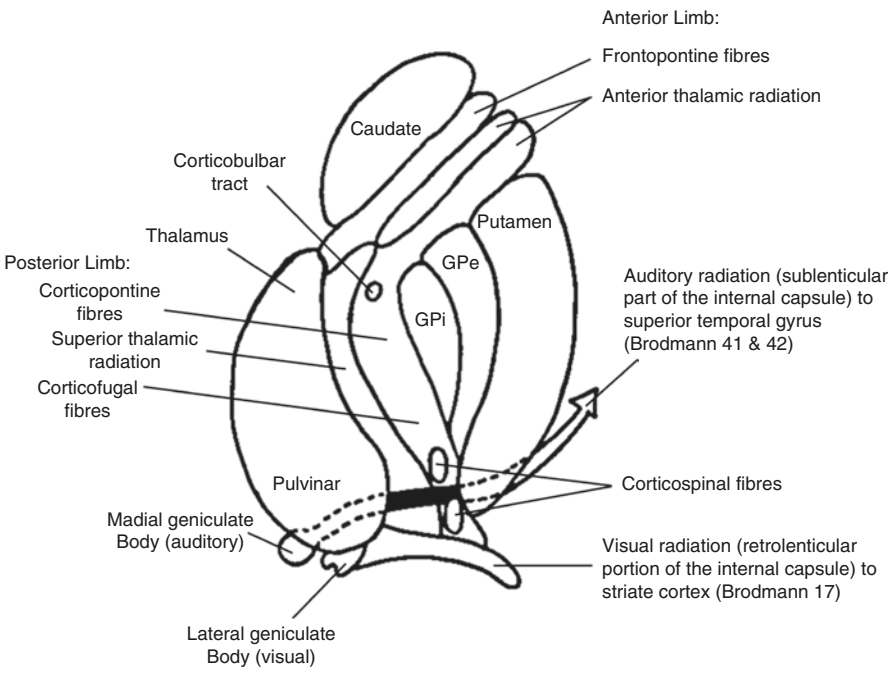

Fig. 9.2 Schematic of coronal cut of stratum showing the anterior and posterior limbs and genu of the internal capsule. *GPi* globus pallidus internal, *GPe* globus pallidus external. Medial surface to left

and caudate, as well as disparate subcortical structures. These fibres fan out above the IC 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 IC is a continuous sheet which forms the medial boundary of the lenticular nucleus 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 funnelled, whereas the superior surface is the direction of fibres destined to move into the corona radiata.

The IC in schizophrenia has been examined using imaging methods by several studies. Multiple studies have consistently shown that compared with controls, patients with schizophrenia displayed significantly lower fractional anisotropy (FA) in the left IC as measured by diffusion tensor imaging [56]. 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 [57–60], whilst others on the anterior limb [61]. Whilst most studies have shown a lateralised FA change, they often disagree on whether it is in the left or right hemisphere [57, 59, 60, 62]. More recent, and perhaps more sensitive, examination has shown FA decrease in schizophrenia in the cerebral peduncle [59] and the corona radiata [60], suggesting this may be a functional change in axon alignment and function rather than specifically and structural one. Interestingly, FA changes in the IC 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 [61], and reductions in IC anisotropy have been linked with poor outcomes in schizophrenia, with right hemispheric changes more significantly associated with positive symptomatology [63, 64]. As IC 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 [58].

Structural MRI studies have suggested significant volume reduction in the bilateral anterior limbs of the IC [65], although more recent examination has shown a significant increase in volume in the anterior limbs [66]. However, multiple reports have shown white matter density is decreased in IC independent of volume [67–69]. Similar to the implications of decreased FA, volumetric IC 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 IC fibres in poor-outcome schizophrenia patients [70].

Myelin-related genes have been examined in the IC in schizophrenia due to the ICs role in the cortico-striato-thalamic circuits [71]. The results are complex, but the

authors show decreased CNP, GALC, MOG and MAG mRNA expression in schizophrenia, as well as increased ALDH1L1 and GFAP mRNA in schizophrenia [72], 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 IC white matter disruption.

Overall, there is considerable evidence for significant disruption of white matter tracts within the IC, although narrowing down the precise causes and effects has proved elusive. As Holleran *et al*. 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' [57]. 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.

9.5 Globus Pallidus

The GP is a ventromedial structure of the basal ganglia. It is flanked laterally by the striatum and inferior to the thalamus. Whilst the GP is structurally a consistent nucleus, functionally it can be split into two sections, the more medial internal part (GPi) and the lateral external part (GPe).

In contrast to the medium-spiny neurons of the striatum the GP is predominantly made up of larger parvalbumin-positive disc-shaped aspiny GABA-ergic neurons with large number of dendrites and pathologically appears far denser than adjacent basal ganglia structures. The GPe, structurally lying immediately medial to the striatum, predominantly receives inputs directly from the striatum by means of a pronounced GABA-ergic pathway, making up the majority of synaptic nuclei within this structure. The primary output of the GPe is composed of GABA-ergic projections to the STN, located inferior of the GPi. In turn the STN has a substantial glutamatergic projection to the GPi tracing an indirect pathway from the striatum via GPe.

The GPi is found more medial than the GPe but still receives a similar direct GABA-ergic inhibitory cluster of projections directly from the striatum. The GPi has two major outputs, the first to the thalamus via two pathways. The lenticular fasciculus is one output pathway which projects via the IC whilst the ansa lenticularis projects ventrally around the IC. These meet at the thalamic fasciculus and terminate in the ventral anterior and ventrolateral parts of the thalamus, which in turn project excitatory glutamatergic pathways to the premotor and frontal cerebral cortices, areas involved in cognition, planning and initiation of movement. This feedback pathway is involved in regulating the level of excitation in the premotor cortex and thus giving a mechanism for basal-thalamic-cortical regulation of movement. The second major Gpi output is a cluster of glutamatergic outputs to the SNr, suggested to regulate nigral DA release, and thus provide a feedback loop for the

nigrostriatal tract. Various experimental manipulations, including microdialysis in rodent and PET in primate models, have shown a role of the GP and STN in regulating somatodendritic DA release in the SN under normal and experimental conditions [73], and probabilistic computation has added to the anatomical argument that the GP is the critical regulatory step from striatal output to the thalamus [74]. This is summarised in Fig. 9.3.

The returning cortical input to the striatum activates inhibitory neurons to the GP, decreasing activity in the tonically active neurons in the GP which then decrease the inhibitory action on ventral anterior and ventrolateral parts of the thalamus. The conclusion of this pathway is therefore disinhibition of thalamic excitation of the cerebral cortex and thus greater activation of the cortex. In the case of the motor cortex activation of the direct pathway would increase the ease of initiation and ease of movement. The GP is also connected with structures involved in reward circuitry such as the NAcc, habenula and the VTA, although further research is required to identify the GP-specific role in these circuits [76, 77].

Structural MRI imaging studies have shown conflicting results, with studies often showing no overall change in size in the GP in schizophrenia but a change in shape, whilst others suggest that GP size is changed. One analysis of basal ganglia relative size and shape suggests that the GP was significantly larger overall, with another study showing increased GP size and altered shape in schizophrenia on the right side only, a lateral change which seems unique within the basal ganglia. Enlargement of basal ganglia structures has typically been found to be related to antipsychotic medication, although the study determining the lateralised effect found no such effect of medication taken at the time of study [15, 78–80].

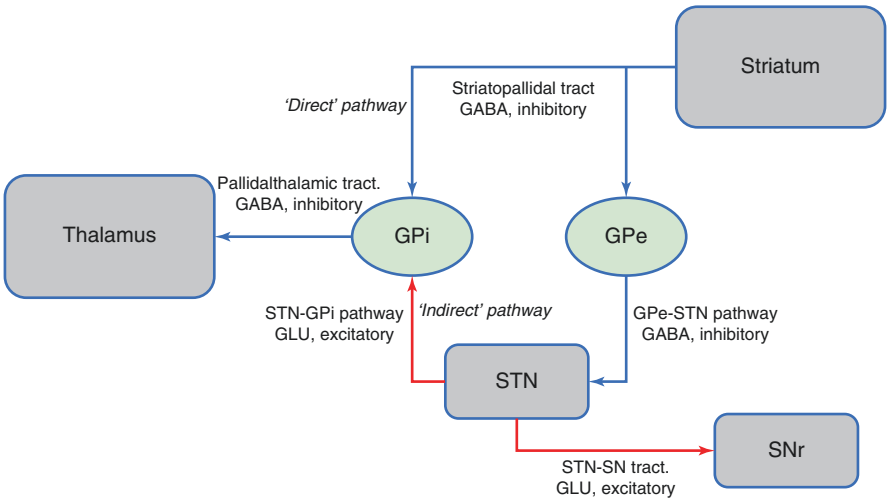

Fig. 9.3 Circuit diagram of the major connections of the GP. Blue—inhibitory pathways, red—excitatory pathways. *STN* sub-thalamic nucleus, *SNr* substantia nigra pars reticulata, *GABA* gamma-amino-butyric acid, *GLU* glutamate [75]

The size increase in GP in schizophrenia has been suggested to be related to the total psychotic symptoms. One study showing GP enlargement in schizophrenia with psychosis also showed GP shrinkage in schizophrenia cases without psychosis, with the GP smaller even than unaffected controls [80]. Dysfunctional interhemispheric connections of the GP has been proposed as the primary site for cognitive disturbance in first-episode schizophrenia measuring negative symptoms and cognitive impairment in functional MRI examination [81].

Despite the intriguing imaging results and the key role the GP plays in regulating striatonigral and striatothalamic circuits, direct neuropathological investigation of the GP is thin on the ground in schizophrenia. One landmark study has reported that the GPi decreased in volume by 20% whilst the GPe was not changed when systematically examined in sections through the structure using histological staining [82]. One early study suggested increased iron, termed 'mineralisation', of the GP in schizophrenia, although follow-up studies failed to replicate this effect [83–85]. As has previously been mentioned, animal studies using microdialysis have revealed that the striatopallidal pathway from both GP nuclei regulates SN and VTA dopaminergic cells. Although so far direct investigation of binding potential change of D_2 receptor in the pallidus using PET show inconclusive results in both schizophrenic patients and high-risk individuals [86, 87].

High-risk individuals have shown more interesting results in other studies. Teenagers at high risk of developing schizophrenia have left GP size increased by a small but significant average of 1% compared to non-high-risk controls, with a more pronounced increase with age. This suggests that the increased size may predate schizophrenia first-onset, and GP enlargement may not be down entirely to antipsychotic action [88].

In a similar finding, voxel-based morphometry examination with structural MRI has shown increased grey matter in the GP in first-degree relatives of schizophrenia patients as well as those patients themselves [89]. GP deformation was also observed in unaffected relatives of schizophrenia patients, albeit to a lesser degree than those suffering with schizophrenia [80].

Although the role of the GP in modulating striatal output to the thalamus and midbrain has good supporting evidence, the GP's role in other, less prominent circuits is not well understood. There have been few good quality studies to investigate the cognitive- and movement-related role of this structure in both normal controls and schizophrenia patients, and a woeful lack of direct examination at the cellular level using any type of pathological techniques. Additionally, the problems of interpreting the results we have obtained are compounded by the known effects of antipsychotic medication. This makes the GP a prime candidate for further examination in schizophrenia from both a basic neuroscientific stance and in future drug development.

9.6 Nucleus Accumbens

Historically, the NAcc has been of interest in neuropsychiatric disorders due to its proposed role in addiction, particularly with morphine, cocaine and amphetamine, thought to be due to drug-mediated release of DA from the VTA and SN. More

recently, nicotine addiction has been suggested to work through this pathway [90, 91]. The NAcc is a basal ganglia nucleus, sometimes described as part of the ventral striatum although it is distinct from the two primary striatal nuclei, the caudate and putamen, and is a central part of the cortico-ganglia-thalamic loop [92]. The NAcc is directly continuous with the main dorsal part of the striatum, and often described as part of the striatal complex. However, it has some structural distinction compared to the putamen and caudate as it is split into a core and a shell [93]. The core is largely continuous with the rest of the striatum and is composed of similar spiny neurons which predominantly form the output neurons of the NAcc, although the shell has independent projections to the bed nucleus of stria terminalis and lateral hypothalamus [93, 94]. The NAcc also receives a distinct collection of DA neurones directly from the VTA, the DA nucleus that lies adjacent to the SN. This is known as the mesolimbic pathway and has been strongly implicated in addiction [95]. Whilst the main output structure for striatal medium spiny neuron axons is the thalamus, major pathways also project to the GP and the NAcc, as well as reciprocal projections back to the DA regions of the VTA and SN (Shepherd 2013). There is a reciprocal feedback loop of GABA projections from the NAcc to the ventral pallidum and VTA, and there are glutamatergic projections from the PFC, hippocampus and amygdala. The amygdala glutamatergic projection to the NAcc in particular has been suggested as key in modulating cue-triggered motivated behaviours [96], and the PFC regulates NAcc dopaminergic output by glutamatergic projection [97]. Hippocampal projections to the NAcc arise from the subiculum, the most inferior part of the hippocampal formation, lying between CA1 and the entorhinal cortex (discussed in Chap. 6). The ventral subiculum exerts a strong regulatory role on activity of DA projections from the VTA via glutamatergic mechanisms localised within the NAcc [98, 99]. The precise pattern of inputs to the NAcc is complicated, but the projections from the cortex, thalamus and amygdaloid are topographically organised (see Groenewegen et al. [100] for review), meaning that only in limited parts of the nucleus do interactions between these inputs occur.

The structure as a whole has evidence of change in schizophrenia, with a 42% decrease in NAcc volume and 50% decrease in neuron number reported [101, 102], but this is in contrast to other studies of the same regions showing no changes [103]. Post-mortem studies have mostly suggested that the NAcc shows no overall change in volume in schizophrenia, although one small scale ($n = 9$) stereological study did report an overall increase in NAcc size [31, 101, 104, 105]. Some imaging studies have suggested decreased volume [16, 106]. The right NAcc and caudate higher neuron numbers in schizophrenia [30], with another study showing no change in NAcc neuron number [31]. The possible causes of such strongly conflicting results may well be down to the stereological methods [33].

The very large ENIGMA project scanning over 2000 schizophrenic brains compared to more than 2500 controls showed the NAcc was smaller in schizophrenia, as well as similar findings in smaller studies [16, 106]. This has not been consistently reported in large imaging studies, with striatal volumes, including the NAcc, showing no change in schizophrenia [82].

The NAcc has a potentially important role in the biology of schizophrenia as it is part of a complex processing loop of cortico-striato-nigral-thalamo-cortical circuits [107], which has been assumed to be a prime system for the elevated DA levels in schizophrenia, based on its functional properties and evidence of antipsychotic drug action [108–110]. DA turnover was not increased in schizophrenic patients but, as assessed by the spiroperidol-binding technique, there was a significant increase in post-synaptic receptor sensitivity. The change in the dopamine receptor occurred in NAcc, putamen and caudate nucleus [111–118]. Ultrastructural examination of the NAcc shows that appearance, size and density of mitochondria were normal in the nucleus accumbens [35], but that NAcc synapses show a 19% increase in the density of asymmetric axospinous synapses in the NAcc but not that in the shell in schizophrenia. Similarly postsynaptic densities of asymmetric synapses had 22% smaller areas in the core NACC but again not in the shell, suggesting increased excitatory input to the NAcc core in schizophrenia [119]. The cortico-striato-nigral-thalamo-cortical circuits have been suggested to be a prime system for the elevated DA levels in schizophrenia, based on its functional properties and evidence of antipsychotic drug action therein [108, 110]. The changes in DA receptors occurred in the NAcc, putamen and caudate nucleus [113, 114]. Initially, studies found no change in possible DA-receptor sensitivity in the NAcc, but one later neuropathological study has reported potential decreased DA-sensitivity change [116, 118].

Amphetamine administration yields an NAcc neurotensin response which can be blocked using a dopamine D1 antagonist, suggesting a physical as well as functional variation in dopamine receptor subtypes throughout the NAcc. These differing regulatory pathways moderated by DA receptors clearly have significant implications for the role of antipsychotic medication in schizophrenia treatment. The NAcc has also been shown to be involved in stress-activated activation of the DA system and thus may be related to schizophrenia symptoms influenced by stress. Information transfer from ventral to dorsal striatum, essentially the mesolimbic pathway, relevant to antipsychotic medication depends on both striato-corticostriatal and striato-nigro-striatal sub-circuits. Although the functional integrity of the former appears to track improvement of positive symptoms of schizophrenia, the latter has received little experimental attention in relation to the illness. Compared with non-refractory patients, treatment-resistant individuals exhibited reduced connectivity between ventral striatum and SN. Furthermore, disturbance to corticostriatal connectivity was more pervasive in treatment-resistant individuals [120]. Controlled treatment of antipsychotic medication in rats such as haloperidol shows significant intermediate-early gene mRNA in the striatum, particularly strongly in the NAcc. In contrast clozapine produces a similar Fos-response in the NAcc but not the rest of the striatum [108, 110]. As with the other basal ganglia, the role of the NAcc is poorly understood given its clear critical role in both the pathophysiology of schizophrenia and in the role antipsychotic medication plays in the treatment of the disorder. Further examination is needed in this structure and the associated subcortical networks, to better target future treatments.

9.7 Substantia Nigra

The substantia nigra (SN) is a paired midbrain structure that lies immediately ventral to the cerebral peduncles at the level of the superior colliculus (Fig. 9.4) and has a critical regulatory role in the CNS. The dysfunction of this structure is implicated in the pathology of several serious illnesses. Substantia nigra translates from the Latin as 'black substance' as it is recognised by its characteristic black/brown-stained appearance, a result of the neuromelanin granules contained within the DA neurons as a by-product of DA metabolism (shown in Fig. 9.5). This is an easily observable phenomenon in Parkinson's disease where decreased DA synthesis causes a loss of neuromelanin formation in these cells and thus the loss of the dark colouration normal to the SN. The SN is the predominant DA-producing structure of the brain, along with smaller DA-producing cell populations in the VTA, hypothalamus and zona incerta.

Structurally the SN is often split into two distinct regions: the SN pars compacta (SNpc) and the SN pars reticulata (SNpr). The SNpc, the inner layer of the SN closest to the cerebral aqueduct, is a densely packed structure containing the large DA-producing neurons, modulated by accompanying interneurons, and is the source of the DA projections to the striatum, GP and the SNpr. Input into the SNpc occurs via GABA-ergic and glutamatergic feedback mechanisms from striatal and GP regions [121–124], with the SNpc receiving almost all its regulatory input from the GP with a small input from the frontal lobe. By contrast, the SNpr is larger but far more diffuse and comprised of much smaller, GABA-neurons than the SNpc, and occupies the outer layer of the SN. These neurons receive the SNpc DA projections and send GABAergic projections to the ventral anterior and ventrolateral thalamus, the superior colliculus and to the pedunculopontine complex, a brainstem nucleus caudal to the SN. These subdivisions have a reciprocal set of internal connections making a functional loop from the SNpc to the striatum, back to the SNpr to regulate the SNpc. The causes of excess SNpc DA in psychosis or decreased SNpc DA in Parkinson's disease are not well understood, but a key focus of interest is the SN-striatal loop. Internal connectivity also occurs via glutamatergic and GABA-modulated interneuron–dendritic interactions, modulating DA activity of the SN both within and between the SNpc and SNpr [121, 125, 126].

In schizophrenia the primary interest in the SN is due to it being the origin of the nigrostriatal pathway, the most prominent SN DA projection with axons from the SNpc DA neurons ascending into the striatum in a topographic manner, although with a distinct cluster that terminates in the dorsal putamen. This pathway is part of the basal ganglia loop, a functional system thought to have an important regulatory role in cognition. DA pathways from the SN and VTA are shown in Fig. 9.6.

DA influence on striatal medium spiny neurons is receptor-specific, with D_1 (excitatory) and D_2 (inhibitory) receptors leading to excitatory and inhibitory striatal responses, which permit discrimination of motor programs to suit the required task, the dominant function of the nigrostriatal pathway. Historically, psychosis has been treated using first-generation antipsychotics, which primarily bind to the D_2 receptors and have slow dissociation rates. D_2 receptors are found in the striatum

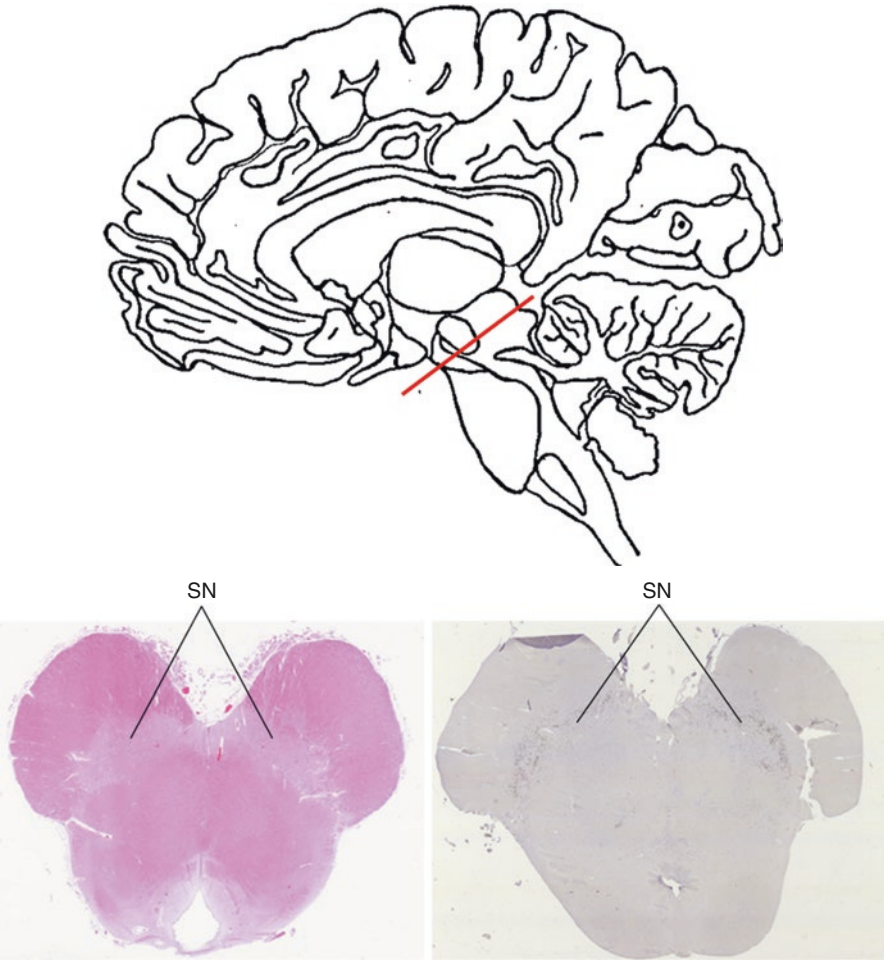

Fig. 9.4 Coronal cuts through midbrain at the level of the superior colliculus, cut indicated by red line on the upper image. Adjacent 10 μm slides stained with H&E (lower left) and cresyl-violet (lower right) histology both show the substantia nigra (SN) clearly by the presence of the large DA-producing neurons

where they modulate SN DA signal from the nigrostriatal pathway into the putamen. There is a strong correlation between therapeutic doses of antipsychotics and binding at the D_2 receptors [123, 124, 127], and D_2 antagonism can cause motor dysfunction such a pseudo-parkinsonism, which remained a problem with these early drug regimes. Second-generation antipsychotic drugs generally have lower rates of D_2 occupancy, decreasing the motor symptoms but often have better therapeutic outcomes. This is thought to be due to their dual action on the serotonin system, primarily through 5-HT_{2A} antagonism in addition to multiple reported sites of action other than dopamine D_2 receptors, including dopamine (D_1, D_3, D_4),

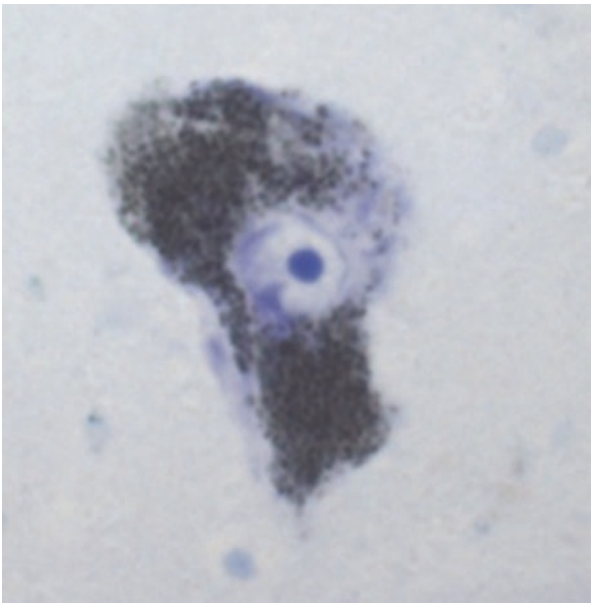

Fig. 9.5 Image of a large DA-producing SN neuron with light cresyl-violet staining. In addition to the clear nucleus and nucleolus, the neuromelanin can be clearly seen in the cytosol. Taken at ×400 magnification

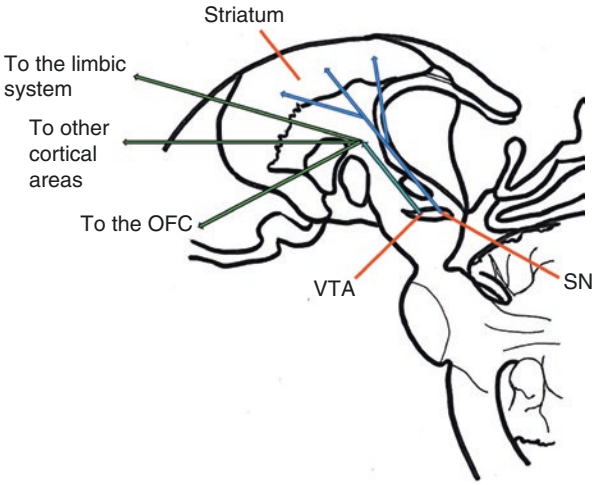

Fig. 9.6 Representation of the layout of the mesolimbic and mesocortical (green) and nigrostriatal (blue) pathways. These DA pathways have been heavily implicated in behavioural regulation, particularly in regard to antipsychotic medication action and addiction. *OFC* orbitofrontal cortex, *VTA* ventral tegmentum area, *SN* substantia nigra

serotonin (5-HT_{1A}, 5-HT_{2C}, 5-HT_6, 5-HT_7), muscarinic cholinergic and histamine receptors [128, 129]. In direct comparisons, there has been no difference in the efficacy of the first-generation antipsychotics and second-generation antipsychotics in acute therapy in schizophrenia at similar doses [130]. However, meta-analysis has shown some evidence that the second-generation antipsychotics may be better tolerated over time [131] and have a greater effect on negative symptoms than the first-generation antipsychotics [132, 133], primarily modulated by the serotonergic effects of the second-generation antipsychotics. Comparison of the effects of these

drugs on cognition have not yielded clear findings, although some mild improvement in cognitive symptoms with the second-generation antipsychotics have been reported [134–136]. As much of the basal ganglia DA system is involved with the motor system, the lack of effect of the first-generation antipsychotics on cognition may not seem surprising. But the causative pathway from elevated nigrostriatal DA to the cortical disruption leading to psychosis is not known, and clearly there are downstream effects from striatal DA-modulated changes critical in regulating cortical function.

In recent years, the SN has become more interesting to those who study psychotic disorders and schizophrenia as the DA hypothesis of schizophrenia has proposed subcortical DA dysfunction, presynaptic-DA dysfunction, underlies many symptoms [11, 137]. This model is based upon DA dysfunction in the striatum [138], and schizophrenia is associated with elevated striatal DA level and synthesis [139, 140]. One of the most interesting findings of recent years is that increased striatal dopamine synthesis capacity is evident in individuals with prodromal schizophrenia symptoms, suggesting that DA abnormalities predate the onset of first-episode psychosis [141]. By contrast, there is no similar elevation in non-psychotic depression [142] or in patients with persistent subclinical psychotic symptoms who have not developed a psychotic disorder, suggesting specificity to psychotic illness [12, 143, 144]. Whilst this focus has been on striatal DA, it should be reiterated that DA is synthesised in the SN and transported along the nigrostriatal pathway, meaning that the SN is the structure behind the extensive striatal DA changes. Direct examination of SN DA neurons suggests that excess DA synthesis is the cause of elevated DA, rather than insufficient DA breakdown. DA is synthesised from tyrosine via a two-step process, tyrosine hydroxylase (TH) converts tyrosine into dihydroxyphenyl-L-alanine, the rate-limiting step of DA synthesis, which is converted by aromatic acid decarboxylase into DA [145]. DA is broken down by two pathways: by dopamine-β-hydroxylase (DBH) to noradrenaline and by catechol O-methyltransferase (COMT) to 3-methoxytyramine. DBH is a vesicle-bound enzyme which has not been investigated well in mental illness, although has a strong role in addiction, whereas COMT exists in both intra- and extracellular forms, with the extracellular form often found in astrocytes, and astrocyte density has been reported to be decreased in the SN in schizophrenia [13]. However, no direct evidence has demonstrated that breakdown pathways have any role in SN DA function [146], in contrast to the PFC where COMT activity has been reported to have a role in working memory [147].

Post-mortem studies have found altered tyrosine hydroxylase mRNA levels, increased amount and variability of TH levels in the SN of schizophrenia patients [144, 148]. TH staining was significantly increased in nigral DA-neurons in schizophrenia, and this was not due to medication effects. These cells did not have elevated DA-mRNA, suggesting that this increases in regulated post-transcriptionally [12, 149], with these cells also having increased somal size, nuclear cross-sectional area and increased nucleolar volume compared with controls, in addition to decreased astrocyte density. Indeed, detailed examination of the DA neurons themselves suggests that their soma and nuclei are physically swollen in schizophrenia, suggesting a very substantial increase in DA synthesis [13].

Whilst we have much to learn about the regulation of the SN in schizophrenia and similar illnesses, the evidence so far suggests that excess SN-striatal DA may not be due to a fault within the SN itself but rather a regulatory issue that most likely originates elsewhere within the basal ganglia. As described above, the SN is part of a complex network which we are only now beginning to functionally examine piece by piece, and we hope that in the near future, the neurophysiology underlying these severe illnesses can be unravelled, and better therapies developed.

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