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Section 1 Background concepts

Chapter 1

Functional neuroanatomy and physiology in movement disorders

Nicola Pavese and David J. Brooks

Introduction

The most common movement disorders, including Parkinson's disease (PD), Huntington's disease (HD), dystonia, and dyskinesias are associated with pathology within the basal ganglia (BG), a group of gray-matter structures situated at the base of the forebrain that are extensively interconnected together as well as with different parts of the cerebral cortex, the thalamus, and other subcortical and brainstem nuclei.

To date, the complex functional organization of this extensive BG network has not been fully elucidated. However, microelectrode recordings in non-human primates and functional neuroimaging studies in humans during the execution of specific motor and/or behavioral tasks imply that the BG are relays in parallel functionally and anatomically segregated circuits, which integrate and focus activity from different cortical and subcortical regions. At least five separate functional loops have been described: (1) motor, (2) oculomotor, (3) orbitofrontal, (4) associative, and (5) limbic. The motor loop subserves preparation and execution of movement while the associative loop mediates executive functions such as planning, decision-making, and working memory. The orbitofrontal loop is activated by reward-related and novel, salient activities, while the limbic loop mediates control of emotions and motivations.

In PD and related disorders, the pathological process of the disease targets dopamine projections to posterior putamen, which mainly impacts on the motor circuit and leads to the occurrence of the classical limb rigidity and bradykinesia of these conditions. However, involvement of other BG areas results in executive functions, reward-related activities, control of emotions and motivations, and behavioral responses becoming abnormal in PD and other neurodegenerative diseases associated with movement disorders.

Functional imaging techniques such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), and blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) have provided the tools for assessing directly the function of brain networks involving the BG in humans and have brought invaluable insight into the pathogenesis of movement disorders.

This chapter will provide a brief overview of BG neuroanatomy and pathophysiological mechanisms underlying the main movement disorders. The findings of functional imaging studies that have enhanced our understanding of BG dysfunction in these conditions will be also outlined.

BG anatomy and physiology in the normal state

The BG comprise four main anatomical structures: the striatum, the globus pallidus, the subthalamic nucleus, and the substantia nigra (Figure 1.1). With the exception of the latter, which is in the midbrain, all the BG nuclei are situated at the base of the forebrain. The striatum is classically considered the input nucleus of the BG. It encompasses the caudate nucleus, the putamen, and the nucleus accumbens. The globus pallidus, which is located medial to the putamen, also consists of two subnuclei: the globus pallidus externa (GPe) and the globus pallidus interna (GPi). Together, the putamen and the adjacent GPe and GPi have the shape of a biconvex lens and are referred to as the lentiform nucleus. Finally, the substantia nigra (SN) is also divided in two parts, the pars compacta (SNc) and

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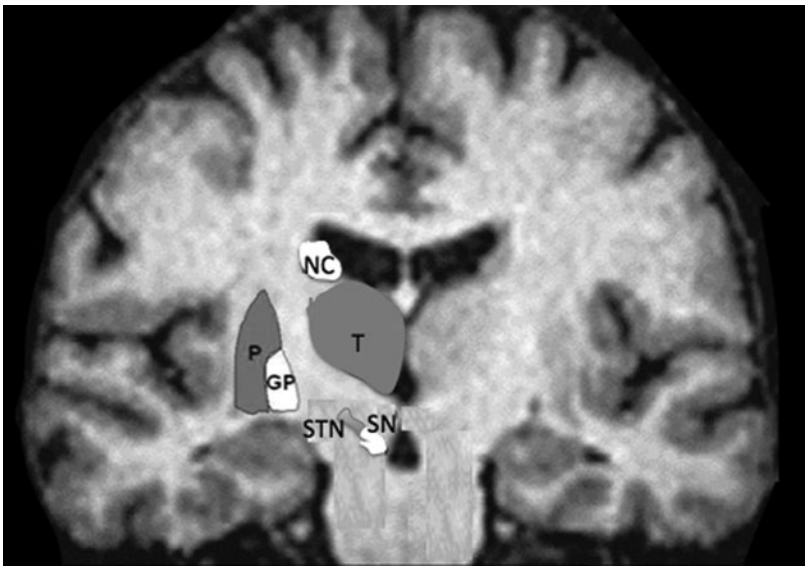

Figure 1.1 Coronal MRI image through the basal ganglia. GP = globus pallidus, NC = nucleus caudate, P = putamen, SN = substantia nigra, STN = subthalamic nucleus, T = thalamus. (See color plate section.)

the pars reticulata (SNr). The SNc contains a large population of dopaminergic neurons that project primarily to the striatum, forming the nigrostrial pathway, the largest dopaminergic tract in the brain.

The functional organization of these structures within the motor loop is still being investigated. The classical model of the BG motor loop, an amplitude model, proposes that signals from the cerebral cortex are conveyed to the BG and then returned back to the cortex after focusing and filtering (Figure 1.2) [1]. In this way, the BG select the appropriate input for the current context and send the appropriate command back to the motor cortex, by suppressing unintended movement and promoting desired ones [1,2]. The striatum is the BG main entry point and receives glutamatergic afferent inputs from all cortical areas including the primary somatosensory cortex (Brodmann areas 4 and 5), the supplementary motor area (6), the thalamus, and dopaminergic afferents from the SNc.

Two pathways with opposing effects originate from the striatal GABAergic medium spiny neurons and project to the GPi, the main output nucleus of the BG [1]. The direct pathway involves monosynaptic outputs from the striatum that inhibit the GPi and the SNr. The indirect pathway involves polysynaptic outputs from the striatum to the GPi via the GPe and the subthalamic nucleus (STN). Striatal GABAergic medium spiny neurons in the indirect pathway inhibit the GPe, whose GABAergic projections in turn inhibit the STN and its glutamatergic excitatory efferents to the GPi and the

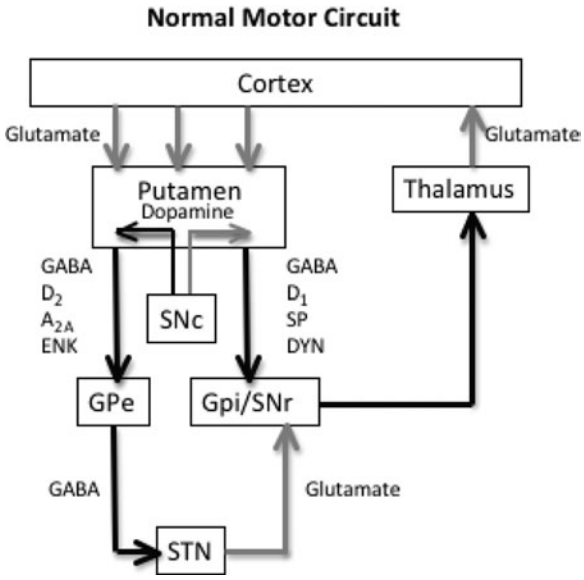

Figure 1.2 Classical model of the basal ganglia. Black arrows indicate inhibitory connections, gray arrows indicate excitatory connections. The thickness of the arrows indicates their activity. A_{2A} = adenosine A_{2A} receptors, DYN = dynorphin, D_1 = dopamine D_1 receptors, D_2 = dopamine D_2 receptors, GPe = globus pallidus externa, ENK = enkephalin, GPi = globus pallidus interna, SNc = substantia nigra pars compacta, SNr = substantia nigra pars reticulata, SP = substance P, STN = subthalamic nucleus.

SNr. Consequently, the direct and indirect pathways have opposing actions on the GPi. Activity of the direct pathway inhibits GPi output, while activity in the indirect pathway facilitates GPi output. Projections from the

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GPi and the SNr inhibit the ventral lateral nucleus of the thalamus, which send excitatory efferents to the cerebral cortex. The net effect is that thalamo-cortical activity is facilitated by the direct pathway and inhibited by the indirect pathway.

Based on this classical model, reduced BG output leads to movement facilitation and increased BG activity leads to movement inhibition. Dopamine is thought to strongly modulate this network by exerting opposing effects on the striatal neurons composing the two pathways. Neurons in the direct pathway express dopamine D_1 receptors and co-express substance P and dynorphin, whereas neurons in the indirect pathway express dopamine D_2 receptors and co-express enkephalin. Dopamine activates dopamine D_1 neurons in the direct pathway and inhibits dopamine D_2 neurons in the indirect pathways, leading to reduced inhibitory BG output to the thalamus and net movement facilitation [1].

The classical amplitude model has served as a good starting point to understand the physiology of the BG and the pathophysiology of both parkinsonian and hyperkinetic disorders. However, in recent years there has been growing evidence that the amplitude model is inadequate, failing to explain a number of aspects of movement disorders including the beneficial effect of pallidotomy on both parkinsonism and dyskinesias [3,4].

It is now clear that, in addition to afferents from the cerebral cortex, the SNc, and thalamus, the BG receive a large number of inputs from other subcortical structures, including the cerebellum, the locus coeruleus, the raphe nuclei, and the pedunculopontine nucleus (PPN) [4]. The latter, with its reciprocal connection with the striatum, the GPi, and the SNr, plays a key role in the control of posture and locomotion.

Moreover, the striatum is not the exclusive entry point of the BG. The STN also has a prominent role as an input station receiving afferents from the cerebral cortex, thalamus, and brainstem. The STN efferents project not only to the GPi /SNr, as originally believed, but also to the GPe, the PPN, and directly to the ventral thalamus. This "hyperdirect" cortico-subthalamic pathway is more effective than the polysynaptic striatal indirect pathway in activating the excitatory STN projections to the GPi, when inhibition of unwanted muscular contractions is required [4].

It is also known that collaterals of the GPi/SNr projections to the ventrolateral and ventral anterior thalamus reach other thalamic regions including the centromedian nucleus, which has motor functions, and the parafascicular nucleus, which is involved in non-motor functions. Both these nuclei project back to motor and non-motor subregions of the striatum, providing a feedback system to regulate BG output [4].

A large number of other internal feedback circuits modulating BG output have also been recognized. There are reciprocal connections between the GPe and the striatum and between the striatum and the dopaminergic neurons in the SNc. Anatomic studies have also demonstrated that the separation of direct and indirect pathways is less than initially thought, due to the presence of extensive collaterals. Additionally, direct dopaminergic innervation from the SNc to the GPe, GPi, STN, SNr, and even the thalamus has been found. These extrastriatal dopaminergic circuits influence BG function by regulating the excitability of individual BG nuclei. It has been suggested that they might have an important role in the development of compensatory mechanisms in response to nigrostriatal dysfunction in early stages of PD [5]. Finally, the large striatal interneuron population (mainly represented by the cholinergic tonically active neurons and GABAergic fast-spiking interneurons) further modulates striatal GABAergic output. None of these additional circuits were taken into account in the classical amplitude model of Penney and Young [1].

The role of dopamine in modulating striatal output has also been reconsidered. The majority of dopaminergic nigrostriatal terminals form both conventional synapses and open contacts with target neurons in the striatum indicating that both phasic short-acting synaptic and bulk long-lasting tonic dopamine release occurs [6]. Phasic dopamine release results as a response to novel or rewarding stimuli whereas tonic dopamine release serves to focus and filter movements in general.

Finally, recordings of neuronal activity in animal models of PD and in humans during functional neurosurgery have revealed that BG firing patterns and neuronal synchronization at different frequencies between BG nuclei and the cortex have an important role in facilitating or inhibiting motor function [7]. In the normal resting state BG neurons fire synchronously with cortex at a frequency of around 50 Hz but parkinsonian states are associated with lower-frequency oscillatory firing patterns which inhibit movement.

In conclusion, the previous view of the BG as being relays in cortical loops acting to focus and filter actions

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is over-simplistic. It is likely that the BG serve as an important center of integration of inputs related to motor, cognitive, and emotional functions, relating learning and execution of appropriate motor and behavioral responses to the context of the situation [4].

Parkinson's disease

The key pathological feature of PD is the presence of intraneuronal fibrillar aggregates, known as Lewy bodies and Lewy neurites. The major component of these neuronal inclusions is an aggregated form of alpha-synuclein, a presynaptic protein that is probably involved in controlling synaptic plasticity. In post-mortem examinations of PD brains, Lewy bodies and Lewy neurites are widely distributed throughout the brain. However, using synuclein immunocytochemistry, Braak and colleagues have suggested that these intraneuronal lesions in PD may evolve sequentially, beginning in the medulla and ascending in a predictable manner throughout vulnerable regions of the gray matter [8]. A six-point staging system has therefore been proposed for PD pathology based upon the progressive sequential involvement of brain structures: medulla oblongata and olfactory structures (stage 1), pons (stage 2), SN and midbrain nuclei (stage 3, when motor symptoms appear), limbic areas (stage 4), and association and primary neocortex (stages 5 to 6) [8].

Based on this staging system, nigrostriatal degeneration, which is the pathological hallmark of PD and leads to the classical motor symptoms of the disease, only occurs in stage 3 of the disease. The neurodegenerative process within the SN is not uniform [9]. The initial neuronal loss involves the lateral ventral tier of the SNc, which projects to dorsolateral posterior putamen. As PD progresses, nigral degeneration extends medially and dorsally into the dorsal tier and the contiguous ventral tegmental area, with consequent loss of nigral projections to the rostral putamen, head of the caudate nucleus, nucleus accumbens, and globus pallidus. The main effect of the degeneration of the nigral neurons is the profound dopamine depletion in the nigrostriatal projections. Fearnley and Lees have suggested that the classical motor signs of PD become manifest when 50% of the nigra compacta cells and 80% of striatal dopamine have been lost [9]. According to the classical amplitude model, reduction of dopamine levels in PD results in increased activity of the

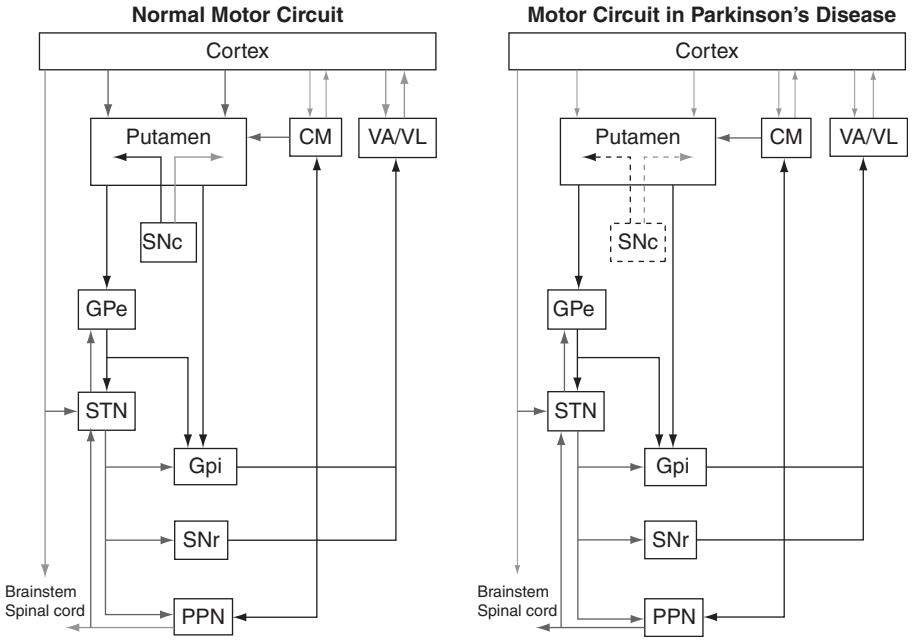

Figure 1.3 New model of the basal ganglia in normal state and in Parkinson's disease. Black arrows indicate inhibitory connections, gray arrows indicate excitatory connections. The thickness of the arrows indicates their activity. CM = centromedian nucleus, GPe = globus pallidus externa, GPi = globus pallidus interna, PPN = pedunculo pontine nucleus, SNc = substantia nigra pars compacta, SNr = substantia nigra pars reticulata, STN = subthalamic nucleus, VA = ventral anterior thalamus, VL = ventrolateral thalamus.

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indirect and reduced activity of the direct striatopallidal pathway. The net effect is increased inhibitory output from GPi/SNr to the ventral thalamus with suppression of movement (Figure 1.3). However, as discussed above, the classical model has a number of significant limitations. Moreover, it does not explain some of the basic clinical symptoms of PD, such as tremor, gait disturbance, and other axial symptoms. Some of the findings of stereotaxic surgery in both PD patients and animal models of the disease are also difficult to explain. Lesions in the motor thalamus and in the GPe do not worsen parkinsonian symptoms, as might be assumed from the amplitude model.

Newer models of PD physiopathology take into account changes in BG activity, and in particular changes in firing patterns and synchrony of neuronal activity [4,7]. Recording through deep-brain stimulation (DBS) electrodes in PD patients as well as electrophysiological studies in animal models have demonstrated abnormal low-frequency synchronization of neuronal activity in BG nuclei including the STN, GPi, GPe, and SNr [10]. Analysis of local field potentials (LFPs) from DBS macro-electrodes has revealed that this oscillatory activity is in the beta frequency range (mean around 18 Hz) in the off-medication state throughout the extrastriatal BG nuclei [11]. It has been suggested that the exaggerated synchronization at the oscillation frequency in a large population of neurons might affect the ability of individual neurons to process and relay specific information, leading to impaired motor control [7]. Abnormal oscillatory activities in the theta band (around 6 Hz) have also been reported in BG nuclei. Interestingly, in the on-medication state, beta activity is reduced and normal high-frequency 50-Hz gamma oscillations are re-established [12]. Excessive dopaminergic stimulation can lead to raised high-frequency activity resulting in involuntary movements. As pallidotomy abolishes both high- and low-frequency activity in the BG, it is able to relieve both parkinsonism and dyskinesias. The aetiology of the aberrant BG oscillatory activity in PD remains to be established. It is likely, however, that these changes are adaptive changes related to dopamine depletion.

Lewy bodies and neurites are not only found in dopamine neurones but also target serotoninergic, noradrenergic, and cholinergic neurons [8]. Impairment of non-dopaminergic neurotransmission is likely to play an important role in the development of non-motor symptoms of PD including sleep disturbance, fatigue, depression, dementia, and autonomic dysfunction.

Functional imaging techniques have been extensively used in vivo to investigate the pathophysiological and pharmacological changes associated with PD. A major advantage of these techniques is that they can provide longitudinal information on the extent and severity of reduced nigrostriatal function in individual patients as they progress through the different stages of their disease. Both positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have shown high sensitivity and specificity for detecting loss of striatal dopamine terminal function in symptomatic patients and subjects at risk for PD, providing valuable insights into the prevalence of pre-clinical disease [13].

Currently three different imaging strategies can be used to quantify presynaptic nigrostriatal dysfunction: (1) Assessment of dopamine synthesis and storage with [^{18}F]-fluorodopa (FDOPA) PET. (2) Measurement of dopamine transporter (DAT) availability with a number of primarily tropane-based PET and SPECT ligands. (3) Detection of reduced vesicular monoamine transporter 2 (VMAT2) binding with [^{11}C]- or [^{18}F]-dihydrotetrabenazine (DTBZ) PET [13].

All of these modalities give similar findings, although PET provides better signal to noise than SPECT. Early Hoehn and Yahr stage 1 PD patients with unilateral disease show bilateral reductions in putamen dopaminergic function but have the most pronounced loss of FDOPA uptake, DTBZ binding, or DAT ligand binding, in the dorsal posterior putamen contralateral to the side of their clinical symptoms. Patients with bilateral disease show more extensive reductions of dopaminergic tracers spreading into the ventral and anterior putamen and dorsal caudate. PD patients with advanced disease show tracer reduction extending to the ventral head of caudate (Figure 1.4) [13]. This posterior-to-anterior gradient of striatal dysfunction evident in PET and SPECT images is consistent with the gradient of nigral degeneration where ventrolateral nigral dopaminergic projections to the dorsal putamen are affected at an earlier stage than the dorsomedial projections to the head of caudate [9].

Levels of striatal dopaminergic dysfunction detected with PET and SPECT correlate well with severity of disability [14,15]. Several studies have reported a significant inverse correlation between stage of disease (rated with the Hoehn and Yahr scale) and FDOPA uptake in both putamen and caudate nucleus. Moreover, both FDOPA uptake and

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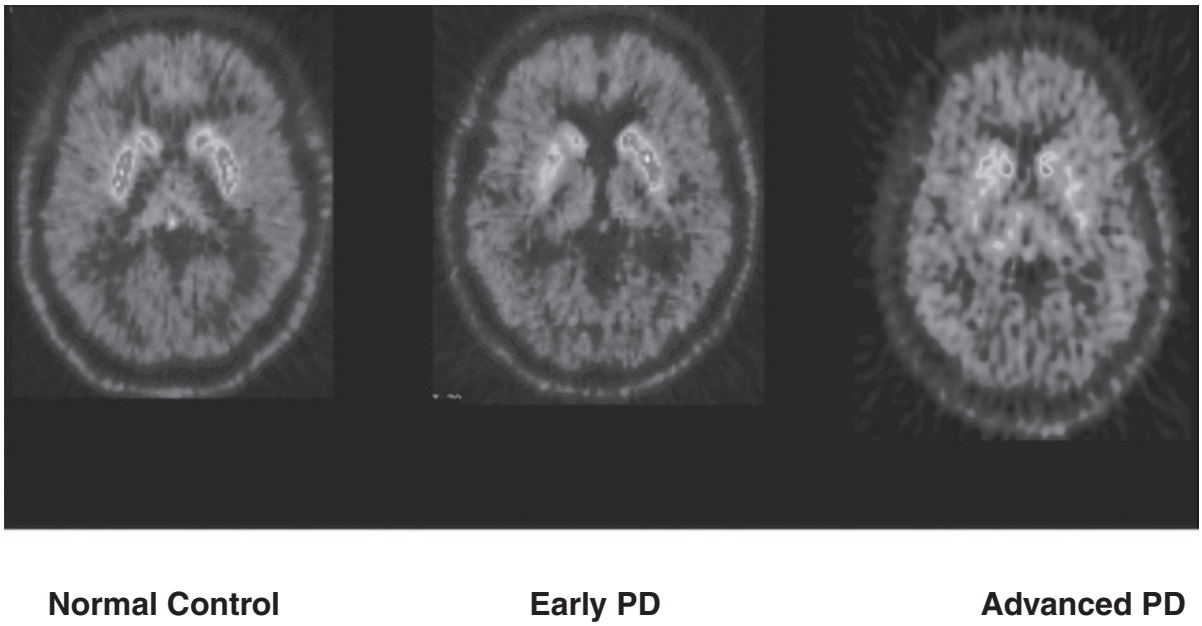

Figure 1.4 [^{18}F]-Fluorodopa PET images in an healthy control and in patients with early and advanced Parkinson's disease. (See color plate section.)

DAT binding in the putamen correlated well with levels of total motor impairment and severity of limb bradykinesia and rigidity (measured with the Unified Parkinson Disease Rating Scale (UPDRS) total motor score and subscores) [14,15].

The FDOPA uptake in the brain mainly reflects the activity of aromatic amino acid decarboxylase (AADC), an enzyme localized in all monoaminergic and not just dopaminergic neurons. As a consequence, this PET ligand can be used to assess the involvement of extrastriatal dopaminergic, serotoninergic, and noradrenergic structures in PD. Compared to controls, patients with advanced PD showed significant FDOPA reductions in the locus coeruleus, midbrain raphe, pallidum, hypothalamus, ventral anterior thalamus, and pineal gland in addition to those seen in the caudate, putamen, and ventral striatum suggesting widespread involvement of the monoaminergic pathways is present in late disease [16].

Voxel-based analysis with statistical parametric mapping (SPM, www.fil.ion.ucl.ac.uk/spm) allows exploratory localization of changes in tracer uptake throughout the entire brain volume. Using this approach, several authors have reported increased FDOPA uptake in the raphe, frontal cortex, and GPi in patients with early PD as their putamen uptake falls [17,18]. These increases are thought to reflect adaptive increases in AADC activity in surviving dopaminergic and other monoaminergic neurons to compensate for the loss of putamen dopamine terminals [18]. These compensatory mechanisms, however, disappear after some years of disease and more advanced patients show normal or reduced tracer uptake in these regions [16].

Several PET ligands have now been developed to assess the involvement of non-dopaminergic transmission in PD and are shedding light on the complex pathology of PD. [^{11}C]-WAY 100635 PET and [^{11}C]-DASB PET are markers for 5-HT1A receptor and serotonin transporter (SERT) binding, respectively. Reductions in [^{11}C]-WAY 100635 in the midbrain of PD patients were found to correlate with severity of tremor [19]. Loss of [^{11}C]-DASB binding has been reported in striatal and limbic areas of PD patients complaining of chronic fatigue, suggesting that serotoninergic transmission may play a role in the genesis of these symptoms [20].

Uptake of the acetylcholine analogs [^{11}C]-MP4A and [^{11}C]-PMP have been used to investigate levels of acetylcholinesterase (AchE) activity in PD patients. Reductions in posterior cortical cholinergic activity have been found in non-demented PD patients that can become global in those with dementia [21].

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A significant reduction in thalamic AChE activity has been reported in PD patients with a history of frequent falls in comparison to healthy controls and PD non-fallers [22]. Such a loss of thalamic cholinergic function is likely to reflect dysfunction/degeneration of the PPN, which is the principal source of cholinergic innervation to the thalamus.

Imaging provides a means of studying in vivo regional cerebral function (under both resting and activating conditions) in humans and in animal models of PD. This has been achieved with different imaging strategies. The most common ones will be briefly summarized in this section.

[^{18}F]-Deoxyglucose (FDG) PET measures the rate of glucose phosphorylation by hexokinase, an index of regional cerebral glucose metabolism (rCMRglc). In the parkinsonian state at rest, covariance analysis can be used to localize abnormal areas of relative hypometabolism and hypermetabolism within structures of the cortical-BG loops providing evidence of abnormal connectivity. Analyses of resting metabolic changes across the brain have identified specific patterns of brain dysfunction in PD and other parkinsonisms, including multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration [23]. The metabolic profile of each of these conditions is distinctive and is potentially useful for discriminating them. In PD, distinct metabolic profiles have been identified that are associated with the akinetic-rigid and tremor-dominant subtypes and with the presence of cognitive dysfunction [24–26]. The akinetic-rigid PD-related profile (PDRP) is characterized by relative hypermetabolism of the lentiform nucleus, thalamus, and pons and relative hypometabolism of the lateral and mesial premotor cortex and parietal areas. Its expression correlates well with measures of bradykinesia and it normalizes after effective dopaminergic therapy [24]. The PD tremor-related metabolic pattern (PDTP) involves hypermetabolism of the cerebello-thalamo-cortical pathways driving parkinsonian tremor [25]. The PD cognitive profile (PDCP) is characterized by metabolic reductions in frontal and parietal association areas and relative increases in the cerebellar vermis and dentate nuclei. Its expression correlates with performance on tests of memory and executive functioning [26].

FDG PET has been used to assess the effects of stereotaxic surgical procedures including pallidotomy and DBS of the GPi, STN and, more recently, PPN on brain function. In general these studies have shown that both pallidotomy and DBS of different targets lead to normalization of the abnormal PDRP (in particular improving cortical metabolism), which usually correlates with the improvement of motor symptoms [27,28].

PET and fMRI enables one to detect regional cerebral activation associated with performance of different tasks. $H_2[^{15}O]$ PET measures changes in regional cerebral blood flow (rCBF) while fMRI detects changes in regional blood oxygenation. Several PET studies have compared changes in rCBF during the execution of simple motor tasks such as finger or joystick movements in PD patients and healthy controls. In comparison to healthy volunteers, PD patients show reduced activation of the rostral supplementary motor area and right dorsolateral prefrontal cortex during the execution of paced joystick movements in freely chosen directions [29]. Similar findings were observed in PD patients during the execution of freely selected fingers movements [30]. PET activation studies have also assessed rCBF changes during imagined performance of paced joystick movements in freely chosen direction (Figure 1.5) [31]. With this paradigm, PD patients showed reduced activation of the prefrontal and mesial premotor cortex, whereas lateral premotor and parietal areas were activated normally. Taken together, these findings support the view that thalamo-frontal activation is reduced in PD. Interestingly, the administration of apomorphine, a powerful dopamine D_1/D_2 agonist, normalized the activation pattern once the patients had switched to an "on" state [32].

Other activation studies have revealed over-activation of compensatory circuits in PD. In particular, cerebellar-lateral parietal-lateral premotor projections are over-active in PD patients during performance of sequential finger movements with one or both hands while medial temporal areas are over-active while solving "Tower of London" problems [33].

Following pallidotomy and DBS of the GPi and STN, $H_2{}^{15}O$ PET studies have shown increased levels of activation of the supplementary motor area and dorsal prefrontal cortex, providing further support that these areas are abnormally hypoactive in PD [34].

fMRI has also been used to investigate changes in local neural activity during sensorimotor and cognitive tests. Blood-oxygenation-level-dependent (BOLD) sequences are sensitive to changes of local blood-oxygenation level as deoxyhemoblobin, but not oxyhemoglobin, is paramagnetic. Task-induced changes in neuronal activity lead to increased regional brain

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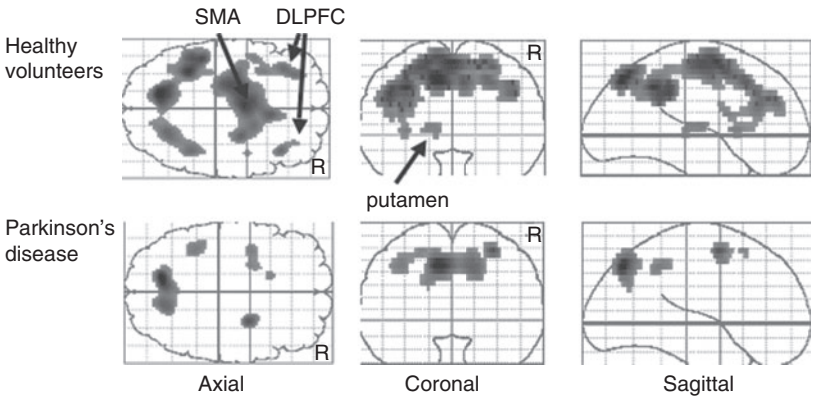

Figure 1.5 Glass brain view of areas of significant activation ($H_2[^{15}O]$ PET) during paced imagination of joystick movements in healthy volunteers and in patients with Parkinson's disease using statistical parametric mapping. All areas shown are significant at the threshold $p < 0.001$. SMA = supplementary motor area, DLPFC = dorsolateral prefrontal cortex.

perfusion and result in raised levels of oxyhemoglobin which can be detected as increased signal by fMRI.

fMRI studies have shown abnormally reduced supplementary motor area and dorsal prefrontal activation and raised lateral premotor and parietal activation in PD patients compared to healthy subjects during sequential manual movements [35,36]. The hyperactivity in premotor and parietal areas has been suggested to represent a compensatory mechanism making use of a less dopamine-dependent dopamine circuit. The relation between levels of BOLD activation and disease severity has been assessed in de novo PD patients during a precision grip force task [37]. A significant negative correlation between BOLD signals and total UPDRS motor scores was found in caudate, putamen, and STN bilaterally and in contralateral GPe, SN, and thalamus. Bradykinesia was the symptom that most consistently correlated with levels of BOLD activation in the BG and thalamus while BOLD activation in the contralateral GPi correlated best with tremor severity. Interestingly, the reduced cortical activity in primary motor cortex and supplementary motor area in de novo PD did not correlate well with severity of motor disability.

fMRI can also detect spontaneous oscillations of BOLD signal during the resting state – so-called default mode imaging. It has been suggested that brain structures that show significantly correlated levels of spontaneous BOLD oscillations belong to synchronized neuronal networks. The amplitude of the low-frequency fluctuations (ALFF) is used as an index of circuit activity level in the resting state. Compared to controls, PD patients at rest show decreased activity in a number of regions, including the supplementary motor cortex, the mesial prefrontal cortex, the right middle frontal gyrus, and the left cerebellum (lobule VII/VIII), as well as increased activity in the right cerebellum (lobule IV/V). This characteristic pattern has been reported to distinguish PD patients from controls with 92% sensitivity and 87% specificity [38]. In summary, fMRI has strong potential to serve as a non-invasive marker of BG function in PD.

Huntington's disease

In HD, the neurodegenerative process leads to progressive loss of striatal GABAergic medium spiny neurons. Based on the classical model of BG connectivity, chorea should arise from greater loss of neurons of the indirect striato-pallidal pathway (Figure 1.6). This would result in decreased inhibitory effect on the GPe, in turn leading to increased inhibition of the STN and its excitatory efferents to the GPi and SNr. The net effect would be reduced inhibitory BG output (GPi and SNr less excited) to thalamus with inappropriately increased thalamo-cortical activity and breakthrough of involuntary movements. The striatal neurons of the indirect pathway express dopamine D_2 receptors while those of the direct pathway express D_1 sites. Given this, the classical model would predict greater loss of striatal D_2 than D_1 receptors in choreic HD. In practice, a parallel loss of both striatal D_1 and D_2 sites is seen, emphasizing the deficiency in the classical view of BG connectivity.

Both PET and SPECT have been used to assess striatal functional integrity in HD.

Reduction of striatal D_2 binding in HD patients and premanifest HD gene carriers have been observed with

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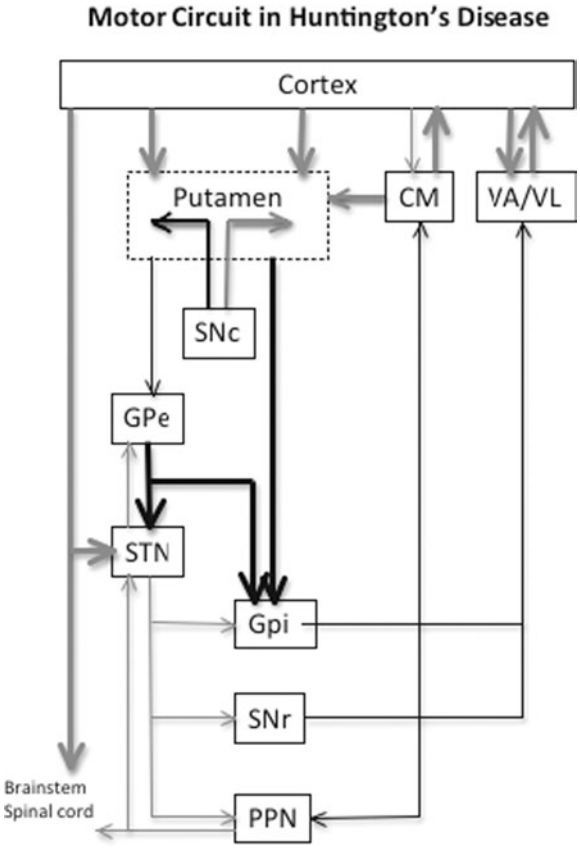

Figure 1.6 Model of the basal ganglia in Huntington's disease. Black arrows indicate inhibitory connections, gray arrows indicate excitatory connections. The thickness of the arrows indicates their activity. CM = centromedian nucleus, GPe = globus pallidus externa, GPi = globus pallidus interna, PPN = pedunculo pontine nucleus, SNc = substantia nigra pars compacta, SNr = substantia nigra pars reticulata, STN = subthalamic nucleus, VA = ventral anterior thalamus, VL = ventrolateral thalamus.

[^{11}C]-raclopride PET and [^{123}I]-IBZM SPECT [39]. At onset of symptoms striatal D_1 and D_2 binding are reduced by 50% and, in agreement with post-mortem studies, the caudate nucleus, in particular its periventricular portion, is more affected than the putamen.

[^{11}C]-raclopride PET has also been used to assess cortical dysfunction in HD patients [40]. Voxel-based interrogation of individual images of [^{11}C]-raclopride binding with SPM has localized significant reductions of frontal and temporal dopamine D_2 receptor availability in both HD patients and premanifest HD gene carriers. Symptomatic HD patients with decreased cortical [^{11}C]-raclopride binding had worse scores on neuropsychological tests assessing attention and executive functions than subjects without cortical dopamine dysfunction, suggesting that reduced cortical D_2 receptor availability may play a role in the pathophysiology of cognitive disturbances in early HD [40].

Progression of HD can be followed objectively by measuring levels of striatal D_2 binding (Figure 1.7). The reported annual loss of striatal [^{11}C]-raclopride binding in clinically affected subjects varies between 3 and 7% across studies, providing a potential tool for monitoring the efficacy of putative neuroprotective new drugs or restorative strategies in HD [39].

It has been proposed that striatal degeneration in HD patients proceeds in an exponential fashion. In a cross-sectional study, a correlation between cytosine–adenosine–guanasine (CAG) repeat length and the estimated loss of striatal D_2 binding was found in HD patients and premanifest HD gene carriers. While CAG repeat length influenced the rate of disease progression, the slopes of the correlation for premanifest HD gene carriers and patients were significantly different, suggesting that the rate of disease progression is faster during the premanifest stages of the disease [41]. However, a longitudinal assessment with three serial [^{11}C]-raclopride PET scans in a cohort of clinically affected HD patients found a linear progression of striatal D_2 loss over a 3-year period [42].

A 2% mean annual loss of striatal dopamine D_1 receptor availability in clinically affected HD patients has been reported with serial [^{11}C]-SCH23390 PET [43]. As striatal medium spiny neurons express opioid, benzodiazepine and cannabinoid receptors, several other PET ligands have been used as markers of their function in HD. [^{11}C]-flumazenil binding to benzodiazepine receptors was reduced in the caudate nucleus of HD patients while reductions of [^{11}C]-diprenorphine binding have been found in striatal and cortical regions [44,45]. Finally, a significant decrease of type 1 cannabinoid receptor (CB1) availability was found throughout the gray matter of the cerebrum, cerebellum, and brainstem in HD patients when compared to controls [46].

The progressive degeneration of striatal neurons associated with HD leads to disruption of fronto-striatal pathways and severe impairment in executive functions. However, primary neurodegeneration of all cortical areas also occurs, though to a lesser extent, and seems to contribute significantly to the cognitive deficit in HD patients [40, 47].

Studies of regional cerebral glucose metabolism with FDG PET and perfusion with [^{99m}TC]-HMPAO

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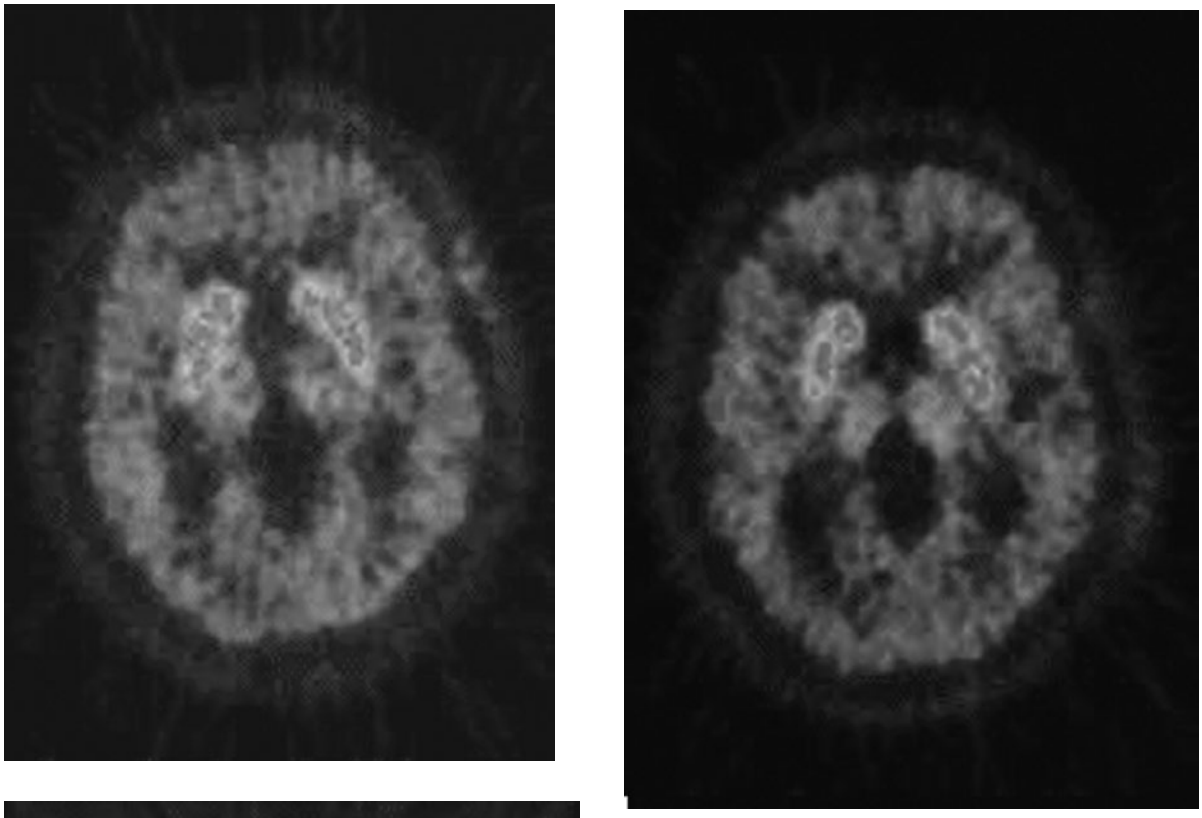

Figure 1.7 Serial [^{11}C]-raclopride scans in a patient with Huntington's disease: (a) baseline; (b) + 28 months; (c) + 41 months. (See color plate section)

and ^{123}IMP SPECT have shown reduced BG, frontal, and temporal function [39]. The heads of the caudate are most affected and, in the majority of these studies, reduced glucose metabolism and hypoperfusion in cortical and subcortical areas correlated with severity of cognitive dysfunction.

Significant reductions in glucose metabolism have also been found in premanifest HD gene carriers. Network analysis has revealed a significant metabolic covariance profile characterized by reductions in striatal and anterior cingulate metabolic activity, associated with relative metabolic increases in the ventrolateral and ventral posterolateral thalamus, cerebellar vermis, and in the primary motor and visual cerebral cortices [48,49]. This HD-related pattern (HDRP) discriminates asymptomatic gene carriers from healthy controls. It has been suggested that the increases in primary motor and visual cortex glucose metabolism compensate for striatal neuronal loss in premanifest HD gene carriers while later decline in these measures is associated with clinical conversion.

$H_2[^{15}O]$ PET was used to assess rCBF changes in HD patients during the execution of paced joystick

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