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

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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 ‘athyromoria’). 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 disruption of ‘auto-activation’. Apathy is 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 a 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; Laplante 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 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 Szwarchbart, 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.
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 interested in learning new things?’ (Starkstein et al., 1992) or ‘Are you concerned about your condition?’ or ‘Are you interested in learning new things?’ (Starkstein et al., 1992) and providing the key to understanding this type of apathy: indeed, emotion and affect may indicate the motivational value of a given ongoing or forthcoming 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).

<table>
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<tr>
<th>Mechanisms</th>
<th>Inability:</th>
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<td>● to associate emotion/affect with behavior</td>
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<tr>
<td>● to accurately decode the affective context that guides behavior</td>
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<td>● to evaluate the consequences of actions in terms of positive or negative outcome</td>
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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)

| Location of the lesions or dysfunctions associated with this mechanism: |
| Orbital and medial PFC (BA 13,14, ventral 10) |

| BA, Brodmann area. |

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<th>Table 1</th>
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<tr>
<td>Emotional–affective processing</td>
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| 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

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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)

| Location of the lesions or dysfunctions associated with this mechanism: |
| Orbital and medial PFC (BA 13,14, ventral 10) |

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 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/Clincial 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-Buchhalter episodic memory test improved by external cues, poor literal 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:

<table>
<thead>
<tr>
<th>Area</th>
<th>Ant. Thalamic nuclei</th>
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<tr>
<td>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:</td>
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<td>Trail-making task: WSCT: Wisconsin sorting card test.</td>
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Table 3
Auto-activation processing

Mechanisms
Difficulties in self-activating thoughts or behavior
Symptoms/Clincial 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:

<table>
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<tr>
<th>Region</th>
<th>ACC, anterior cingulate cortex, BA, Brodmann area CN, caudate nucleus GP, internal portion of the globus pallidus, MD, medial-dorsal, SFG, superior frontal gyrus</th>
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<tr>
<td>Impairment in specific subsets of the executive functions associated with cognitive inertia:</td>
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<tr>
<td>Cognitive and Limbic territories of the basal ganglia (large uni- or bilateral CN lesions, GPi, MD thalamus)</td>
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<tr>
<td>Medial PFC (medial SFG dorsal and ventral ACC) (BA: medial 9/10, 24, 25, 32), large frontal lesions, frontal white matter lesions</td>
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According to the above data, one may expect apathy to occur after lesions of the ventral striatum (Selemion and Goldman-Rakic, 1985; Vetaryan and Pandya, 1991) as well as to the ‘core’ structure of the ventral striatum (Selemion 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) thalamus, 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 (Seleston and Goldman-Rakic, 1985; Arikuni and Kubota, 1986; Saint-Cyr et al., 1990; Yeterian and Pandya, 1991; Eblen and Graybiel, 1995). Seleston 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 blunt; 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 arrhythmomania). 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; Lehemebre 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 akinnesia, 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...
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 patho-
logical 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 struc-
tures 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 signif-
icant 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](https://example.com/figure3.png)

**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 mesocorticollimbic 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., 1992) 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 over-activity 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 DL-PFC 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

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

References


