Cerebral Cortex July 2006;16:916-928
doi:10.1093/cercor/bhj043
Advance Access publication October 5, 2005

Apathy and the Functional Anatomy of the Prefrontal Cortex–Basal Ganglia Circuits

Richard Levy and Bruno Dubois

Fédération de Neurologie and INSERM U610, Hôpital de la Salpêtrière, Paris, France

The clinical signs grouped under the concept of apathy are a common feature of prefrontal and basal ganglia lesions or dysfunctions and can therefore help to improve our understanding of the functional anatomy of the prefrontal–basal ganglia system. Apathy is here defined as a quantitative reduction of voluntary, goal-directed behaviors. The underlying mechanisms responsible for apathy can be divided into three subtypes of disrupted processing: 'emotional–affective', 'cognitive' and 'auto-activation'. Apathy due to the disruption of 'emotional–affective' processing refers to the inability to establish the necessary linkage between emotional–affective signals and the ongoing or forthcoming behavior. It may be related to lesions of the orbital–medial prefrontal cortex or to the related subregions (limbic territory) within the basal ganglia (e.g. ventral striatum, ventral pallidum). Apathy due to the disruption of 'cognitive' processing refers to difficulties in elaborating the plan of actions necessary for the ongoing or forthcoming behavior. It may be related to lesions of the dorsolateral prefrontal cortex and the related subregions (associative territory) within the basal ganglia (e.g. dorsal caudate nucleus). The disruption of 'auto-activation' processing refers to the inability to self-activate thoughts or self-initiate actions contrasting with a relatively spared ability to generate externally driven behavior. It is responsible for the most severe form of apathy and in most cases the lesions affect bilaterally the associative and limbic territories of the internal portion of the globus pallidus. It characterizes the syndrome of 'auto-activation deficit' (also known as 'psychic akinesia' or 'athymormia'). This syndrome implies that direct lesions of the basal ganglia output result in a loss of amplification of the relevant signal, consequently leading to a diminished extraction of this signal within the frontal cortex. Likewise, apathy occurring in Parkinson's disease could be interpreted as secondary to the loss of spatial and temporal focalization of the signals transferred to the frontal cortex. In both situations (direct basal ganglia lesions and nigro-striatal dopaminergic loss), the capacity of the frontal cortex to select, initiate, maintain and shift programs of actions is impaired.

Introduction

In this review article, we consider apathy from a novel perspective. Apathy is not defined here as the clinical consequence of a 'lack of motivation' — a rather blurred and inhomogeneous psychological concept — but as an observable behavioral syndrome consisting in a quantitative reduction of voluntary (or goal-directed) behaviors. Therefore, apathy occurs when the systems that generate and control voluntary actions are altered. These systems are mostly represented by different, but closely interconnected, subregions of the prefrontal cortex (PFC) and of the basal ganglia. And indeed, apathy is one of the most frequent behavioral changes associated with diseases or lesions affecting either the PFC or the basal ganglia. It can thus be viewed as the consequence of lesions or dysfunctions of the PFC–basal ganglia functional axis. From this perspective, apathy may provide fruitful hypotheses regarding the functional anatomy of the basal ganglia and its reciprocal relationship with the frontal lobes. Accordingly, we have attempted in this review to support this theoretical framework by data derived from clinical observations and experimental studies in humans.

What is Apathy?

Apathy is conventionally defined as an 'absence or lack of feeling, emotion, interest or concern'. To clarify the concept of apathy for practical medical purposes, Robert Marin proposed that apathy corresponds to a 'lack of motivation not attributable to diminished level of consciousness, cognitive impairment or emotional distress' (Marin, 1991, 1996). It is unlikely that the concept of 'lack of motivation' represents the underlying mechanism responsible for apathy because it is a projective psychological interpretation of a given behavioral state. Indeed, as a syndrome, apathy should be objectively measurable, independently of any psychological interpretation. In this view, apathy is seen as a quantitative reduction of actions compared to the previous behavior, despite the patient's environmental or physical constraints remaining unchanged. Therefore, one should be cautious when stating that a subject is apathetic if the reduction of actions is contemporary to physical impairments (such as a paresis or an altered consciousness). The reduction of actions can be reversed, at least partially, under strong solicitation from the external environment, testifying to a contrast between a deep alteration of self-generated behaviors and a relative preservation of externally driven ones. In consequence, we propose to define apathy as *the quantitative reduction of self-generated voluntary and purposeful behaviors*. It is therefore observable and can be quantified. According to the proposed definition, apathy is a pathology of voluntary action or goal-directed behavior (GDB) and the underlying mechanism(s) responsible for apathy may be seen as dysfunctions occurring at the level of elaboration, execution and control of GDB (Brown and Pluck, 2000).

A potential source of confusion lies in the difficulty of clinically and conceptually differentiating apathy from depression. Depression is defined, according to the World Health Organization's international classification of diseases, as a syndrome consisting in a permanent abnormal mood (at least for two consecutive weeks) and a marked diminished interest or

pleasure and decreased energy associated to at least one of the following symptoms: loss of confidence, excessive guilt, recurrent thoughts of death, poor concentration, sleep disturbance, and change in appetite or weight. Apathy is not a clinical criterion of depression but can be one of the clinical expressions of a depressed state (Marin *et al.*, 1993, 1994). The mechanism(s) by which depression induces apathy has not been totally elucidated. However, in depression, the generation of voluntary actions based on cognitive control has been found more effortful than in normal subjects (Hartlage *et al.*, 1993; Harvey *et al.*, 2005). At rest, depressed patients also exhibit an hypometabolism in the dorsolateral prefrontal cortex (DLPFC) (Drevets, 2000; Mayberg, 2003), an area essential for the generation of behavior based on internal guidance (Goldman-Rakic, 1987) contrasting with an hypermetabolism in the subgenual portion of the anterior cingulate cortex (Drevets, 2001; Mayberg, 2003), an area activated by negative emotions and affects such as depressed mood (for a review, see Phan *et al.*, 2002). It is thus very likely that apathy in depression results from an alteration of the emotional and affective processing via: (i) a marked sensitivity to emotionally negative situations inducing a negative bias interfering with attention resources and executive functions; or (ii) as the consequence of anhedonia (insensitivity to pleasure), which limits the will to perform actions. However, as developed below, apathy, in general, can result from several different mechanisms and not only from an altered processing of emotion and affect. In addition, it is obvious that apathy can occur in the absence of depression and indeed, in most neurological diseases, apathy is not the consequence of depression. Moreover, in neurological diseases such as Alzheimer and Parkinson's diseases, where apathy and depression can coexist in a given patient, they have been shown to be different in terms of the correlation with other signs and symptoms and in terms of the location of the lesions (Marin *et al.*, 1994; Levy *et al.*, 1998; Anderson *et al.*, 1999; Kuzis *et al.*, 1999). In short, apathy is a symptom that can be observed in depression but may also occur without depression and, when both are present in a given patient they may be clinically and anatomically independent.

Apathy: A Pathology of the Prefrontal–Basal Ganglia Circuits

Apathy is often present after direct lesions of the PFC (Luria, 1980; Eslinger and Damasio, 1985; Fuster, 1997; Stuss, 2000). It is also a common clinical feature of basal ganglia diseases. It can be observed in neurodegenerative diseases such as Parkinson's disease (PD) (Aarsland *et al.*, 1999, 2001; Isella *et al.*, 2002; Pluck and Brown, 2002; Starkstein *et al.*, 1992), Huntington's disease (Craufurd *et al.*, 2001; Hamilton *et al.*, 2003; Thompson *et al.*, 2002) and progressive supranuclear palsy (PSP) (Aarsland *et al.*, 2001; Litvan *et al.*, 1996a, 1998). Apathy is also frequently encountered after focal lesions of specific structures of the basal ganglia such as the caudate nuclei, the internal pallidum and the medial–dorsal thalamic nuclei (Ali-Cherif *et al.*, 1984; Laplane *et al.*, 1989; Mendez *et al.*, 1989; Bhatia and Marsden, 1994; Engelborghs *et al.*, 2000; Ghika-Schmid and Bogousslavsky, 2000).

Apathy is therefore one of the clinical consequences of the disruption of the PFC–basal ganglia axis, one of the functional systems involved in the generation and control of self-generated purposeful behavior. The anatomical relationship between these structures has been repeatedly demonstrated in the monkey from the first studies of Kemp and Powell (1970) using fiber degeneration techniques to the most recent and sophisticated techniques of pathway labeling using viral polysynaptic retrograde tracers (Middleton and Strick, 2002). From this perspective, a prefrontal-like syndrome (including apathy as one of its clinical manifestations) can be encountered following diseases that mainly involve the basal ganglia. For instance, apathy represents one of the most important clinical features of PSP (Litvan *et al.*, 1996a, 1998), in which the most severe neuronal loss affects the basal ganglia, in contrast to a mild degree of direct prefrontal damage (Hauw *et al.*, 1994; Litvan *et al.*, 1996b). This suggests that apathy can also be the consequence of a 'prefrontal-like' syndrome due to lesions mostly affecting the basal ganglia. Similarly, physiological and lesion studies in the monkey found a similarity in the neuronal activation or deficits in behavioral tasks whether the target was within the PFC or in the basal ganglia (Battig *et al.*, 1960; Rosvold and Szwarcbart, 1964; Divac *et al.*, 1967; Butters and Rosvold, 1968; Iversen, 1979; Alexander *et al.*, 1980; Friedman *et al.*, 1990; Levy *et al.*, 1997; Kimura *et al.*, 2003). However, more subtle clinical analyses may reveal functional differences between lesions affecting the PFC or the basal ganglia and between different anatomical and functional territories (e.g. cognitive and limbic territories) within the PFC and the basal ganglia, ruling out redundancy and favoring the functional specificity of each structure or circuit. And indeed, PFC–basal ganglia anatomical and functional networks are multiple, according to the relative segregation of PFC–basal ganglia–PFC circuits (Alexander *et al.*, 1986; Middleton and Strick, 2002; Haber, 2003). Given the heterogeneity of the anatomical and functional organization of the PFC–basal ganglia system, several questions can be raised regarding apathy: Do the PFC and the basal ganglia contribute equally to apathy? Does one PFC–basal ganglia circuit contribute more than others to apathy? Do all the PFC–basal ganglia circuits contribute to apathy but through different mechanisms?

Proposed Underlying Mechanisms Responsible for Apathy (see Table 1–3)

As several steps are necessary to achieve GDB (processing of external and internal determinants that influence the intention to act, elaboration of the plan of actions, initiation, execution, feedback control of the behavioral response, etc.) (see Fig. 1), apathy may arise from dysfunctions occurring at any of these steps. It is thus likely that the physiopathology of apathy is not a single entity but multiple, depending on which specific process or macrofunction is disrupted during the completion of GDB. In line with this notion, Stuss *et al.* (2000) proposed dividing apathetic syndromes into three subtypes: 'emotional', 'cognitive' and 'behavioral'. In the present review we shall likewise distinguish between three subtypes (or groups) of mechanisms, although we would like to rename the behavioral subtype: it can no longer be maintained under this wording, since apathy itself is considered as behavioral (i.e. an 'observable state'). Our observation of patients leads us to replace it with the concept of 'auto-activation deficit'. This refers to a fundamental deficit of activation of behavior that is not primarily due to an 'emotional' or a 'cognitive' deficit and can be reversed by external stimulation ('hetero-activation'). This mechanism is associated with the most severe apathetic states.

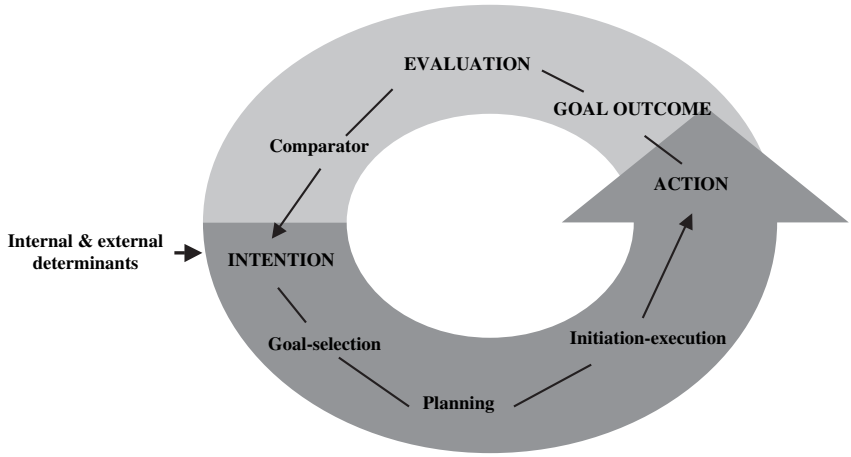

Figure 1. Model of organization of goal-directed behaviors. Adapted from Brown and Pluck (2000).

This division into three groups of mechanisms is based on clinical observations of patients with brain lesions affecting the PFC and the basal ganglia. Each of the three groups of mechanisms can be ascribed to lesions of different PFC–basal ganglia territories as follows: 'emotional–affective' to the orbital–medial PFC and presumably to its connected region within the striatum, namely the ventral striatum, 'cognitive' to the lateral PFC (and to its striatal input, namely the dorsal caudate nuclei) and 'auto-activation' to basal ganglia lesions that usually affect both the cognitive and limbic territories [bilateral GPi (internal portion of the globus pallidus) or bilateral paramedian thalamic lesions] and also the dorsal–medial aspect of the PFC (see Table 1–3).

Apathy Related to Disruption of 'Emotional–Affective' Processing

This form refers to a reduction in GDB due to an inability to associate affective and emotional signals with ongoing and forthcoming behaviors. Emotions and affect are necessary to decode the context of a given behavior and to provide its motivational value. Any change in the linkage between emotion–affect and behavior may lead to apathy, either by reducing the willingness to perform actions (loss of will, loss of goals, emotional blunting) and maintain them to their completion or by diminishing one's ability to evaluate the consequences of future actions (Eslinger and Damasio, 1985). Apathy related to a disruption of 'emotional–affective' processing may typically be assessed in apathy scales by questions such as 'Does anything interest you?' Are you concerned about your condition?' Are you interested in learning new things?' (Marin, 1991; Starkstein *et al.*, 1993; Robert *et al.*, 2002), and by tasks, such as the gambling (Bechara *et al.*, 1994) or reversal (Rolls *et al.*, 1994; Czernecki *et al.*, 2002) tasks, which investigate the ability to modulate one's behavior as a function of reward.

Brain Lesions Inducing Apathy Through the Orbital–Medial Stream

In humans, lesions of the orbital–medial PFC are often associated with apathy. For instance, apathy is one of the major signs of frontotemporal dementia (FTD) and is present in >90% of patients at the early stage of FTD (mostly affecting the orbital and medial PFC at that stage of the disease) (Pasquier, 1999; Rahman, 1999; Lough, 2001; Rosen *et al.*, 2002a). After focal orbital and medial PFC lesions, patients often take hours to complete actions that usually take minutes or they remain unable to make a decision or undertake a plan of actions (Eslinger and Damasio, 1985). How can one explain these behaviors? Emotional blunting is one of the main features of orbital–medial PFC dysfunction (Rosen *et al.*, 2002b; Boone *et al.*, 2003) and provides the key to understanding this type of apathy: indeed, emotion and affect may indicate the motivational value of a given ongoing or forthcoming behavior and orient decision making. In patients with focal orbital and medial PFC lesions, there is evidence that a decreased reactivity to emotion and sensitivity to reward results in a decision-making deficit, i.e. an inability to accurately evaluate the consequences of their own choices and actions on an affective and emotional basis, and therefore induces a quantitative decrease in GDB (Eslinger and Damasio, 1985; Bechara *et al.*, 1994; Bechara *et al.*, 2000). The conclusion that apathy resulting from lesions of the orbital–medial PFC is due to a decreased impact of emotion and

Table 1
Emotional-affective processing

Mechanisms
Inability: • to associate emotion/affect with behavior • to accurately decode the affective context that guides behavior • to evaluate the consequences of actions in terms of positive or negative outcome
Symptoms/Clinical signs/Assessment
Quantitative reduction of voluntary actions associated with: • emotional blunting (reactivity to emotional situations is poor and short live) • loss of interest to daily-life activities, situations or stimuli that were previously considered as motivating Assessed in apathy scales by questions such as "Does anything interest you?"; Are you concerned about your condition?" or "Are you interested in learning new things?" (Starkstein *et al.,* 1992) • decreased reward sensitivity, assessed by the reversal tasks (Rolls *et al.,* 1994) • errors in decision-making in real-life situations due to inaccurate interpretation of the positive or negative outcome of a given choice, leading in some cases to impulsivity (increased number of involuntary actions) but also to apathy (decreased number of voluntary actions). It can be assessed by the Gambling task (Bechara *et al.,* 1994) • decreased involvement in affective aspects of life (social interpersonal conduct, sexual life, decline in personal hygiene)
no depressive state
not necessarily associated with cognitive deficits
not necessarily reversed by strong external solicitation
Location of the lesions or dysfunctions associated with this mechanism: Orbital and medial PFC (BA 13, 14, ventral 10)
(Limbic territories of the basal ganglia [ventral striatum, ventral pallidum])

BA, Brodmann area.

Table 2
Cognitive processing

Mechanisms

Impairment in the elaboration of plans of actions (rule-finding, set-shifting, maintenance of goals and subgoals, strategies to retrieve information)

Symptoms/Clinical signs/ Assessment

Quantitative reduction of voluntary actions associated with a cognitive inertia:
i.e. default in planning and organizing goals for the future and slowness and latency of responses after stimulation

Impairment in specific subsets of the executive functions associated with cognitive inertia:
- self-generation of rules (decreased number of criteria in the WSCT)
- set-shifting (preservations in the WSCT, slowness and errors in TMT part B)
- strategies to self-retrieve information from episodic or semantic memory (deficit in the free recall in the Grober-Buschke episodic memory test improved by external cueing, poor litteral fluency contrasting with better performances in categorical fluency)
- difficulties in maintaining information in working memory (digit span, and subgoals in planning tasks (Tower of London)
- no depressive state
- not necessarily associated with emotional-affective deficits
- not necessarily reversed by strong external solicitation

Location of the lesions or dysfunctions associated with this mechanism:
Dorsolateral PFC
(BA 9/46/Lateral 10)
Cognitive territory of the basal ganglia: Dorsal CN, GPi (L-D-M), SNpr (R-L), Pv MD & Ant. Thalamic nuclei

Ant., anterior; BA, Brodmann area; CN, caudate nucleus; D, dorsal; GPi, internal portion of the globus pallidus; L, lateral; M, medial; MD, medial–dorsal; PV, parvocellular; R, rostral; TMT: Trail-making task; WSCT: Wisconsin sorting card test.

Table 3
Auto-activation processing

Mechanisms

Difficulties in self-activating thoughts or behavior

Symptoms/Clinical signs/Assessment

- quantitative reduction of voluntary actions associated with:
- a loss of spontaneous activation of mental set and emotional response
- lack of self-generation of thoughts (mental emptiness)
- emotional responses are short lived
- sharp contrast between the drastic quantitative reduction of self-generated actions and the normal production of behaviors in response to external solicitation

It can be assessed in apathy scales by questions such as "Does someone has to tell you what to do each day?" or "Do you need a push to get started on things?" (Starkstein *et al.,* 1992)

Location of the lesions or dysfunctions associated with this mechanism:
Cognitive and Limbic territories of the basal ganglia (large uni-or bilateral CN lesions, GPi, MD thalamus)

Medial PFC (medial SFG/ dorsal and ventral ACC) (BA: medial 9/10, 24, 25, 32), large frontal lesions, frontal white matter lesions

ACC, anterior cingulate cortex; BA, Brodmann area; CN, caudate nucleus; GPi, internal portion of the globus pallidus; MD, medial–dorsal; SFG, superior frontal gyrus.

affect on ongoing or forthcoming behaviors is supported by several lines of evidence from anatomy, electrophysiology and functional imaging. First, anatomically, the orbital–medial PFC is connected to limbic (e.g. amygdala, subiculum, ventral tegmental area) and visceromotor (e.g. hypothalamus, periaqueductal gray matter) brain regions (Carmichael and Price, 1994; 1995; Öngur and Price, 2000), whereas its most lateral subregion is reciprocally connected to the sensory cortices (primary olfactory, gustatory and somatosensory cortices and association visual and auditory cortices) (Barbas, 1995; Carmichael and Price, 1995; Cavada *et al.*, 2000). Altogether, these inputs from limbic structures and from all the sensory systems are very likely the anatomical background that provides the affective or emotional flow of information that is necessary for the orbital-medial PFC to influence the ongoing or forthcoming behavior (Barbas, 1988; Carmichael and Price, 1995; Carmichael and Price, 1996; Öngur and Price, 2000). Second, behavioral and electrophysiological studies in the monkey and recent imaging studies in humans indicate that the orbital and medial PFC is essential to provide the contextual value of reward and consequently to integrate the rewarding value of a stimulus into behavior (Rolls *et al.*, 1989; Critchley and Rolls, 1996; Thut *et al.*, 1997; Tremblay and Schultz, 1999; Hollerman *et al.*, 2000; O'Doherty *et al.*, 2000, 2001, 2003; Rolls, 2000; Schultz *et al.*, 2000; Knutson *et al.*, 2001, 2003; Elliott *et al.*, 2003). In particular, the influence of the medial–orbital PFC is essential when the context requires the subject to adapt his/her behavior to maintain a positive outcome and anticipate the rewarding value of a forthcoming behavior. Electrophysiological studies in the monkey have demonstrated that neurons in the orbital–medial PFC were activated by the contextual (or relative) value of a potential reward rather than by its absolute value: if an animal is hungry, a glucose solution will become attractive and activate orbital neurons. In contrast, when the animal reaches satiety, the self-same neurons no longer discharge (Rolls *et al.*, 1989; Critchley and Rolls, 1996). Along the same line of research, in a stimulus–reward association task, neurons in the orbital–medial PFC were activated by reward 'A' (preferred by the monkey) but not by reward 'B' (less appreciated). However, when reward 'B' was presented in conjunction with reward 'C' (an even less appreciated reward), the orbital–medial PFC neurons previously activated by reward 'A' were now activated by reward 'B', but not by reward 'C' (Tremblay and Schultz, 1999). Taken together, these data indicate that lesions or dysfunctions of the orbital and medial PFC can lead to an insensitivity to reward, which may in turn lead to a decreased number of voluntary actions (which may be associated with impulsive and reflexive responses to endogenous or environmental percepts).

The orbital and medial PFC projects to the medial and ventral portion of the head, body and tail of the caudate nuclei (Selemon and Goldman-Rakic, 1985; Yeterian and Pandya, 1991) as well as to the 'core' structure of the ventral striatum (Selemon and Goldman-Rakic, 1985; Haber *et al.*, 1995). Output from these striatal regions terminates in the medial and ventral pallidum and in the medial portion of the substantia nigra pars reticulata (Haber *et al.*, 1995; Haber, 2003). The pallido-thalamic projections terminate in the magnocellular part of the medial–dorsal (MD) thalami, which in turn project to the orbital and ventral–medial PFC (Haber, 2003). In addition, this relatively segregated cortico-subcortico-cortical loop is also connected with the amygdala (Russchen *et al.*, 1985; Fudge *et al.*, 2002) and can thus be considered as a 'limbic loop'. Several physiological studies (cell recordings) in monkeys have confirmed the involvement of the ventral portion of the striatum in a functional axis with the orbital–ventral PFC: indeed, the ventral striatal neurons also seem to play a major role in integrating the affective or emotional value of a given stimulus into the ongoing behavior (Apicella *et al.*, 1991; Schultz *et al.*, 1992; Hollerman *et al.*, 1998). The main patterns of neural discharge are an anticipatory response to a forthcoming reward and double coding (reward and motor preparation).

According to the above data, one may expect apathy to occur after lesions of the ventral striatum. In humans, reports of the clinical consequences of a lesion restricted to the ventral part of the striatum (nucleus accumbens) or to other limbic structures of the basal ganglia are scarce (Mendez *et al.*, 1989; Calder *et al.*, 2004). These studies did not report decreased GDB

as a consequence of ventral striatum lesions, although larger lesions including the ventral striatum (combined with more dorsal areas of the basal ganglia) are associated with very severe apathetic states (Bhatia and Marsden, 1994). Furthermore, no description of apathy was reported after direct ventral striatal lesions in the monkey although these lesions are associated with pathological changes in reward processing (Butters and Rosvold, 1968; Stern and Passingham, 1994, 1995, 1996). From these data, it can be concluded either that ventral striatal lesions are insufficient to produce apathy or that previous studies, focusing on other scientific issues overlooked this particular syndrome (although the latter is unlikely as apathy induces an obvious, spontaneous abnormal behavioral state).

Taken together, this set of data suggests that: (i) apathy may result from a lesion of the orbital and medial PFC; (ii) apathy may in this case be related to a disruption of affective and emotional processing; and (iii) apathy has not been clearly demonstrated after ventral striatal lesions despite the close anatomical and functional relationship between the orbital and medial PFC and ventral areas of the basal ganglia and the involvement of the ventral striatum in reward processing.

Apathy Related to Disruption of 'Cognitive' Processing

This form, which can be called 'cognitive inertia', refers to the reduction in GDB due to impairments in the cognitive functions needed to elaborate the plan of actions. It results from impairments in several executive functions that are needed to plan and carry out GDB, such as impairments in planning, working memory, rule-finding and set-shifting. Patients may therefore be apathetic as a result of working memory and planning deficits (maintenance and mental manipulation of goals and subgoals), difficulty in generating new rules or strategies or difficulty in shifting from one mental and behavioral set to another. Specific cognitive tasks, such as the Wisconsin Card Sorting task (rule-finding, maintenance and set-shifting), the Tower of London task (planning) or the literal fluency task (self-activation of cognitive strategies), can be used to detect this cognitive inertia.

Brain Lesions Inducing Apathy Through the Dorsolateral Stream

A reduction of GDB can be secondary to lesions of the lateral PFC due to impairments of executive functions. The lateral PFC, represented by the dorsolateral (BA 9/46), ventrolateral (12, 44, 45, 47) and frontopolar (lateral 10) regions (for reviews, see Goldman-Rakic, 1987; Fuster, 1997; Petrides and Pandya, 1999), is an essential node in the neural network subserving executive functions, as pinpointed by different experimental approaches including neuropsychology and functional imaging studies in humans as well as lesion and single-cell recording studies in the monkey (for reviews, see Goldman-Rakic, 1987; Fuster, 1997; Miller and Cohen, 2001; Stuss and Knight, 2002). Several of the cognitive dysfunctions that are observed after lateral lesions may contribute to a significant reduction in GDB. In particular, impairments in planning, rule-finding, set-shifting, working memory and the self-activation of strategies for retrieval in declarative memory are often observed after lateral PFC lesions (Milner, 1964; Chorover and Cole, 1966; Luria, 1980; Milner, 1982; Petrides and Milner, 1982; Shallice, 1982; Knight, 1984; Stuss and Benson, 1984; Owen *et al.*, 1990; Ferreira *et al.*, 1998; Sarazin *et al.*, 1998; Thompson-Schill *et al.*, 2002; Godefroy, 2003). It is thus easily understandable that planning and working memory impairments, through difficulties in sequencing ideas, maintaining mental representation of goals and subgoals and manipulating them, may abort the elaboration of GDB, thereby quantitatively (and qualitatively) reducing GDB. And indeed, a 'cognitive inertia' is frequently observed in patients with lateral lesions, associated with difficulties in activating mental strategies to generate rules, retrieve words or retrieve information from declarative memory. This loss of self-activation of cognitive strategies may quantitatively impoverish behavior.

The lateral portion of the PFC is tightly connected with the caudate nucleus. There is a gradient from the dorsal to the ventral portion of the caudate nuclei that corresponds to projections from the dorsolateral and ventrolateral portions of the PFC respectively (Selemon and Goldman-Rakic, 1985; Arikuni and Kubota, 1986; Saint-Cyr *et al.*, 1990; Yeterian and Pandya, 1991; Eblen and Graybiel, 1995). Selemon and Goldman-Rakic (1985) have shown that these projections extend dorsally along the rostrocaudal axis of the striatum. These anatomical findings support a functionally coherent circuit: lesions of the dorsal portion of the caudate nucleus induce impairments in tasks that are also altered after dorsolateral PFC lesions, such as spatial delayed and delayed alternation tasks (Dean and Davis, 1958; Rosvold *et al.*, 1958; Battig *et al.*, 1960; Divac *et al.*, 1967; Butters and Rosvold, 1968; Iversen, 1979). Moreover, electrophysiological studies focusing on the head of the caudate nuclei have demonstrated patterns of neural activation similar to those observed in the dorsolateral PFC during working memory or sequencing tasks (Rolls *et al.*, 1983; Caan *et al.*, 1984; Hikosaka *et al.*, 1989; Kimura *et al.*, 2003). In functional imaging, activation in the dorsal portion of the head of the caudate nuclei was found during working memory tasks and, more importantly, during planning tasks (Baker *et al.*, 1996; Owen *et al.*, 1996; Levy *et al.*, 1997). Taken together, these data suggest that the dorsal portion of the caudate nuclei (in particular the head) is a key structure in an anatomical–functional network in combination with the dorsolateral PFC which mostly contributes to executive functions.

Therefore, it is not surprising that, in humans, unilateral or bilateral lesions of the dorsal portion of the head of the caudate nucleus are associated with a massive apathetic syndrome (Richfield *et al.*, 1987; Mendez *et al.*, 1989; Caplan *et al.*, 1990; Bhatia and Marsden, 1994; Kumral *et al.*, 1999) in combination with a cognitive inertia, consistently found when behavioral disturbances are present (Mendez *et al.*, 1989; Kumral *et al.*, 1999). In patients with dorsal caudate lesions, cognitive inertia is very likely the mechanism that explains apathy through difficulty in generating new rules or strategies or difficulty in shifting from one mental and behavioral set to another. Indeed, in patients with caudate lesions, impairment of executive functions includes planning, working memory, set-shifting, ability to activate or generate cognitive strategies (e.g. those used to retrieve semantic or episodic information from memory), and temporal ordering.

Taken together, this set of data suggests that: (i) apathy may result from lesions of the lateral PFC and from lesions of the dorsal (associative) territories of the basal ganglia, in particular lesions of the dorsal portion of the head of the caudate nucleus; and (ii) apathy may in this case be related to a disruption of cognitive processing that can be called cognitive inertia and which refers to a dysexecutive syndrome, mostly related to difficulties in elaborating new patterns of behavior.

Apathy Related to an 'Auto-activation' Deficit

This form refers to difficulties in activating thoughts or initiating the motor program necessary to complete the behavior. Patients with an 'auto-activation' deficit exhibit the most severe form of apathy, characterized by difficulties in self-initiating actions or thoughts ('mental emptiness'), contrasting with relatively spared, externally driven responses. It seems likely that the 'auto-activation' deficit results from a failure to reach the threshold of initiation/activation of thoughts or actions when subjects should behave on an internal basis but not in automatic response to perception. This syndrome can be assessed, in apathy scales, by questions contrasting self- and externally driven behaviors in activities of daily living such as 'Does someone have to tell you what to do each day?' 'Do you need a push to get started on things?' (Starkstein *et al.*, 1992) and by the evidence of a severe spontaneous inertia that can be reversed by external stimulation in the absence of depressive mood.

Brain Lesions Inducing Apathy through Basal Ganglia-related Self-generation of Actions

One of the most severe forms of apathy, called 'athymhormia' or 'auto-activation' deficit, has been reported after focal basal ganglia lesions (Laplane *et al.*, 1981, 1984, 1989; Ali-Cherif *et al.*, 1984; Habib and Poncet, 1988; Starkstein *et al.*, 1989; Bogousslavsky *et al.*, 1991). This syndrome consists in a loss of spontaneous activation that seems to affect both cognitive and emotional responses. Patients tend to remain quietly in the same place or position all day long, without speaking or taking any spontaneous initiative. When questioned, patients express the feeling that their mind is empty. The decreased number of spontaneous voluntary actions is clearly associated with a drastic drop in the number of the patient's daily activities. Affect is usually flattened with anhedonia and emotional responses are blunted; any reactivity to emotional situations is poor and short-lived. One of the most important features of this syndrome is that it can be temporarily reversed by external stimulation and, when solicited, patients can produce relevant answers and behaviors. In other words, there is a sharp contrast between the drastic quantitative reduction of self-generated actions and the normal production of behaviors in response to external solicitation. However, while the patients are globally apathetic, one can observe involuntary stereotypic and pseudo-compulsive behaviors or thoughts (such as arythmomania). This apathetic syndrome is generally due to restricted and specific lesions in the basal ganglia, in most cases affecting, bilaterally, the internal portion of the pallidum (Sawada *et al.*, 1980; Klawans *et al.*, 1982; Pulst *et al.*, 1983; Ali-Cherif *et al.*, 1984; Laplane *et al.*, 1984; Strub, 1989; Lugaresi *et al.*, 1990). It should be noted that a very similar syndrome has been described after bilateral striato-pallidal lesions (Laplane *et al.*, 1981; Pulst *et al.*, 1983; Uitti *et al.*, 1985; Peters *et al.*, 1988; Katz *et al.*, 1989; Krauss *et al.*, 1991; Lehembre and Graux, 1992), uni- or bilateral large lesions of the caudate nucleus (Laplane *et al.*, 1981; Pulst *et al.*, 1983; Stein *et al.*, 1984; Pardal *et al.*, 1985; Habib and Poncet, 1988; Mendez *et al.*, 1989; Trillet *et al.*, 1990; Caplan *et al.*, 1990; Godefroy *et al.*, 1992), and lesions of the MD and anterior nuclei of the thalamus and the deep frontal white matter (Laplane *et al.*, 1988; Bogousslavsky *et al.*, 1991; van Domburg *et al.*, 1996). These areas within the basal ganglia are without doubt limbic and associative territories, which probably explains the absence of extrapyramidal motor signs in this syndrome. On the one hand, one may hypothesize that the 'auto-activation' deficit reflects the summation of the disruption of emotional and cognitive processing. On the other hand, it may be due to an impairment of elementary functions, devoted to auto-activation. According to the latter hypothesis, auto-activation may represent a central function of the basal ganglia (see below), and the fact that the lesions responsible for this syndrome are located in cognitive and limbic territories could be interpreted as the non-motor expression of an 'auto-activation' deficit. By extension, we may question the relationship between 'auto-activation' deficit and some of the signs usually considered as 'motor' signs, notably those referred to as akinesia, such as a diminished number of movements, delayed initiation and freezing, suggesting that these 'motor' signs may arise from the same elementary mechanisms as those leading to 'auto-activation' deficit, but in the domain of movement and gesture.

'Auto-activation' deficit may occur after frontal lesions affecting the frontal deep white matter [close to the medial PFC (Laplane *et al.*, 1988)]. In addition, 'auto-activation' deficit observed after basal ganglia lesions bears similarities to the results of direct lesions of the dorsal–medial PFC. Indeed, a reduction of spontaneous behaviors is often found after direct lesions of the medial wall of the frontal lobes, including the dorsal–medial PFC (medial BA 9 and dorsal–medial 10), the premotor medial frontal cortex [supplementary eye field (SEF), supplementary motor area (SMA)] and the dorsal part of the anterior cingulate cortex (ACC; BA 24 and 32). Distinct clinical syndromes can be observed according to the location and extent of the lesions within the medial wall of the frontal lobes. For instance, extensive bilateral lesions of the medial wall (in general after an ischemic stroke in the territories of the anterior cerebral arteries) may result in an 'akinetic mutism', a clinical state in which patients do not spontaneously speak or move (Mega and Cohenour, 1997; Kumral *et al.*, 2002; Anderson *et al.*, 2003; Nagaratnam *et al.*, 2004). Cortical or subcortical lesions affecting the anterior portion of the medial wall of the dominant hemisphere may produce a motor transcortical aphasia, in which one can observe a sharp decrease in spontaneous speech contrasting with normal language abilities in repetition tasks, again indicating that the impairment mostly concerns the ability to self-generate verbal output (Ardila and Lopez, 1984). More caudal lesions of the medial wall (affecting mostly the SMA and the contiguous ACC region) are responsible for a reduction of self-initiated movement, called 'motor neglect', characterized by an under-utilization of the contralateral arm in spontaneous conditions (Laplane and Degos, 1983; von Giesen *et al.*, 1994). In the monkey, a clinical syndrome of this type is induced by experimental lesions of the medial wall (including the dorsal portion of the ACC): the monkeys exhibit a sharp decrease in self-initiation of voluntary movements, contrasting with the total sparing of externally triggered actions (Thaler *et al.*, 1988, 1995). In the same line of research, several studies using positron emission tomography in humans have shown that the regional cerebral blood flow in the mesial frontal cortex (and in particular the rostral SMA) was associated with the self-generation of motor actions but not with externally cued ones (Deiber *et al.*, 1991; Jahanbashi *et al.*, 1992; Jenkins *et al.*, 2000). This set of clinical, behavioral and imaging data suggests that lesions of the dorsal–medial PFC are associated with an apathetic syndrome largely explained by the subject's inability to self-activate (or generate) actions, whereas these

actions can be elaborated and performed under strong and sustained external stimulation. These data also suggest a functional continuum along the rostral-caudal axis of the medial regions of the frontal lobes from cognitive and emotional functions to motor functions devoted to self-initiation of action and thought.

Taken together, this set of data suggests that: (i) apathy may result from basal ganglia lesions located in the associative and limbic territories (in particular in the GPi); (ii) these lesions are associated with a particular pattern of apathy ('auto-activation' deficit) in which self-generated actions are drastically reduced, contrasting with a relative preservation of externally-driven actions; and (iii) 'auto-activation' deficit after basal ganglia lesions bears similarities to the results of direct lesions of the dorsal–medial PFC. However, it has not yet been possible to demonstrate that the lesioned areas within the basal ganglia are preferentially connected to the areas within the medial PFC.

What Apathy Tells Us about the Functions of the Prefrontal–Basal Ganglia Circuits

Role of the Basal Ganglia

'Auto-activation' deficit suggests that basal ganglia lesions induce a failure to activate the output structures, in particular the frontal lobes, when behavior depends upon internalized guidance (Fig. 2). This failure of cortical activation is clearly demonstrated by the deep prefrontal hypometabolism observed in PSP and in the auto-activation deficit due to focal basal ganglia lesions (D'Antona *et al.*, 1985; Leenders *et al.*, 1988; Laplane *et al.*, 1989; Baron, 1994). It is thus possible to propose that the disruption of the PFC–basal ganglia–PFC loops at the level of the basal ganglia may lead to apathy because basal ganglia processing is no longer able to generate the relevant neural signal at the level of its output targets in the prefrontal cognitive and limbic territories (or in the medial PFC). How can one model the deficit of activation of the PFC targets? Several studies have promoted the concept of a relative segregation of the frontal–basal ganglia loops organized in parallel pathways throughout the basal ganglia (Alexander *et al.*, 1986; Hoover and Strick, 1993; Wichmann and DeLong, 1993; Albin *et al.*, 1995; Middleton and Strick, 2000). This 'segregation' model suggests that one of the main aspects of information processing within the basal ganglia is the selection of specific signals, which may correspond to the actions or thoughts generated by the frontal lobes (Tremblay and Filion, 1989; Tremblay *et al.*, 1989; Vitek *et al.*, 1990; Brotchie *et al.*, 1991; Bar-Gad and Bergman, 2001; Kimura *et al.*, 2003). However, an alternative view, taking into account the progressive convergent funneling of fibers and the increased ratio of the number of cortical neurons to the number of striatal or pallidal neurons, points rather to a concentration/convergence model favoring integrative processing rather than selection (Percheron and Filion, 1991; Yelnik, 2002). These two apparently opposite views can easily be reconciled in the light of self-generation of action and its related pathological state, apathy. Indeed, segregation and convergence may be complementary: temporal–spatial focalization could be essential to select the relevant signal, whereas convergence may be necessary to amplify it. Both types of processing may favor the emergence of a clear-cut signal from the background noise in the output structures (the frontal targets). Consequently, in normal conditions, one may propose that the PFC internalizes the information from the external and internal environments needed to make a decision about possible actions to be elaborated and performed. Neural signals corresponding to the thoughts or actions generated by the PFC are then processed by the basal ganglia in order to validate the most relevant signal. Validation processing may be translated into the extraction of the relevant signal from noise to be readdressed to the output target, namely the PFC. The very specific general architecture of the basal ganglia combining the relative spatial segregation into parallel anatomical and parallel circuits and the relative progressive concentration of fibers throughout the basal ganglia may favor the extraction of the relevant signal from background noise by selecting (parallel loops) and amplifying (i.e. concentrating) it. These 'extracted' signals are

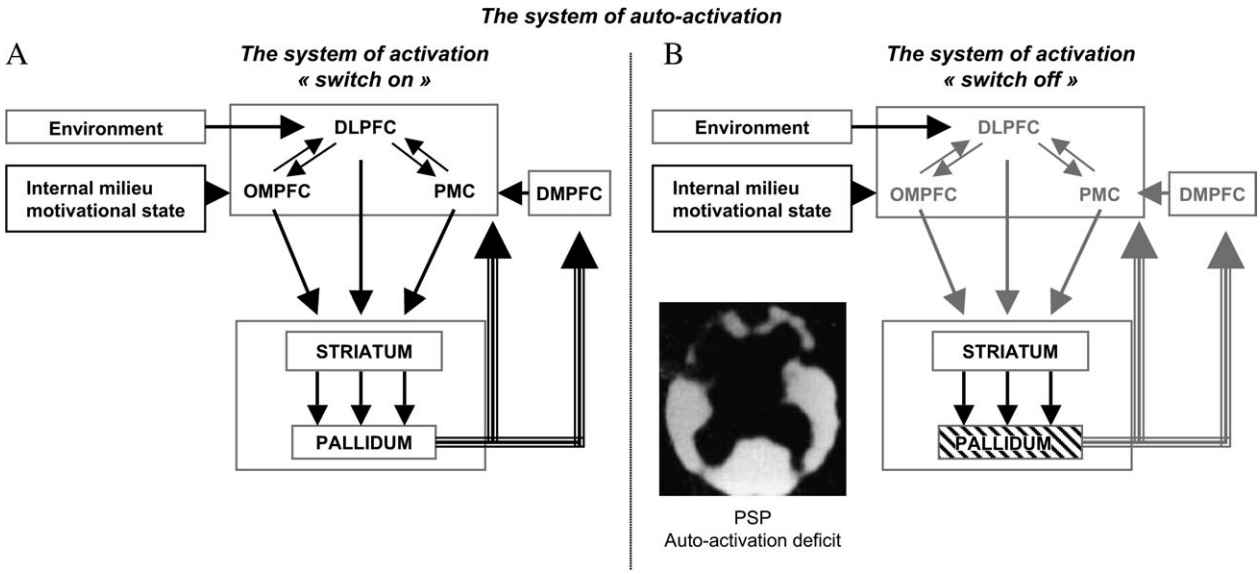

Figure 2. A model for apathy after direct lesions of the basal ganglia. (*A*) In the normal state. (*B*) When the basal ganglia output is damaged. PET scan image showing a frontal hypometabolism in PSP. PMC, premotor cortex; PSP, progressive supranuclear palsy.

ultimately transferred to the PFC, where a clear-cut signal can be detected and contributes to disambiguating decision-making and maintaining or modifying the ongoing behavior. In pathological situations, if there is a focal destruction within the basal ganglia subregions involved in affective–cognitive processing, the signal emerging from the basal ganglia is diminished, the ongoing behavior is not validated (i.e. not amplified) at the level of the PFC and could be difficult to maintain, and the forthcoming one (if it is not reflexive) is not activated. Above all, if the destruction is massive in these areas, no signal is ultimately transferred to the prefrontal cortex (Fig. 3). A related but alternative proposal could be that, from the GPi, the main functional route of output fibers terminates in the medial PFC. Since the medial PFC could be considered an essential node in order to self-generate action (i.e. in the absence of external drive), a GPi lesion or diminished activation may 'switch off' the medial PFC and lead to an 'auto-activation' deficit, contrasting with a relative sparing of externally driven behavior (Fig. 2).

In sum, an 'auto-activation' deficit results from the inability of voluntary thoughts or actions to reach the activation threshold due to a decreased signal-to-noise ratio at the level of the PFC. In this case, a basal ganglia lesion or dysfunction reduces the ability to select and amplify the relevant signal. This syndrome may represent the pathological mirror of one of the central functions of the basal ganglia: namely, the auto-activation of behavior.

Role of Dopamine

If an apathetic syndrome resulting from a focal lesion within the striatum, the globus pallidus or the thalamus can be explained by a disruption of a functional circuit leading to a failure of activation in the prefrontal targets, how can one explain apathy in PD, where there are virtually no direct lesions of these structures but rather a cascade of dysfunctions secondary to the loss of striatal dopamine innervation? Recently, using Starkstein's apathy scale (Starkstein *et al.*, 1992), we demonstrated a significant difference in the severity of apathy between the 'off' and 'on' states in fluctuating PD patients, suggesting that apathy in PD is at least partly a dopamine-dependent syndrome (Czernecki *et al.*, 2002).

Classically, dopamine is associated with reward processing, as demonstrated by studies in rodents and monkeys using the techniques of electrical self-stimulation of the brain under dopamine-receptor blockade (Rolls, 1976), self-administration of dopamine substances (Fibiger *et al.*, 1987; Koob, 1992), behavioral observations following dopamine release (Robbins and Everitt, 1996) and single cell recordings in dopaminergic neurons coupled with behavior (Schultz *et al.*, 1997). What emerges from this literature is that dopamine may act as a modulating system that favors reward-dependent learning. For instance, dopaminergic neurons may signal discrepancies between the predicted reward as the result of a given behavior and the reward that the subject eventually receives (Schultz *et al.*, 1997; Tobler *et al.*, 2003). In addition, dopamine may also code uncertainty of reward delivery (Fiorillo *et al.*, 2003). Both mechanisms may suggest a possible role for dopamine signals in attention-based learning and evaluating the odds in decision-making based on potentially unpredicted rewarding events. As the reward processing circuit involves the orbital–PFC–ventral striatum circuit, the influence of dopamine on reward processing may act through a modulation of this circuit

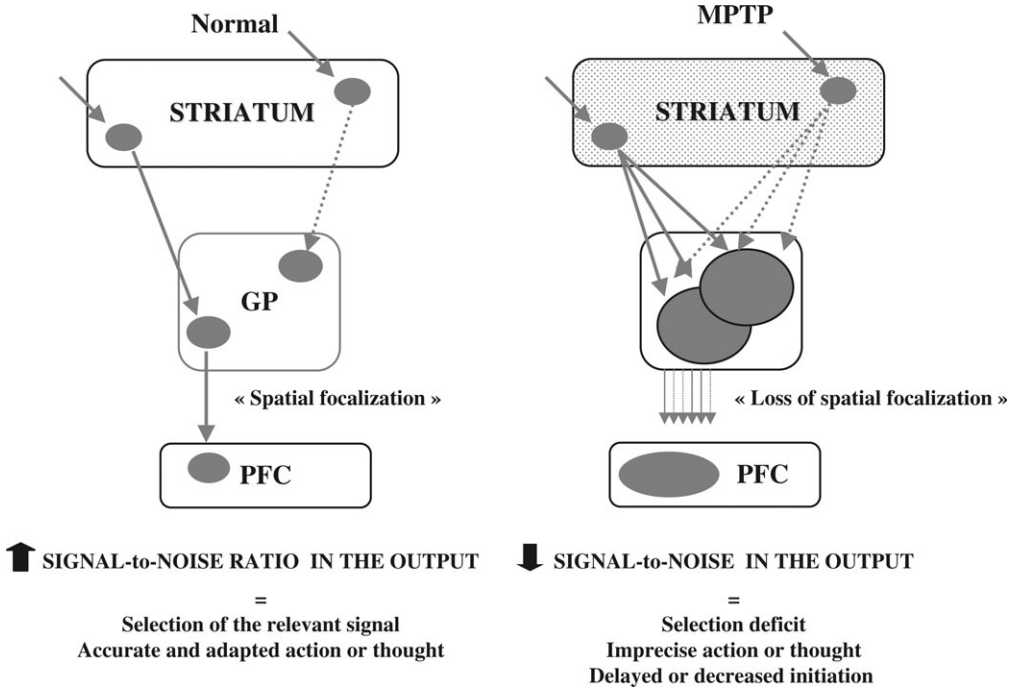

Figure 3. A model for apathy after dopaminergic nigro-striatal denervation, as seen in Parkinson's disease and in an animal model of Parkinsonism (MPTP-lesioned monkey). (*A*) In the normal state. Arrows in the striatum represent (electrical) activation in distinct striatal territories. This is followed by a cascade of activation/inhibition in discrete areas in the downstream brain structures. The neural signal mediated in this pathway is spatially and temporally focalized. (*B*) In MPTP-lesioned monkey, a similar striatal activation is followed by larger, overlapping activated areas in downstream structures, leading to a loss of spatial and temporal focalization. Adapted from the experiment described in normal and MPTP-lesioned monkeys in Tremblay and Filion's articles (Tremblay and Filion, 1989; Tremblay *et al.*, 1989) regarding activation in the striatum and the pallidum. GP, globus pallidus; PFC, prefrontal cortex.

via the meso-cortico-limbic pathway. In consequence, one may hypothesize that apathy in PD patients falls within the subtype of 'emotional affective' mechanisms and may result from a dysfunction of the orbital-medial PFC-ventral striatum circuit. However, several data suggest that apathy in PD is not due to a disruption of 'emotional–affective' processing: (i) apathy is present in PD even at relatively early stages and in the absence of dementia (Starkstein *et al.*, 1992; Aarsland *et al.*, 1999; Czernecki *et al.*, 2002; Isella *et al.*, 2002; Pluck and Brown, 2002), when the dopaminergic mesocorticolimbic pathway is supposed to be relatively spared (Javoy-Agid and Agid, 1980; Ruberg and Agid, 1988); and (ii) tasks used to assess reward sensitivity and the effect of changes in reward contingencies, such as the gambling (Bechara *et al.*, 1994) and reversal (Rolls *et al.*, 1994) tasks, which are sensitive to lesions of the orbital–medial PFC–ventral striatum loop, were not found to be impaired in PD patients, even in patients tested while 'off' levodopa therapy (Czernecki *et al.*, 2002).

Considering that the severity of dopamine depletion is not uniform within the striatum in PD, an alternative hypothesis is that different clinical consequences can be expected depending on which functional territories (motor, cognitive, affective) are affected by the dopamine depletion. Therefore, apathy in PD may result from the disruption of 'cognitive' processing usually mediated by the dorsolateral PFC–dorsal caudate nucleus circuit. This is in agreement with the fact that cognitive dysfunction in PD resembles that of patients with direct dorsolateral PFC lesions (Pillon *et al.*, 2002) and that dopamine denervation of the alternative target, i.e. the orbital–medial PFC–ventral striatum circuit, is significantly less severe. Another hypothesis is to consider that apathy is one of several clinical syndromes due to the same elementary dysfunction. This proposal follows the suggestion made by Rolls (1999, p. 198) that dopamine is a 'nonspecific modulator that only sets the thresholds of firing in striatal neurons regardless of what type of information these neurons carry as far as the information is relevant from the cortical perspective'. In this framework, apathy (like many of the parkinsonian signs) can result from the inability of the basal ganglia to validate the relevant signal that is transferred to the PFC. A series of important experiments by Filion and Tremblay (Tremblay and Filion, 1989; Tremblay *et al.*, 1989; Filion and Tremblay, 1991) illustrates this point. In a first group of experiments, the dorsal striatum was electrically stimulated at a distant location in normal monkeys. Each stimulation induced the firing of distinct groups of pallidal neurons and two distant striatal stimulations resulted in no overlap of activation in the globus pallidus. This spatial focalization of activation may be an important feature of the selection of actions because it could be translated to the output structure and particularly to the frontal cortex. A second group of experiments, performed in MPTP-lesioned monkeys, showed that two distant stimulations within the striatum led to overlapping responses within the pallidum. This loss of spatial focalization by decreasing the ratio of the relevant signals to noise may lead to a failure to extract the relevant signal in the output structures (the frontal cortex). In addition, the overactivity of the GABAergic output neurons of the GPi may lead to an excessive and global inhibition of the thalamocortical circuits and thereby hypoactivates the frontal regions involved in the generation of actions based on self-guidance. In support to this view, several functional imaging studies in non-demented PD patients have shown that while PD patients were asked to perform a freely selected volitional motor task, at 'off' state, an hypometabolism was observed in the medial frontal cortex (mostly in the rostral supplementary motor area) and in the DLPFC as compared to normal controls (Playford *et al.*, 1992; Jahanshahi *et al.*, 1995; Samuel *et al.*, 1997). This hypometabolism was reversed by apomorphine, a dopamine agonist (Jenkins *et al.*, 1992) and by internal pallidotomy (Samuel *et al.*, 1997). We thus hypothesize that, following striatal dopamine depletion, both defaults in selection and signal amplification contribute to apathy because the output structures can no more disambiguate the relevant signal and this may cause problems in decision-making, inducing aborted or delayed responses (Fig. 3).

Conclusion

David Marsden entitled his famous Robert Wartenberg lecture 'The Mysterious Function of the Basal Ganglia' (1982). Since then, many important data have been collected that have helped to clarify the functions of the basal ganglia. However, even if 'mysterious' may no longer be applied to basal ganglia functions, many issues remain the subject of debate or are still fairly obscure. Yet, as we have seen, a clinical and conceptual perspective of the functional anatomy of the frontal–basal ganglia circuits can be derived from the study of apathy. It enables the clinician to propose working hypotheses to model the dysfunctions leading to various clinical syndromes. From this perspective, we should like to emphasize three points. (i) From a clinical point of view, apathy is a syndrome related to a reduction in goal-directed behavior. (ii) Anatomically, apathy can be secondary to dysfunctions or lesions of the PFC. As the PFC is functionally and anatomically heterogeneous, subtypes of apathy depend on which PFC region is affected. Accordingly, apathy occurs in diseases affecting the basal ganglia, in particular caudate nuclei, GPi and MD thalamic lesions, because these diseases disrupt associative and limbic pathways from/to the PFC. (iii) From a pathophysiological point of view, we propose that apathy may be explained by the impact of lesions or dysfunctions of the basal ganglia, because these lesions or dysfunctions lead to a loss of amplification of the relevant signal and/or to a loss of temporal and spatial focalization, both of which result in a diminished extraction of the relevant signal within the frontal cortex, thereby inhibiting the capacity of the frontal cortex to select, initiate, maintain and shift programs of action.

Notes

Address correspondence to Richard Levy, Fédération de Neurologie, Hôpital de la Salpêtrière, 47, bd de l'hôpital, 75651 Paris cedex 13, France. Email: richard.levy@psl.aphp.fr.

Funding to pay the Open Access publication charges for this article was provided by INSERM, France.

References

Aarsland D, Larsen JP, Lim NG, Janvin C, Karlsen K, Tandberg E, Cummings JL (1999) Range of neuropsychiatric disturbances in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 67:492–496.

Aarsland D, Litvan I, Larsen JP (2001) Neuropsychiatric symptoms of patients with progressive supranuclear palsy and Parkinson's disease. J Neuropsychiatry Clin Neurosci 13:42–49.

Albin RL, Young AB, Penney JB (1995) The functional anatomy of disorders of the basal ganglia. Trends Neurosci 18:63–64.

Alexander GE, Witt ED, Goldman-Rakic PS (1980) Neuronal activity in the prefrontal cortex, caudate nucleus and medio-dorsal thalamic nucleus during delayed response performance of immature and adult rhesus monkey. Soc Neurosci Abstr 6:86.
Alexander GE, Delong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 9:357–381.
Ali-Cherif A, Royere ML, Gosset A, Poncet M, Salamon G, Khalil R (1984) Troubles du comportement et de l'activité mentale après intoxication oxycarbonée. Lésions pallidales bilatérales. Rev Neurol (Paris) 140:401–405.
Andersson S, Krogstad JM, Finset A (1999) Apathy and depressed mood in acquired brain damage: relationship to lesion localization and psychophysiological reactivity. Psychol Med 29:447–456.
Anderson CA, Arciniegas DB, Huddle DC, Leehey MA (2003) Akinetic mutism following unilateral anterior cerebral artery occlusion. J Neuropsychiatry Clin Neurosci 15:385–386.
Apicella P, Ljungberg T, Scarnati E, Schultz W (1991) Responses to reward in monkey dorsal and ventral striatum. Exp Brain Res 85:491–500.
Ardila A, Lopez MV (1984) Transcortical motor aphasia: one or two aphasias? Brain Lang 22:350–353.
Arikuni T, Kubota K (1986) The organization of prefrontocaudate projections and their laminar origin in the macaque monkey: a retrograde study using HRP-gel. J Comp Neurol 244:492–510.
Baker SC, Rogers RD, Owen AM, Frith CD, Dolan RJ, Frackowiak RS, Robbins TW (1996) Neural systems engaged by planning: a PET study of the Tower of London task. Neuropsychologia 34:515–526.
Bar-Gad I, Bergman H (2001) Stepping out of the box: information processing in the neural networks of the basal ganglia. Curr Opin Neurobiol 11:689–695.
Barbas H (1988) Anatomic organization of basoventral and mediodorsal visual recipient prefrontal regions in the rhesus monkey. J Comp Neurol 276:313–342.
Barbas H (1995) Pattern in the cortical distribution of prefrontally directed neurons with divergent axons in the rhesus monkey. Cereb Cortex 5:158–165.
Baron JC (1994) [Consequences of lesions of the basal ganglia for cerebral metabolic activity: clinical implications]. Rev Neurol (Paris) 150:599–604.
Battig K, Rosvold HE, Mishkin M (1960) Comparison of the effect of frontal and caudate lesions on delayed response and alternation in monkeys. J Comp Physiol Psychol 53:400–404.
Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50:7–15.
Bechara A, Damasio H, Damasio AR (2000) Emotion, decision making and the orbitofrontal cortex. Cereb Cortex 10:295–307.
Bhatia KP, Marsden CD (1994) The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain 117:859–876.
Bogousslavsky J, Regli F, Delaloye B, Delaloye-Bischof A, Assal G, Uske A (1991) Loss of psychic self-activation with bithalamic infarction. Neurobehavioural, CT, MRI and SPECT correlates. Acta Neurol Scand 83:309–316.
Boone KB, Miller BL, Swartz R, Lu P, Lee A (2003) Relationship between positive and negative symptoms and neuropsychological scores in frontotemporal dementia and Alzheimer's disease. J Int Neuropsychol Soc 9:698–709.
Brotchie P, Iansek R, Horne MK (1991) Motor function of the monkey globus pallidus. I. Neuronal discharge and parameter of movement. Brain 114:1667–1683.
Brown RG, Pluck G (2000) Negative symptoms: the 'pathology' of motivation and goal-directed behaviour. Trends Neurosci 23:412–417.
Butters N, Rosvold HE (1968) Effect of caudate and septal nuclei lesions on resistance to extinction and delayed alternation. J Comp Physiol Psychol 65:397–403.
Caan W, Perrett DI, Rolls ET (1984) Responses of striatal neurons in the behaving monkey. 2. Visual processing in the caudal neostriatum. Brain Res 290:53–65.
Calder AJ, Keane J, Lawrence AD, Manes F (2004) Impaired recognition of anger following damage to the ventral striatum. Brain 127:1958–1969.
Caplan LR, Schmahmann JD, Kase CS, Feldmann E, Baquis G, Greenberg JP, Gorelick PB, Helgason C, Hier DB (1990) Caudate infarcts. Arch Neurol 47:133–143.
Carmichael ST, Price JL (1994) Architectonic subdivision of the orbital and medial prefrontal cortex in the macaque monkey. J Comp Neurol 346:366–402.
Carmichael ST, Price JL (1995) Sensory and premotor connections of the orbital and medial prefrontal cortex of macaque monkeys. J Comp Neurol 363:642–664.
Carmichael ST, Price JL (1996) Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. J Comp Neurol 371:179–207.
Carter CS, Macdonald AM, Botvinick M, Ross LL, Stenger VA, Noll D, Cohen JD (2000) Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. Proc Natl Acad Sci USA 97:1944–1948.
Cavada C, Company T, Tejedor J, Cruz-Rizzolo RJ, Reinoso-Suarez F (2000) The anatomical connections of the macaque monkey orbitofrontal cortex. A review. Cereb Cortex 10:220–242.
Chorover SL, Cole M (1966) Delayed alternation performance in patients with cerebral lesions. Neuropsychologia 4:1–7.
Craufurd D, Thompson JC, Snowden JS (2001) Behavioral changes in Huntington Disease. Neuropsychiatry Neuropsychol Behav Neurol 14:219–226.
Critchley HD, Rolls ET (1996) Hunger and satiety modify the responses of olfactory and visual neurons in the primate orbitofrontal cortex. J Neurophysiol 75:1673–1686.
Cummings JL (1997) The neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology 48 (Suppl 6): S10-16.
Czernecki V, Pillon B, Houeto JL, Pochon JB, Levy R, Dubois B (2002) Motivation, reward, and Parkinson's disease: influence of dopatherapy. Neuropsychologia 40:2257–2267.
D'Antona R, Baron JC, Samson Y, Serdaru M, Viader F, Agid Y, Cambier J (1985) Subcortical dementia: frontal cortex hypometabolism detected by positron tomography in patients with progressive supranuclear palsy. Brain 108:785–799.
Dean WH, Davis GD (1958) Behavior changes following caudate lesions in rhesus monkeys. J Neurophysiol 22:165–187.
Deiber MP, Passingham RE, Colebatch JG, Friston KJ, Nixon PD, Frackowiak RS (1991) Cortical areas and the selection of movement: a study with positron emission tomography. Exp Brain Res 84:393–402.
Divac I, Rosvold HE, Scwarcbart MK (1967) Behavioural effects of selective ablation of the caudate nucleus. J Comp Physiol Psych 63:184–190.
Drevets WC (2000) Neuroimaging studies of mood disorders. Biol Psychiatry 15:813–29.
Eblen F, Graybiel AM (1995) Highly restricted origin of prefrontal cortical inputs to striosomes in the macaque monkey. J Neurosci 15:5999–6013.
Elliott R, Newman JL, Longe OA, Deakin JF (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.
Engelborghs S, Marien P, Pickut BA, Verstraeten S, De Deyn PP (2000) Loss of psychic self-activation after paramedian bithalamic infarction. Stroke 31:1762–1765.
Eslinger PJ, Damasio AR (1985) Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. Neurology 35:1731–1741.
Ferreira CT, Verin M, Pillon B, Levy R, Dubois B, Agid Y (1998) Spatiotemporal working memory and frontal lesions in man. Cortex 34:83–98.
Fibiger HC, LePiane FG, Jakubovic A, Phillips AG (1987) The role of dopamine in intracranial self-stimulation of the ventral tegmental area. J Neurosci 7:3888–3896.

Filion M, Tremblay L (1991) Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res 547:142–151.
Fiorillo CD, Tobler PN, Schultz W (2003) Discrete coding of reward probability and uncertainty by dopamine neurons. Science 299:1898–1902.
Friedman HR, Janas J, Goldman-Rakic PS (1990) Enhancement of metabolic activity in the diencephalon of monkeys performing working memory tasks: a 2-deoxyglucose study in behaving monkeys. J Cogn Neurosci 2:18–31.
Fudge JL, Kunishio K, Walsh P, Richard C, Haber SN (2002) Amygdaloid projections to ventromedial striatal subterritories in the primate. Neuroscience 110:257–275.
Fuster JM (1997) The prefrontal cortex. New York: Raven Press.
Ghika-Schmid F, Bogousslavsky J (2000) The acute behavioral syndrome of anterior thalamic infarction: a prospective study of 12 cases. Ann Neurol 48:220–227.
Godefroy O (2003) Frontal syndrome and disorders of executive functions. J Neurol 250:1–6.
Godefroy O, Rousseaux M, Leys D, Scheltens P, Pruve JP (1992) Frontal lobe dysfunction in unilateral lenticulo-striate infarcts. Arch Neurol 49:1285–1289.
Goldman-Rakic PS (1987) Circuitry of primate prefrontal cortex and regulation of behaviour by representational memory. In: Handbook of physiology (Plum F, Mountcastle U, eds), pp. 373–417. Washington, DC: The American Physiological Society.
Haber SN (2003) The primate basal ganglia: parallel and integrative networks. J Chem Neuroanat 26:317–330.
Haber SN, Kunishio K, Mizobuchi M, Lynd-Balta E (1995) The orbital and medial prefrontal circuit through the primate basal ganglia. J Neurosci 15:4851–4867.
Habib M, Poncet M (1988) Perte de l'élan vital, de l'intérêt et de l'affectivité (syndrome athymormique) au cours des lésions lacunaires des corps striés. Rev Neurol (Paris) 144:571–577.
Hamilton JM, Salmon DP, Corey-Bloom J, Gamst A, Paulsen JS, Jerkins S, Jacobson MW, Peavy G (2003) Behavioural abnormalities contribute to functional decline in Huntington's disease. J Neurol Neurosurg Psychiatry 74:120–122.
Hartlage S, Alloy LB, Vazquez C, Dykman B (1993) Automatic and effortful processing in depression. Psychol Bull 113:247–78.
Harvey PO, Fossati P, Pochon JB, Levy R, Le Bastard G, Lehericy S, Allilaire JF, Dubois B (2005) Cognitive effort and brain resources in major depression: a fMRI study using the n-back task. Neuroimage 26:860–869.
Hauw JJ, Daniel SE, Dickson D, Horoupian DS, Jellinger K, Lantos PL, McKee A, Tabaton M, Litvan I (1994) Preliminary NINDS neuropathologic criteria for Steele–Richardson–Olszewski syndrome (progressive supranuclear palsy). Neurology 44:2015–2019.
Hikosaka O, Sakamoto M, Usui S (1989) Functional properties of monkey caudate neurons. III. Activities related to expectation of target and reward. J Neurophysiol 61:814–832.
Hollerman JR, Tremblay L, Schultz W (1998) Influence of reward expectation on behavior-related neuronal activity in primate striatum. J Neurophysiol 80:947–963.
Hollerman JR, Tremblay L, Schultz W (2000) Involvement of basal ganglia and orbitofrontal cortex in goal-directed behavior. Prog Brain Res 126:193–215.
Hoover JE, Strick PL (1993) Multiple output channels in the basal ganglia. Science 259:819–821.
Isella V, Melzi P, Grimaldi M, Iurlaro S, Piolti R, Ferrarese C, Frattola L, Appollonio I (2002) Clinical, neuropsychological, and morphometric correlates of apathy in Parkinson's disease. Mov Disord 17:366–371.
Iversen SD (1979) Behaviour after neostriatal lesions in animals. In: The neostriatum (Divac I, Oberg RGE, eds), pp. 195–210. Oxford: Pergamon Press.
Javoy-Agid F, Agid Y (1980) Is the mesocortical dopaminergic system involved in Parkinson's disease. Neurology 30:1326–1330.
Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ (1995) Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain 118:913–33.
Jenkins IH, Jahanshahi M, Jueptner M, Passingham RE, Brooks DJ (2000) Self-initiated versus externally triggered movements. II. The effect of movement predictability on regional cerebral blood flow. Brain 123:1216–28.
Katz DI, Alexander MP, Seliger GM, Bellas DN (1989) Traumatic basal ganglia hemorrhage: clinicopathologic features and outcome. Neurology 39:897–904.
Kemp JM, Powell TPS (1970) The cortico-striate projections in the monkey. Brain 93:525–546.
Kimura M, Matsumoto N, Okahashi K, Ueda Y, Satoh T, Minamimoto T, Sakamoto M, Yamada H (2003) Goal-directed, serial and synchronous activation of neurons in the primate striatum. Neuroreport 14:799–802.
Klawans HL, Stein RW, Tanner CM, Goetz CG (1982) A pure parkinsonian syndrome following acute carbon monoxide intoxication. Arch Neurol 39:302–304.
Knight RT (1984) Decreased response to novel stimuli after prefrontal lesions in man. Electroencephalogr Clin Neurophysiol 59:9–20.
Knutson B, Fong GW, Adams CM, Varner JL, Hommer D (2001) Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport 12:3683–3687.
Knutson B, Fong GW, Bennett SM, Adams CM, Hommer D (2003) A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. Neuroimage 18:263–272.
Koob GF (1992) Neural mechanisms of drug reinforcement. Ann NY Acad Sci 654:171–191.
Krauss JK, Mohadjer M, Wakhloo AK, Mundinger F (1991) Dystonia and akinesia due to pallidoputaminal lesions after disulfiram intoxication. Mov Disord 6:166–170.
Kumral E, Evyapan D, Balkir K (1999) Acute caudate vascular lesions. Stroke 30:100–108.
Kumral E, Bayulkem G, Evyapan D, Yunten N (2002) Spectrum of anterior cerebral artery territory infarction: clinical and MRI findings. Eur J Neurol 9:615–624.
Kuzis G, Sabe L, Tiberti C, Merello M, Leiguarda R, Starkstein SE (1999) Explicit and implicit learning in patients with Alzheimer disease and Parkinson disease with dementia. Neuropsychiatry Neuropsychol Behav Neurol 12:265–269.
Laplane D, Degos JD (1983) Motor neglect. J Neurol Neurosurg Psychiatry 46:152–158.
Laplane D, Widlocher D, Pillon B, Baulac M, Binoux F (1981) [Obsessional-type compulsive behavior caused by bilateral circumscribed pallidostriatal necrosis. Encephalopathy caused by a wasp sting]. Rev Neurol (Paris) 137:269–276.
Laplane D, Baulac M, Widlocher D, Dubois B (1984) Pure psychic akinesia with bilateral lesions of basal ganglia. J Neurol Neurosurg Psychiatry 47:377–385.
Laplane D, Dubois B, Pillon B, Baulac M (1988) Perte d'auto-acitvation psychique et activité mentale stéréotypée par lésion frontale. Rev Neurol (Paris) 144:564–570.
Laplane D, Levasseur M, Pillon B, Dubois B, Baulac M, Mazoyer B, Tran Dinh S, Sette G, Danze F, Baron JC (1989) Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions. A neuropsychological, magnetic resonance imaging and positron tomography study. Brain 112 (Pt 3):699–725.
Leenders KL, Frackowiak R, Lees AJ (1988) Steele–Richardson–Olszewsky syndrome. Brain energy metabolism, blood flow and fluorodopa uptake measured by positron emission tomography. Brain 111:615–630.
Lehembre P, Graux P (1992) [Athymormia, arithmomania or stercoral compulsion in multiple infarcts of the corpus striatum]. Ann Med Psychol (Paris) 150:699–701.
Levy ML, Cummings JL, Fairbanks LA, Masterman D, Miller BL, Craig AH, Paulsen JS, Litvan I (1998) Apathy is not depression. J Neuropsychiatry Clin Neurosci 10:314–319.
Levy R, Friedman HR, Davachi L, Goldman-Rakic PS (1997) Differential activation of the caudate nucleus in primates performing spatial and nonspatial working memory tasks. J Neurosci 17:3870–3882.

Litvan I, Hauw JJ, Bartko JJ, Lantos PL, Daniel SE, Horoupian DS, McKee A, Dickson D, Bancher C, Tabaton M, Jellinger K, Anderson DW (1996a) Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. J Neuropathol Exp Neurol 55:97–105.

Litvan I, Mega MS, Cummings JL, Fairbanks L (1996b) Neuropsychiatric aspects of progressive supranuclear palsy. Neurology 47:1184–1189.

Litvan I, Paulsen JS, Mega MS, Cummings JL (1998) Neuropsychiatric assessment of patients with hyperkinetic and hypokinetic movement disorders. Arch Neurol 55:1313–1319.

Lough S, Gregory C, Hodges JR (2001) Dissociation of social cognition and executive function in frontal variant frontotemporal dementia. Neurocase 7:123–130.

Lugaresi A, Montagna P, Morreale A, Gallassi R (1990) 'Psychic akinesia' following carbon monoxide poisoning. Eur Neurol 30:167–169.

Luria AR (1980) Higher cortical functions in man. New York: Basic Books.

Marin RS (1991) Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci 3:243–254.

Marin RS (1996) Apathy: concept, cyndrome, neural mechanisms, and treatment. Semin Clin Neuropsychiatry 1:304–314.

Marin RS, Firinciogullari S, Biedrzycki RC (1993) The sources of convergence between measures of apathy and depression. J Affect Disord 28:117–124.

Marin RS, Firinciogullari S, Biedrzycki RC (1994) Group differences in the relationship between apathy and depression. J Nerv Ment Dis 182:235–239.

Marsden CD (1982) The mysterious function of the basal ganglia: the Robert Wartenberg lecture. Neurology 32:514–539.

Mayberg HS (2003) Positron emission tomography imaging in depression: a neural systems perspective. Neuroimaging Clin N Am 13:805–15.

Mega MS, Cohenour RC (1997) Akinetic mutism: disconnection of frontal-subcortical circuits. Neuropsychiatry Neuropsychol Behav Neurol 10:254–259.

Mendez MF, Adams NL, Lewandowski KS (1989) Neurobehavioral changes associated with caudate lesions. Neurology 39:349–354.

Middleton FA, Strick PL (2000) Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. Brain Cogn 42:183–200.

Middleton FA, Strick PL (2002) Basal-ganglia 'projections' to the prefrontal cortex of the primate. Cereb Cortex 12:926–935.

Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Annu Rev Neurosci 24:167–202.

Milner B (1964) Some effects of frontal lobectomy in man. In: The frontal granular cortex and behaviour (Warren JM, Akert K, eds), pp. 313–334. New York: McGraw-Hill.

Milner B (1982) Some cognitive effects of frontal-lobe lesions in man. Philos Trans R Soc Lond B Biol Sci 298:211–226.

Nagaratnam N, Nagaratnam K, Ng K, Diu P (2004) Akinetic mutism following stroke. J Clin Neurosci 11:25–30.

O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F, Kobal G, Renner B, Ahne G (2000) Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. Neuroreport 11: 893–897.

O'Doherty J, Kringelbach ML, Rolls ET, Hornak J, Andrews C (2001) Abstract reward and punishment representations in the human orbitofrontal cortex. Nat Neurosci 4:95–102.

O'Doherty J, Critchley H, Deichmann R, Dolan RJ (2003) Dissociating valence of outcome from behavioral control in human orbital and ventral prefrontal cortices. J Neurosci 23:7931–7939.

Öngur D, Price JL (2000) The organization of network within the orbital and medial prefrontal cortex of, rats, monkeys, and humans. Cereb Cortex 10:206–219.

Owen AM, Downes JJ, Sahakian BJ, Polkey CE, Robbins TW (1990) Planning and spatial working memory following frontal lobe lesions in man. Neuropsychologia 28:1021–1034.

Owen AM, Doyon J, Petrides M, Evans AC (1996) Planning and spatial working memory: a positron emission tomography study in humans. Eur J Neurosci 8:353–364.

Pardal MM, Micheli F, Asconape J, Paradiso G (1985) Neurobehavioral symptoms in caudate hemorrhage: two cases. Neurology 35:1806–1807.

Pasquier F, Lebert F, Lavenu I, Guillaume B (1999) The clinical picture of frontotemporal dementia: diagnosis and follow-up. Dement Geriatr Cogn Disord 10 Suppl 1:10–14.

Percheron G, Filion M (1991) Parallel processing in the basal ganglia: up to a point [Letter]. Trends Neurosci 14:55–56.

Peters HA, Levine RL, Matthews CG, Chapman LJ (1988) Extrapyramidal and other neurologic manifestations associated with carbon disulfide fumigant exposure. Arch Neurol 45:537–540.

Petrides M, Milner B (1982) Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. Neuropsychologia 20:249–262.

Petrides M, Pandya DN (1999) Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. Eur J Neurosci 11:1011–1036.

Phan KL, Wager T, Taylor SF, Liberzon I (2002) Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16:331–348.

Pillon B, Boller F, Levy R, Dubois B (2002) Cognitive deficits in Parkinson's disease. In: Handbook of neuropsychology (Boller F, Grafman J, eds). Amsterdam: Elsevier.

Playford ED, Jenkins IH, Passingham RE, Nutt J, Frackowiak RS, Brooks DJ (1992) Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study. Ann Neurol 32:151–61.

Pluck GC, Brown RG (2002) Apathy in Parkinson's disease. J Neurol Neurosurg Psychiatry 73:636–642.

Pulst SM, Walshe TM, Romero JA (1983) Carbon monoxide poisoning with features of Gilles de la Tourette's syndrome. Arch Neurol 40:443–444.

Rahman S, Sahakian BJ, Hodges JR, Rogers RD, Robbins TW (1999) Specific cognitive deficits in mild frontal variant frontotemporal dementia. Brain 122 (Pt 8):1469–1493.

Richfield EK, Twyman R, Berent S (1987) Neurological syndrome following bilateral damage to the head of the caudate nuclei. Ann Neurol 22:768–771.

Robbins TW, Everitt BJ (1996) Neurobehavioural mechanisms of reward and motivation. Curr Opin Neurobiol 6:228–236.

Robert PH, Clairet S, Benoit M, Koutaich J, Bertogliati C, Tible O, Caci H, Borg M, Brocker P, Bedoucha P (2002) The apathy inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. Int J Geriatr Psychiatry 17:1099–1105.

Rolls ET (1976) The neurophysiological basis of brain-stimulation reward. In: Brain stimulation reward (Wauquier A, Rolls ET, eds), pp 65–87. Amsterdam: North Holland.

Rolls ET (2000) The orbitofrontal cortex and reward. Cereb Cortex 10:284–294.

Rolls ET, Thorpe SJ, Maddison SP (1983) Responses of striatal neurons in the behaving monkey. I. Head of the caudate nucleus. Behav Brain Res 7:179–210.

Rolls ET, Sienkiewicz ZJ, Yaxley S (1989) Hunger modulates the responses to gustatory stimuli of single neurons in the caudolateral orbitofrontal cortex of the macaque monkey. Eur J Neurosci 1:53–60.

Rolls ET, Hornak J, Wade D, McGrath J (1994) Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. J Neurol Neurosurg Psychiatry 57:1518–1524.

Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M, Feiwell R, Kramer JH, Miller BL (2002a) Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology 58:198–208.

Rosen HJ, Hartikainen KM, Jagust W, Kramer JH, Reed BR, Cummings JL, Boone K, Ellis W, Miller C, Miller BL (2002b) Utility of clinical criteria in differentiating frontotemporal lobar degeneration (FTLD) from AD. Neurology 58:1608–1615.

Rosvold HE, Mishkin M, Szwarbach MK (1958) Effects of subcortical lesions in monkeys on visual-discrimination and single-alternation performance. J Comp Physiol Psychol 51:437–444.
Rosvold HE, Szwarcbart MK (1964) Neural structures involved in delayed-response performance. In: The frontal granular cortex and behavior (Warren JM and Akert K, eds), pp. 1–15. New York: McGraw-Hill.
Ruberg M, Agid Y (1988) Dementia in Parkinson's disease. In: Handbook of psychopharmacology (Iversen L, Iversen SD, Snyder SH, eds), pp. 157–205. New York: Plenum Press.
Russchen FT, Bakst I, Amaral DG, Price JL (1985) The amygdalostriatal projections in the monkey. An anterograde tracing study. Brain Res 329:241–257.
Saint-Cyr JA, Ungerleider LG, Desimone R (1990) Organization of visual cortical inputs to the striatum and subsequent ouputs to the pallido-nigral complex in the monkey. J Comp Neurol 298:129–156.
Samuel M, Ceballos-Baumann AO, Turjanski N, Boecker H, Gorospe A, Linazasoro G, Holmes AP, DeLong MR, Vitek JL, Thomas DG, Quinn NP, Obeso JA, Brooks DJ (1997) Pallidotomy in Parkinson's disease increases supplementary motor area and prefrontal activation during performance of volitional movements an H2(15)O PET study. Brain 120:1301–1313.
Sarazin M, Pillon B, Giannakopoulos P, Rancurel G, Samson Y, Dubois B (1998) Clinicometabolic dissociation of cognitive functions and social behavior in frontal lobe lesions. Neurology 51:142–148.
Sawada Y, Takahashi M, Ohashi N, Fusamoto H, Maemura K, Kobayashi H, Yoshioka T, Sugimoto T (1980) Computerised tomography as an indication of long-term outcome after acute carbon monoxide poisoning. Lancet 1:783–784.
Schultz W, Apicella P, Scarnati E, Ljungberg T (1992) Neuronal activity in monkey ventral striatum related to the expectation of reward. J Neurosci 12:4595–4610.
Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. Science 275:1593–1599.
Schultz W, Tremblay L, Hollerman JR (2000) Reward processing in primate orbitofrontal cortex and basal ganglia. Cereb Cortex 10:272–284.
Selemon LD, Goldman-Rakic PS (1985) Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkeys. J Neurosci 5:776–794.
Shallice T (1982) Specific impairments of planning. Philos Trans R Soc Lond B Biol Sci 298:199–209.
Stanton GB, Goldberg ME, Bruce CJ (1988) Frontal eye field efferents in the macaque monkey: I. Subcortical pathways and topography of striatal and thalamic terminal fields. J Comp Neurol 271:473–492.
Starkstein SE, Berthier ML, Leiguarda R (1989) Psychic akinesia following bilateral pallidal lesions. Int J Psychiatry Med 19:155–164.
Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG (1993) Apathy following cerebrovascular lesions. Stroke 24:1625–1630.
Starkstein SE, Mayberg HS, Preziosi TJ, Andrezejewski P, Leiguarda R, Robinson RG (1992) Reliability, validity, and clinical correlates of apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 4:134–139.
Stein RW, Kase CS, Hier DB, Caplan LR, Mohr JP, Hemmati M, Henderson K (1984) Caudate hemorrhage. Neurology 34:1549–1554.
Stern CE, Passingham RE (1994) The nucleus accumbens in monkeys (*Macaca fascicularis*): I. The organization of behaviour. Behav Brain Res 61:9–21.
Stern CE, Passingham RE (1995) The nucleus accumbens in monkeys (*Macaca fascicularis*). III. Reversal learning. Exp Brain Res 106:239–247.
Stern CE, Passingham RE (1996) The nucleus accumbens in monkeys (*Macaca fascicularis*): II. Emotion and motivation. Behav Brain Res 75:179–193.
Strub RL (1989) Frontal lobe syndrome in a patient with bilateral globus pallidus lesions. Arch Neurol 46:1024–1027.
Stuss DT, Benson DF (1984) Neuropsychological studies of the frontal lobes. Psychol Bull 95:3–28.
Stuss DT, Knight RT (2002) Principles of frontal lobe function. Oxford: University Press.
Stuss DT, Van Reekum R, Murphy KJ (2000) Differentiation of states and causes of apathy. In: The Neuropsychology of emotion (Borod JC, ed.), pp. 340–363. Oxford: Oxford University Press.
Thaler DE, Rolls ET, Passingham RE (1988) Neuronal activity of the supplementary motor area (SMA) during internally and externally triggered wrist movements. Neurosci Lett 93:264–269.
Thaler D, Chen YC, Nixon PD, Stern CE, Passingham RE (1995) The functions of the medial premotor cortex. I. Simple learned movements. Exp Brain Res 102:445–460.
Thompson JC, Snowden JS, Craufurd D, Neary D (2002) Behavior in Huntington's disease: dissociating cognition-based and mood-based changes. J Neuropsychiatry Clin Neurosci 14:37–43.
Thompson-Schill SL, Jonides J, Marshuetz C, Smith EE, D'Esposito M, Kan IP, Knight RT, Swick D (2002) Effects of frontal lobe damage on interference effects in working memory. Cogn Affect Behav Neurosci 2:109–120.
Thut G, Schultz W, Roelcke U, Nienhusmeier M, Missimer J, Maguire RP, Leenders KL (1997) Activation of the human brain by monetary reward. Neuroreport 8:1225–1228.
Tobler PN, Dickinson A, Schultz W (2003) Coding of predicted reward omission by dopamine neurons in a conditioned inhibition paradigm. J Neurosci 23:10402–10410.
Tremblay L, Filion M (1989) Responses of pallidal neurons to striatal stimulation in intact waking monkeys. Brain Res 498:1–16.
Tremblay L, Schultz W (1999) Relative reward preference in primate orbitofrontal cortex. Nature 398:704–708.
Tremblay L, Filion M, Bedard PJ (1989) Responses of pallidal neurons to striatal stimulation in monkeys with MPTP-induced parkinsonism. Brain Res 498:17–33.
Trillet M, Croisile B, Tourniaire D, Schott B (1990) Perturbations de l'activité motrice volontaire et lésions des noyaux caudés. Rev Neurol (Paris) 146:338–344.
Uitti RJ, Rajput AH, Ashenhurst EM, Rozdilsky B (1985) Cyanide-induced parkinsonism: a clinicopathologic report. Neurology 35: 921–925.
van Domburg PH, ten Donkelaar HJ, Notermans SL (1996) Akinetic mutism with bithalamic infarction. Neurophysiological correlates. J Neurol Sci 139:58–65.
Vitek JL, Ashe J, DeLong MR, Alexander GE (1990) Altered somatosensory response properties of neurons in the 'motor' thalamus of MPTP parkinsonian monkeys. Soc Neurosci Abstr 16:425.
von Giesen HJ, Schlaug G, Steinmetz H, Benecke R, Freund HJ, Seitz RJ (1994) Cerebral network underlying unilateral motor neglect: evidence from positron emission tomography. J Neurol Sci 125:29–38.
Wichmann T, DeLong MR (1993) Pathophysiology of parkinsonian motor abnormalities. In: Advances in neurology (Narabayashi H, Nagatsu T, Yanagisawa N, Muzino Y, eds). New York: Raven Press.
Yelnik J (2002) Functional anatomy of the basal ganglia. Mov Disord 17 Suppl 3:S15-21.
Yeterian EH, Hoesen GWV (1978) Cortico-striate projections in the rhesus monkey: the organization of certain cortico-caudate connections. Brain Res 139:43–63.
Yeterian EH, Pandya DN (1991) Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys. J Comp Neurol 312:43–67.