

The cognitive functions of the caudate nucleus

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ABSTRACT

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 basal ganglia are functionally delineated along corticostriatal lines, and that a modular conception of the respective functions of various nuclei is useful. Here we examine the specific role of the caudate nucleus, and in particular, how this differs from that of the putamen. This review considers converging evidence from multiple domains including anatomical studies of corticostriatal circuitry, neuroimaging studies of healthy volunteers, patient studies of performance deficits on a variety of cognitive tests, and animal studies of behavioural control. We conclude that the caudate nucleus contributes to behaviour through the excitation of correct action schemas and the selection of appropriate sub-goals based on an evaluation of action-outcomes; both processes fundamental to successful goal-directed action. This is in contrast to the putamen, which appears to subservise cognitive functions more limited to stimulus-response, or habit, learning. This modular conception of the striatum is consistent with hierarchical models of cortico-striatal function through which adaptive behaviour towards significant goals can be identified (motivation; ventral striatum), planned (cognition; caudate) and implemented (sensorimotor coordination; putamen) effectively.

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Abbreviations: ACA, anterior cingulate area; Ach, acetylcholine; APV, 2-amino-5-phosphonovaleric acid; BLA, basolateral amygdala; BOLD, blood-oxygenation level dependent; caudate (DL), dorsolateral caudate; caudate (VM), ventromedial caudate; cdm-GPi, caudodorsomedial globus pallidus (internal segment); cl-SNr, caudolateral substantia nigra pars reticulata; DLPFC, dorsolateral prefrontal cortex; DS, dorsal striatum; DTI, diffusion tensor imaging; EDS, extra-dimensional shift; FEF, frontal eye fields; fMRI, functional magnetic resonance imaging; HD, Huntington's disease; l-dopa, levodopa; l-VAmc, lateral ventral anterior nucleus of thalamus pars magnocellularis; lDS, lateral dorsal striatum; m-VAmc, medial ventral anterior nucleus of thalamus pars magnocellularis; mdm-GPi, dorsomedial globus pallidus (internal segment); MDmc, magnocellular subnucleus of mediodorsal nucleus of the thalamus; MDpl, parvocellular subnucleus of mediodorsal nucleus of the thalamus; mDS, medial dorsal striatum; NMDA, N-methyl-D-aspartic acid; PD, Parkinson's disease; PET, positron emission tomography; PFC, prefrontal cortex; pm-MD, posteromedial mediodorsal nucleus of the thalamus; rCBF, regional cerebral blood flow; rd-SNr, rostromedial substantia nigra pars reticulata; rl-GPi, rostromedial globus pallidus (internal segment); rm-SNr, rostromedial substantia nigra pars reticulata; S-R, stimulus-response; SMA, supplementary motor area; TMS, transcranial magnetic stimulation; vl-GPi, ventrolateral globus pallidus (internal segment); vl-SNr, ventrolateral substantia nigra pars reticulata; VIm, ventrolateral nucleus of thalamus pars medialis; VL0, ventrolateral nucleus of thalamus pars oralis; VP, ventral posterior nucleus of the thalamus; VS, ventral striatum.

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1. Introduction

Traditionally the basal ganglia have been associated with motor processes, although evidence for their role in parallel cognitive functions is mounting (for a review, see [Middleton and Strick, 2000](#)). In this review we are concerned with the striatum, composed of the putamen (or medial dorsal striatum in rodents) and the caudate nucleus (or lateral dorsal striatum). In particular, we focus on human, non-human primate, and rodent investigations in order to define the cognitive functions of the striatum, and especially to differentiate the functions of the caudate from those of the putamen.

The different roles of the caudate and putamen in higher level learning and memory tasks have been examined in animals using behavioural, lesion, and pharmacological techniques. In humans, a common approach for investigating the function of these areas has been to study the deficits that accompany basal ganglia pathology such as that found in Parkinson's disease (PD) and Huntington's disease (HD). In addition, recent functional neuroimaging studies using Positron Emission Tomography (PET) and functional magnetic resonance imaging (fMRI) have provided important new insights into striatal structure and function in the healthy human brain. Pharmacological manipulations have also been conducted to investigate the role of dopamine, a neurotransmitter that is crucial to normal striatal function, in cognitive tasks involving the caudate.

In this review, we consider converging evidence from multiple domains and conclude that the caudate plays a critical role in supporting the planning and execution of strategies and behaviour required for achieving complex goals, i.e. in action-outcome learning that subserves goal-directed action. This is in contrast to the putamen, which appears to subserve cognitive functions more limited to stimulus-response, or habit, learning.

2. Anatomical considerations

2.1. Basal ganglia anatomy

In humans and non-human primates, 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 ([Nolte, 1999](#)). In non-primates the anatomy is similar. For the purpose of this cross-species review the dorsal striatum (DS) in rats will be considered to correspond to the caudate and putamen in primates. Further, anatomical and functional studies in rats suggests that, without the clear defining border of the internal capsule, the medial dorsal striatum (mDS) roughly corresponds to the primate caudate and the lateral dorsal striatum (lDS) to the putamen ([Joel and Weiner, 2000](#)). The ventral striatum (VS) will be viewed synonymously across rodents and primates (including humans).

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 ([Alexander et al., 1986](#)), which emphasizes the functional inter-relationships between the neocortex and the striatum (see [Fig. 1](#)). 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.

Examinations of striatal anatomical and functional connections broadly support the parallel loop model of striatal organization ([Alexander et al., 1986](#); [Nakahara et al., 2002](#)). Anterograde and retrograde tracer studies, as well as electrophysiological studies have been conducted to determine anatomical and functional connectivity in animals. Three main loops will be discussed here: the limbic loop (involving mainly ventral striatal areas), the sensorimotor loop (involving caudal areas), and the associative loop (involving dorsal and rostral areas). The limbic loop comprises the ventromedial striatum, including the nucleus accumbens, and the rostral, ventral caudate nucleus, and putamen, which receive frontal input from the orbital and medial prefrontal cortex ([Haber et al., 2000](#); [Kunishio and Haber, 1994](#)). In contrast, the associative loop involves the head of caudate and most rostral putamen, which receive input from the dorsolateral prefrontal cortex, pre-supplementary motor area, posterior parietal cortex ([Parent, 1990](#); [Parent and Hazrati, 1995](#)). The sensorimotor loop involves caudal and lateral aspects of the putamen, and receives input from the primary and supplementary motor areas as well as somato-sensory cortex ([Alexander and Crutcher, 1990](#)). Thus, the topography of the different loops in the striatum suggests that functional divisions of the basal ganglia do not strictly coincide with anatomical boundaries. One can conceive of basal ganglia function along gradients: the dorsal (mainly associative loop) to ventral (limbic) gradient and the anterior (associative) to posterior (sensorimotor) gradient.

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 MRI to determine anatomical connectivity. A DTI study by [Lehericy et al. \(2004\)](#) found that the head of the caudate was connected primarily to medial, ventral, and dorsolateral prefrontal cortex, the frontal

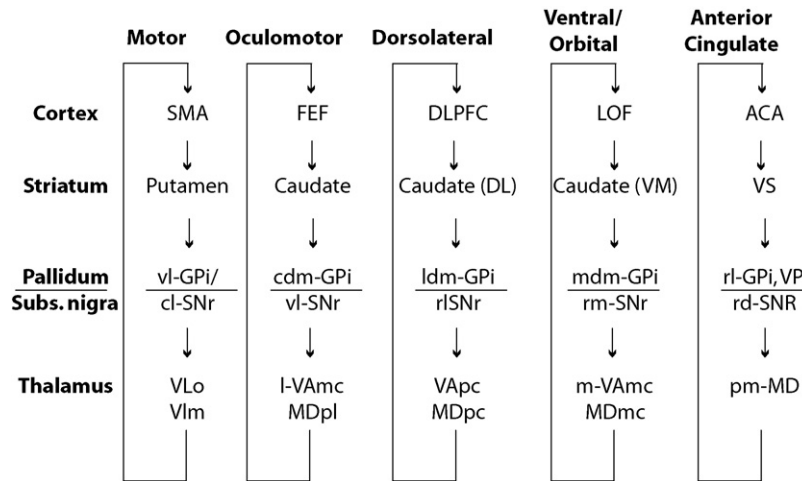


Fig. 1. The dorsal and ventral striatum are differentially connected to discrete prefrontal cortical regions in segregated corticostriatal circuits (adapted from Alexander et al., 1986). The putamen plays a critical role within the so called ‘motor circuit’ whilst the caudate forms part of the oculomotor, 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, l-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., 1986).

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, consistent with animal work mentioned above. The connectivity patterns held both when tracing from the striatum to cortical areas and when tracing from cortical areas back to the striatum. Taken together, both the animal and human work point to anatomical parcellations that correspond well to the proposed associative, sensorimotor, and limbic loops, involving more dorsal, caudal, and ventral striatal structures, respectively.

2.2. Functional connections of 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 PET and fMRI studies has demonstrated that different areas of the striatum have distinct patterns of functional connectivity with the cerebral cortex (Postuma and Dagher, 2006). The results of this analysis were also consistent with the concept of segregated corticostriatal connections, as described in parallel loop models (Alexander et al., 1986). 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) (Bestmann et al., 2004), and also induces focal dopamine release in the putamen, but not the caudate (Strafella et al., 2003). Stimulation over dorsolateral prefrontal cortex, however, increases neural activity and dopamine release in the caudate, but not the putamen (Knoch et al., 2006; Strafella et al., 2001). Thus, non-invasive measures of anatomical and functional connectivity in humans demonstrate a clear link between the caudate and executive frontal areas, in contrast to the putamen’s links to more basic sensorimotor regions.

As a final note, we have restricted our review of caudate function to the head of the caudate nucleus, and do not consider in detail the body or tail. These latter structures receive projections from ventrolateral prefrontal regions as well as inferior temporal regions, and appear to be involved in visual stimulus-response learning and visual working memory functions (Lawrence et al., 1998b; Middleton and Strick, 1996).

3. Animal research into striatal function

Historically, two seemingly disparate models of dorsal striatal function have emerged from animal research: (1) the conception of the striatum as a habit mechanism, and (2) the conception of the striatum as a mechanism for flexibility and switching. It is becoming clear that different components of the striatum (corresponding to the putamen/lateral dorsal striatum and caudate/medial dorsal striatum, respectively) may contribute to both of these processes within the broader framework of distinct corticostriatal circuits. As is outlined below, whilst there is growing evidence that lateral regions of the dorsal striatum support instrumental stimulus-response habits, the medial dorsal

striatum appears to contribute to a distinct form of instrumental behaviour, that of goal-directed action. The major distinction being that whilst the former is a rigid and automatic form of stimulus-bound behaviour, the latter depends on representations of goal value and of the contingencies between actions and their consequences. In contrast to the role of the dorsal striatum in instrumental behaviour, the ventral striatum, long argued to subserve a distinct function from its dorsal counterpart (Robbins and Everitt, 1992) appears to support Pavlovian influences over behaviour (Balleine, 2005). As is described below, these functional dissociations fit well within neuroanatomical models of cortico-striatal function (Parkinson et al., 2000a), as dissociable regions of PFC project across the striatum in a somewhat segregated and parallel manner (Berendse et al., 1992; Haber et al., 2000) as was first postulated by Alexander et al. (1986).

3.1. *The dorsal striatum and habit*

Consistent with the anatomical and functional connectivity dissociations listed above, studies of animals have demonstrated functional dissociations across the striatum, and between striatal regions and associated brain structures. It has often been argued that the dorsal striatum underlies habit learning, that is, the development of stimulus-response (S-R) mappings in the control of skill automaticity (Wise, 1996), for review see Poldrack and Packard (2003). For example, lesions of the caudate-putamen have been shown to impair delayed response, alternation behaviour and visual discrimination learning (Butters and Rosvold, 1968; Divac, 1968, 1972; Reading et al., 1991).

Evidence has also emerged to suggest that the striatum is a site for the consolidation of S-R learning—infusions of dopamine agonists into the striatum after a training session has been completed improves subsequent performance, and the enhancement is selective with respect to corticostriatal circuit and function. For example, post-training intra-dorsal striatal infusions of dopamine improve radial arm maze win-stay performance, a measure of S-R learning (Viaud and White, 1989), whilst post-training intra-ventral striatal infusions of dopamine improve autoshaping, a Pavlovian preparation which measures anticipatory motivational arousal (Oscos et al., 1988).

However, this simple conceptualisation of dorsal striatum function has been questioned: research focusing on the medial versus lateral striatum, a rough attempt to delineate caudate from putamen in the rat, has suggested different functions for these two areas (Carr and Wilkie, 1997; Hiroi and White, 1991; Reading et al., 1991; Viaud and White, 1989; White and Viaud, 1991). For example, lesions of the medial striatum but not lateral striatum impair certain spatial tasks (those that are sensitive to hippocampal manipulations (Devan et al., 1999), consistent with the projections this region receives from the hippocampus). There is also growing evidence (reviewed below) to suggest that the medial striatum (or caudate) is involved in flexibility of responding. In addition, the neurobiological processes operating within the caudate are different from other striatal zones.

3.2. *The medial striatum and flexible behaviour*

There is a body of evidence in the animal literature which has concluded that the caudate is critical for aspects of response switching, including cognitively driven strategy switching (Ragozzino, 2003). So, whilst manipulations of the medial dorsal striatum (mDS) do not impair initial acquisition of instrumental behaviours (Pisa and Cyr, 1990; Ragozzino and Choi, 2004), they do affect the ability of animals to stop, change or regulate their instrumental behaviour when task contingencies, or goal values, change. For

example, lesions of the mDS (but not lateral dorsal striatum (IDS) when also assessed) impair inhibitory control (Brasted et al., 1999; Eagle and Robbins, 2003), disrupt reversal learning (Collins et al., 2000; Pisa and Cyr, 1990; Ragozzino and Choi, 2004; Ragozzino et al., 2002) and disrupt the ability to switch between different strategies (response-based versus visual cue-based) when appropriate to do so (Ragozzino et al., 2002). Further, extracellular microdialysis in the mDS has shown that whilst levels of acetylcholine (ACh) do not fluctuate during the initial acquisition of an instrumental task, they increase significantly in response to changes in response contingencies and return to baseline once animals acquire the new response strategy (Ragozzino and Choi, 2004). Analysis of errors that are made by animals with a dysfunctional mDS suggests a selective deficit in being able to maintain a new response pattern, rather than inhibiting a previously successful one. In contrast, the medial wall of the PFC projects across the mDS and has been shown to be critical for inhibition of previously learnt associations (Dias et al., 1996; Rhodes and Killcross, 2004). Therefore, these two structures together may control ultimate selection by suppressing out-of-date behaviour on the one hand (PFC) and supporting new appropriate strategies on the other (caudate).

3.3. *Actions and habits—a dual system perspective on instrumental behaviour*

The idea that instrumental conditioning based on S-R principles could provide a full account of human (or even rodent) purposive behaviour has not stood up to conceptual or empirical analysis. Humans perform acts and pursue complex behaviour over protracted periods of time in order to satisfy specific goals. If the goal value changes or becomes less appropriate to satisfy the needs of the individual, then the goal changes and behaviour is adapted accordingly. Indeed, Tolman (1932) argued that behaviour was driven by cognitive representations of the goal of actions. Contemporary theories now favour a dual-process model of instrumental learning: a simple, though less flexible, S-R system and a cognitive knowledge-based system (Dickinson and Balleine, 1994). Several important behavioural paradigmatic approaches support the existence of both habits and goal-directed actions in rats and primates. Extended lever-training in rodents leads to habitual control over behaviour which can be assessed using devaluation procedures (Adams and Dickinson, 1981). Animals will readily learn to press a lever to receive a food reinforcer, or outcome. Such lever-pressing could be accomplished by either an S-R habit system, or a goal-directed action system. The critical distinction between the two is that the goal-directed action system maintains an active representation of the outcome, or goal, such that a change in the outcome value, or a change in the animal's motivational state should change behaviour. For example, an animal learns to press a lever for a cinnamon flavoured solution. Subsequently, away from the testing apparatus, the value of the cinnamon flavour is reduced, either by satiating the animal on the flavour (sensory-specific satiety) or by inducing a learned taste-aversion to the flavour, through illness. Finally, the animal is given the opportunity to press the lever again in a test session. The test is carried out in extinction so that the animal has to perform based on its memory, i.e. this tests what representations are supporting behaviour. If an S-R process is controlling behaviour, the animal should continue to press because the sight of the lever (stimulus) elicits lever-pressing (response) and no representation of the now devalued cinnamon enters into the process. In contrast, goal-directed processes should suppress lever-pressing because the memory of the cinnamon will no longer represent an appetitive goal (indeed it should elicit disgust). It should be of no surprise that

rodents are perfectly capable of suppressing behaviour in this sort of situation (Adams and Dickinson, 1981; Balleine and Dickinson, 1991, 1998b). However, after an extended period of training, lever pressing appears to become resistant to devaluation, that is, animals will continue to press a lever even if the outcome for which they are responding has been devalued (Dickinson et al., 1995). This provides the first stage of evidence for the existence of at least two instrumental response systems.

Manipulations of the contingency between actions and outcomes can also indicate whether behaviour is controlled by an S-R or goal-directed system. Because S-R behaviour is, by definition, stimulus bound, changes in the contingency between responses and outcomes should not affect performance. Indeed, as mentioned above with regard to different reinforcement schedules, it has been demonstrated that the development of habitual control seems fastest when the contingency between actions and outcomes is least perceivable. In a test session, one can degrade the contingency between responding and reinforcement simply by presenting reinforcers “for free” irrespective of an animal's behaviour (Balleine and Dickinson, 1998a; Dickinson and Dawson, 1987; Hammond, 1980). This approach can be used to assay behaviour for goal-directed properties.

Research in rats and primates has explored the extent to which corticostriatal circuitry contributes to goal-directed learning and incentive motivation. For example, there is evidence that both the ventral striatum and the caudate could support goal-directed action selection. However, to date, evidence for a role of the ventral striatum in value representations is somewhat equivocal (Corbit et al., 2001; de Borchgrave et al., 2002; Parkinson et al., 1999, 2000b) and its role in instrumental behaviour may be best described as providing a stimulus-induced motivational influence on the performance (Balleine, 2005; Parkinson et al., 2000a; Wyvell and Berridge, 2000). In other words, providing a means through which conditioned stimuli in the environment can affect the direction and vigour of ongoing behaviour (sometimes called incentive salience; Dickinson and Balleine, 2002). This stimulus-bound motivational influence is an important factor in behaviour, but is dissociable, theoretically and empirically from goal-directed action.

Emerging evidence suggests that the caudate nucleus may be a more likely source for goal-directed behaviour. A series of elegant studies by Balleine and colleagues have provided direct evidence for this contention (and see Yin and Knowlton, 2006). For example, lesions of the posterior mDS, carried out pre- or post-training disrupt the ability of rats to respond to changes in the value of the goal (outcome devaluation) and to changes in the contingency between actions and outcomes (Yin et al., 2005b). Inactivation of the mDS with either muscimol or the NMDA antagonist APV had a similarly profound effect on goal-directed behaviour, though none of the manipulations impaired outcome or response discrimination (Yin et al., 2005a,b). The specificity of these effects is demonstrated by the fact that lesions of the anterior mDS or of the IDS do not impair goal-directed behaviour (Yin et al., 2004). Indeed, inactivation of the IDS actually enhances sensitivity to outcome devaluation (Yin et al., 2006) supporting previous suggestions of competition between different response selection mechanisms, in this case actions and habits.

In addition, the striatum receives inputs from areas that are likely to represent outcome expectation. For example, projections from the basolateral amygdala (BLA), orbital and medial PFC interface along the medial axis of the striatum including both the ventral striatum proper and also the overlying caudate (Berendse et al., 1992). The BLA, considered to be a cortical-like afferent to caudate and ventral striatum corticostriatal circuitry, is critical for incentive learning (Balleine et al., 2003). Further, electrophysiological recordings of BLA neurons in vivo have also shown that a

predominant function is to code the expected outcome following the presentation of a predictive stimulus, i.e. stimulus-outcome neurons (Schoenbaum et al., 1998). The firing pattern of these neurons reflects the value of the expected outcome and track changes in that value. As such, these neurons conform to one of the defining requirements of goal-directed action: a flexible representation of the goal. Other neurons in the BLA fire in the delay between a response and the outcome, suggesting an expectation of the goal following a response. This pattern is consistent with the second requirement for goal-directed action: knowledge of the contingency between actions and outcomes. Further, this response-based pattern of activity appears to be provided to the BLA by the orbital prefrontal cortex, as the information is lost from the BLA if its afferent orbitofrontal cortex has been lesioned (Saddoris et al., 2005). It has also been demonstrated that competition between S-R and A-O systems takes place along the medial wall of the PFC. The medial PFC in rats can be segregated anatomically incorporating infralimbic and prelimbic cortices (Berendse et al., 1992). These regions project across the striatum in a parallel manner, consistent with models of corticostriatal circuitry (Alexander et al., 1986) and may correspond to Brodmann's areas 25 and 32, respectively. In recent functional work focusing on goal-directed behaviour it has been shown that whilst selective lesions of the infralimbic cortex result in animals that are controlled by goal-directed mechanisms, lesions of the prelimbic cortex produce the opposite; habit-based animals insensitive to changes in goal values (Killcross and Coutureau, 2003). This result provides a clear neural-based indication of the existence of these two separable processes. Indeed, the goal-directed system can be reinstated in overtrained animals through transient inactivation of the infralimbic cortex (Coutureau and Killcross, 2003). Thus, of the various learning processes that can support motivated behaviour, recent evidence suggests that the caudate and its associated corticostriatal circuitry underlies goal-directed action i.e. the selection of behaviour based on the changing values of goals and a knowledge of which actions lead to what outcomes. An important outstanding question is to whether the medial caudate subserves goal-directed behaviour for both appetitive (above) and aversive outcomes—is valence independent. Whilst little work has addressed this issue directly, there is evidence from single-unit recording work in macaques that neurons in the caudate code for both appetitive or aversive outcomes, though they may fire in a manner that discriminates the valence of the expected outcome (Yamada et al., 2004; Ravel et al., 2003). As such, there is some evidence to support a general role for the mDS, or caudate, in goal-directed behaviour irrespective of outcome valence.

4. Parkinson's disease as a model for examining caudate dysfunction in humans

Parkinson's disease (PD) is probably the most-studied of all the basal ganglia disorders, and as such, is a principal source of information about human striatal function. Patients with PD develop deficits across a wide range of cognitive functions, including memory, attention, planning, and skill learning. Many of these functions are crucial for guiding action in the pursuit of goals.

4.1. 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 (Jellinger, 2001). 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 dorsomedial projection of the nigrostriatal tract is to the head of the caudate nucleus (Bernheimer et al., 1973). 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 (Rinne et al., 1989). In addition, correlations exist between dopaminergic depletion of the caudate nucleus and neuropsychological performance (Bruck et al., 2001; Marie et al., 1999), although these findings have not been universally corroborated (Broussolle et al., 1999; Rinne et al., 2000).

As PD is a progressive neurodegenerative disease, recent 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 (Kish et al., 1988). 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 (Yeterian and Pandya, 1991). 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) (Yeterian and Pandya, 1991), are relatively spared in early PD, which may leave functions which are maximally dependent on this circuitry relatively intact.

It is 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 (Agid et al., 1987a), 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 (Byrne et al., 1989; Gibb et al., 1989). Finally, patients with PD have dopamine depletion within the frontal cortex itself (Scatton et al., 1983) 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 (Agid et al., 1987b) 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 caudate 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.

4.2. Cognitive deficits in PD

About 20% of patients with PD develop frank dementia (Brown and Marsden, 1984), but less severe cognitive impairments are

common even at the earliest stages of the disease (Downes et al., 1989). The pattern of these impairments is often described as predominantly 'executive', resembling that produced by circumscribed frontal-lobe lesions (Owen et al., 1992). '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 (Morris et al., 1990). Many willed actions involve executive processes, particularly when the action or response is novel or complex (Norman and Shallice, 1986) such as pursuing a long-term goal requiring the completion of multiple intermediate subgoals and behaviour. A variety of functions fall under 'executive' control, including directing attention to a relevant stimulus and inhibition of irrelevant stimuli, switching attention between different processes, coding and checking of the contents of memory storage, and planning. 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. Morris et al., 1990), suggests that an equivalence between the prefrontal cortex and executive functioning cannot be assumed. Moreover, as damage to different regions of the caudate nucleus in non-human species produces deficits that often resemble the effects of damage to their corresponding targets of projection within the prefrontal cortex (Divac et al., 1967), it is entirely unclear whether executive deficits in PD reflect predominantly their cortical (frontal-lobe) or subcortical (striatal) damage.

Attentional set-shifting is probably the most widely studied executive deficit in PD, and impairments have been reported in both cognitive and motor domains (Cools et al., 1984; Downes et al., 1989; Owen et al., 1992; Van Spaendonck et al., 1996). In the cognitive domain, attentional set-shifting performance has been studied most extensively using tests of visual discrimination learning (e.g. Downes et al., 1989; Owen et al., 1992). Using such tasks, a number of studies have shown that PD patients, like patients with frontal-lobe damage, are more impaired when an attentional shift is required between two competing perceptual dimensions such as 'colour' and 'number' (a so-called 'extra-dimensional shift', EDS), than when a shift is required between two different values of the same dimension such as 'blue' and 'red' (a so-called 'intra-dimensional shift', IDS (Roberts et al., 1988)). This EDS-specific deficit in PD has been further delineated into two cognitively distinct processes, 'perseveration' and 'learned irrelevance' (Owen et al., 1993; Slabosz et al., 2006). 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) (Mackintosh, 1973). Owen et al. (1993) 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 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. 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

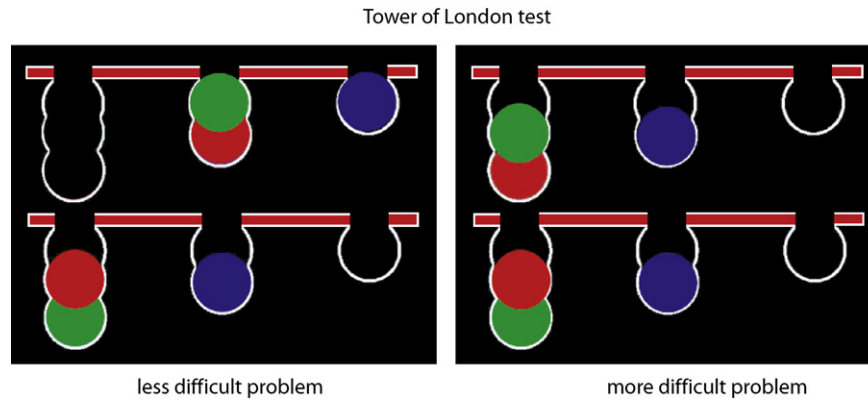


Fig. 2. The top part of the figure shows two trials from the computerised version of Tower of London task (Owen et al., 1990). The balls in the bottom half of the screen must be moved around to match the goal arrangement in the top half of the screen. The problem shown on the left requires three moves. A more difficult, four-move problem is shown on the right side of the figure.

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 (Owen et al., 1993). Thus, in early PD (when pathology is most likely to be focused on the rostradorsal portion of the head of the caudate nucleus), ‘frontal-like’ attentional set-shifting 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.

In general these results are typical of studies that have sought to investigate the precise nature of executive deficits in early PD; that is to say, performance is often compromised on ‘frontal-lobe’ 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 Owen, 2004). 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 (Owen et al., 1990, 1992). In this 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 of the tasks described above, which have been used to explore goal-directed behaviour in non-human species, 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’ (Owen et al., 1990). Like frontal-lobe patients, early PD patients make significantly more ‘between search errors’ than matched healthy controls (Owen et al., 1992). 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 (Owen et al., 1996b). One interpretation of this result is that, whilst PD patients can perform this complex search 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 sub-set of boxes based on their changing value and to modify subsequent behaviour accordingly.

Perhaps the best example of a failure of goal-directed action in early PD comes from the behaviour of such patients on the Tower of London Test of planning (Shallice, 1982). In the computerised version of this task (see Fig. 2), patients are required to move a set of three coloured balls around in ‘pockets’ or ‘socks’ to match a goal arrangement presented at the top of the screen (Owen et al., 1990). Successful performance on the Tower of London task typically involves a number of stages; the overall situation is considered by assessing the initial and goal states with reference to differences in the positions and overall configuration of the balls, a series of sub-goals is defined, a sequence of moves is generated to attain these sub-goals, this sequence is refined and revised according to the results of mental rehearsal and, finally, the correct solution is executed. Functional neuroimaging studies of the Tower of London task (see Figs. 3 and 4) have shown that increasing the difficulty of the problem (e.g. by increasing the number of sub-goals) results in increased activity in the caudate nucleus (Dagher et al., 1999;

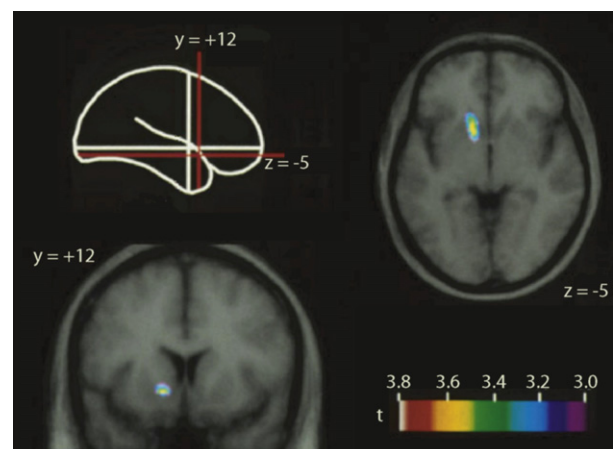


Fig. 3. Average PET subtraction images shown superimposed upon the corresponding averaged MRI scan for the healthy control subjects performing the Tower of London test. The schematic (top left), illustrates the approximate position of the coronal ($y = +12$) and sagittal slices ($z = -5$) shown. Subtraction of easy Tower of London planning problems from more difficult Tower of London planning problems yielded the focal changes in blood flow shown as a t -statistic image, whose range is coded by the colour scale at the bottom right of the figure. Both sections illustrate the regional cerebral blood flow increase in the left caudate nucleus during difficult planning problems (Owen et al., 1996a).

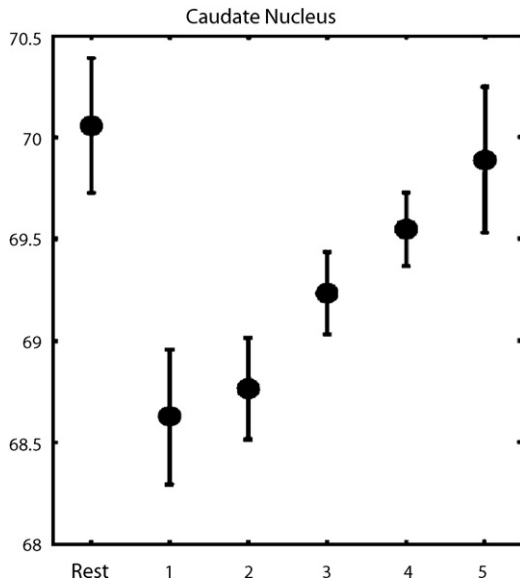


Fig. 4. The caudate nucleus is involved in the cognitive component of the Tower of London task. The relative regional cerebral blood flow (rCBF) is plotted (y-axis) as a function of task complexity level (x-axis). The relative rCBF in the caudate nucleus correlated with task complexity (Dagher et al., 1999).

Owen et al., 1996a), whereas simply increasing the number of moves involved results in increased activity in the putamen (Dagher et al., 1999). A number of computerised models of problem solving have been constructed that are capable of performing the Tower of London task (e.g. Anderson, 1993; Dehaene and Changeux, 1997; Newell and Simon, 1972). One particularly successful model is the Soar production system (Newell, 1990). Soar has no difficulty in maintaining current goals, the current problem state and other task relevant information during problem solving. However, the model does run into difficulty when there is no clear choice as to which move is the most beneficial in a given context. Under these conditions, the program creates a temporary sub-goal to resolve the conflict. This situation arises during the Tower of London task when moving one of the balls directly into its target location prevents additional moves that are necessary to complete the entire problem. This complex task requirement can only be resolved via a “shunting” manoeuvre by which the crucial ball is placed in a temporary (i.e. sub-goal) location.

The performance of patients with mild PD on the Tower of London test of planning is characterized by prolonged initial *thinking time* (see Fig. 4); that is, the time spent planning a solution and selecting between various sub-goals prior to its execution (Owen et al., 1992). In addition, a recent study of eye-gaze behaviour in PD has revealed that during this initial planning period, the patients behaviour is characterized by a failure to attend appropriately to the goals of the task (Hodgson et al., 2002). In one recent functional neuroimaging study, impaired right caudate nucleus activity was observed in patients with mild PD (when compared to healthy controls) during difficult Tower of London problems, whilst frontal-lobe activity was shown to be intact in this patient group (Dagher et al., 2001). Unlike patients with mild PD, patients with frontal-lobe damage do not exhibit prolonged initial thinking times on the Tower of London task and they also require more moves to reach the appropriate solution (Owen et al., 1990).

It seems likely that these subtle differences between the performance of patients with circumscribed lesions of the frontal-lobe and that of patients with mild PD may provide some important clues about the role of the caudate nucleus in cognition.

For example, whilst 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 the caudate nucleus may contribute to performance through the excitation of correct action schemas and the selection of appropriate sub-goals based on an evaluation of action-outcomes; both processes fundamental to successful goal-directed action.

4.3. Pharmacological studies of dopaminergic function 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 (Gotham et al., 1988; Lange et al., 1992). L-Dopa, a precursor primarily affecting levels of dopamine in the central nervous system (Maruyama et al., 1996), 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 (Frank et al., 2004; Gotham et al., 1988; Kulisevsky et al., 1996; Lange et al., 1992; Swainson et al., 2000). For example, Gotham et al. (1988), 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. Swainson et al. (2000) 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 (Owen et al., 1996a), but performed significantly better than medicated patients on a test of reversal learning that appears to depend more on ventral frontal and striatal regions (Dias et al., 1996). 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. (2001) 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 (e.g. Dias et al., 1996). Because the effect of L-dopa stems mainly from its ability to elevate dopamine levels (Maruyama et al., 1996) in the striatum (Hornykiewicz, 1974), 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 (Cools et al., 2001). 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. (2004) 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. (1999) 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 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 search tasks described above (Elliott et al., 1997; Mehta et al., 2000), which is known to be sensitive both to early PD (Owen et al., 1992) and to the effects of L-dopa in PD patients (Lange et al., 1992).

4.4. Comparison with other diseases affecting caudate 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 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 (Douaud et al., 2006; Hedreen and Folstein, 1995). The striosomes in the dorsal regions of the caudate nucleus are connected primarily with the dorsolateral frontal cortex, whilst 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 (Lawrence et al., 1998a, 1996), including the tests of attentional set-shifting, planning and working memory described above.

5. Functional neuroimaging

5.1. Methodology

Although clues about the functions of the caudate nucleus can be gleaned from comparisons between patients with PD (or HD) and patients with frontal-lobe damage, it is not possible to delineate the exact contributions of different striatal regions to behaviour on the basis of studies in patients alone as, even in the early stages of disease, the pathology in these neurodegenerative conditions is undoubtedly somewhat distributed and likely involves 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 subcortical 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 60–120 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. Talairach and Tournoux, 1988), 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 (Friston et al., 1991), or t-maps (Worsley et al., 1992), are then generated and the stereotaxic coordinates (x, y, z), of local maxima are calculated within the standardized stereotaxic system.

5.2. Functional neuroimaging studies of the caudate nucleus

Several neuroimaging studies of the striatum have been conducted, and a selection of these that focus on specific functions of the caudate are reviewed here. As found in the patient literature, the caudate is implicated in a variety of executive processes. In particular, tasks that require processes critical for goal-directed action seem to robustly activate the caudate. A defining element of goal-directed action is the expectation of an outcome prior to, or during, choice behaviour. Expectation of particular contingencies after particular actions is crucial to the shaping of willed behaviour, and there is accumulating evidence that the caudate plays a role in this process.

In an elegant series of studies by Tricomi et al. (2004), the respective importance of reward and punishment *per se*, anticipation of a reward/punishment outcome, and action-outcome contingency were disentangled. In the first experiment, neural response to reward was measured. A visual stimulus (up, down, or sideways arrow) appeared indicating an increase, decrease, or no change in subjects' monetary compensation level, and subjects simply pressed a button in response to the cue. In the second experiment, anticipation of an outcome was also measured. An anticipatory cue appeared before the arrows, indicating that a reward or punishment arrow would occur in 3 s. The reward or punishment arrow appeared at the expected time, and subjects again responded with a simple button press. In the third experiment, subjects' perception of action-outcome contingency was also manipulated. The anticipatory cue was still present, but consisted of two types. One type was the same as before: it simply indicated upcoming reward or punishment. The other type, however, required subjects to press their choice of buttons. Subjects were told that the subsequent reward or punishment was contingent upon their choice (though it was not). Across the experiments, the caudate was found to be reliably active only in the conditions that subjects felt that their response determined the outcome. There was no reliable caudate activity to the presentation of reward or punishment on its own. Similarly, time-locked anticipation of a reward or punishment (which was not contingent upon subjects' responses) also did not activate the caudate. However, when subjects believed that after the anticipatory cue, their choice of button press would determine the reward outcome, the head of the caudate was reliably active. Moreover, the authors also found that the magnitude of caudate activity was correlated with subjective ratings of control over the outcome.

The action-outcome requirement for caudate involvement can be found in other work, even when no decision is made by the

subjects (Knutson et al., 2001a,b, 2000). The outcome (obtaining reward or avoiding punishment) in these studies is instead determined by the subject's speed of response in a target detection task. Subjects are aware that the outcome is dependent on speed of response, and the task is difficult enough that correct performance is not guaranteed (thus the action is non-trivial). Therefore, the activity in the caudate cannot be attributed to decision-making alone. Tricomi et al. (2004) suggest that the action-contingency interpretation of caudate function may reconcile differences in caudate activity observed in prior studies: studies in which subjects' decisions or reaction time determine the outcome generally find activity in the caudate (Delgado et al., 2000, 2004; Elliott et al., 2000; Knutson et al., 2001a,b, 2000). When responses do not determine the outcome (or only non-effortful responses are necessary) then the caudate does not respond (Berns et al., 2001; Breiter et al., 2001; Elliott et al., 2003; McClure et al., 2003; O'Doherty et al., 2006; O'Doherty et al., 2003; Seymour et al., 2004). Therefore, the caudate seems to be sensitive to reinforcement of action, rather than to rewards in and of themselves.

Importantly, it does not appear to matter whether the rewards that reinforce the action are extrinsic or intrinsic, or even whether they are merely imagined (and not forthcoming). In a study of perceptual category learning (Tricomi et al., 2006), Japanese subjects for whom the English phonemes [r] and [l] are indistinct performed an identification task of the words "road" and "load". This task induces learning, but only when performance feedback is present (McCandliss et al., 2002). Each subject performed alternating runs of training with and without feedback, followed by performance of a card guessing task with monetary reward and punishment outcomes. This allowed comparison of activity patterns elicited by an intrinsic reward (learning to distinguish two phonemes) and extrinsic reward (earning money). Feedback processing during the perceptual phoneme task activated the caudate bilaterally, as did reward processing during the card-guessing task. Moreover, because of the within-subjects design, the authors were able to determine that the time course of activity in the caudate during feedback processing was similar in both tasks. The caudate activity was more sustained both in correct trials during perceptual learning, and monetary reward during card guessing. Therefore, for motivated subjects, performance feedback appeared to be as rewarding as monetary gain, and the caudate is sensitive to outcomes with either intrinsic or extrinsic value. Further, in a different study looking at food choices in hungry volunteers, caudate activity was observed when subjects were choosing preferred foods from a menu, even though they never received the actual tastes, but merely generated an expectation of what the foods would be like (Arana et al., 2003). The results of this study and the work described above implicate the caudate in a variety of executive, goal-directed behaviours, particularly where the outcome is perceived as desirable by the individual.

The activity of the caudate in goal-directed behaviour can be observed not just during individual actions, but also actions that occur in a social context (see Montague et al., 2006, for a review). For example, one study (King-Casas et al., 2005) used a 'trust' game, in which pairs of players engaged in 10 rounds of monetary exchanges. On each round, one player (the investor) was endowed with a certain amount of money. The investor could keep the money, or invest it with the other player (the trustee). If invested, the amount was tripled, and the trustee then decided what fraction to send back to the investor. The authors used two MR scanners to measure neural activity in both players simultaneously (Montague et al., 2002). The results showed that the caudate was the only area with an increased response to benevolent reciprocity (i.e. one person shows an increase in trusting the other person, signified by giving more money to that person in the economic exchange) than

malevolent reciprocity (i.e. one person gives less money, signifying a decrease in trust). Correspondingly, increases in benevolent reciprocity, or trust, had a greater effect on the behaviour of the other person than decreases in trust. That is, increases in trust by the trustee correlated positively with changes in investment by the investor, whereas decreases did not show a behavioural correlate. Thus, a decrease in trust has no predictive information for future behaviour, and the caudate is not active. An increase in trust does change behaviour, causing the investor to evaluate how much more to give next time. This condition also involves an increase in the expectation that a subject has of the positive nature of their contingent interactions with the trustee. The caudate is again implicated in the evaluation of the action-outcome contingencies underlying goal-directed behaviour in order to obtain a reward (in this case, money).

The role of the caudate in the complex interactions between social influences and reward is also highlighted by two recent studies examining modulation of caudate activity by perceptions of moral character, and altruistic punishment (ref). In the first study, participants played an economic trust game with opponents portrayed as having praiseworthy, neutral, or suspect moral character. The perceived moral character influenced caudate activity during economic feedback (monetary gain or loss during the trust exchange). When participants had an expectation about their partner's moral character, the caudate response was diminished, as was the reliance on feedback of monetary outcome. Thus, the authors suggest that moral beliefs affect economic decision-making through modulations in the caudate. These modulations subsequently influence the adjustment of choices based on trial-and-error feedback.

A natural response to violations of trust is to punish the offender. In a study of altruistic punishment (ref), participants could punish opponents (monetarily) who violated trust in an economic exchange game. The authors found that the caudate was active when participants were able to punish opponents, and participants with the strongest activations in the caudate were willing to incur the greatest costs in order to punish. This can be interpreted in two ways: that higher punishment induces stronger satisfaction, resulting in greater caudate activity, or, that higher caudate activity reflects greater expected satisfaction from punishment, which then causes greater investments in punishment. The latter interpretation is consistent with goal-directed behaviour resulting in actions that are motivated by anticipated rewards. As mentioned earlier, the anticipated reward need not be monetary, but can be as abstract as the satisfaction derived from punishment of trust violations.

Many neuroimaging studies have also implicated the caudate in set-shifting such as that required to complete the Wisconsin Card Sorting Task (Berg, 1948; Milner, 1963; Stewart et al., 2001). Whilst at face value a task such as the WCST may not appear to involve or disentangle goal-directed actions (relative to other executive functions and behavioural processes), as the patient studies described above demonstrate, there is a clear conceptual similarity between making volitional shifts in behavioural strategy and choosing optimal goal-directed actions. As such, "shifting" undoubtedly taps into the process by which actions are chosen based on the expectations of their consequences. However, in neuroimaging, it is important to disentangle brain activity due to simple execution of the shift from brain activity due to the cognitive decision to shift. Monchi et al. (2006) did this in an fMRI study using a similar card sorting task. Several conditions were included in order to separate activity related to (a) retrieving the sorting rule (the cue that indicated by what rule the cards should be sorted); (b) execution of a shift (done by including a 'continuous shift' condition, in which subjects shifted on every trial, and

therefore no decision about whether or not to shift had to be made); and (c) the cognitive decision to subsequently execute a shift. The results demonstrated that the caudate is not activated by the simple execution of the shift, but rather the cognitive decision to shift. During blocks when subjects were continuously shifting, and no evaluation or decision to shift was required, just a new response, the caudate was not active. However, when evaluation and a decision to change set are required, the caudate was active.

Taken together, these studies demonstrate how the caudate is in a prime position to aid goal-directed learning, as it is sensitive to action contingencies and evaluation of subsequent outcomes. The data from neuroimaging studies suggest that the following properties appear necessary to drive the caudate: (1) some form of goal-directed action, with a perception that the outcome is contingent upon behaviour; (2) knowledge of the outcome, or feedback (generally most informative when it is unpredictable); and (3) incentive, with can be either extrinsically or intrinsically valuable, and can occur in individual and social contexts. In short, the caudate nucleus is ideally poised to guide behaviour based on response-dependent feedback to obtain an outcome that is valued by the subject.

5.3. Functional neuroimaging in neurodegenerative disorders

Neuroimaging of neurodegenerative disorders is potentially a very powerful tool, combining behavioural observations of neurological patients with corresponding neural activation differences. However, 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. (1998) observed abnormal blood flow in the basal ganglia in patients with PD during performance of both the Tower of London planning task and the spatial working memory test described above; both tasks that have been shown to recruit the caudate nucleus (and dorsolateral frontal cortex) in healthy volunteers (Owen et al., 1996a; see Figs. 3 and 5). The abnormal striatal activation pattern in the PD patients was accompanied by a performance deficit, similar to that seen in patients with frontal-lobe damage, although no abnormalities in regional cerebral blood flow were observed in the prefrontal cortex. 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. A second study (Dagher et al., 2001) replicated this

pattern of abnormal blood flow in the basal ganglia in PD, with normal blood flow in the cortex, again using the Tower of London task in patients. Moreover, previous pathological (Paulus and Jellinger, 1991; Rinne et al., 1989) and ^{18}F -dopa PET studies (which use radioactively tagged L-dopa to measure dopamine uptake in the brain) have confirmed a correlation between caudate dopamine loss and neuropsychological performance in PD patients (Marie et al., 1999), suggesting a preferential role for this system in cognitive impairment (Ito et al., 2002).

In one recent study, the role of the caudate nucleus in the executive 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 (Lewis et al., 2003). 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 (Lewis et al., 2003). 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 executive performance by guiding the selection of responses necessary to achieve the goals of the task in hand by initiating the required action contingencies and evaluating the subsequent outcomes.

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 (Berent et al., 1988; Hasselbalch et al., 1992). Furthermore, measures of resting caudate metabolism have been shown to correlate with performance of the Wisconsin Card Sorting Task, the clinical 'standard' of attentional set-shifting ability described above (Hasselbalch et al., 1992). Lawrence et al. (1998c) examined the relationship between positron emission tomography measures of striatal neuronal loss and cognitive function in HD patients and in presymptomatic HD mutation carriers. Striatal medium-spiny neurons express dopamine receptors and thus, dopamine receptor binding potentials provide an index of basal ganglia pathology. A direct relationship was

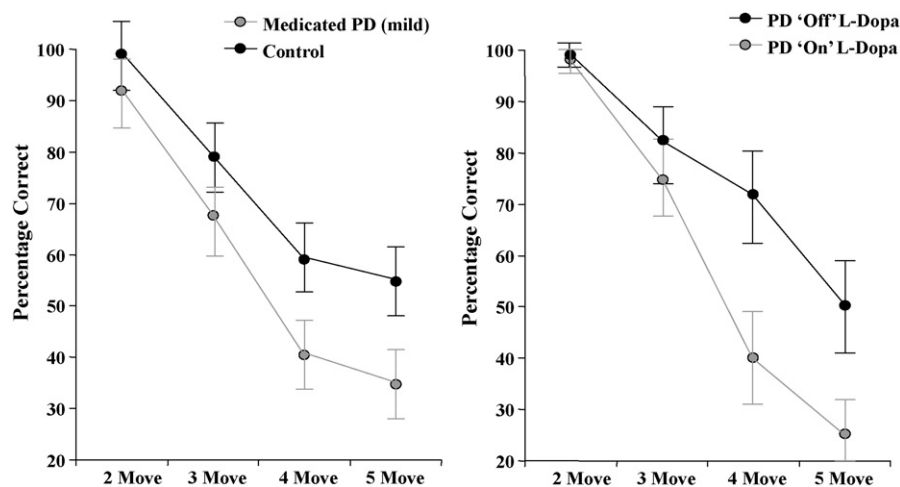


Fig. 5. Performance of patients with mild Parkinson's disease on the Tower of London test of planning (left). Compared to age matched healthy volunteers, the Parkinson's patients are significantly impaired, particularly at the more difficult 4 and 5 move problems. Adapted from Owen et al. (1992). Performance of patients with Parkinson's disease on the Tower of London test of planning when 'on' and 'off' L-Dopa medication (right). L-Dopa significantly improves performance on the task, suggesting a dopaminergic substrate for the deficit observed in the patients. Adapted from Lange et al. (1992).

observed between impaired executive function and caudate dopamine D2 receptor binding potentials, suggesting that executive dysfunction in HD, which includes deficits in attentional set-shifting, is indeed related to caudate neuronal loss (Lawrence et al., 1998c).

6. 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 corticostriatal lines and the convergence of several research domains, including anatomical studies of corticostriatal circuitry, neuroimaging studies of healthy volunteers, patient studies of performance deficits on a variety of cognitive tests, and animal studies of behavioural control have focused the search for the neural mechanisms of goal-directed action on the striatum and, in particular, on the caudate nucleus.

For example, measures of anatomical and functional connectivity in humans, non-human primates, and rats demonstrate a clear link between the caudate and regions of the frontal lobe known to be responsible for 'executive' functions. Executive tasks invariably require the generation and monitoring of appropriate strategies, and evaluation of potential outcomes for successful performance. In the animal literature, the caudate and its associated corticostriatal circuitry have also been shown to underlie the selection of behaviour based on the changing values of goals and knowledge of which actions lead to what outcomes, i.e. goal-directed action.

Neuropsychological studies of patients with early Parkinson's disease have shown a tendency for specific impairments in 'frontal-like' executive tasks. 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 patients, the pathology in the striatum is most likely to be focused on the rostradorsal portion of the head of the caudate nucleus. Similarly, in early Huntington's disease, another neurodegenerative disorder that affects the integrity of the caudate nucleus, deficits are most apparent in tasks that require the selection of appropriate sub-goals based on an evaluation of action-outcomes; both processes fundamental to successful goal-directed action.

Finally, neuroimaging studies in healthy volunteers and in patients also provide evidence for the involvement of the caudate nucleus in goal-directed action. In particular, tasks that activate the caudate nucleus typically require that the outcome is contingent upon behaviour, knowledge of that outcome, and some incentive that makes the goal desirable in some way.

It is interesting to note the cross-species commonalities in prefrontal cortex and caudate function. For example, the aforementioned studies of Parkinson's disease show dissociations in the prefrontal and striatal contributions to disease impairments, such that prefrontal cortex monitors performance and appropriate strategy, whereas the striatum initiates and maintains correct responses. Parallel interpretations of animal work can be made. For example, acetylcholine manipulations in striatum affect choosing of the correct response, whereas lesions of prefrontal cortex impact upon the use of action-outcome or stimulus-response strategies.

Thus, the cumulative evidence from converging methodologies demonstrates that the caudate nucleus represents action-outcome contingencies, which subserve adaptable goal-directed behaviour. This is in contrast to its nearest neighbour, the putamen, which appears to be involved in simpler, less flexible types of behaviour such as habit learning and stimulus-response associations. These simpler mechanisms are still important to normal behaviour

across species, in part because they free up attentional and memory 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 (Redgrave et al., 1999) through which adaptive behaviour towards significant goals can be identified (motivation; ventral striatum), planned (cognition; caudate) and implemented (sensorimotor coordination; putamen) effectively.

Given the evidence described above, it is remarkable that the behaviour influenced by the caudate ranges from a rat's decision to press a lever to a human's decision about how much to trust a partner in a financial exchange. On the surface, it may seem implausible that the caudate can contribute to such a range of behaviours, from a simple binary choice to a complex decision with emotional, rational, and social contingencies to be considered. Effective behaviour, and hence optimal survival, is accomplished by selecting the most appropriate actions whilst suppressing inappropriate ones as quickly and as cleanly as possible. Selection is a matter of prioritization, firstly of goals and then of means to achieve those goals. As such, selection can occur not just at the behavioural level, but at many different points, notably at the motivational and cognitive levels. Thus, the underlying requirement in many different situations is a representation of an outcome that is contingent on an action. The number of factors to be considered that are influenced by the outcome may increase perceived behavioural complexity, but we suggest that this complex behaviour is still subserved by the action-outcome representation in the caudate nucleus.

References

- Adams, C.D., Dickinson, A., 1981. Instrumental responding following reinforcer devaluation. *Quart. J. Exp. Psychol. Sect. B—Comp. Physiol. Psychol.* 33, 109–121.
- Agid, Y., Javoy-Agid, E., Ruberg, M., 1987a. Biochemistry of neurotransmitters in Parkinson's disease. In: Marsden, C.D., Fahn, S. (Eds.), *Movement Disorders*. Butterworth, London, pp. 166–230.
- Agid, Y., Ruberg, M., Dubois, B., Pillon, B., 1987b. Anatomoclinical and biochemical concepts of subcortical dementia. In: Stahl, S.M., Iversen, S.D., Goodman, E.C. (Eds.), *Cognitive Neurochemistry*. Oxford University Press, Oxford, pp. 248–271.
- Alexander, G.E., Crutcher, M.D., 1990. Functional architecture of basal ganglia circuits—neural substrates of parallel processing. *Trends Neurosci.* 13, 266–271.
- Alexander, G.E., DeLong, M.R., Strick, P.L., 1986. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu. Rev. Neurosci.* 9, 357–381.
- Anderson, J.J., 1993. *Rules of Mind*. Erlbaum, Hillsdale, NJ.
- Arana, F.S., Parkinson, J.A., Hinton, E., Holland, A.J., Owen, A.M., Roberts, A.C., 2003. Dissociable contributions of the human amygdala and orbitofrontal cortex to incentive motivation and goal selection. *J. Neurosci.* 23 (29), 9632–9638.
- Balleine, B., Dickinson, A., 1991. Instrumental performance following reinforcer devaluation depends upon incentive learning. *Quart. J. Exp. Psychol. Sect. B—Comp. Physiol. Psychol.* 43, 279–296.
- Balleine, B.W., 2005. Neural bases of food-seeking: affect, arousal and reward in corticostriatal limbic circuits. *Physiol. Behav.* 86, 717–730.
- Balleine, B.W., Dickinson, A., 1998a. Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. *Neuropharmacology* 37, 407–419.
- Balleine, B.W., Dickinson, A., 1998b. The role of incentive learning in instrumental outcome reevaluation by sensory-specific satiety. *Anim. Learn. Behav.* 26, 46–59.
- Balleine, B.W., Killcross, A.S., Dickinson, A., 2003. The effect of lesions of the basolateral amygdala on instrumental conditioning. *J. Neurosci.* 23, 666–675.
- Berendse, H.W., Galisdegraaf, Y., Groenewegen, H.J., 1992. Topographical organization and relationship with ventral striatal compartments of prefrontal corticostriatal projections in the rat. *J. Comp. Neurol.* 316, 314–347.
- Berent, S., Giordani, B., Lehtinen, S., Markel, D., Penney, J.B., Buchtel, H.A., Starosta-Rubinstein, S., Hichwa, R., Young, A.B., 1988. Positron emission tomographic scan investigations of Huntington's disease: cerebral metabolic correlates of cognitive function. *Ann. Neurol.* 23, 541–546.
- Berg, E.A., 1948. A simple objective technique for measuring flexibility in thinking. *J. Gen. Psychol.* 39, 15–22.
- Bernheimer, H., Birkmayer, W., Hornykiewicz, O., Jellinger, K., Seitelberger, F., 1973. Brain dopamine and the syndromes of Parkinson and Huntington. Clinical, morphological and neurochemical correlations. *J. Neurol. Sci.* 20, 415–455.

- Berns, G.S., McClure, S.M., Pagnoni, G., Montague, P.R., 2001. Predictability modulates human brain response to reward. *J. Neurosci.* 21, 2793–2798.
- Bestmann, S., Baudewig, J., Siebner, H.R., Rothwell, J.C., Frahm, J., 2004. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. *Eur. J. Neurosci.* 19, 1950–1962.
- Brasted, P.J., Robbins, T.W., Dunnett, S.B., 1999. Distinct roles for striatal subregions in mediating response processing revealed by focal excitotoxic lesions. *Behav. Neurosci.* 113, 253–264.
- Breiter, H.C., Aharon, I., Kahneman, D., Dale, A., Shizgal, P., 2001. Functional imaging of neural responses to expectancy and experience of monetary gains and losses. *Neuron* 30, 619–639.
- Broussolle, E., Dentesangle, C., Landais, P., Garcia-Larrea, L., Pollak, P., Croisile, B., Hibert, O., Bonnefoi, F., Galy, G., Froment, J.C., Comar, D., 1999. The relation of putamen and caudate nucleus 18F-Dopa uptake to motor and cognitive performances in Parkinson's disease. *J. Neurol. Sci.* 166, 141–151.
- Brown, R.G., Marsden, C.D., 1984. How common is dementia in Parkinson's disease? *Lancet* 2, 1262–1265.
- Bruck, A., Portin, R., Lindell, A., Laihin, A., Bergman, J., Haaparanta, M., Solin, O., Rinne, J.O., 2001. Positron emission tomography shows that impaired frontal lobe functioning in Parkinson's disease is related to dopaminergic hypofunction in the caudate nucleus. *Neurosci. Lett.* 311, 81–84.
- Butters, N., Rosvold, H.E., 1968. Effect of caudate and septal nuclei lesions on resistance to extinction and delayed-alternation. *J. Comp. Physiol. Psychol.* 65, 397–403.
- Byrne, E.J., Lennox, G., Lowe, J., Godwin-Austen, R.B., 1989. Diffuse Lewy body disease: clinical features in 15 cases. *J. Neurol. Neurosurg. Psychiatry* 52, 709–717.
- Carr, J.A.R., Wilkie, D.M., 1997. Ordinal, phase, and interval timing. In: Bradshaw, C.M., Szabadi, E. (Eds.), *Time and Behaviour: Psychological and Neurobehavioural Analyses*, vol. 120. Elsevier Science B.V., Amsterdam, pp. 265–327.
- Collins, P., Wilkinson, L.S., Everitt, B.J., Robbins, T.W., Roberts, A.C., 2000. The effect of dopamine depletion from the caudate nucleus of the common marmoset (*Callithrix jacchus*) on tests of prefrontal cognitive function. *Behav. Neurosci.* 114, 3–17.
- Cools, A.R., van den Bercken, J.H., Horstink, M.W., van Spaendonck, K.P., Berger, H.J., 1984. Cognitive and motor shifting aptitude disorder in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 47, 443–453.
- Cools, R., Barker, R.A., Sahakian, B.J., Robbins, T.W., 2001. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. *Cereb. Cortex* 11, 1136–1143.
- Corbit, L.H., Muir, J.L., Balleine, B.W., 2001. The role of the nucleus accumbens in instrumental conditioning: evidence of a functional dissociation between accumbens core and shell. *J. Neurosci.* 21, 3251–3260.
- Coutureau, E., Killcross, S., 2003. Inactivation of the infralimbic prefrontal cortex reinstates goal-directed responding in overtrained rats. *Behav. Brain Res.* 146, 167–174.
- Dagher, A., Owen, A.M., Boecker, H., Brooks, D.J., 1999. Mapping the network for planning: a correlational PET activation study with the Tower of London task. *Brain* 122 (Pt 10), 1973–1987.
- Dagher, A., Owen, A.M., Boecker, H., Brooks, D.J., 2001. The role of the striatum and hippocampus in planning: a PET activation study in Parkinson's disease. *Brain* 124, 1020–1032.
- de Borchgrave, R., Rawlins, J.N., Dickinson, A., Balleine, B.W., 2002. Effects of cytotoxic nucleus accumbens lesions on instrumental conditioning in rats. *Exp. Brain Res.* 144, 50–68.
- Dehaene, S., Changeux, J.P., 1997. A hierarchical neuronal network for planning behaviour. *Proc. Natl. Acad. Sci. U.S.A.* 94, 13293–13298.
- Delgado, M.R., Nystrom, L.E., Fissell, C., Noll, D.C., Fiez, J.A., 2000. Tracking the hemodynamic responses to reward and punishment in the striatum. *J. Neurophysiol.* 84, 3072–3077.
- Delgado, M.R., Stenger, V.A., Fiez, J.A., 2004. Motivation-dependent responses in the human caudate nucleus. *Cereb. Cortex* 14, 1022–1030.
- Devan, B.D., McDonald, R.J., White, N.M., 1999. Effects of medial and lateral caudate-putamen lesions on place- and cue-guided behaviors in the water maze: relation to thigmotaxis. *Behav. Brain Res.* 100, 5–14.
- Dias, R., Robbins, T.W., Roberts, A.C., 1996. Dissociation in prefrontal cortex of affective and attentional shifts. *Nature* 380, 69–72.
- Dickinson, A., Balleine, B., 1994. Motivational control of goal-directed action. *Anim. Learn. Behav.* 22, 1–18.
- Dickinson, A., Balleine, B., 2002. The role of learning in the operation of motivational systems. In: Pashler, H., Gallistel, R. (Eds.), *Steven's Handbook of Experimental Psychology*, vol. 3 (Learning, Motivation, and Emotion) John Wiley & Sons, New York, pp. 497–533.
- Dickinson, A., Balleine, B., Watt, A., Gonzalez, F., Boakes, R.A., 1995. Motivational control after extended instrumental training. *Anim. Learn. Behav.* 23, 197–206.
- Dickinson, A., Dawson, G.R., 1987. The role of the instrumental contingency in the motivational control of performance. *Quart. J. Exp. Psychol. Sect. B—Comp. Physiol. Psychol.* 39, 77–93.
- Divac, I., 1968. Effects of prefrontal and caudate lesions on delayed response in cats. *Acta Biol. Exp. (Warsz)* 28, 149–167.
- Divac, I., 1972. Delayed alternation in cats with lesions of the prefrontal cortex and the caudate nucleus. *Physiol. Behav.* 8, 519–522.
- Divac, I., Rosvold, H.E., Szwarcbart, M.K., 1967. Behavioral effects of selective ablation of the caudate nucleus. *J. Comp. Physiol. Psychol.* 63 (2), 184–190.
- Douaud, G., Gaura, V., Ribeiro, M.-J., Lethimonnier, F., Maroy, R., Verny, C., Krystkowiak, P., Damier, P., Bachoud-Levi, A.-C., Hantraye, P., Remy, P., 2006. Distribution of grey matter atrophy in Huntington's disease patients: a combined ROI-based and voxel-based morphometric study. *NeuroImage* 32, 1562–1575.
- Downes, J.J., Roberts, A.C., Sahakian, B.J., Evenden, J.L., Morris, R.G., Robbins, T.W., 1989. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. *Neuropsychologia* 27, 1329–1343.
- Eagle, D.M., Robbins, T.W., 2003. Inhibitory control in rats performing a stop-signal reaction-time task: effects of lesions of the medial striatum and d-amphetamine. *Behav. Neurosci.* 117, 1302–1317.
- Elliott, R., Friston, K.J., Dolan, R.J., 2000. Dissociable neural responses in human reward systems. *J. Neurosci.* 20, 6159–6165.
- Elliott, R., Newman, J.L., Longe, O.A., Deakin, J.F., 2003. Differential response patterns in the striatum and orbitofrontal cortex to financial reward in humans: a parametric functional magnetic resonance imaging study. *J. Neurosci.* 23, 303–307.
- Elliott, R., Sahakian, B.J., Matthews, K., Bannerjee, A., Rimmer, J., Robbins, T.W., 1997. Effects of methylphenidate on spatial working memory and planning in healthy young adults. *Psychopharmacology (Berlin)* 131, 196–206.
- Frank, M.J., Seeberger, L.C., O'Reilly, R.C., 2004. By carrot or by stick: cognitive reinforcement learning in Parkinsonism. *Science* 306, 19403.
- Friston, K.J., Frith, C.D., Liddle, P.F., Frackowiak, R.S., 1991. Comparing functional (PET) images: the assessment of significant change. *J. Cereb. Blood Flow Metab.* 11, 690–699.
- Gibb, W.R., Luthert, P.J., Janota, I., Lantos, P.L., 1989. Cortical Lewy body dementia: clinical features and classification. *J. Neurol. Neurosurg. Psychiatry* 52, 185–192.
- Gotham, A.M., Brown, R.G., Marsden, C.D., 1988. 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. *Brain* 111 (Pt 2), 299–321.
- Haber, S.N., Fudge, J.L., McFarland, N.R., 2000. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J. Neurosci.* 20, 2369–2382.
- Hammond, L.J., 1980. The effect of contingency upon the appetitive conditioning of free-operant behavior. *J. Exp. Anal. Behav.* 34, 297–304.
- Hasselbalch, S.G., Oberg, G., Sorensen, S.A., Andersen, A.R., Waldemar, G., Schmidt, J.F., Fenger, K., Paulson, O.B., 1992. Reduced regional cerebral blood flow in Huntington's disease studied by SPECT. *J. Neurol. Neurosurg. Psychiatry* 55, 1018–1023.
- Hedreen, J.C., Folstein, S.E., 1995. Early loss of neostriatal striosome neurons in Huntington's disease. *J. Neuropathol. Exp. Neurol.* 54, 105–120.
- Hiroi, N., White, N.M., 1991. The amphetamine conditioned place preference—differential involvement of dopamine receptor subtypes and 2 dopaminergic terminal areas. *Brain Res.* 552, 141–152.
- Hodgson, T.L., Tiesman, B., Owen, A.M., Kennard, C., 2002. Abnormal gaze strategies during problem solving in Parkinson's disease. *Neuropsychologia* 40, 411–422.
- Hornykiewicz, O., 1974. The mechanisms of action of L-DOPA in Parkinson's disease. *Life Sci.* 15, 1249–1259.
- Ito, K., Nagano-Saito, A., Kato, T., Arahata, Y., Nakamura, A., Kawasumi, Y., Hatano, K., Abe, Y., Yamada, T., Kachi, T., Brooks, D.J., 2002. Striatal and extrastriatal dysfunction in Parkinson's disease with dementia: a 6-[¹⁸F]fluoro-L-dopa PET study. *Brain* 125, 1358–1365.
- Jellinger, K.A., 2001. The pathology of Parkinson's disease. *Adv. Neurol.* 86, 55–72.
- Joel, D., Weiner, I., 2000. The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. *Neuroscience* 96, 451–474.
- Killcross, S., Coutureau, E., 2003. Coordination of actions and habits in the medial prefrontal cortex of rats. *Cereb. Cortex* 13, 400–408.
- King-Casas, B., Tomlin, D., Anen, C., Camerer, C.F., Quartz, S.R., Montague, P.R., 2005. Getting to know you: reputation and trust in a two-person economic exchange. *Science* 308, 78–83.
- Kish, S.J., Shannak, K., Hornykiewicz, O., 1988. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiological and clinical implications. *N. Engl. J. Med.* 318, 876–880.
- Knoch, D., Treyer, V., Regard, M., Muri, R.M., Buck, A., Weber, B., 2006. Lateralized and frequency-dependent effects of prefrontal rTMS on regional cerebral blood flow. *NeuroImage* 31, 641–648.
- Knutson, B., Adams, C.M., Fong, G.W., Hommer, D., 2001a. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J. Neurosci.* 21, RC159.
- Knutson, B., Fong, G.W., Adams, C.M., Varner, J.L., Hommer, D., 2001b. Dissociation of reward anticipation and outcome with event-related fMRI. *Neuroreport* 12, 3683–3687.
- Knutson, B., Westdorp, A., Kaiser, E., Hommer, D., 2000. fMRI visualization of brain activity during a monetary incentive delay task. *NeuroImage* 12, 20–27.
- Kulisevsky, J., Avila, A., Barbanj, M., Antonijon, R., Berthier, M.L., Gironell, A., 1996. Acute effects of levodopa on neuropsychological performance in stable and fluctuating Parkinson's disease patients at different levodopa plasma levels. *Brain* 119, 2121–2132.
- Kunishio, K., Haber, S.N., 1994. Primate cingulo-striatal projection: limbic striatal versus sensorimotor striatal input. *J. Comp. Neurol.* 350, 337–356.
- Lange, K.W., Robbins, T.W., Marsden, C.D., James, M., Owen, A.M., Paul, G.M., 1992. L-Dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. *Psychopharmacology (Berlin)* 107, 394–404.

- Lawrence, A.D., Hodges, J.R., Rosser, A.E., Kershaw, A., French-Constant, C., Rubinsztein, D.C., Robbins, T.W., Sahakian, B.J., 1998a. Evidence for specific cognitive deficits in preclinical Huntington's disease. *Brain* 121 (Pt 7), 1329–1341.
- Lawrence, A.D., Sahakian, B.J., Hodges, J.R., Rosser, A.E., Lange, K.W., Robbins, T.W., 1996. Executive and mnemonic functions in early Huntington's disease. *Brain* 119 (Pt 5), 1633–1645.
- Lawrence, A.D., Sahakian, B.J., Robbins, T.W., 1998b. Cognitive functions and corticostriatal circuits: insights from Huntington's disease. *Trends Cogn. Sci.* 2, 379–388.
- Lawrence, A.D., Weeks, R.A., Brooks, D.J., Andrews, T.C., Watkins, L.H., Harding, A.E., Robbins, T.W., Sahakian, B.J., 1998c. The relationship between striatal dopamine receptor binding and cognitive performance in Huntington's disease. *Brain* 121 (Pt 7), 1343–1355.
- Lehericy, S., Ducros, M., Van de Moortele, P.F., Francois, C., Thivard, L., Poupon, C., Swindale, N., Ugurbil, K., Kim, D.S., 2004. Diffusion tensor fiber tracking shows distinct corticostriatal circuits in humans. *Ann. Neurol.* 55, 522–529.
- Lewis, S.J., Dove, A., Robbins, T.W., Barker, R.A., Owen, A.M., 2003. Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *J. Neurosci.* 23, 6351–6356.
- Mackintosh, N.J., 1973. Stimulus selection: learning to ignore stimuli that predict no change in reinforcement. In: Hinde, R.A., Stevenson-Hinde, J. (Eds.), *Constraints on Learning*. Academic Press, London, pp. 75–96.
- Marie, R.M., Barre, L., Dupuy, B., Viader, F., Defer, G., Baron, J.C., 1999. Relationships between striatal dopamine denervation and frontal executive tests in Parkinson's disease. *Neurosci. Lett.* 260, 77–80.
- Maruyama, W., Naoi, M., Narabayashi, H., 1996. 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.* 139, 141–148.
- McCandliss, B.D., Fiez, J.A., Protopapas, A., Conway, M., McClelland, J.L., 2002. Success and failure in teaching the [r]-[l] contrast to Japanese adults: tests of a Hebbian model of plasticity and stabilization in spoken language perception. *Cogn. Affect. Behav. Neurosci.* 2, 89–108.
- McClure, S.M., Berns, G.S., Montague, P.R., 2003. Temporal prediction errors in a passive learning task activate human striatum. *Neuron* 38, 339–346.
- Mehta, M.A., Calloway, P., Sahakian, B.J., 2000. Amelioration of specific working memory deficits by methylphenidate in a case of adult attention deficit/hyperactivity disorder. *J. Psychopharmacol.* 14, 299–302.
- Mehta, M.A., Sahakian, B.J., McKenna, P.J., Robbins, T.W., 1999. Systemic sulpiride in young adult volunteers simulates the profile of cognitive deficits in Parkinson's disease. *Psychopharmacology (Berlin)* 146, 162–174.
- Middleton, F.A., Strick, P.L., 1996. The temporal lobe is a target of output from the basal ganglia. *Proc. Natl. Acad. Sci.* 93, 8683–8687.
- Middleton, F.A., Strick, P.L., 2000. Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. *Brain Cogn.* 42, 183–200.
- Milner, B., 1963. Effects of brain lesions on card sorting. *Arch. Neurol.* 9, 90–100.
- Monchi, O., Petrides, M., Strafella, A.P., Worsley, K.J., Doyon, J., 2006. Functional role of the basal ganglia in the planning and execution of actions. *Ann. Neurol.* 59, 257–264.
- Montague, P.R., Berns, G.S., Cohen, J.D., McClure, S.M., Pagnoni, G., Dhamala, M., Wiest, M.C., Karpov, I., King, R.D., Apple, N., Fisher, R.E., 2002. Hyperscanning: simultaneous fMRI during linked social interactions. *Neuroimage* 16, 1159–1164.
- Montague, P.R., King-Casas, B., Cohen, J.D., 2006. Imaging valuation models in human choice. *Annu. Rev. Neurosci.* 29, 417–448.
- Morris, R.G., Downes, J.J., Robbins, T.W., 1990. The nature of the dysexecutive syndrome in Parkinson's disease. In: Gilhooly, K.J., Leane, M.T.G., Logie, R.H., Erdos, G. (Eds.), *Lines of Thinking*, vol. 2. John Wiley & Sons, Chichester, pp. 247–258.
- Nakahara, K., Hayashi, T., Konishi, S., Miyashita, Y., 2002. Functional MRI of macaque monkeys performing a cognitive set-shifting task. *Science* 295, 1532–1536.
- Newell, A., 1990. *Unified Theories of Cognition*. Harvard University Press, Cambridge.
- Newell, A., Simon, H., 1972. *Human Problem Solving*. Prentice-Hall, Englewood Cliffs, NJ.
- Nolte, J., 1999. *The Human Brain: An Introduction to Its Functional Anatomy*. Mosby, Inc., St. Louis.
- Norman, W., Shallice, T., 1986. Attention to action. In: Davidson, R.J., Schwartz, G.E., Shapiro, D. (Eds.), *Consciousness and Self Regulation: Advances in Research and Theory*, vol. 4. Plenum, New York, pp. 1–18.
- O'Doherty, J.P., Buchanan, T.W., Seymour, B., Dolan, R.J., 2006. Predictive neural coding of reward preference involves dissociable responses in human ventral midbrain and ventral striatum. *Neuron* 49, 157–166.
- O'Doherty, J.P., Dayan, P., Friston, K., Critchley, H., Dolan, R.J., 2003. Temporal difference models and reward-related learning in the human brain. *Neuron* 38, 329–337.
- Oscos, A., Martinez Jr., J.L., McGaugh, J.L., 1988. Effects of post-training D-amphetamine on acquisition of an appetitive autoshaped lever press response in rats. *Psychopharmacology (Berlin)* 95, 132–134.
- Owen, A.M., 2004. Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. *Neuroscientist* 10, 525–537.
- Owen, A.M., Beksinska, M., James, M., Leigh, P.N., Summers, B.A., Marsden, C.D., Quinn, N.P., Sahakian, B.J., Robbins, T.W., 1993. Visuospatial memory deficits at different stages of Parkinson's disease. *Neuropsychologia* 31, 627–644.
- Owen, A.M., Downes, J.J., Sahakian, B.J., Polkey, C.E., Robbins, T.W., 1990. Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia* 28, 1021–1034.
- Owen, A.M., Doyon, J., Dagher, A., Sadikot, A., Evans, A.C., 1998. Abnormal basal ganglia outflow in Parkinson's disease identified with PET. Implications for higher cortical functions. *Brain* 121 (Pt 5), 949–965.
- Owen, A.M., Doyon, J., Petrides, M., Evans, A.C., 1996a. Planning and spatial working memory: a positron emission tomography study in humans. *Eur. J. Neurosci.* 8, 353–364.
- Owen, A.M., James, M., Leigh, P.N., Summers, B.A., Marsden, C.D., Quinn, N.P., Lange, K.W., Robbins, T.W., 1992. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain* 115 (Pt 6), 1727–1751.
- Owen, A.M., Morris, R.G., Sahakian, B.J., Polkey, C.E., Robbins, T.W., 1996b. Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampotomy in man. *Brain* 119 (Pt 5), 1597–1615.
- Parent, A., 1990. Extrinsic connections of the basal ganglia. *Trends Neurosci.* 13, 254–258.
- Parent, A., Hazrati, L.N., 1995. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Res. Brain Res. Rev.* 20, 91–127.
- Parkinson, J.A., Cardinal, R.N., Everitt, B.J., 2000a. Limbic cortico-ventral striatal systems underlying appetitive conditioning. In: Uylings, H.B.M., Van Eden, C.G., De Bruin, J.P.C., Feenstra, M.G.P., Pennartz, C.M.A. (Eds.), *Progress in Brain Research*, vol. 126. Elsevier Science, pp. 263–285.
- Parkinson, J.A., Olmstead, M.C., Burns, L.H., Robbins, T.W., Everitt, B.J., 1999. Dissociation in effects of lesions of the nucleus accumbens core and shell on appetitive Pavlovian approach behavior and the potentiation of conditioned reinforcement and locomotor activity by D-amphetamine. *J. Neurosci.* 19, 2401–2411.
- Parkinson, J.A., Willoughby, P.J., Robbins, T.W., Everitt, B.J., 2000b. Disconnection of the anterior cingulate cortex and nucleus accumbens core impairs Pavlovian approach behavior: further evidence for limbic cortical-ventral striatopallidal systems. *Behav. Neurosci.* 114, 42–63.
- Paulus, W., Jellinger, K., 1991. The neuropathologic basis of different clinical subgroups of Parkinson's disease. *J. Neuropathol. Exp. Neurol.* 50, 743–755.
- Pisa, M., Cyr, J., 1990. Regionally selective roles of the rat's striatum in modality-specific discrimination learning and forelimb reaching. *Behav. Brain Res.* 37, 281–292.
- Poldrack, R.A., Packard, M.G., 2003. Competition among multiple memory systems: converging evidence from animal and human brain studies. *Neuropsychologia* 41, 245–251.
- Postuma, R.B., Dagher, A., 2006. Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. *Cereb. Cortex* 16, 1508–1521.
- Ragozzino, M.E., 2003. Acetylcholine actions in the dorsomedial striatum support the flexible shifting of response patterns. *Neurobiol. Learn. Mem.* 80, 257–267.
- Ragozzino, M.E., Choi, D., 2004. Dynamic changes in acetylcholine output in the medial striatum during place reversal learning. *Learn. Mem.* 11, 70–77.
- Ragozzino, M.E., Jih, J., Tzavos, A., 2002. Involvement of the dorsomedial striatum in behavioral flexibility: role of muscarinic cholinergic receptors. *Brain Res.* 953, 205–214.
- Ravel, S., Legallet, E., Apicella, P., 2003. Responses of tonically active neurons in the monkey striatum discriminate between motivationally opposing stimuli. *J. Neurosci.* 23, 8489–8497.
- Reading, P.J., Dunnett, S.B., Robbins, T.W., 1991. Dissociable roles of the ventral, medial and lateral striatum on the acquisition and performance of a complex visual stimulus-response habit. *Behav. Brain Res.* 45, 147–161.
- Redgrave, P., Prescott, T.J., Gurney, K., 1999. The basal ganglia: a vertebrate solution to the selection problem? *Neuroscience* 89, 1009–1023.
- Rhodes, S.E., Killcross, S., 2004. Lesions of rat infralimbic cortex enhance recovery and reinstatement of an appetitive Pavlovian response. *Learn. Mem.* 11, 611–616.
- Rinne, J.O., Portin, R., Ruottinen, H., Nurmi, E., Bergman, J., Haaparanta, M., Solin, O., 2000. Cognitive impairment and the brain dopaminergic system in Parkinson disease: [¹⁸F]fluorodopa positron emission tomographic study. *Arch. Neurol.* 57, 470–475.
- Rinne, J.O., Rummukainen, J., Paljarvi, L., Rinne, U.K., 1989. Dementia in Parkinson's disease is related to neuronal loss in the medial substantia nigra. *Ann. Neurol.* 26, 47–50.
- Roberts, A.C., Robbins, T.W., Everitt, B.J., 1988. The effects of intradimensional and extradimensional shifts on visual discrimination learning in humans and non-human primates. *Q. J. Exp. Psychol. B* 40, 321–341.
- Robbins, T.W., Everitt, B.J., 1992. Functions of dopamine in the dorsal and ventral striatum. *Semin. Neurosci.* 4, 119–127.
- Saddorri, M.P., Gallagher, M., Schoenbaum, G., 2005. Rapid associative encoding in basolateral amygdala depends on connections with orbitofrontal cortex. *Neuron* 46, 321–331.
- Scatton, B., Javoy-Agid, F., Rouquier, L., Dubois, B., Agid, Y., 1983. Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. *Brain Res.* 275, 321–328.
- Schoenbaum, G., Chiba, A.A., Gallagher, M., 1998. Orbitofrontal cortex and basolateral amygdala encode expected outcomes during learning. *Nat. Neurosci.* 1, 155–159.

- Seymour, B., O'Doherty, J.P., Dayan, P., Koltzenburg, M., Jones, A.K., Dolan, R.J., Friston, K.J., Frackowiak, R.S., 2004. Temporal difference models describe higher-order learning in humans. *Nature* 429, 664–667.
- Shallice, T., 1982. Specific impairments of planning. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 298, 199–209.
- Slabosz, A., Lewis, S.J., Smigajewicz, K., Szymura, B., Barker, R.A., Owen, A.M., 2006. The role of learned irrelevance in attentional set-shifting impairments in Parkinson's disease. *Neuropsychology* 20, 578–588.
- Stewart, L., Meyer, B.-U., Frith, U., Rothwell, J., 2001. Left posterior BA37 is involved in object recognition: a TMS study. *Neuropsychologia* 39, 1–6.
- Strafella, A.P., Paus, T., Barrett, J., Dagher, A., 2001. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J. Neurosci.* 21, RC157.
- Strafella, A.P., Paus, T., Fraraccio, M., Dagher, A., 2003. Striatal dopamine release induced by repetitive transcranial magnetic stimulation of the human motor cortex. *Brain* 126, 2609–2615.
- Swanson, R., Rogers, R.D., Sahakian, B.J., Summers, B.A., Polkey, C.E., Robbins, T.W., 2000. Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: possible adverse effects of dopaminergic medication. *Neuropsychologia* 38, 596–612.
- Talairach, J., Tournoux, P., 1988. *Co-Planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging*. Thieme, New York.
- Tolman, E.C., 1932. *Purposive Behavior in Animals and Men*. Appleton-Century-Crofts, New York.
- Tricomi, E., Delgado, M.R., McCandliss, B.D., McClelland, J.L., Fiez, J.A., 2006. Performance feedback drives caudate activation in a phonological learning task. *J. Cogn. Neurosci.* 18, 1029–1043.
- Tricomi, E.M., Delgado, M.R., Fiez, J.A., 2004. Modulation of caudate activity by action contingency. *Neuron* 41, 281–292.
- Van Spaendonck, K.P., Berger, H.J., Horstink, M.W., Buytenhuijs, E.L., Cools, A.R., 1996. Executive functions and disease characteristics in Parkinson's disease. *Neuropsychologia* 34, 617–626.
- Viaud, M.D., White, N.M., 1989. Dissociation of visual and olfactory conditioning in the neostriatum of rats. *Behav. Brain Res.* 32, 31–42.
- White, N.M., Viaud, M., 1991. Localized intracaudate dopamine-D2 receptor activation during the post-training period improves memory for visual or olfactory conditioned emotional responses in rats. *Behav. Neural Biol.* 55, 255–269.
- Wise, S.P., 1996. The role of the basal ganglia in procedural memory. *Semin. Neurosci.* 8, 39–46.
- Worsley, K.J., Evans, A.C., Marrett, S., Neelin, P., 1992. A three-dimensional statistical analysis for CBF activation studies in human brain. *J. Cereb. Blood Flow Metab.* 12, 900–918.
- Wyvell, C.L., Berridge, K.C., 2000. Intra-accumbens amphetamine increases the conditioned incentive salience of sucrose reward: enhancement of reward "wanting" without enhanced "liking" or response reinforcement. *J. Neurosci.* 20, 8122–8130.
- Yamada, H., Matsumoto, N., Kimura, M., 2004. Tonic active neurons in the primate caudate nucleus and putamen differentially encode instructed motivational outcomes of action. *J. Neurosci.* 7, 3500–3510.
- Yeterian, E.H., Pandya, D.N., 1991. Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys. *J. Comp. Neurol.* 312, 43–67.
- Yin, H.H., Knowlton, B.J., 2006. The role of the basal ganglia in habit formation. *Nat. Rev. Neurosci.* 7, 464–476.
- Yin, H.H., Knowlton, B.J., Balleine, B.W., 2004. Lesions of dorsolateral striatum preserve outcome expectancy but disrupt habit formation in instrumental learning. *Eur. J. Neurosci.* 19, 181–189.
- Yin, H.H., Knowlton, B.J., Balleine, B.W., 2005a. Blockade of NMDA receptors in the dorsomedial striatum prevents action-outcome learning in instrumental conditioning. *Eur. J. Neurosci.* 22, 505–512.
- Yin, H.H., Knowlton, B.J., Balleine, B.W., 2006. Inactivation of dorsolateral striatum enhances sensitivity to changes in the action-outcome contingency in instrumental conditioning. *Behav. Brain Res.* 166, 189–196.
- Yin, H.H., Ostlund, S.B., Knowlton, B.J., Balleine, B.W., 2005b. The role of the dorsomedial striatum in instrumental conditioning. *Eur. J. Neurosci.* 22, 513–523.