



Review

The role of the basal ganglia in learning and memory: Neuropsychological studies

Jessica A. Grahn^{a,*}, John A. Parkinson^b, Adrian M. Owen^a

^a MRC Cognition and Brain Sciences Unit, Cambridge, UK

^b School of Psychology, University of Wales, Bangor, UK

ARTICLE INFO

Article history:

Received 10 September 2008

Received in revised form

10 November 2008

Accepted 11 November 2008

Available online 18 November 2008

Keywords:

Parkinson's disease

Basal ganglia

Learning and memory

ABSTRACT

In recent years, a common approach to understanding how the basal ganglia contribute to learning and memory in humans has been to study the deficits that occur in patients with basal ganglia pathology, such as Parkinson's disease and Huntington's disease. Pharmacological manipulations in patients and in healthy volunteers have also been conducted to investigate the role of dopamine, a neurotransmitter that is crucial for normal striatal functioning. When combined with powerful functional neuroimaging methods such as positron emission tomography and functional magnetic resonance imaging, such studies can provide important new insights into striatal function and dysfunction in humans. In this review, we consider this broad literature in an attempt to define a specific role for the caudate nucleus in learning and memory, and in particular, how this role may differ from that of the putamen. We conclude that the caudate nucleus contributes to learning and memory through the excitation of correct action schemas and the selection of appropriate sub-goals based on an evaluation of action-outcomes; both processes that are fundamental to all tasks involve goal-directed action.

© 2008 Elsevier B.V. All rights reserved.

Contents

1. Introduction	53
2. Anatomical considerations, structural and functional connectivity	54
3. Neuropathology in Parkinson's disease	55
4. Cognitive deficits in PD	55
5. Pharmacological studies of learning and memory in Parkinson's disease	57
6. Comparison with other diseases affecting basal ganglia function	58
7. Functional neuroimaging in Parkinson's disease and Huntington's disease	58
8. Conclusions	59
Acknowledgements	59
References	59

1. Introduction

Parkinson's disease (PD) is the most widely studied of the basal ganglia disorders, and as such, is the principal source of information from humans about striatal function and dysfunction. Studies of patients with PD suggest that the characteristic clinical symptoms of bradykinesia, rigidity and resting tremor are frequently accompanied by impairments in cognitive function. Although between 15 and 20% of PD patients develop a frank dementia [1], less severe cognitive impairment is a well-recognized feature early in the disease that has been shown to be an important predictor for quality

of life [2,3]. These cognitive deficits take many forms, but deficits on tests of learning and memory are common [4,5]. Moreover, some of these impairments have been shown to be extremely sensitive to the effects of controlled L-Dopa withdrawal [6], suggesting that they have a predominantly dopaminergic substrate. Dopaminergic neuronal loss represents the primary neuropathology in PD and occurs predominantly in the nigrostriatal tract and to a lesser extent in the mesocortical pathway where neurons project from the ventral tegmental area and the medial substantia nigra *pars compacta* [7]. Recent functional neuroimaging studies exploring cognitive deficits in this patient group suggest a role for disruption in both the nigrostriatal [8,9] and mesocortical [10,11] pathways.

In this review, we will consider this literature in an attempt to define whether the basal ganglia play any specific role in learning

* Corresponding author. Tel.: +44 1223 355294 fax: +44 1223 359062.

E-mail address: jessica.grahn@mrc-cbu.cam.ac.uk (J.A. Grahn).

and memory. In particular, we will assess how the functions of the caudate nucleus may differ from those of the putamen.

2. Anatomical considerations, structural and functional connectivity

In humans, the basal ganglia comprise the striatum (the caudate and the putamen, linked together through the fundus), the ventral striatum (the nucleus accumbens and most ventral aspects of caudate and putamen), the globus pallidus (internal and external sectors), the substantia nigra, and the subthalamic nucleus [12]. The caudate and putamen are the main input nuclei to the basal ganglia, receiving axons from nearly all parts of cortex apart from primary visual, auditory, and olfactory cortices. The caudate and putamen are reciprocally interconnected with the substantia nigra (nigrostriatal tract), and most of the basal ganglia output is sent via the substantia nigra and globus pallidus. An influential model for understanding how the various basal ganglia nuclei relate to one another (and to the cortex) has been the concept of cortico-striatal loops [13], which emphasises the functional inter-relationships between the neocortex and the striatum. According to this model, widespread topographically organized cortical projections converge upon the striatum, and project back, via the pallidal, nigral and thalamic output structures, to discrete cortical regions. Information is processed at each level before being relayed back to the cortex, or directed via the brainstem to motor output structures (Fig. 1).

Although the invasive tract tracing methods used to delineate neuroanatomical connections in non-human animals are inapplicable to humans, diffusion tensor imaging (DTI) is a non-invasive magnetic resonance technique that allows demonstration of white matter fiber tracts *in vivo*. In white matter, water diffusion is higher along the direction of fiber bundles (due to axonal organization and the myelin sheath). This *anisotropy* is measured with magnetic resonance imaging (MRI) to determine anatomical connectivity. Examination of striatal anatomical and functional connections using this method broadly supports the parallel loop model of striatal organization [13,14]. For example, a DTI study by Lehericy and colleagues [15] found that the head of the caudate was connected primarily to medial, ventral, and dorsolateral prefrontal cortex, the

frontal pole, and the pre-supplementary motor area. The rostral putamen was connected to similar cortical structures, but in general, the caudate fibers were more rostral than those of the anterior putamen. The caudate connectivity pattern was in contrast to that of the posterior putamen, which was connected to primary sensory and motor areas and the posterior supplementary motor area, and also in contrast to the ventral striatum, which was connected to orbitomedial frontal cortex, amygdala, hippocampus, and temporal pole, which is broadly consistent with relevant studies in non-human species. The connectivity patterns held both when tracing from the striatum to cortical areas and when tracing from cortical areas back to the striatum.

In addition to anatomical connectivity, functional connectivity of the striatum in humans has been investigated. Functional connectivity measures the statistical tendency for different brain regions to be active simultaneously, and thus does not necessarily rely upon direct (monosynaptic) anatomical connections. A recent meta-analysis of 126 positron emission tomography (PET) and functional MRI (fMRI) studies has demonstrated that different areas of the striatum have distinct patterns of functional connectivity with the cerebral cortex [16]. The results of this analysis were also consistent with the concept of segregated cortico-striatal connections, as described in parallel loop models ([13] also see Fig. 1 above). Whereas the putamen showed a high degree of coactivation with primary cortical motor areas, the caudate was coactive with higher level cognitive areas, such as the dorsolateral prefrontal cortex, rostral anterior cingulate, and inferior frontal gyri.

This pattern of connectivity has been further confirmed in humans through the use of transcranial magnetic stimulation (TMS). TMS is a non-invasive method of exciting cortical neurons via a weak electric current that is induced in the tissue by a rapidly changing magnetic field. The method is ideal for stimulating the cortical surface, although deeper structures such as the striatum are generally beyond reach. However, the effects of stimulating surface regions on deeper structures can be measured using other techniques such as PET and fMRI, thereby providing important clues about likely patterns of connectivity. For example, stimulation of motor cortex increases activity in the putamen (measured using fMRI) [17], and also induces focal dopamine release in the putamen, but not the caudate [18]. Stimulation over dorsolateral

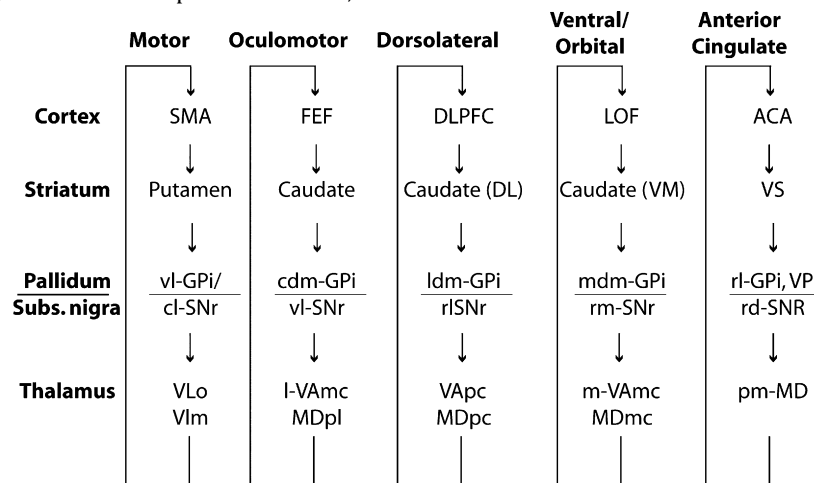


Fig. 1. The dorsal and ventral striatum are differentially connected to discrete prefrontal cortical regions in segregated cortico-striatal circuits (adapted from Alexander et al. [13]). The putamen plays a critical role within the so-called 'motor circuit' while the caudate forms part of the oculomotor, dorsolateral and ventral/orbital circuits. SMA = supplementary motor area, vl-GPi = ventrolateral globus pallidus (internal segment), cl-SNr = caudolateral substantia nigra pars reticulata, VLo = ventrolateral nucleus of thalamus pars oralis, VIm = ventrolateral nucleus of thalamus pars medialis, FEF = frontal eye fields, cdm-GPi = caudodorsomedial globus pallidus (internal segment), vl-SNr = ventrolateral substantia nigra pars reticulata, I-VAmc = lateral ventral anterior nucleus of thalamus pars magnocellularis, MDpl = parvocellular subnucleus of mediodorsal nucleus of the thalamus, DLPFC = dorsolateral prefrontal cortex, Caudate (DL) = dorsolateral caudate, Caudate (VM) = ventromedial caudate, mdm-GPi = dorsomedial globus pallidus (internal segment), rm-SNr = rostromedial substantia nigra pars reticulata, m-VAmc = medial ventral anterior nucleus of thalamus pars magnocellularis, MDmc = magnocellular subnucleus of mediodorsal nucleus of the thalamus, ACA = anterior cingulate area, VS = ventral striatum, rl-GPi = rostromedial globus pallidus (internal segment), VP = ventral posterior nucleus of the thalamus, rd-SNr = rostromedial substantia nigra pars reticulata, pm-MD = posteromedial mediodorsal nucleus of the thalamus (adapted from Alexander et al. [13]).

prefrontal cortex, however, increases neural activity and dopamine release in the caudate, but not the putamen [19,20]. Thus, non-invasive measures of anatomical and functional connectivity in humans demonstrate a clear link between the caudate nucleus and frontal-lobe areas, in contrast to the putamen's links to more basic sensorimotor regions.

3. Neuropathology in Parkinson's disease

Dopaminergic neuronal loss represents the primary neuropathology in PD and occurs predominantly in one of the four main dopamine pathways in the brain; the nigrostriatal tract. Another dopamine pathway, the mesocortical pathway (which does not involve the striatum, but rather directly links the ventral tegmentum and medial substantia nigra *pars compacta* to frontal areas) is also dopaminergically depleted, but to a lesser degree [7]. Although the striatum as a whole is compromised in PD, some conclusions can still be drawn about the role of the caudate nucleus specifically. For example, the main output of the dorso-medial projection of the nigrostriatal tract is to the head of the caudate nucleus [21]. Interestingly, a correlation between the loss of dopaminergic neurons that project to the caudate and the degree of dementia in PD patients has been reported [22]. In addition, correlations exist between dopaminergic depletion of the caudate nucleus and neuropsychological performance [23,24] although these findings have not been universally corroborated [25,26].

As PD is a progressive neurodegenerative disease, anatomical and neuropathological evidence suggests that the evolving pattern of cognitive impairments observed in these patients may be best explained in terms of the spatiotemporal progression of dopamine depletion within the striatum and the terminal distribution of its cortical afferents. This is highlighted by a detailed post-mortem neurochemical analysis which shows uneven patterns of striatal dopamine loss in patients dying with idiopathic PD [27]. The study confirms that the putamen is more severely depleted than the caudate nucleus, and also shows that the caudal putamen is more affected than the rostral portions. Within the caudate nucleus, dopamine depletion is greatest (to a maximum of about 90%) in the most rostradorsal extent of the head of this structure, an area which is heavily connected with dorsolateral regions of the frontal-lobe [28]. The rostradorsal regions of the caudate nucleus are most likely subjected to greater disruption by the disease and probably at an earlier stage of its progression. By contrast, ventral regions of the caudate, which are preferentially connected with more ventral regions of the frontal-lobe (including the ventrolateral prefrontal cortex) [28], are relatively spared in early PD, which may leave functions which are maximally dependent on this circuitry relatively intact.

Although this “traditional” view that the pathological process in PD starts by degeneration of dopaminergic neurons in the substantia nigra fits with the apparent progression of cognitive deficits in the disease, it has recently been challenged by Braak and colleagues [29]. It is also important to acknowledge that other factors may play a role in the cognitive deficits observed in PD. For example, non-dopaminergic forms of pathology, including noradrenergic, serotonergic and cholinergic deafferentation of the cortex also occur in PD [30], and may play a significant role in some of the cognitive deficits observed. Similarly, cortical Lewy bodies, which may occur even in the early stages of PD, may play a contributory role [31,32]. Finally, patients with PD have dopamine depletion within the frontal cortex itself [33] through degeneration of the mesocortical dopamine pathway. However, this system is known to be less severely affected (50% depletion) than the nigrostriatal dopamine system in PD [34] and possibly at a later stage of the disease process.

In summary, given the relatively large numbers of patients available for study (compared, for example, to HD) PD is the best available model of basal ganglia dysfunction in humans, although

its specificity in this regard is likely to decrease as the disease progresses. Thus, studies of ‘de novo’ patients, or at least those in the earliest stages of the disease, are a primary source of information about the likely cognitive functions of the caudate nucleus in humans.

4. Cognitive deficits in PD

In the last 20 years, an enormous number of studies have reported cognitive deficits in non-demented groups of patients with PD (e.g. [4,5,35–42]). A central model for much of this work has been the concept of cortico-striatal loops described above ([13]; also see Fig. 1), which emphasises the functional inter-relationships between the neocortex and the basal ganglia. Of particular interest is the fact that the principal target of basal ganglia outflow appears to be the frontal-lobes. Although many of these studies report poor performance on tests of learning and memory, these deficits are by no means specific; rather they appear to reflect a more general impairment of executive functions early in the disease process. ‘Executive’ processes have been defined as cognitive mechanisms by which performance is optimized in situations requiring the simultaneous operation of a number of different processes [43]. Many test of memory and learning involve executive processes, particularly when the action or response is novel or complex [44]. Executive processes are also central to all tasks that involve directing attention to a relevant stimulus (e.g., a stimulus to be remembered) and/or inhibition of irrelevant stimuli as well as tests that require switching attention between different processes or the coding and checking of the contents of memory storage. The frontal-lobes have long been known to play an important role in executive functioning, although the fact that the ‘dysexecutive syndrome’ may be observed in patients with damage to other brain regions (e.g. [43]), suggests that an equivalence between the prefrontal cortex and executive functioning cannot be assumed. Moreover, as damage to different regions of the basal ganglia in non-human species produces deficits that often resemble the effects of damage to their corresponding targets of projection within the prefrontal cortex [45] it is entirely unclear whether executive deficits in PD reflect predominantly their cortical (frontal-lobe) or subcortical (striatal) damage. A logical approach to this problem is to compare the behaviour of patients with early PD to that of patients with circumscribed excisions of the frontal cortex.

One of the most widely studied cognitive impairments in PD is a profound and somewhat specific deficit in tests of visual discrimination learning [4,46–48]. During such tasks, PD patients, like patients with frontal-lobe damage, are more impaired when they are required to learn that an attentional shift is required between two competing perceptual dimensions such as ‘colour’ and ‘number’ (a so-called ‘extra-dimensional shift’, EDS), than when learning that a shift is required between two different values of the same dimension such as ‘blue’ and ‘red’ (a so-called ‘intra-dimensional shift’, IDS [49]). This EDS deficit in PD has been further delineated into two cognitively distinct learning processes, ‘perseveration’ and ‘learned irrelevance’ [40,50]. Perseveration refers to an inability to disengage attention from a previously relevant dimension at the EDS stage of learning (e.g., to stop responding on the basis of colour). In contrast, learned irrelevance which was developed originally within the framework of classical animal learning theory, refers to the inability to attend to, or to learn about, information which has previously been shown to be irrelevant (e.g., to start responding to colour, when it has previously been irrelevant) [51]. Owen et al. [40] contrasted two EDS conditions that allowed perseveration (but not learned irrelevance) or learned irrelevance (but not perseveration), respectively, in patients with PD and a group of patients with circumscribed frontal-lobe removals. In one sense, these two conditions can be considered to be sub-goals of the broader set-shifting task, requiring the participant to cease responding to one

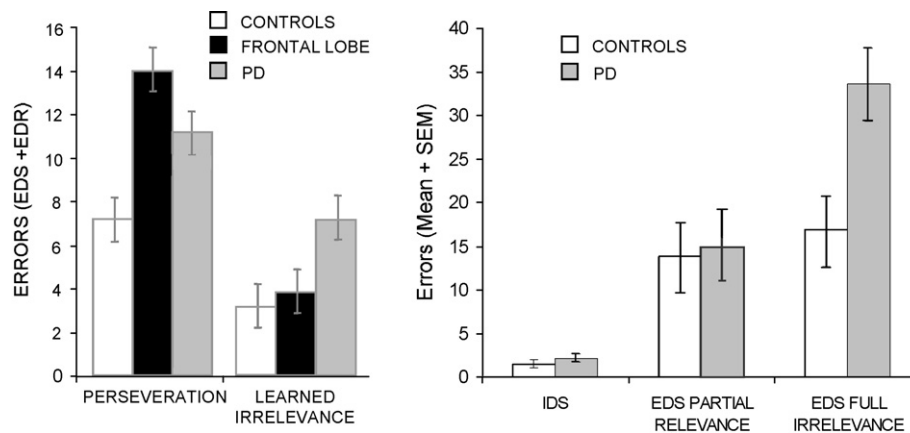


Fig. 2. Learned irrelevance in Parkinson's disease: Left graph (adapted from Owen et al. [40]): Compared to controls, frontal-lobe EDS performance is impaired in the perseveration EDS but not in the learned irrelevance EDS. In contrast, non-mediated patients with mild PD are equally and significantly impaired in both conditions. Right Graph (adapted from Slabosz et al. [50]): Compared to controls, PD patients are significantly impaired at learning that a stimulus is fully irrelevant, but not that it is only partially irrelevant. Bars represent standard error of the mean.

set of stimuli on the one hand, and to engage a second (competing) set of stimuli (which have previously been randomly paired with reinforcement) on the other (Fig. 2).

The group of neurosurgical patients with frontal-lobe excisions made significantly more errors than controls in the 'perseveration' condition, but performed normally in the 'learned irrelevance' condition. In contrast, a group of non-medicated PD patients in the early stages of the disease were equally and significantly impaired in both sub-goals, failing both to disengage from the previously relevant dimension and to orient attention to the previously irrelevant dimension [40]. This effect was explored further in a recent study by Slabosz et al. [50] in which a novel visual discrimination tasks was used to assess the effects of *variable* dimensional relevance in PD patients and in controls. The patients made more errors than controls in a condition in which they had to learn prior to the EDS that target dimension was completely irrelevant, but not in a condition in which the dimension was partially reinforced, confirming that learned irrelevance is a significant factor in accounting for visual discrimination learning deficits in PD. Taken together, these studies suggest that in early PD (when pathology is most likely to be focused on the rostradorsal portion of the head of the caudate nucleus), 'frontal-like' visual discrimination learning deficits are observed, but they are rather broader and involve more sub-components of the task than those seen after direct damage to the frontal-lobe.

These results described above are typical of findings from studies that have sought to investigate the precise nature of learning and memory deficits in early PD; that is to say, performance is often compromised on tests that involve the integration of multiple sub-goals, although frequently, when the tasks are decomposed into their constituents elements, the PD and frontal-lobe patients appear to be impaired for quite different reasons (for a review, see [52]). For example, like frontal-lobe patients, patients with mild (medicated) PD are impaired on a test of spatial working memory, which requires the selection between, and sequencing of, a series of sub-goals for successful overall performance [4,53]. This test is essentially a modification of a task used by Passingham [54] to examine the effects of prefrontal cortex lesions in primates, and is conceptually similar to the radial arm maze which has been successfully used to assess working memory in rats [55]. In the human version of the task, participants are required to search through an array of 'boxes' on a touch sensitive screen for hidden 'tokens', avoiding boxes that have been checked previously and shown to contain a token on a previous search. Like many tests of learning and memory that have been shown to be sensitive to deficit in PD, successful performance of this test involves the selection of behaviour (e.g., a particular sequence of boxes to search) based on

the changing values of goals (e.g., whether any given box has previously been used to conceal a token or not) and a knowledge of which actions lead to what outcomes (e.g., that selecting a particular box has already revealed no hidden token). Thus, as participants search through the boxes, an ongoing secondary task (or sub-goal), is to take note of those boxes that have previously been associated with reward and to avoid them. Failure to do so leads to an increase in 'between search errors' [53]. Like frontal-lobe patients, PD patients with mild disease make significantly more 'between search errors' than matched healthy controls [4]. However, unlike the frontal-lobe group, the PD patients are not impaired in terms of 'within search errors' (returns to boxes previously opened and shown to be empty earlier in the same search) and their impairment in 'between search errors' cannot be explained in terms of an inappropriate task strategy [56]. One interpretation of this result is that, while PD patients can perform this complex memory task, carrying out effective searches and adopting a similar overall approach (or strategy) to controls, they are unable to alternate effectively between important sub-goals; notably, to take note of a specific subset of boxes based on their changing value and to modify subsequent behaviour accordingly.

Further comparisons between studies also suggest that some aspects of cognitive function may be affected earlier in the course of PD than others. For example, Bradley et al. [37] found that patients with mild to moderate PD were impaired on a test of visuospatial working memory, whilst performance on an analogous test of verbal working memory was unaffected. Similarly, both Postle et al. [42] and Owen et al. [57] have demonstrated that, whilst spatial working memory is impaired in medicated patients with mild PD, working memory for visual shapes is relatively preserved. While this pattern of impairments may simply reflect a disproportionate involvement of spatial processing deficits in PD [58], an alternative possibility is that the spatial memory tasks used in these studies differ from the non-spatial memory tasks in terms of their underlying executive requirements.

Several studies have investigate this possibility directly by comparing the performance of groups of patients with PD on learning and memory tests which are known to tap demonstrably different aspects of executive function [4,6,36,59]. For example, one cross-sectional study of patients with PD clearly demonstrated that L-Dopa medicated and non-medicated patients at different stages of the disease can be differentiated in terms of their performance on a test of spatial memory span [4]. In this task, patients are required to remember sequences of colour-changing boxes on a computer screen. After each successful trial, the number of boxes changing in the next sequence is increased, from two up to a maximum of

nine boxes. Performance is scored according to the highest level at which the patient successfully recalls the sequence of boxes (so-called ‘memory span’). A significant impairment was observed in patients who were medicated and had severe clinical symptoms, but not in patients who were either medicated or non-medicated with mild disease [4]. It is unlikely that dopaminergic medication contributed significantly to this deficit as a parallel study of ten patients with severe PD has demonstrated that L-Dopa improves, rather than impairs, performance on the spatial span task [6].

This pattern of impaired spatial span performance in severe PD and intact spatial span in early PD contrasts markedly with the performance of these same groups on the more complex spatial search task described above [4]. In fact, medicated PD patients with both mild and severe clinical symptoms make more errors than matched controls on that task and a non-significant trend towards impairment was even observed in a non-medicated PD group of patients with extremely mild disease [4,5].

These results clearly demonstrate that patients at different stages of PD can be differentiated in terms of their performance on two tests of spatial memory that make different demands of executive processes. Among the patients with PD, there is an apparent increase in severity and broadening of spatial memory impairments as patients show increasing clinical disability. Thus, when the task simply involved the retention and recall of a spatial sequence within working memory, deficits were only observed in a subgroup of patients with severe clinical symptoms. By contrast, when the task required the active manipulation of spatial information within working memory and the identification and implementation of organizational strategies, deficits were observed in medicated patients with both mild and severe clinical symptoms. Because of the controlled nature and design of these tests, these differences cannot simply be explained in terms of the concurrent deterioration of motor function in these patients. The results do, in fact, concur fully with more extensive neuropsychological evaluations of these same patient groups which suggest that the pattern of learning and memory impairment in PD emerges and subsequently progresses according to a defined sequence which evolves in parallel with the motor deficits that characterize the disorder [4,5]. This apparent ‘progression’ on tests which are known to emphasize different aspects of executive function could simply reflect a global difference in cognitive capacity between patients with mild and severe PD. This seems unlikely, however, since similar groups of patients cannot be distinguished in terms of their performance on ‘non-frontal’ tests of visual recognition memory [5].

It seems likely that the subtle differences in performance between patients with circumscribed lesions of the frontal-lobe and patients with mild PD on test of learning and memory combined with the apparent broadening of executive deficits that co-occurs with the deterioration of motor function in PD may provide some important clues about the role of the caudate nucleus in healthy cognition. For example, while several of the studies discussed above suggest that the frontal-lobe contributes to complex executive tasks by generating and/or monitoring appropriate strategies and evaluating outcomes, the subtly different behaviour of patients with PD suggests that striatal pathology may interfere with performance on the same tasks at a more fundamental level; specifically, by failing to excite the correct action schemas and the selection of appropriate sub-goals based on an evaluation of action-outcomes, both processes fundamental to all tasks that require successful goal-directed action.

5. Pharmacological studies of learning and memory in Parkinson’s disease

So-called ‘on/off’ studies have been used to demonstrate a specific relationship between executive cognitive deficits and

dopaminergic pathology in PD [6,35]. L-Dopa, a precursor primarily affecting levels of dopamine in the central nervous system [60], typically ameliorates the motor symptoms of PD, although the effects on cognition are more variable. Thus, deleterious as well as beneficial effects have been reported [6,35,61,62]. For example, Gotham et al. [35], observed beneficial effects of dopaminergic medication on some cognitive tasks, but detrimental effects on others and speculated that the L-Dopa dose necessary to restore normal levels of dopamine to the striatum may ‘overdose’ any area where dopamine depletion is less severe, such as the prefrontal cortex. Swanson et al. [62] explored this issue directly using tasks that have been differentially associated with specific components of frontostriatal circuitry. Non-medicated PD patients were impaired on a spatial recognition memory task that has been shown to involve the dorsolateral frontal cortex [63], but performed significantly better than medicated patients on a test of reversal learning that appears to depend more on ventral frontal and striatal regions [64]. It was suggested that the medication dose sufficient to restore function to dorsal frontostriatal circuitry effectively overdoses and impairs function in the less affected ventral frontostriatal circuitry. This important result was followed up by Cools et al. [65] who demonstrated both beneficial and deleterious effects of dopaminergic medication in the same group of patients with PD on cognitive tasks that were selected according to their known dependence on different components of frontostriatal circuitry. Thus, whereas withdrawal of L-Dopa in PD impaired task set-shifting, which is assumed to involve the dorsolateral frontal cortex and its associated circuitry, it improved performance on probabilistic reversal learning, which is assumed to involve the ventrolateral frontal cortex and its associated circuitry, and orbitofrontal regions and the ventral striatum [64]. Because the effect of L-Dopa stems mainly from its ability to elevate dopamine levels [60] in the striatum [66], the authors suggested that the observed effects on task set-shifting and reversal learning are most likely due to effects of dopamine in the dorsal and ventral striatum, respectively [65]. However, given the role of the mesocortical dopamine projection in PD, by which neurons project from the ventral tegmental area and the medial substantia nigra *pars compacta* to the frontal-lobes, a direct effect on the frontal-lobe cannot be ruled out. In one influential study drawing on a computational model of the basal ganglia dopamine system, Frank et al. [67] successfully reconciled some of the apparently contradictory effects of dopaminergic medication in PD. In a procedural learning task, patients off medication were better at learning to avoid choices that resulted in negative outcomes than they were at learning from positive outcomes. Dopamine medication reversed this bias, demonstrating how both cognitive enhancements and impairments can arise from medication in PD, depending on the task being performed.

Broadly speaking, the results of ‘on/off’ studies in PD also concur closely with the few relevant pharmacological studies that have been conducted in healthy volunteers. For example, Mehta et al. [68] used the dopaminergic D2 receptor antagonist sulpiride (with the striatum as its presumed major site of action) to investigate the role of striatal dopamine in cognitive functioning. Following sulpiride administration, impairments were found on many executive learning and memory tasks, the overall pattern of deficits being similar to that found in early PD. In contrast, the indirect catecholamine agonist methylphenidate (Ritalin), *improves* performance in healthy volunteers on the spatial memory task described above [69,70], which is known to be sensitive both to early PD [4] and to the effects of L-Dopa in PD patients [6]. PET and SPECT studies that have explored the relationship between other cognitive tasks and components of the dopamine system have found that dopaminergic activity modulates a range of frontal executive-type cognitive processes, such as working memory, attentional functioning, and sequential organization [71,72].

6. Comparison with other diseases affecting basal ganglia function

The pattern of neuropsychological deficits in early PD described above is also broadly similar to that observed in other disorders that affect the integrity of the caudate nucleus. For example, Huntington's disease (HD) is an autosomal, dominantly inherited neurodegenerative disorder characterized phenotypically by motor, cognitive and affective disturbances. Pathologically, the most striking changes in HD are found in the striatum. Neuronal loss begins with the striosome compartment of the head of the caudate nucleus and progresses in a dorsal to ventral direction [73]. The striosomes in the dorsal regions of the caudate nucleus are connected primarily with the dorsolateral frontal cortex, while those in ventral regions of the caudate nucleus receive inputs from limbic related areas. In the earliest stages of HD (as well as in pre-clinical carriers of the mutation) when the damage may be relatively restricted to the head of the caudate nucleus, the cognitive deficits are relatively circumscribed, and include impairments in several tasks that involve the selection and execution of specific action schemas in the context of broad and complex goals [74–77], including the tests of visual discrimination learning and spatial working memory described above.

7. Functional neuroimaging in Parkinson's disease and Huntington's disease

Although clues about the functions of the basal ganglia can be gleaned from behavioural studies of patients with PD (or HD), it is not possible to delineate the exact contributions of different striatal regions to behaviour on the basis of these studies alone; even in the early stages of disease, the pathology is likely to be distributed and involve a number of anatomical regions and neurochemical systems. In recent years, however, functional neuroimaging techniques such as PET and fMRI have provided a unique opportunity for assessing the relationship between patterns of cortical and sub-cortical activation and different aspects of cognitive processing in healthy control volunteers and in patients with neuropathological disorders. These techniques measure the increase in oxygenated blood flow to the local vasculature that accompanies neural (synaptic) activity in different brain areas. PET measures regional cerebral blood flow (rCBF) directly, by determining the spatial distribution of a positron-emitting tracer, ^{15}O , throughout the brain, during a 6–120 s time window. fMRI measures a correlate of rCBF: the change in magnetic resonance signal that occurs when levels of oxygenated (diamagnetic) as opposed to deoxygenated (paramagnetic) haemoglobin increases in areas with recent neural activity. This 'Blood Oxygenation Level Dependent' (BOLD) contrast effect is detected using special MR protocols. In both PET and fMRI, the subject typically performs the task of interest (e.g., a memory task), in one scan or set of scans and a 'control' task requiring many, but not all, of the same motoric, perceptual and cognitive components during another scan or set of scans. The data are then usually transformed into a standardized stereotaxic coordinate system (e.g. [77]), so they can be averaged across all subjects, and subtraction images are generated. These images represent the difference in blood flow occurring across the brain during the task of interest and during the 'control' task. Statistical parametric maps [78], or t-maps [79], are then generated and the stereotaxic coordinates (x, y, z), of local maxima are calculated within the standardized stereotaxic system.

Neuroimaging of neurodegenerative disorders is potentially a very powerful tool, combining behavioural observations of neurological patients with corresponding neural activation differences. However, unlike imaging in healthy volunteers, this approach is very much in its infancy and only a few studies have so far been conducted. In one early study, Owen et al. [8] observed abnormal

blood flow in patients with PD in both the caudate nucleus and the internal segment of the globus pallidus when difficult and easy versions of a spatial working memory test conceptually similar to the one described above were compared. The abnormal basal ganglia activation pattern in the PD patients was accompanied by a performance deficit, similar to that seen previously in patients with frontal-lobe damage, although no abnormalities in regional cerebral blood flow were observed in the prefrontal cortex when the conditions were compared. This observation suggests that the striatum (and specifically, the caudate nucleus) is the likely neural substrate for the deficit observed in these patients on these tasks. Recent work by Lozza and colleagues [80] with ^{18}F -dopa PET scanning (which uses radioactively tagged L-dopa to measure dopamine uptake in the brain) found that hypometabolism in a network of brain areas including the striatum and ventromedial frontal cortex was correlated with performance on tests of strategy, planning, and working memory. Other ^{18}F -dopa PET studies, and, more directly, pathological [26,81] studies have confirmed a correlation between caudate dopamine loss and neuropsychological performance in PD patients [24], suggesting a preferential role for this system in cognitive impairment [82].

Monchi and others [83,84] examined set-shifting in PD patients and controls using fMRI, and found decreased cortical activation in the patient group that was dependent on the caudate nucleus involvement in the task. In another recent study, the role of the caudate nucleus in the working memory deficits that are observed in PD was explored using fMRI in a design that compared matched groups of patients selected according to whether they were executively impaired or not [85]. Two groups of patients with mild disease, who were well matched on a range of clinical and neuropsychological measures, but differed in terms of their executive impairments, underwent event-related fMRI during a novel working memory task that assessed multiple components of performance simultaneously [85]. The results revealed selective impairments in working memory that were associated with reduced activity in the caudate nucleus in the executively impaired sub-group of patients with PD, but not in the executively unimpaired sub-group of patients. This observation suggests again that the caudate nucleus contributes to tests of learning and memory by guiding the selection of responses necessary to achieve the goals of the task in hand and by initiating the required action contingencies and evaluating the subsequent outcomes (Fig. 3).

Neuroimaging in patients with early HD also suggests that the neural substrate of many of the observed cognitive deficits centres on the caudate nucleus. For example, PET and SPECT measures of caudate atrophy in HD correlate strongly with performance on many executive tasks [86,87]. Furthermore, measures of resting caudate metabolism have been shown to correlate with performance of the Wisconsin Card Sorting Task, the clinical 'standard' of visual discrimination learning described above [86,87] examined the relationship between PET measures of striatal neuronal loss and cognitive function in HD patients and in presymptomatic HD mutation carriers. Striatal medium-spiny neurons express dopamine

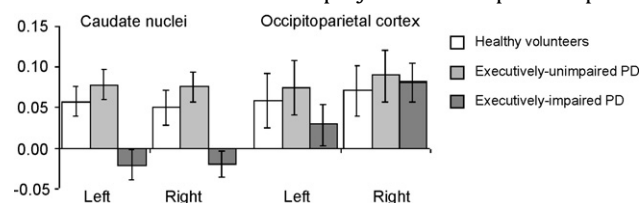


Fig. 3. (Adapted from Lewis et al. [85]). Regional mean fMRI signal during a working memory task. The subgroup of PD patients with executive impairment demonstrated significant underactivation compared with executively unimpaired patients in the caudate nucleus, but not in a 'control' occipitoparietal region. During retrieval (no manipulation), caudate underactivation was also observed in the executively impaired subgroup of patients.

receptors and thus, dopamine receptor binding potentials provide an index of basal ganglia pathology. A direct relationship was observed between impaired executive function and caudate dopamine D2 receptor binding potentials, suggesting that executive dysfunction in HD, which includes deficits in visual discrimination learning, is indeed related to caudate neuronal loss [88].

8. Conclusions

It is widely accepted that the basal ganglia as a whole are broadly responsible for sensorimotor coordination, including response selection and initiation. However, it has become increasingly clear that regions of the striatum can be functionally delineated along cortico-striatal lines. The convergence of several research domains in humans, including neuropsychological and neuropharmacological studies in patients, anatomical studies of cortico-striatal circuitry and neuroimaging studies of both patients and healthy volunteers, have focused the search for the neural mechanisms of goal-directed action on the striatum and, in particular, on the caudate nucleus. In particular, measures of anatomical and functional connectivity in healthy humans, concur with the available data in non-human primates and in rats in demonstrating a clear link between the caudate nucleus and regions of the frontal-lobe known to be responsible for 'executive' functions. Many tests of learning and memory make executive demands by requiring the generation and monitoring of appropriate strategies and the evaluation of potential outcomes for successful performance. Neuropsychological studies of patients with early PD have shown a tendency for relatively specific impairments in tests of learning and memory that make demands on executive processes. Importantly, however, these deficits are rather broader and involve more sub-components of the tasks than those seen after direct damage to the frontal-lobe. In these early-in-the-course patients, the pathology in the striatum is focused predominantly on the rostradorsal portion of the head of the caudate nucleus suggesting this as the most parsimonious locus for the effects observed. Similarly, in early Huntington's disease, another neurodegenerative disorder that affects the integrity of the caudate nucleus, deficits are most apparent in learning and memory tasks that require the selection of appropriate sub-goals based on an evaluation of action-outcomes; both processes fundamental to successful goal-directed action.

In summary, the cumulative evidence from converging methodologies in humans suggests a rather fundamental role for the caudate nucleus in representing action-outcome contingencies, which subserves adaptable goal-directed behaviour across many tests of learning and memory. Thus, whereas the prefrontal cortex appears to monitor performance and select appropriate strategies, the striatum, and more specifically the caudate nucleus, may be responsible for initiating and maintaining correct responses. These simpler mechanisms are crucial for all forms of normal behaviour, not just those involving learning and memory, because they free up attentional resources required for more complicated cognitive functions. This modular conception of the parts of the striatum is consistent with hierarchical models of cortico-striatal function [89] through which adaptive behaviour towards significant goals can be identified, planned and implemented effectively.

Acknowledgements

The authors would like to gratefully acknowledge Trevor W. Robbins, Barbara J. Sahakian, Angela Roberts, Aleksandra Slabosz, Roger Barker and Simon Lewis, all of whom contributed significantly to work described in this review.

References

- [1] Brown RG, Marsden CD. How common is dementia in Parkinson's disease? *Lancet* 1984;2:1262–5.
- [2] Karlson KH, Larsen JP, Tandberg E, Maland JG. Quality of life measurements in patients with Parkinson's disease: a community-based study 1998. *Eur J Neurol* 1998;5(5):443–50.
- [3] Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? *J Neurol Neurosurg Psychiatry* 2000;69:308–12.
- [4] Owen AM, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, et al. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain* 1992;115:1727–51. Pt 6.
- [5] Owen AM, Beksinska M, James M, Leigh PN, Summers BA, Marsden CD, et al. Visuospatial memory deficits at different stages of Parkinson's disease. *Neuropsychologia* 1993;31:627–44.
- [6] Lange KW, Robbins TW, Marsden CD, James M, Owen AM, Paul GM. L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. *Psychopharmacol (Berl)* 1992;107:394–404.
- [7] Jellinger KA. The pathology of Parkinson's disease. *Adv Neurol* 2001;86:55–72.
- [8] Owen AM, Doyon J, Dagher A, Sadikot A, Evans AC. Abnormal basal ganglia outflow in Parkinson's disease identified with PET. Implications for higher cortical functions. *Brain* 1998;121:949–65. Pt 5.
- [9] Dagher A, Owen AM, Boecker H, Brooks DJ. The role of the striatum and hippocampus in planning: a PET activation study in Parkinson's disease. *Brain* 2001;124:1020–32.
- [10] Cools R, Stefanova E, Barker RA, Robbins TW, Owen AM. Dopaminergic modulation of high-level cognition in Parkinson's disease: the role of the prefrontal cortex revealed by PET. *Brain* 2002;125:584–94.
- [11] Mattay VS, Tessitore A, Callicott JH, Bertolino A, Goldberg TE, Chase TN, et al. Dopaminergic modulation of cortical function in patients with Parkinson's disease. *Ann Neurol* 2002;51:156–64.
- [12] Nolte J. *The human brain: an introduction to its functional anatomy*. St Louis: Mosby, Inc.; 1999.
- [13] Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986;9:357–81.
- [14] Nakahara K, Hayashi T, Konishi S, Miyashita Y. Functional MRI of macaque monkeys performing a cognitive set-shifting task. *Science* 2002;295:1532–6.
- [15] Lehericy S, Ducros M, Van de Moortele PF, Francois C, Thivard L, Poupon C, et al. Diffusion tensor fiber tracking shows distinct corticostriatal circuits in humans. *Ann Neurol* 2004;55:522–9.
- [16] Postuma RB, Dagher A. Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. *Cereb Cortex* 2006;16:1508–21.
- [17] Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. *Eur J Neurosci* 2004;19:1950–62.
- [18] Strafella AP, Paus T, Fraraccio M, Dagher A. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. *Brain* 2003;126:2609–15.
- [19] Knoch D, Treyer V, Regard M, Muri RM, Buck A, Weber B. Lateralized and frequency-dependent effects of prefrontal rTMS on regional cerebral blood flow. *Neuroimage* 2006;31:641–8.
- [20] Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J Neurosci* 2001;21. RC157.
- [21] Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. *J Neurol Sci* 1973;20:415–55.
- [22] Rinne JO, Portin R, Ruottinen H, Nurmi E, Bergman J, Haaparanta M, et al. Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]fluorodopa positron emission tomographic study. *Arch Neurol* 2000;57:470–5.
- [23] Bruck A, Portin R, Lindell A, Laihinne A, Bergman J, Haaparanta M, et al. Positron emission tomography shows that impaired frontal lobe functioning in Parkinson's disease is related to dopaminergic hypofunction in the caudate nucleus. *Neurosci Lett* 2001;311:81–4.
- [24] Marie RM, Barre L, Dupuy B, Viader F, Defer G, Baron JC. Relationships between striatal dopamine denervation and frontal executive tests in Parkinson's disease. *Neurosci Lett* 1999;260:77–80.
- [25] Broussolle E, Dentesangle C, Landais P, Garcia-Larrea L, Pollak P, Croisile B, et al. The relation of putamen and caudate nucleus 18F-Dopa uptake to motor and cognitive performances in Parkinson's disease. *J Neurol Sci* 1999;166:141–51.
- [26] Rinne JO, Rummukainen J, Paljarvi L, Rinne UK. Dementia in Parkinson's disease is related to neuronal loss in the medial substantia nigra. *Ann Neurol* 1989;26:47–50.
- [27] Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiologic and clinical implications. *N Engl J Med* 1988;318:876–80.
- [28] Yeterian EH, Pandya DN. Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys. *J Comp Neurol* 1991;312:43–67.
- [29] Braak H, Tredicia KD, Rübä U, de Vosb RAI, Steurb ENHJ, Braaka E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197–211.

- [30] Agid Y, Javoy-Agid E, Ruberg M. Biochemistry of neurotransmitters in Parkinson's disease. In: Marsden CD, Fahn S, editors. *Movement disorders*. London: Butterworth; 1987. p. 166–230.
- [31] Byrne EJ, Lennox G, Lowe J, Godwin-Austen RB. Diffuse Lewy body disease: clinical features in 15 cases. *J Neurol Neurosurg Psychiatry* 1989;52:709–17.
- [32] Gibb WR, Luthert PJ, Janota I, Lantos PL. Cortical Lewy body dementia: clinical features and classification. *J Neurol Neurosurg Psychiatry* 1989;52:185–92.
- [33] Scatton B, Javoy-Agid F, Rouquier L, Dubois B, Agid Y. Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. *Brain Res* 1983;275:321–8.
- [34] Agid Y, Ruberg M, Dubois B, P. Anatomoclinical and biochemical concepts of subcortical dementia. In: Stahel SM, I.S.D., Goodman EC, editors. *Cognitive neurochemistry*. Oxford: Oxford University Press; 1987. p. 248–71.
- [35] Gotham AM, Brown RG, Marsden CD. 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. *Brain* 1988;111:299–321. Pt 2.
- [36] Morris RG, Downes JJ, Sahakian BJ, Evenden JL, Heald A, Robbins TW. Planning and spatial working memory in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1988;51:757–66.
- [37] Bradley VA, Welch JL, Dick DJ. Visuospatial working memory in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1989;52:1228–35.
- [38] Cooper JA, Sagar HJ, Jordan N, Harvey NS, Sullivan EV. Cognitive impairment in early, untreated Parkinson's disease and its relationship to motor disability. *Brain* 1991;114:2095–122.
- [39] Cooper JA, Sagar HJ, Sullivan EV. Short-term memory and temporal ordering in early Parkinson's disease: effects of disease chronicity and medication. *Neuropsychologia* 1993;31:933–49.
- [40] Owen AM, Roberts AC, Hodges JR, Summers BA, Polkey CE, Robbins TW. Contrasting mechanisms of impaired attentional set shifting in patients with frontal lobe damage or Parkinson's disease. *Brain* 1993;116:1159–79.
- [41] Owen AM, Sahakian BJ, Hodges JR, Summers BA, Polkey CE, Robbins TW. Dopamine-dependent fronto-striatal planning deficits in early Parkinson's disease. *Neuropsychology* 1995;9:126–40.
- [42] Postle BR, Jonides J, Smith EE, Corkin S, Growdon JH. Spatial, but not object, delayed response is impaired in early Parkinson's disease. *Neuropsychology* 1997;11:171–9.
- [43] Morris RG, Downes JJ, Robbins TW. The nature of the dysexecutive syndrome in Parkinson's disease. In: Gilhooly KJ, Leane MTG, Logie RH, Erdos G, editors. *Lines of thinking, vol. 2*. Chichester: John Wiley & Sons; 1990. p. 247–58.
- [44] Norman W, Shallice T. Attention to action. In: Davidson RJ, Schwartz GE, Shapiro D, editors. *Consciousness and self-regulation: advances in research and theory, vol. 4*. New York: Plenum; 1986. p. 1–18.
- [45] Divac I. Effects of prefrontal and caudate lesions on delayed response in cats. *Acta Biol Exp (Warsz)* 1967;28:149–67.
- [46] Cools AR, van den Bercken JH, Horstink MW, van Spaendonck KP, Berger HJ. Cognitive and motor shifting aptitude disorder in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1984;47:443–53.
- [47] Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. *Neuropsychologia* 1989;27:1329–43.
- [48] Van Spaendonck KP, Berger HJ, Horstink MW, Buytenhuijs EL, Cools AR. Executive functions and disease characteristics in Parkinson's disease. *Neuropsychologia* 1996;34:617–26.
- [49] Roberts AC, Robbins TW, Everitt BJ. The effects of intradimensional and extradimensional shifts on visual discrimination learning in humans and non-human primates. *Q J Exp Psychol B* 1988;40:321–41.
- [50] Slabosz A, Lewis SJ, Smigajewicz K, Szymura B, Barker RA, Owen AM. The role of learned irrelevance in attentional set-shifting impairments in Parkinson's disease. *Neuropsychology* 2006;20:578–88.
- [51] Mackintosh NJ. Stimulus selection: learning to ignore stimuli that predict no change in reinforcement. In: Hinde RA, Stevenson-Hinde J, editors. *Constraints on learning*. London: Academic Press; 1973. p. 75–96.
- [52] Owen AM. Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. *Neuroscientist* 2004;10:525–37.
- [53] Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW. Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia* 1990;28:1021–34.
- [54] Passingham RE. Memory of monkeys (*Macaca mulatta*) with lesions in prefrontal cortex. *Behav Neurosci* 1985;99(3):21.
- [55] Olton DS. Spatially organised behaviours of animals: behavioural and neurological studies. In: Potegal M, editor. *Spatial abilities*, 325. New York: Academic Press; 1982. p. 360.
- [56] Owen AM, Morris RG, Sahakian BJ, Polkey CE, Robbins TW. Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampotomy in man. *Brain* 1996;119:1597–615. Pt 5.
- [57] Owen AM, Iddon JL, Hodges JR, Summers BA, Robbins TW. Spatial and non-spatial working memory at different stages of Parkinson's disease. *Neuropsychologia* 1997;35:519–32.
- [58] Le Bras C, Pillon B, Damier P, Dubois B. At which steps of spatial working memory processing do striatofrontal circuits intervene in humans? *Neuropsychologia* 1999;37:83–90.
- [59] Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt PM. Cambridge Neuropsychological Test Automated battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. *Dementia* 1994;5:266–81.
- [60] Maruyama W, Naoi M, Narabayashi H. The metabolism of L-DOPA and L-threo-3,4-dihydroxyphenylserine and their effects on monoamines in the human brain: analysis of the intraventricular fluid from parkinsonian patients. *J Neurol Sci* 1996;139:141–8.
- [61] Kulisevsky J, Avila A, Barbanjo M, Antonijoa R, Berthier ML, Gironell A. Acute effects of levodopa on neuropsychological performance in stable and fluctuating Parkinson's disease patients at different levodopa plasma levels. *Brain* 1996;119:2121–32.
- [62] Swanson R, Rogers RD, Sahakian BJ, Summers BA, Polkey CE, Robbins TW. Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia* 2000;38:596–612.
- [63] Owen AM, Doyon J, Petrides M, Evans AC. Planning and spatial working memory: a positron emission tomography study in humans. *Eur J Neurosci* 1996;8:353–64.
- [64] Dias R, Robbins TW, Roberts AC. Dissociation in prefrontal cortex of affective and attentional shifts. *Nature* 1996;380:69–72.
- [65] Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb Cortex* 2001;11:1136–43.
- [66] Hornykiewicz O. The mechanisms of action of L-dopa in Parkinson's disease. *Life Sci* 1974;15:1249–59.
- [67] Frank MJ, Seeberger LC, O'Reilly RC. By carrot or by stick: cognitive reinforcement learning in Parkinsonism. *Science* 2004;306:19403.
- [68] Mehta MA, Sahakian BJ, McKenna PJ, Robbins TW. Systemic sulpiride in young adult volunteers simulates the profile of cognitive deficits in Parkinson's disease. *Psychopharmacol (Berl)* 1999;146:162–74.
- [69] Elliott R, Sahakian BJ, Matthews K, Bannerjee A, Rimmer J, Robbins TW. Effects of methylphenidate on spatial working memory and planning in healthy young adults. *Psychopharmacol (Berl)* 1997;131:196–206.
- [70] Mehta MA, Calloway P, Sahakian BJ. Amelioration of specific working memory deficits by methylphenidate in a case of adult attention deficit/hyperactivity disorder. *J Psychopharmacol* 2000;14:299–302.
- [71] Cropley VL, Fujita M, Innis RB, Nathan PJ. Molecular imaging of the dopaminergic system and its association with human cognitive function. *Biol Psychiatry* 2006;59:898–907.
- [72] Aalto S, Brück A, Laine M, Nägren K, Rinne JO. Frontal and temporal dopamine release during working memory and attention tasks in healthy humans: a positron emission tomography study using the high-affinity dopamine D2 receptor ligand [¹¹C]FLB 457. *J Neurosci* 2005;25:2471–7.
- [73] Hedreen JC, Folstein SE. Early loss of neostriatal striosome neurons in Huntington's disease. *J Neuropathol Exp Neurol* 1995;54:105–20.
- [74] Lawrence AD, Sahakian BJ, Hodges JR, Rosser AE, Lange KW, Robbins TW. Executive and mnemonic functions in early Huntington's disease. *Brain* 1996;119:1633–45. Pt 5.
- [75] Lawrence AD, Hodges JR, Rosser AE, Kershaw A, French-Constant C, Rubinstztein DC, et al. Evidence for specific cognitive deficits in preclinical Huntington's disease. *Brain* 1998;121:1329–41. Pt 7.
- [76] Lawrence AD, Sahakian BJ, Robbins TW. Cognitive functions and corticostriatal circuits: insights from Huntington's disease. *Trends Cognit Sci* 1998;2:379–88.
- [77] Talairach J, Tournoux P. *Co-planar stereotaxic atlas of the human brain: 3-dimensional proportional system: an approach to cerebral imaging*. New York: Thieme; 1988.
- [78] Friston KJ, Frith CD, Liddle PF, Frackowiak RS. Comparing functional (PET) images: the assessment of significant change. *J Cereb Blood Flow Metab* 1991;11:690–9.
- [79] Worsley KJ, Evans AC, Marrett S, Neelin P. A three-dimensional statistical analysis for CBF activation studies in human brain. *J Cereb Blood Flow Metab* 1992;12:900–18.
- [80] Lozza C, Baron JC, Eidelberg D, Mentis MJ, Carbon M, Marié RM. Executive processes in Parkinson's disease: FDG-PET and network analysis. *Hum Brain Mapp* 2004;22:236–45.
- [81] Paulus W, Jellinger K. The neuropathologic basis of different clinical subgroups of Parkinson's disease. *J Neuropathol Exp Neurol* 1991;50:743–55.
- [82] Ito K, Nagano-Saito A, Kato T, Arahata Y, Nakamura A, Kawasumi Y, et al. Striatal and extrastriatal dysfunction in Parkinson's disease with dementia: a 6-[¹⁸F]fluoro-L-dopa PET study. *Brain* 2002;125:1358–65.
- [83] Monchi O, Petrides M, Doyon J, Postuma RB, Worsley K, Dagher A. Neural bases of set-shifting deficits in Parkinson's disease. *J Neurosci* 2004;24:702–10.
- [84] Monchi O, Petrides M, Mejia-Constrain B, Strafella AP. Cortical activity in Parkinson's disease during executive processing depends on striatal involvement. *Brain* 2007;130:233–44.
- [85] Lewis SJ, Dove A, Robbins TW, Barker RA, Owen AM. Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *J Neurosci* 2003;23:6351–6.
- [86] Berent S, Giordani B, Lehtinen S, Markel D, Penney JB, Buchtel HA, et al. Positron emission tomographic scan investigations of Huntington's disease: cerebral metabolic correlates of cognitive function. *Ann Neurol* 1988;23:541–6.
- [87] Hasselbalch SG, Oberg G, Sorensen SA, Andersen AR, Waldemar G, Schmidt JF, et al. Reduced regional cerebral blood flow in Huntington's disease studied by SPECT. *J Neurol Neurosurg Psychiatry* 1992;55:1018–23.
- [88] Lawrence AD, Weeks RA, Brooks DJ, Andrews TC, Watkins LH, Harding AE, et al. The relationship between striatal dopamine receptor binding and cognitive performance in Huntington's disease. *Brain* 1998;121:1343–55. Pt 7.
- [89] Redgrave P, Prescott TJ, Gurney K. The basal ganglia: a vertebrate solution to the selection problem? *Neuroscience* 1999;89:1009–23.