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Apathy and the basal ganglia

Abstract We should like to emphasize the following points: 1. Apathy is defined here as a quantified and observable behavioral syndrome consisting in a quantitative reduction of voluntary (or goal-directed) behaviors; 2. Therefore, apathy occurs when the systems that generate and control voluntary actions are altered; 3. These systems are mostly represented by the different subregions embedded in the Prefrontal cortex (PFC) and in the basal ganglia regions that are closely connected with the PFC; 4. In consequence, clinically, apathy is a prefrontal syndrome either due to direct lesions of the PFC or to lesions of basal ganglia areas that are closely related to the PFC; 5. Apathy is not a single entity but rather heterogeneous. Several different mechanisms may lead to apathy; Because there are several anatomical-functional prefrontal-basal ganglia circuits, the underlying mechanisms responsible for apathy may differ according to which prefrontal-basal ganglia circuit is affected; 6. In this context, apathy is the macroscopic results of the disruption of one or several elementary steps necessary for goal-directed behavior that are subserved by different prefrontal-basal ganglia circuits; 7. Intense apathy is related to caudate nucleus and GPi, disrupting associative and limbic pathways from/to the PFC; 8. in progressive supranuclear palsy (PSP) and focal lesions (caudate nuclei, GPi), apathy may be due to a loss of PFC activation; 9. In Parkinson's disease (PD), apathy may be due to a loss of signal focalization; 10. More globally, we propose that apathy may be explained by the impact of lesions or dysfunctions of the BG, 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.

Key words Striatum · pallidum · prefrontal cortex · executive functions · cognition · neuropsychologia · Parkinson's disease · progressive supranuclear palsy

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Introduction

Apathy is a common feature of many pathological states involving lesions or dysfunctions located within the prefrontal-basal ganglia system. It can be observed in neurodegenerative diseases such as Parkinson's disease (PD) [1, 2, 47, 83, 98], Huntington's disease [23, 43, 104] and progressive supranuclear palsy (PSP) [3, 65, 66]. 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 [6, 13, 38, 57, 76]. In this review article, we will attempt to revisit the concept of apathy in order to propose a better understanding of its physiopathology and subsequently to improve our knowledge of the role of the prefrontal-basal ganglia system.

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The concept of apathy

Apathy is conventionally defined as an "absence or lack of feeling, emotion, interest or concern". Robert Marin proposed that apathy corresponds to a "lack of motivation not attributable to diminished level of consciousness, cognitive impairment or emotional distress" [69, 70]. This definition appears problematic for several reasons: First, "motivation" is a psychological concept that encompasses several different theories from behavioral to social psychology and it is therefore difficult to propose a consensus on its definition and overall to transfer this concept to the level of its physiopathological basis. Second, defining apathy as a "lack of motivation" is an inference resulting from a psychological interpretation of a given behavioral state. Third, apathy may be the clinical expression of several different underlying mechanisms.

An alternative approach is to view apathy as a quantitative reduction of actions compared to previous behavior, despite the patient's environmental or physical constraints remaining unchanged. In other words, 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 this definition, apathy is a pathology of voluntary action or goal-directed behavior (GDB) and the underlying mechanisms responsible for apathy may be seen as dysfunctions occurring at the level of elaboration, execution and control of GDB [17]. 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, etc.), apathy may arise from dysfunctions occurring at any of the steps required to achieve a GDB. It is thus likely that the physiopathology of apathy is not a single entity but multiple, depending on which specific process is disrupted during the completion of GDB. In line with this notion, we propose dividing apathetic syndromes into three subtypes: 'emotional', 'cognitive' and 'auto-activation'. Apathy related to disruption of 'emotional' processing refers to a reduction in GDB due to an inability to associate affective and emotional signals with ongoing and forthcoming behaviors. Any change in the linkage between emotion-affect and behavior may lead to apathy, either by reducing the willingness to perform (loss of will, loss of goals, emotional blunting) and maintain actions to their completion or by diminishing one's ability to evaluate the consequences of future actions [31]. Apathy related to disruption of 'cognitive' processing refers to the reduction in GDB due to impairments in the cognitive functions needed to elaborate the plan of actions. These functions are usually gathered under the heading of 'executive functions'. Patients may therefore be apathetic as a result of working memory 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. Apathy related to an 'auto-activation' deficit 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.

Based on the large body of evidence, each of the three groups of mechanisms responsible for apathy can be ascribed to dysfunctions of different territories within the PFC and the basal ganglia as follows: 'emotional-affective' to the orbital-medial PFC and to a lesser extend to the limbic territories of the basal ganglia (ventral striatum, ventral pallidum), 'cognitive' to the lateral PFC and the cognitive territory of the basal ganglia (dorsal caudate nucleus, dorsal pallidum) and 'auto-activation' to both cognitive limbic territories of the basal ganglia and to a lesser extend to the dorsal-medial PFC. However, this distinction should be considered as a general framework as lesions or dysfunctions within the prefrontal-basal ganglia system are rarely superimposed to this relative functional segregation.

Apathy is not depression

Apathy can be a one of the clinical signs of a depression [71, 72]. In this case, apathy is a symptom due to depression. Apathy in depression may be the consequence of anhedonia (insensitivity to pleasure) or of a marked sensitivity to emotionally negative situations inducing a negative biais interfering with attention resources and executive functions. However, in many medical situation apathy can be totally independent from depression: for instance, in neurological diseases such as Alzheimer's and PD, apathy and depression are not similar in terms of the correlation with other signs and symptoms and the location of the lesions [7, 55, 62, 72]. In sum, apathy is a symptom that can be observed in depression but apathy can occur without depression and when both are present in a given patient, they may be clinically and anatomically independent.

Apathy in Parkinson's disease

The frequency of apathy in PD varies between 16.5 and 42 %, according to different studies [2, 3, 25, 26, 47, 83, 87, 97]. Apathy does not correlate with the duration and

severity of the disease [97] and the frontal atrophy on MRI or CT-scan. However, apathy do correlate with the dysexecutive syndrome [17, 47, 97], the existence of dementia [17], the index of the activities of daily living and the daily dose of L-dopa [47].

There are many dysfunctions that can be considered as potential candidates to produce apathy in PD (lesions to: dopamine ascending pathways including nigro-striatal and meso-cortico-limbic pathways, cholinergic pathway, noradrenergic and serotoninergic ascending pathways, direct cortical lesions in associative cortices). For instance, a recent study has reported that apathy was inversely correlated with a marker of both dopamine and noradrenaline transporter ([11C]RTI-32 binding) in the ventral striatum [85]. Using Starkstein's apathy scale [97], we demonstrated a significant difference in the severity of apathy between the 'off' and 'on' states in fluctuating PD patients, indicating that apathy in PD is at least partly a dopamine-dependent syndrome [25]. This dopamine-dependent effect is likely to occur via the impact of striatal dopamine dysfunction and the cascade of dysfunctions within the basal ganglia circuits: According to this hypothesis, in a recent study, we have shown that bilateral deep brain stimulation in the subthalamic nuclei may significantly improves apathy in PD [25]. By which mechanisms, striatal dopamine depletion induces apathy in PD patients?

Classically, dopamine is associated with reward processing [52, 86, 88, 95]. The influence of dopamine on reward processing may act through a modulation of the orbital-medial PFC and the ventral striatum via the meso-cortico-limbic pathway. As a consequence, one may hypothesize that apathy in PD patients falls into the subtype of the "emotional"mechanism and may result from a dysfunction of the orbital-medial PFC-ventral striatum circuit. However, there are several data that suggest that apathy in PD is not due to a disruption of 'emotional-affective' processing: 1) apathy is present in PD even at relatively early stages and in the absence of dementia [2, 3, 25, 26, 47, 83, 87, 97], i.e., at stages in which the dopamine mesocorticolimbic pathway is relatively spared [92]; 2) Tasks used to assess reward sensitivity and changes in reward contingencies, such as the gambling [12], reversal [90] and object alternation tasks, which are sensitive to lesions of the orbital-medial PFC-VS loop, were not found to be impaired in PD patients, even in patients tested while 'off' levodopa therapy [25, 34].

What other alternative hypotheses can be proposed to explain apathy in PD patients? At a very global level, one hypothesis could be that apathy in PD results from the disruption of the 'cognitive' processing usually mediated by the dorsolateral PFC-dorsal caudate nucleus circuit, as cognitive dysfunction in PD resembles that of patients with direct dorsolateral PFC lesions [82]. At a more elementary level, apathy (as many of the parkinsonian signs) can result from the inability for the basal ganglia to validate the relevant signal that is transferred to the PFC. A series of important experiments by Filion and Tremblay [32, 105, 106] 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 this time 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). We hypothesize that this contributes to some form of apathy because it may be difficult for the output structures to disambiguate the relevant signal and this may cause problems in decision-making, inducing aborted or delayed responses.

Apathy in other diseases affecting the basal ganglia

Apathy in PSP

Apathy represents one of the most important clinical features of PSP, where it is considered as almost constant (more than 90 % of the patients) [64, 65] and often more severe than in PD [3]. This neurodegenerative disease is characterized by severe neuronal loss in the basal ganglia contrasting with a mild degree of direct prefrontal pathology [44, 64]. This suggests that apathy is the consequence of a "prefrontal-like" syndrome due to lesions mostly affecting the basal ganglia. In consequence, the massive hypometabolism of the anterior portion of the frontal lobes [27, 33, 59], in particular in the superior lateral and medial PFC [14, 46, 59] that correlates with the behavioral syndrome, can be interpreted as the result of a deafferentation prefrontal syndrome due to basal ganglia lesions.

Apathy following focal lesions of the basal ganglia

Apathy (often called 'abulia' or 'psychic akinesia' when it is intense), can be seen after uni- or bilateral caudate lesions [13, 20]. According to Bathia and Marsden [13], it affects about 28 % of the patients with focal lesions of the caudate nucleus. Patients exhibit a lack of initiative for usual daily activities leading to a drastic decrease in

their spontaneous behaviors, which may be partially reversed by external and strong solicitation [13, 54]. It is associated with a slowness and a latency of responses after stimulation. This behavior cannot be related to depressive disorders but it could be associated with flattened affect and emotional blunting.

Apathy has been observed with lesions located in the dorsal area of the head of the caudate nucleus [76]. Based on data from anatomical, electrophysiological and lesion studies in the monkeys [5, 29, 36, 40, 48, 50, 63, 96, 112] as well as from functional imaging studies in humans [78], the dorsal portion of the caudate nuclei (in particular the head) should be considered as key structures in an anatomical-functional network, in combination with the dorsolateral PFC, which mostly contributes to executive functions. It is thus likely that apathy resulting from lesions in the dorsal portion of the caudate nuclei is due to a dysexecutive syndrome (in particular, difficulties in generating new rules or strategies or difficulty in shifting from one mental and behavioral set to another) rather than to an emotional or motivational dysfunction. This pattern of dysfunction can be refered to as 'Cognitive inertia' and represents the expression of apathy in the sphere of executive functions.

So far, in human, there is no report of apathy following lesions located in isolation to the ventral striatum, However, one should note that reports of isolated ventral striatal lesions are very few [19, 76]. Nevertheless, several lines of data indirectly suggest that the ventral striatal dysfunction may contribute to an "emotional" form of apathy: 1) the ventral striatum receives dense and direct connections from the orbital-medial PFC [41, 96]; 2) Lesions to this PFC region is associated with emotional blunting, reward insensitivity and apathy [67, 91]; 3) the role of the ventral striatum in reward processing has been pinpointed by many experimental approaches [8, 18, 45, 94, 100].

One of the most intense forms of apathy, called 'athymhormia' or 'psychic auto-activation' deficit, has been reported after focal basal ganglia lesions [6, 15, 56, 57, 97]. This syndrome consists in a loss of spontaneous activation in three different domains: behavior, cognition and emotion. 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 when they are not stimulated. Affect is usually flattened with anhedonia and emotional responses are blunted; any reactivity to emotional situations is poor and short live. One of the most important features of this syndrome is that it can be partially and temporarily reversed by external stimulation and, when solicited, patients can produce relevant answers and behaviors. It is often associated with stereotypic and pseudo-compulsive behaviors or thoughts (such as arythmomania). In other words, there is a sharp contrast between the drastic quantitative reduction of self-generated actions and the relatively normally executed externally-driven behaviors. This syndrome, according to the tripartite subdivision of mechanisms responsible for apathy, clearly falls into the category of 'auto-activation' deficit. This apathetic syndrome is in general due to restricted and specific lesions in the basal ganglia, in most cases affecting, bilaterally, the internal portion of the pallidum [6, 51, 56, 68, 84, 93, 103]. It can also be seen after bilateral striato-pallidal lesions [49, 53, 58, 60, 81, 84, 108], uni- or bilateral lesions of the head of the caudate nucleus [20, 39, 42, 58, 76, 79, 84, 107], and lesions of the MD and anterior nuclei of the thalamus and the deep frontal white matter [15, 109]. These areas within the basal ganglia are without doubt limbic and cognitive territories, which probably explains the absence of extrapyramidal motor signs in this syndrome. On the one hand, one may hypothesize that the 'psychic 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 more elementary functions, devoted to auto-activation (related to specific areas within the dorsal-medial PFC). 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. It is thus interesting to note the close relationship between 'auto-activation' deficit and some of the signs usually classified 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.

'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. 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 [10, 14, 27, 57, 59]. In the above pathological situations there are destructive lesions in the limbic and cognitive territories of the input (striatum) and/or output structures (GPi) of the basal ganglia. 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 strongly emphasized the concept of a relative segregation of the frontal-basal ganglia loops organized in parallel pathways throughout the basal ganglia [4, 77]. This 'segrega-

tion' model suggests that one of the main aspects of information processing within the basal ganglia could be the selection of specific signals, which may correspond to the actions or thoughts generated by the frontal lobes [9, 16, 50, 105, 106, 110]. 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 [80, 111]. 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, the PFC internalizes the information from the external and internal environments needed to make a decision about potential 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 re-addressed 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 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.

Assessment and management of apathy

Assessment tools

Assessing apathy relies at first hand on the information collected about the patients from the caregivers and from specific questionnaires performed by the patients: three questionnaires specifically assess apathy: the "Apathy evaluation scale" [69], the Apathy scale [98] and the "Apathy inventory" [87]. The emotional dimension can be assessed in such questionnaires by items such as "does anything interest you?"; Are you concerned about your condition?" Are you interested in learning new things?" Emotional mechanisms may also be assessed by tasks such as the gambling [12] or reversal [25, 90] tasks, which investigate the ability to modulate one's behavior as a function of reward. The cognitive dimension is not well represented in the apathy questionnaires but it may be tested by 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), that may be useful to detect a cognitive 'inertia'. The "auto-activation" dimension is characterized by an intense apathy affecting both the "cognitive" and the "emotional" dimensions. Several items on the apathy questionnaires may point out the contrast between auto- and hetero-activation of behavior ("Does someone has to tell you what to do each day?""Do you need a push to get started on things?").

Treatment

Current treatments of apathy are unsatisfactory. The available treatments for apathy, regardless of the underlying etiology, have only been tested in open-trials or in case studies: among them, one should consider methylphenidate, an amphetamine derived drug used in attention deficit-hyperactivity disorder syndrome [21], bupropion [22], amantidine [73], selegiline [73] and bromocriptine [11, 28]. When targeting more specifically apathy in PD patients, L-dopa has some positive but incomplete effect [25]. Results regarding STN DBS are encouraging for the short-term outcome [26, 35]. However, it seems to early to declare DBS effective on apathy. Particularly, the long term effect of DBS on apathy remains to be determined. Anticholinesterase inhibitors are promising, based on results obtained in large double-blind, placebo control studies on behavioral syndromes (including apathy) in Alzheimer's disease and in dementia with Lewy bodies [24, 30, 37, 61, 75] and from the first results in PD [1, 61, 74].

References

1. Aarsland D, Hutchinson M, Larsen JP (2003) Cognitive, psychiatric and motor response to galantamine in Parkinson's disease with dementia. Int J Geriatr Psychiatr 18(10):937–941
2. Aarsland D, Larsen JP, Lim NG, Janvin C, Karlsen K, Tandberg E et al. (1999) Range of neuropsychiatric disturbances in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 67(4):492–496
3. Aarsland D, Litvan I, Larsen JP (2001) Neuropsychiatric symptoms of patients with progressive supranuclear palsy and Parkinson's disease. J Neuropsychiatry Clin Neurosci 13(1): 42–49
4. Alexander GE, Delong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annual Review of Neurosciences 9:357–381
5. 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. Society of Neuroscience Abstract 6:86
6. Ali-Cherif A, Royere ML, Gosset A, Poncet M, Salamon G, Khalil R (1984) Behavior and mental activity disorders after carbon monoxide poisoning, Bilateral pallidal lesions. Rev Neurol (Paris) 140(6–7):401–405
7. 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(2): 447–456
8. Apicella P, Ljungberg T, Scarnati E, Schultz W (1991) Responses to reward in monkey dorsal and ventral striatum. Exp Brain Res 85(3):491–500
9. 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(6): 689–695
10. Baron JC (1994) Consequences of lesions of the basal ganglia on cerebral metabolic activity: clinical implications. Rev Neurol (Paris) 150(8–9): 599–604
11. Barrett K (1991) Treating organic abulia with bromocriptine and lisuride: four case studies. J Neurol Neurosurg Psychiatr 54(8):718–721
12. Bechara A, Damasio AR, Damasio H, Anderson SW (1994) Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50(1–3):7–15
13. Bhatia KP, Marsden CD (1994) The behavioural and motor consequences of focal lesions of the basal ganglia in man. Brain 117(Pt 4):859–876
14. Blin J, Baron JC, Dubois B et al. (1988) PET studies in a model of subcortical dementia: Progressive supra-nuclear palsy. In: AA et al. (ed) Senile dementia and Alzheimer's disease. J Libbey, London, pp 73–80
15. 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(5):309–316
16. Brotchie P, Iansek R, Horne MK (1991) Motor function of the monkey globus pallidus. I. Neuronal discharge and parameter of movement. Brain 114: 1667–16683
17. Brown RG, Pluck G (2000) Negative symptoms: the 'pathology' of motivation and goal-directed behaviour. Trends Neurosci 23(9):412–417
18. 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
19. Calder AJ, Keane J, Lawrence AD, Manes F (2004) Impaired recognition of anger following damage to the ventral striatum. Brain 127(Pt 9): 1958–1969
20. Caplan LR, Schmahmann JD, Kase CS et al. (1990) Caudate Infarcts. Arch Neurol 47:133–143
21. Chatterjee A, Fahn S (2002) Methylphenidate treats apathy in Parkinson's disease. J Neuropsychiatry Clin Neurosci 14(4):461–462
22. Corcoran C, Wong ML, O'Keane V (2004) Bupropion in the management of apathy. J Psychopharmacol 18(1): 133–135
23. Craufurd D, Thompson JC, Snowden JS (2001) Behavioral changes in Huntington Disease. Neuropsychiatry Neuropsychol Behav Neurol 14(4):219–226
24. Cummings JL, Nadel A, Masterman D, Cyrus PA (2001) Efficacy of metrifonate in improving the psychiatric and behavioral disturbances of patients with Alzheimer's disease. J Geriatr Psychiatry Neurol 14(2): 101–108
25. Czernecki V, Pillon B, Houeto JL, Pochon JB, Levy R, Dubois B (2002) Motivation, reward, and Parkinson's disease: influence of dopatherapy. Neuropsychologia 40(13):2257–2267
26. Czernecki V, Pillon B, Houeto JL, Welter ML, Mesnage V, Agid Y et al. (2005) Does bilateral stimulation of the subthalamic nucleus aggravate apathy in Parkinson's disease? J Neurol Neurosurg Psychiatry 76(6):775–779
27. D'Antona R, Baron JC, Samson Y et al. (1985) Subcortical dementia: frontal cortex hypometabolism detected by positon tomography in patients with progressive supranuclear palsy. Brain 108:785–799
28. Debette S, Kozlowski O, Steinling M, Rousseaux M (2002) Levodopa and bromocriptine in hypoxic brain injury. J Neurol 249(12):1678–1682
29. Divac I, Rosvold HE, Scwarcbart MK (1967) Behavioural effects of selective ablation of the caudate nucleus. J Comp Physiol Psych 63:184–190
30. Edwards KR, Hershey L, Wray L, Bednarczyk EM, Lichter D, Farlow M et al. (2004) Efficacy and safety of galantamine in patients with dementia with Lewy bodies: a 12-week interim analysis. Dement Geriatr Cogn Disord 17(Suppl 1):40–48
31. Eslinger PJ, Damasio AR (1985) Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. Neurology 35(12):1731–1741
32. Filion M, Tremblay L (1991) Abnormal spontaneous activity of globus pallidus neurons in monkeys with MPTP-induced parkinsonism. Brain Res 547: 142–151
33. Foster NL, Gilman S, Berent S et al. (1988) Cerebral hypometabolism in progressive supranuclear palsy studied with positon emission tomography. Ann Neurol 24:399–406
34. Freedman M, Oscar-Berman M (1986) Elective delayed response deficits in Parkinson's and Alzheimer's disease. Arch Neurol 43:886–890
35. Funkiewiez A, Ardouin C, Krack P, Fraix V, Van Blercom N, Xie J et al. (2003) Acute psychotropic effects of bilateral subthalamic nucleus stimulation and levodopa in Parkinson's disease. Mov Disord 18(5):524–530
36. Fuster JM (1997) The prefrontal cortex, 2nd edn. Raven Press, New York
37. Gauthier S, Feldman H, Hecker J, Vellas B, Ames D, Subbiah P et al. (2002) Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. Int Psychogeriatr 14(4):389–404
38. Ghika-Schmid F, Bogousslavsky J (2000) The acute behavioral syndrome of anterior thalamic infarction: a prospective study of 12 cases. Ann Neurol 48(2):220–227

39. Godefroy O, Rousseaux M, Leys D, Scheltens P, Pruve JP (1992) Frontal lobe dysfunction in unilateral lenticulo-striate infarcts. Arch Neurol 49: 1285–1289
40. Goldman-Rakic PS (1987) Circuitry of primate prefrontal cortex and regulation of behaviour by representational memory. In: Plum F, Mouncastle U (eds) Handbook of Physiology (Vol. 5). Washington: The American Physiological Society, pp 373–417
41. 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
42. Habib M, Poncet M (1988) Loss of vitality, of interest and of the affect (athymhormia syndrome) in lacunar lesions of the corpus striatum. Rev Neurol (Paris) 144(10):571–577
43. Hamilton JM, Salmon DP, Corey-Bloom J, Gamst A, Paulsen JS, Jerkins S et al. (2003) Behavioural abnormalities contribute to functional decline in Huntington's disease. J Neurol Neurosurg Psychiatry 74(1):120–122
44. Hauw JJ, Daniel SE, Dickson D, Horoupian DS, Jellinger K, Lantos PL et al. (1994) Preliminary NINDS neuropathologic criteria for Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). Neurology 44(11):2015–2019
45. Hollerman JR, Tremblay L, Schultz W (1998) Influence of reward expectation on behavior-related neuronal activity in primate striatum. J Neurophysiol 80(2):947–963
46. Hosaka K, Ishii K, Sakamoto S, Mori T, Sasaki M, Hirono N et al. (2002) Voxel-based comparison of regional cerebral glucose metabolism between PSP and corticobasal degeneration. J Neurol Sci 199(1–2):67–71
47. Isella V, Melzi P, Grimaldi M, Iurlaro S, Piolti R, Ferrarese C et al. (2002) Clinical, neuropsychological, and morphometric correlates of apathy in Parkinson's disease. Mov Disord 17(2): 366–371
48. Iversen SD (1979) Behaviour after neostriatal lesions in animals. In: Divac I, Oberg RGE (eds) The neostriatum. Pergamon, Oxford, pp 195–210
49. Katz DI, Alexander MP, Seliger GM, Bellas DN (1989) Traumatic basal ganglia hemorrhage: clinicopathologic features and outcome. Neurology 39(7):897–904
50. Kimura M, Matsumoto N, Okahashi K, Ueda Y, Satoh T, Minamimoto T et al. (2003) Goal-directed, serial and synchronous activation of neurons in the primate striatum. Neuroreport 14(6): 799–802
51. Klawans HL, Stein RW, Tanner CM, Goetz CG (1982) A pure parkinsonian syndrome following acute carbon monoxide intoxication. Arch Neurol 39(5):302–304
52. Koob GF (1992) Neural mechanisms of drug reinforcement. Ann N Y Acad Sci 654:171–191
53. Krauss JK, Mohadjer M, Wakhloo AK, Mundinger F (1991) Dystonia and akinesia due to pallidoputaminal lesions after disulfiram intoxication. Mov Disord 6(2):166–170
54. Kumral E, Evyapan D, Balkir K (1999) Acute caudate vascular lesions. Stroke 30(1):100–108
55. 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(4): 265–269
56. Laplane D, Baulac M, Widlocher D, Dubois B (1984) Pure psychic akinesia with bilateral lesions of basal ganglia. J Neurol Neurosurg Psychiatry 47(4): 377–385
57. Laplane D, Levasseur M, Pillon B, Dubois B, Baulac M, Mazoyer B et al. (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
58. 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(4):269–276
59. 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
60. Lehembre P, Graux P (1992) Athymormia, arithmomania or stercoral compulsion in multiple infarcts of the corpus striatum. Ann Med Psychol (Paris) 150(9):699–701
61. Leroi I, Brandt J, Reich SG, Lyketsos CG, Grill S, Thompson R et al. (2004) Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease. Int J Geriatr Psychiatry 19(1):1–8
62. Levy ML, Cummings JL, Fairbanks LA, Masterman D, Miller BL, Craig AH et al. (1998) Apathy is not depression. J Neuropsychiatry Clin Neurosci 10(3): 314–319
63. 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(10):3870–3882
64. Litvan I, Hauw JJ, Bartko JJ, Lantos PL, Daniel SE, Horoupian DS et al. (1996) Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. J Neuropathol Exp Neurol 55(1):97–105
65. Litvan I, Mega MS, Cummings JL, Fairbanks L (1996) Neuropsychiatric aspects of progressive supranuclear palsy. Neurology 47(5):1184–1189
66. Litvan I, Paulsen JS, Mega MS, Cummings JL (1998) Neuropsychiatric assessment of patients with hyperkinetic and hypokinetic movement disorders. Arch Neurol 55(10):1313–1319
67. Lough S, Gregory C, Hodges JR (2001) Dissociation of social cognition and executive function in frontal variant frontotemporal dementia. Neurocase 7(2):123–130
68. Lugaresi A, Montagna P, Morreale A, Gallassi R (1990) 'Psychic akinesia' following carbon monoxide poisoning. Eur Neurol 30(3):167–169
69. Marin RS (1991) Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci 3(3):243–254
70. Marin RS (1996) Apathy: Concept, Syndrome, Neural Mechanisms, and Treatment. Semin Clin Neuropsychiatry 1(4):304–314
71. Marin RS, Firinciogullari S, Biedrzycki RC (1993) The sources of convergence between measures of apathy and depression. J Affect Disord 28(2):117–124
72. Marin RS, Firinciogullari S, Biedrzycki RC (1994) Group differences in the relationship between apathy and depression. J Nerv Ment Dis 182(4):235–239
73. Marin RS, Fogel BS, Hawkins J, Duffy J, Krupp B (1995) Apathy: a treatable syndrome. J Neuropsychiatry Clin Neurosci 7(1):23–30
74. McKeith I (2004) Dementia in Parkinson's disease: common and treatable. Lancet Neurol 3(8):456
75. McKeith IG, Grace JB, Walker Z, Byrne EJ, Wilkinson D, Stevens T et al. (2000) Rivastigmine in the treatment of dementia with Lewy bodies: preliminary findings from an open trial. Int J Geriatr Psychiatry 15(5):387–392
76. Mendez MF, Adams NL, Lewandowski KS (1989) Neurobehavioral changes associated with caudate lesions. Neurology 39(3):349–354
77. Middleton FA, Strick PL (2000) Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. Brain Cogn 42(2):183–200

78. 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
79. Pardal MM, Micheli F, Asconape J, Paradiso G (1985). Neurobehavioral symptoms in caudate hemorrhage: two cases. Neurology 35(12):1806–1807
80. Percheron G, Fillion M (1991) Parallel processing in the basal ganglia: up to a point (letter). Trends Neurosci 14: 55–56
81. Peters HA, Levine RL, Matthews CG, Chapman LJ (1988) Extrapyramidal and other neurologic manifestations associated with carbon disulfide fumigant exposure. Arch Neurol 45(5):537–540
82. Pillon B, Boller F, Levy R, Dubois B (2002) Cognitive deficits in Parkinson's disease. In: Boller F, Grafman J (eds) Handbook of Neuropsychology (vol 6). Elsevier, Amsterdam
83. Pluck GC, Brown RG (2002) Apathy in Parkinson's disease. J Neurol Neurosurg Psychiatry 73(6):636–642
84. Pulst SM, Walshe TM, Romero JA (1983) Carbon monoxide poisoning with features of Gilles de la Tourette's syndrome. Arch Neurol 40(7):443–444
85. Remy P, Doder M, Lees A, Turjanski N, Brooks D (2005) Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain 128(6):1314–1322
86. Robbins TW, EverittBJ (1996)Neurobehavioural mechanisms of reward and motivation. Curr Opin Neurobiol 6(2): 228–236
87. Robert PH, Clairet S, Benoit M, Koutaich J, Bertogliati C, Tible O et al. (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(12): 1099–1105
88. Rolls ET (1976) The neurophysiological basis of brain-stimulation reward. In: AW, Rolls ET (ed) Brain stimulation reward. North-Holland, Amsterdam, pp 65–87
89. Rolls ET (1999) The brain and emotion. Oxford: Oxford University Press
90. 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(12):1518–1524
91. Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M et al. (2002) Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology 58(2): 198–208
92. Ruberg M, Agid Y (1988) Dementia in Parkinson's disease. In: Iversen L, Iversen SD, Snyder SH (eds) Handbook of Psychopharmacology (Vol. 20: Psychopharmacology of aging nervous system). Plenum, New York, pp 157–205
93. Sawada Y, Takahashi M, Ohashi N, Fusamoto H, Maemura K, Kobayashi H et al. (1980) Computerised tomography as an indication of long-term outcome after acute carbon monoxide poisoning. Lancet 1(8172): 783–784
94. Schultz W, Apicella P, Scarnati E, Ljungberg T (1992). Neuronal activity in monkey ventral striatum related to the expectation of reward. J Neurosci 12(12):4595–4610
95. Schultz W, Dayan P, Montague PR (1997) A neural substrate of prediction and reward. Science 275(5306): 1593–1599
96. Selemon LD, Goldman-Rakic PS (1985) Longitudinal topography and interdigitation of corticostriatal projections in the rhesus monkeys. J Neurosci 5:776–794
97. Starkstein SE, Berthier ML, Leiguarda R (1989) Psychic akinesia following bilateral pallidal lesions. Int J Psychiatry Med 19(2):155–164
98. 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(2):134–139
99. Stein RW, Kase CS, Hier DB, Caplan LR, Mohr JP, Hemmati M et al. (1984) Caudate hemorrhage. Neurology 34(12):1549–1554
100. Stern CE, Passingham RE (1994) The nucleus accumbens in monkeys (Macaca fascicularis): I The organization of behaviour. Behav Brain Res 61(1):9–21
101. Stern CE, Passingham RE (1995) The nucleus accumbens in monkeys (Macaca fascicularis). III. Reversal learning. Exp Brain Res 106(2): 239–247
102. Stern CE, Passingham RE (1996) The nucleus accumbens in monkeys (Macaca fascicularis): II. Emotion and motivation. Behav Brain Res 75(1–2):179–193
103. Strub RL (1989) Frontal lobe syndrome in a patient with bilateral globus pallidus lesions. Arch Neurol 46(9):1024–1027
104. 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(1):37–43
105. 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
106. Tremblay L, Fillion M (1989) Responses of pallidal neurons to striatal stimulation in intact waking monkeys. Brain Res 498:1–16
107. Trillet M, Croisile B, Tourniaire D, Schott B (1990) Disorders of voluntary motor activity and lesions of caudate nuclei. Rev Neurol (Paris) 146(5):338–344
108. Uitti RJ, Rajput AH, Ashenhurst EM, Rozdilsky B (1985) Cyanide-induced parkinsonism: a clinicopathologic report. Neurology 35(6):921–925
109. van Domburg PH, ten Donkelaar HJ, Notermans SL (1996) Akinetic mutism with bithalamic infarction. Neurophysiological correlates. J Neurol Sci 139(1):58–65
110. 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
111. Yelnik J (2002) Functional anatomy of the basal ganglia. Mov Disord 17 (Suppl 3):S15–S21
112. Yeterian EH, Pandya DN (1991) Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys. J Comp Neurol 312:43–67