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Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment

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Normal maintenance of human motivation depends on the integrity of subcortical structures that link the prefrontal cortex with the limbic system. Structural and functional disruption of different networks within these circuits alters the maintenance of spontaneous mental activity and the capacity of affected individuals to associate emotions with complex stimuli. The clinical manifestations of these changes include a continuum of abnormalities in goal-oriented behaviours known as apathy. Apathy is highly prevalent in Parkinson's disease (and across many neurodegenerative disorders) and can severely affect the quality of life of both patients and caregivers. Differentiation of apathy from depression, and discrimination of its cognitive, emotional, and auto-activation components could guide an individualised approach to the treatment of symptoms. The opportunity to manipulate dopaminergic treatment in Parkinson's disease allows researchers to study a continuous range of motivational states, from apathy to impulse control disorders. Parkinson's disease can thus be viewed as a model that provides insight into the neural substrates of apathy.

Introduction

Apathy is a behavioural syndrome that consists of a set of simultaneous behavioural, affective, and cognitive features. Apathy can be defined as a state of decreased motivation that manifests as a decrease in goal-directed behaviours, and can be variably characterised by reduced interests or emotions that cannot be attributed to diminished level of consciousness, cognitive impairment, or emotional distress.^{1,2} The observable phenomenon of apathy is related to four subdomains: decrease in emotional resonance (reward deficiency syndrome), depression, decrease in cognitive interests (executive dysfunction), and absence of spontaneous activation of mental processes (auto-activation deficit).^{3,4} In psychology, subdomains are defined as each one of the discrete components that contribute differentially to the manifestation of a cognitive or behavioural syndrome or construct.⁵ The contribution of these subdomains of apathy can vary from patient to patient, so their discrimination in particular patients could guide an individualised approach to the treatment of symptoms that lead to diminished goal-directed behaviours.

Awareness of the importance of neuropsychiatric and cognitive symptoms, including apathy, in the management of patients with Parkinson's disease has increased in the past decade. An effort has been made to describe mood disorders in Parkinson's disease in more detail in an attempt to distinguish apathy from depression,^{6,7} recognising that the emotional expression of apathy largely overlaps with anhedonia, which is also a part of depression.⁸ Isolated apathy, which is not related to cognitive impairment or depression, has been recorded at early and advanced stages of Parkinson's disease.^{9,10} Apathy can be regarded as an independent nosological entity caused by dysfunction of different but interrelated subdomains and neural circuits, and it is increasingly recognised as a syndrome with distinct targets for pharmacotherapy.¹¹ Validated scales assessing specific cognitive, motivational, and depressive symptoms can be used to differentiate apathy from depression, and

discriminate its cognitive, emotional, and auto-activation subdomains.

In this Review, we focus on apathy in Parkinson's disease, discussing its prevalence, clinical relevance, phenomenology, neuropsychological correlates, and response to treatments. We propose a model with the aim of linking the separate subdomains of apathy with different neurobiological correlates, thus providing an operative framework for the clinical classification of apathetic syndromes and the selection of appropriate treatments.

Syndromes and substrates of apathy

Conceptual issues

Motivation is a psychological feature that arouses an organism to act towards a desired goal, both eliciting and sustaining goal-directed behaviours.¹² Motivation in healthy human beings acts as an inner drive elicited by physical needs (eg, eating and drinking), but also by pleasurable and aversive stimuli, as coded by reward-based and punishment-based learning, which attach motivational importance to otherwise neutral environmental stimuli.^{13–15} The notion of apathy as a clinical syndrome was built from original case reports and lesional studies describing patients with fairly well preserved cognition who showed a striking absence of observable spontaneous active behaviours, but who were still capable of reacting and behaving almost normally in response to external stimulation.^{16,17} Many descriptive epithets have been ascribed to this unique combination of an absence of self-initiated goal-directed actions—giving the patient the aspect of indifference, flattening of affect, or emptiness of mind—and diminished responsiveness to stimuli. The different terms used to describe the features of apathy can be regarded as describing a continuum of severity of reduced motivated behaviours, up to the most severe forms of akinetic mutism, abulia, athymhormia, or auto-activation deficits. At present, decreased goal-directed behaviours in neurodegenerative diseases are generally categorised as apathy, irrespective of their severity.

Discrimination of apathetic syndromes to guide treatment

Apathy is a clinically relevant and potentially treatable impairment of motivated human behaviour. Identification of the different components of apathy could help to determine the treatment approach for individual patients.¹⁸ Four major subdomains of goal-directed behaviour variably contribute (in isolation or, more frequently, in combination) to apathy: reward deficiency syndrome, depression, executive dysfunction, and auto-activation failure (figure 1).

Reward deficiency syndrome refers to a state of emotional blunting or absence of emotional resonance, which prevents an individual from attaching motivational values and pleasure to environmental or inner stimuli.¹² Blunted affect in isolated apathy should be clinically differentiated from apathy caused by negative affect. In major depression, sadness is accompanied by a substantial reduction in effortful and sustained positively motivated behaviours.¹⁹ A large overlap between apathy and depression exists, with a series of common features. However, some emotions and thoughts are more specific to depression, so their presence or absence helps to separate depression from apathy (figure 2). Clinical diagnosis of apathy should therefore be based on the presence of symptoms that cause decreased goal-directed behaviours, along with the absence of prominent depressive symptoms.

Results from many studies have shown that executive dysfunction is the most consistent neuropsychological correlate of apathy in neurodegeneration.^{11,20} The dysfunction of executive networks makes it difficult to redirect attention to novel stimuli, manipulate complex external or internal information, or generate plans for the future. These deficits lead to a decrease in cognitive interests and a state of so-called cognitive inertia, which restricts the search for or the enjoyment of previous or new interests.²

Finally, apathy might also result from auto-activation deficits, which are the result of an inability to activate oneself—ie, to spontaneously activate mental processing, without external stimulation. Auto-activation deficits prevent a patient from engaging with the external world and the *milieu intérieur* (their own internal thoughts and emotions),^{21–23} leading to a state of mental emptiness, in which the patient has “nothing to say” and “nothing matters” to them.^{22,23}

Neural substrates of apathy

The development of reward deficiency syndrome has been associated with the dysfunction of circuits implicated in reward-related learning that connect the orbitomedial and ventromedial prefrontal cortex with the amygdala and nucleus accumbens.^{24,25} This syndrome would be produced by predominant degeneration of cortical structures in frontotemporal dementia or progressive supranuclear palsy, by predominantly subcortical degeneration in Huntington’s disease, or by the denervation of ascending

mesostriatal, mesolimbic, and mesocortical dopaminergic pathways, as in Parkinson’s disease.^{26,27}

When apathy coexists with depression, reduction in motivated behaviours is associated with a dysfunctional network that is shown by hyperactivity of the subgenual cingulate cortex (BA25), and hypometabolism of both the dorsolateral prefrontal cortex and the dorsal anterior cingulate cortex (BA24b).^{28–30} With recovery from depression, metabolism in the dorsal anterior cingulate cortex is restored and goal-directed behaviours improve.^{31,32} Apathy in the context of executive dysfunction is related to decreased activity in a network that encompasses the dorsolateral prefrontal cortex, lateral aspects of the caudate nucleus and putamen, the anterior cingulate cortex, and the posterior parietal cortex.³³

Finally, auto-activation deficit has been reported in patients with bilateral lesions involving subcortical structures that disconnect the medial and lateral prefrontal cortex and the supplementary motor area from the limbic system.^{22,23,34} This connection is basically driven by the caudate nucleus and the anterior cingulate cortex,³⁵ which has a major role in regulating the expression of emotional responses and the association of emotions with complex stimuli.^{36,37}

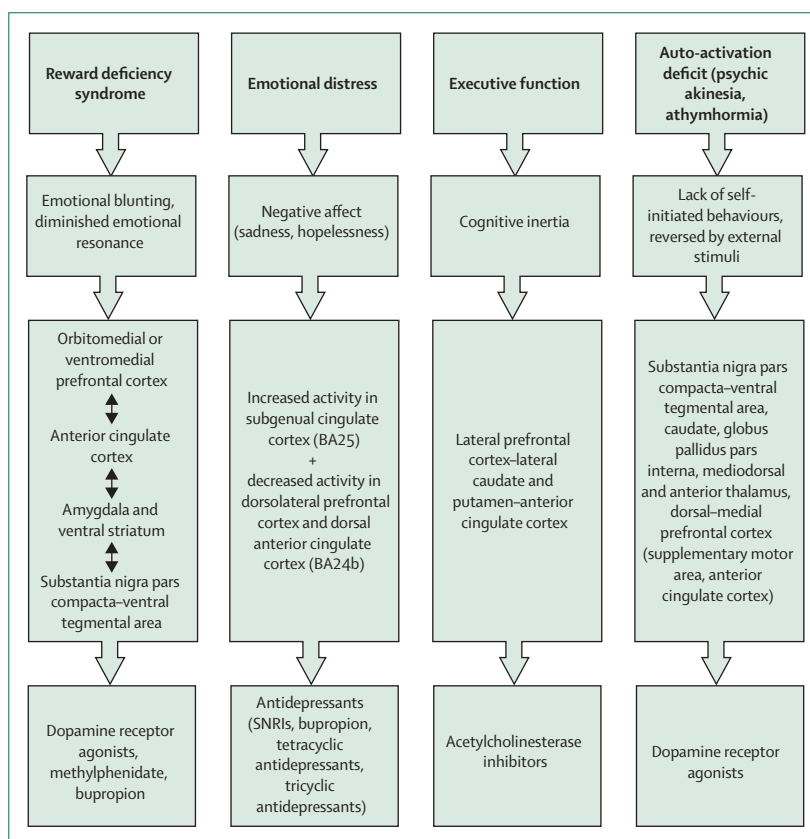


Figure 1: Apathy subdomains, neural substrates, and potential treatments

Various symptoms leading to decreased goal-directed behaviours are associated with dysfunction in different neural circuits and structures, and potentially respond to different treatment strategies. SNRI=serotonin–noradrenaline reuptake inhibitor.

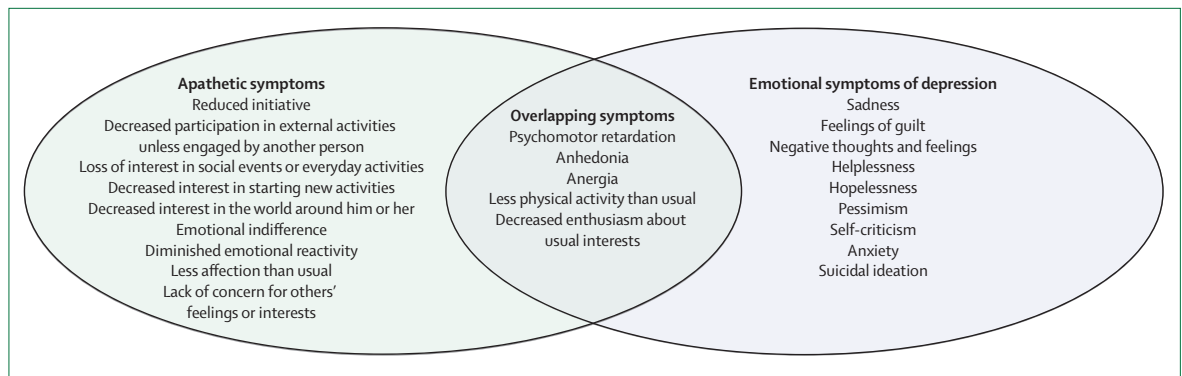


Figure 2: Differential diagnosis of apathy and depression by exclusive and overlapping symptoms

A focused clinical interview might help to distinguish apathetic symptoms (characterised by diminished activities, interests, and emotions) from the emotional symptoms of depression (characterised by the enhancement of negative thoughts, beliefs, and emotions).

Panel 1: Case study 1—apathy and depression signalling Parkinson's disease onset

A patient started to develop symptoms of Parkinson's disease at age 46 years, with a prodromal phase characterised by a complete hypodopaminergic behavioural syndrome. Fatigue had been the first and was still the main complaint. The patient had a major loss of motivation at work; he abandoned all leisure activities and was inactive, "in need of rest" each weekend. He was anxious, felt vulnerable, and had lost his self-confidence. The only motor complaints were micrographic writing and irregular steps when playing tennis. Family history was positive: his father had developed Parkinson's disease at age 79 years and his sister at age 36 years, whereas his younger brother was in good health. Genetic testing showed α -synuclein duplication. On the first examination he had mild hypomimia, mild stooped posture, and right-side akinetic-rigid syndrome. Cognition was normal. He was severely apathetic (Starkstein Apathy Scale [SAS] score 28/42) and had moderately severe depression and anxiety. After 6 months of treatment with 8 mg ropinirole, motivation had greatly improved but was not back to normal (SAS score 14/42), whereas depression and anxiety had disappeared. After 1 year on 12 mg ropinirole, the patient stated, "my motivation is back". He started to play tennis again, which had always been his passion; he enjoyed staying with his children; he was gardening and had plenty of plans for future activities. Motor evaluation showed mild improvement compared with baseline, and cognitive-behavioural evaluation was normal (SAS score 7/42).

All these neural systems are richly innervated by the mesolimbic–mesocortical pathway and its dopaminergic afferents from the substantia nigra pars compacta and the ventral tegmental area,³⁸ and by the nigrostriatal dopamine system that provides dopamine to the putamen, dorsolateral caudate nucleus, and prefrontal cortex (figure 1).^{27,39} However, serotonergic, cholinergic, and noradrenergic neurotransmitter systems are also crucial for the functionality of these circuits, interconnecting the amygdala, ventral striatum, and prefrontal cortex.⁴⁰

Despite the conceptual, scientific, and practical interest of dissecting out the different components that might underlie the development of apathetic behaviours, an important point to acknowledge is that apathy symptoms and their respective neurobiologies overlap and might be difficult to separate in clinical practice.

Apathy in Parkinson's disease

Prevalence and clinical relevance

Apathy is a frequent neuropsychiatric disturbance that can precede the onset of the first motor symptoms of Parkinson's disease (panel 1).⁴¹ Depending on the diagnostic methods used, apathy is diagnosed in 20–36% of new-onset patients who have not been treated with drugs.^{42–44} In early-stage Parkinson's disease, apathy seems to decrease after introduction of dopaminergic treatment, but its frequency increases again to 40% in patients without dementia and to 60% in patients with dementia after 5–10 years of disease.^{45–48} Apathy has been described mainly in the context of progressive cognitive deterioration in various neurodegenerative diseases, including Alzheimer's disease. Apathy has also been reported to occur as a separate and isolated behavioural symptom in Parkinson's disease.^{10,49} Cluster analyses⁴⁶ have identified subgroups of patients with Parkinson's disease with predominant or isolated apathy, representing a distinct behavioural syndrome that is associated with specific clinical and demographic correlates, neuropsychological features, and different disease progression. Specifically, patients with Parkinson's disease who have apathy are more likely to be men and to be older than patients with Parkinson's disease without apathy. Apathy in Parkinson's disease has also been related to more severe motor impairment, worse executive dysfunction, and a higher risk of developing dementia than Parkinson's disease without apathy.^{50,51} As such, apathy is a key symptom of the worsening of Parkinson's disease as the disease progresses, predictive of decreased functioning in activities of daily living,⁵² decreased response to treatment, poor outcome, and diminished quality of life,^{43,50,53} and it is a major contributor to caregiver emotional distress.⁵⁴

The multidimensional nature of apathy

Denervation deficits involving multiple neurotransmitters and heterogeneous pathological changes in different brain regions are characteristic of Parkinson's disease. Accordingly, apathy in patients with Parkinson's disease is

multidimensional and caused by dysfunction in different neural systems.^{7,55} Both dopaminergic denervation and cholinergic abnormalities affect the lateral and medial regions of the prefrontal cortex in Parkinson's disease. Degeneration of mesencephalic dopaminergic neurons at Braak stage III of the disease leads to dopamine depletion in the mesocortical and mesolimbic systems,⁵⁶ and the spread of synucleinopathy to subcortical and cortical dopamine projection areas further impairs their functionality during Braak stages IV and V.^{57,58} Delineation of the different components that can lead to apathy is crucial to the planning of therapeutic strategies.

Many studies have shown a robust association between the degree of apathy (but not depression) and the degree of executive dysfunction in Parkinson's disease.^{47,59,60} Nevertheless, when patients with Parkinson's disease are assessed using more comprehensive neuropsychological batteries, a wider spectrum of deficits appears in those with apathy compared with patients without apathy.^{10,50} Besides having more executive dysfunction, patients with apathy also show impairment in global cognitive function and in performance on cognitive tasks that are more dependent on the temporal lobes (eg, delayed verbal memory, semantic verbal fluency, and confrontation naming) than do patients without apathy.^{10,50} These findings help to explain why apathy seems to herald dementia in Parkinson's disease.⁵⁰ Furthermore, in studies that included highly selected patients with isolated apathy without concomitant depression or dementia, the syndrome also seemed to be related to facial-emotion recognition deficits, suggesting dysfunction of the mesolimbic circuits,^{61,62} but preserved performance on decision-making tasks. This latter, apparently paradoxical protective effect was suggested to be related to more widespread degeneration of the ventral tegmental area in patients with apathy. In these patients with similar dopamine deficiency in both the dorsal and ventral striatum, dopaminergic drugs would not exert an overdosing effect on limbic structures, but would lead them to a state of decreased dopaminergic stimulation.^{10,63,64}

Neurophysiological studies of the functionality of the connection between the ventral striatum and medial prefrontal cortex that have measured the feedback-related negativity wave⁶⁵ (an event-related potential associated with negative performance outcome) reinforce the role of emotional blunting in the development of isolated apathy in Parkinson's disease.⁶⁶ In patients without dementia, the amplitude of the feedback-related negativity—an event-related potential associated with performance outcome valence—was significantly reduced in those with Parkinson's disease and isolated apathy compared with those without apathy and healthy controls. This finding suggests that apathy in this subset of patients results from impaired incentive processing and a compromised mesocorticolimbic pathway.⁶⁶

The multidimensional nature of apathy in Parkinson's disease is also clearly evidenced in studies^{6,7,67,68} that have

comprehensively assessed the presence of depression, apathy, anhedonia, and cognition in patients without dementia. Anhedonia seems to be common to both apathy and depression, making it useless for differential diagnosis in clinical practice.^{6,7} Conversely, whereas apathy seems specifically related to blunted affect, decreased intellectual curiosity, and executive dysfunction, depression seems to be linked to the presence of sadness, dysphoria, negative emotions, and increased anxiety (figure 2).^{6,7} As with apathy, anxiety can also appear in isolation without depression. Anxiety itself can lead to avoidance, which also negatively affects goal-directed behaviour.

The use of specific rating instruments for each one of these subdomains^{69–71} might help to disentangle at a single-patient level the different aspects contributing to decreased goal-directed behaviours.

Lesions and neuroimaging

Anatomical and imaging reports have provided evidence that network abnormalities within the prefrontal cortex–striatal circuit can lead to apathetic behaviour.^{2,3} Apathy has been described in association with focal lesions of the prefrontal cortex,⁷² caudate nucleus, internal globus pallidus, and medial–dorsal thalamic nuclei,^{73,74} and is also a common clinical feature reported in association with several neurodegenerative diseases, including Parkinson's disease,⁷⁵ Alzheimer's disease, frontotemporal dementia,⁷⁶ Huntington's disease,⁷⁷ and progressive supranuclear palsy.⁷⁸

Classically, apathy is the result of a disruption of emotional-affective mechanisms linked to the ventromedial prefrontal cortex, amygdala, and ventral striatum³ (figure 3) and frequently reported in patients with the behavioural variant of frontotemporal dementia.⁷⁶ In these patients, imaging studies⁷⁶ have shown that severity of apathy is related to orbitofrontal cortex abnormalities with grey matter atrophy in the dorsal anterior cingulate cortex and dorsolateral prefrontal cortex. In Alzheimer's disease, the degree of apathy severity has been linked to neurofibrillary tangles and volume loss in the medial prefrontal cortex, including the anterior cingulate cortex.⁷⁶ Accordingly, other functional imaging studies^{79–82} have shown an association between apathy and hypometabolism in the medial orbitofrontal cortex and anterior cingulate cortex.

Of particular interest are neuroimaging reports in Parkinson's disease of a dysfunction of dopaminergic transmission in the mesocorticolimbic pathway that might underlie apathetic behaviour. In this regard, PET studies⁸³ with the dopamine D2 and D3 receptor antagonist [¹¹C]raclopride have shown several differences in dopaminergic binding and transmission between patients with Parkinson's disease with apathy and those without apathy. Notably, [¹¹C]raclopride binding potential was increased in the orbitofrontal cortex, cingulate cortex, dorsolateral prefrontal cortex, amygdala, and

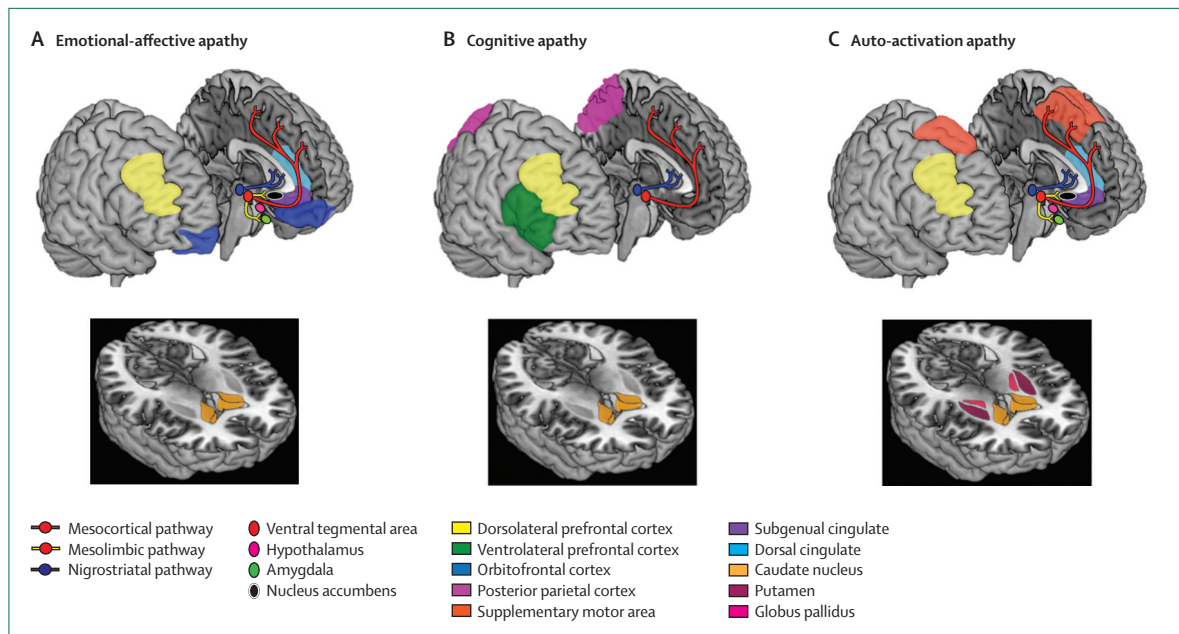


Figure 3: Neural networks subserving different apathetic syndromes

The upper set of images show the cortical regions and ascending nigrostriatal (blue), mesolimbic (yellow), and mesocortical (red) dopaminergic pathways associated with the emotional-affective, cognitive, and auto-activation subdomains of apathy. The lower set of images show the subcortical basal ganglia regions associated with each subdomain of apathy. Clinically relevant apathy is typically associated with bilateral dysfunction. Dorsolateral prefrontal cortex–caudate circuits are key structures implicated in any form of apathy. Orbitofrontal and subgenual cingulate dysfunction contribute to emotional-affective symptoms (A). Ventrolateral prefrontal cortex and posterior parietal dysfunction is involved in cognitive apathy (B). Supplementary motor or diffuse basal ganglia dysfunction, comprising bilateral caudate–putamen or pallidum, are reported in apathy with prominent auto-activation deficit (C).

striatum in patients with apathy, implying either a reactive increase in D2 and D3 receptor expression or a reduction in endogenous synaptic dopamine, or both. Furthermore, methylphenidate challenge led to a smaller reduction in [^{11}C]raclopride binding potential in patients with apathy than in those without apathy, providing evidence for reduced capacity for endogenous dopamine release in the mesocorticolimbic system of patients with apathy. Additional PET studies⁸⁴ with [^{11}C]RTI-32, a ligand with affinity for both dopamine and noradrenaline transporters, showed that the degree of apathy severity was inversely associated with [^{11}C]RTI-32 binding in the ventral striatum in patients with Parkinson's disease. In a recent study⁸⁵ exploring risk factors associated with apathy after deep brain stimulation of the subthalamic nucleus (STN-DBS), increased apathy was only related to reduced preoperative metabolism within the right ventral striatum, as assessed with ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET 3 months before surgery. Overall, these neuroimaging studies⁸⁶ suggest that apathy in Parkinson's disease might result from a severe dopamine depletion state in the mesocorticolimbic system, leading to impaired emotional reactivity and poor decision-making processes.

Behavioural and imaging abnormalities in the same cortical regions involving the mesocorticolimbic system have also been recorded with excess dopaminergic stimulation, which results in behavioural addictions.^{87–89}

These findings provide evidence of a behavioural spectrum disorder, ranging from a hyperdopaminergic syndrome (including impulse control disorders) to hypodopaminergic levels associated with apathy, anxiety, and depression, as described in the withdrawal dopaminergic syndromes.^{83,90–93}

Besides the emotional-affective syndrome, apathy might also be associated with a disruption of cognitive functions. This form of apathy is generally associated with an impairment in those executive functions (selection, planning, working memory, and set-shifting) needed to elaborate an action plan. This cognitive apathy might result from brain lesions affecting either the lateral (ie, dorsolateral and ventrolateral) prefrontal cortex or the caudate nucleus.² Several functional imaging studies^{94,95} in patients with Parkinson's disease without dementia have supported this hypothesis, showing that these patients can present with abnormal activation at the level of the dorsolateral or ventrolateral prefrontal cortex and caudate nucleus during executive tasks. Results from glucose metabolism studies^{96–98} with ^{18}F -FDG PET in Parkinson's disease have shown that apathy severity is associated with metabolic activity in different cognitive regions, including the inferior medial frontal gyrus, cingulate cortex, insula, cuneus, and temporoparietal region.

In the severe form of apathy in which the auto-activation subdomain is predominantly impaired, the combined effect of lesions of the basal ganglia, thalamus,

and cortex on the dorsal–medial prefrontal cortex (ie, supplementary motor area and anterior cingulate cortex) generally results in dysfunction of both cognitive and emotional neural networks.²

Apathy after deep brain stimulation in Parkinson's disease

Postoperative apathy is a frequent observation after STN-DBS in Parkinson's disease.^{9,99,100} The context in which apathy occurs is crucial to an understanding of underlying mechanisms. A long-term follow-up study¹⁰¹ showed frequent early but transient apathy occurring in patients in the first postoperative months. In a small proportion of patients followed up over 5 years, permanent apathy developed in parallel with worsening of dysexecutive syndrome and appearance of dementia. This early postoperative apathy does not occur in all patients. It is potentially reversible and both occurrence and improvement depend on patient management.^{92,102} Panel 2 describes the clinical features of early reversible postoperative apathy.

In a 2013 randomised study¹⁰³ comparing STN-DBS to best medical treatment in Parkinson's disease, the frequency of apathy did not differ during the 2 years of follow-up, showing absence of early postoperative apathy when STN-DBS is accompanied by optimised medical treatment. The highest reported frequency of new-onset apathy during the first year after STN-DBS was 50% of the patients.⁸³ This unusually high rate appeared in the context of a study⁸³ addressing the mechanisms of postoperative apathy. The increased incidence of apathy can be explained by a deviation from the recommended and usual postoperative management.¹⁰² All patients were completely withdrawn from dopamine agonists immediately after surgery and levodopa was greatly reduced to the minimally required dose, with a parallel increase in stimulation parameters.⁹¹ Half of the patients developed apathy in the course of the first year of follow-up, and half of those also developed depression at the same time. The full dopamine withdrawal syndrome consisted of a triad of apathy, anxiety, and depression, with apathy being the most common symptom.

By contrast with the rapid onset of the syndrome seen after withdrawal of dopamine agonists in non-operated patients with impulse control disorders,⁹³ apathy was reported to occur with a mean delay of 4–5 months in the patients who had had surgery. This withdrawal syndrome with predominant apathy occurring after a combination of successful STN-DBS-related motor improvement and a substantial decrease in dopaminergic treatment was associated with diffuse mesolimbic and mesocortical dopaminergic denervation.⁸³ Targeting of the sensorimotor subthalamic territory with DBS to improve off-period akinesia does not prevent diffusion of current to parts of the non-motor associative and limbic subthalamic territories. STN-DBS itself has a positive effect on off-period apathy, contributing to improvement of off-period

cognitive and emotional aspects in apathy.^{92,104–106} However, with regard to the on-period motivational aspects of the antiparkinsonian drugs, a slowly progressive desensitisation of the psychotropic effects of dopaminergic treatment after drug decrease¹⁰⁷ explains why the hypodopaminergic withdrawal syndrome in patients on chronic STN-DBS typically occurs with a substantial delay of several months after surgery^{83,92} (unlike the much more acute withdrawal syndrome after cessation of dopamine agonists in patients not receiving chronic STN-DBS).⁹³

The potential to reverse postoperative apathy after D2 or D3 receptor stimulation with oral dopamine receptor agonists^{108,109} clearly suggests a Parkinson's disease-related symptom that has been unmasked by a decrease in drug treatment. That is, postoperative apathy is not induced by current diffusion to non-motor territories of the subthalamic nucleus, as had been postulated in the absence of an association between reduction in drug treatment and occurrence of apathy.¹⁰⁰ The only predictive factor for occurrence of apathy during the first year after surgery is the presence of preoperative non-motor fluctuations. Furthermore, imaging has confirmed increased mesocorticolimbic denervation in postoperative patients with apathy.⁸³ Apathy, most often expressed as “fatigue” by the patient, is part of the non-motor off-period in patients with non-motor fluctuations. Taken together, this evidence implies that a more severe mesolimbic and mesocortical dopaminergic denervation translates into non-motor fluctuations with dopaminergic treatment in the same way that the severity of motor fluctuations depends on nigrostriatal dopaminergic denervation.¹¹⁰

Long-term, treatment-resistant postoperative apathy tends to develop in association with levodopa-resistant frontal dysexecutive syndrome, and can be explained by diffuse cortical synucleinopathy^{2,10,50,56,111,112} rather than by STN-DBS on its own. Although dementia might be a part of Parkinson's disease progression,^{113,114} in the young and largely cognitively preserved populations of patients with Parkinson's disease who are generally selected for deep brain stimulation, overall cognition, including frontal dysexecutive syndrome, is relatively stable^{115,116} in the first years after STN-DBS, although in a small proportion of patients, surgery itself can induce cognitive deterioration.¹¹⁷ Surgical treatment of Parkinson's disease has given rise to a new phenotype of patients with advanced Parkinson's disease who have little akinesia, no tremor or rigidity, and little dyskinesia, and are mainly disabled by frontal dementia, apathy, and levodopa-resistant axial motor features.¹¹⁸

Different mechanisms might therefore underlie early and potentially reversible postoperative apathy and more tardive non-reversible apathy. Whereas the early and potentially reversible form of apathy occurs in the context of withdrawal of dopaminergic drugs, the tardive non-reversible form seems more related to cognitive deterioration and progression of synucleinopathy, which is transmitted by projection neurons to their target

Panel 2: Case study 2—isolated postoperative apathy with auto-activation deficit

A patient aged 57 years had been operated for severe disabling Parkinson's disease with onset at age 40 years. He had given up his job 4 years previously because of severe motor fluctuations with inability to walk in the off-state. For the past 2 years, he had been unable to leave his home because of sudden-onset disabling off-periods. He stayed busy at home though, helping with the computer system of his wife's business and mending computers as a hobby. The patient had a marked response to levodopa (Unified Parkinson's Disease Rating Scale motor score changing from 80/108 in off-drug to 20/108 in on-drug conditions). Cognitive assessment was normal. Preoperative drugs consisted of 1500 mg levodopa and 4 mg pramipexole. After surgery, on bilateral subthalamic stimulation using standard parameters, his motor state improved rapidly with disappearance of his severe off-drug parkinsonism. The patient had become fully autonomous and dopaminergic treatment could be stopped altogether. After 5 months, the patient had progressively diminished his activities, triggering unsuccessful trials of antidepressive treatment with citalopram, and then again with mirtazapine. When the patient came back to the surgical centre, stimulation parameters and his motor state had remained stable and he was still without dopaminergic treatment. However, he had developed a severe isolated apathy (Starkstein Apathy Scale score 36/42) without depression (Beck Depression Inventory 15/63) or anxiety. The following is from a videotaped discussion with the patient and his wife:

Question: "What were the things you liked to do before surgery?"

Patient: "I liked to play with computers, build computers. I spent a lot of time even though it was very frustrating as I was shaking a lot."

Question: "And presently?"

Patient: "Not at all. I haven't got any motivation to do it."

Question (referring to the single levodopa dose that the patient received for a levodopa test): "What happened when you took your levodopa yesterday?"

Patient: "When I took the levodopa yesterday, my brain cleared, and I was able to start reading a book I had been meaning to read for a long time, but I just couldn't get the interest up."

Question: "What about your daily activities? You need to be pushed?"

Patient: "Yes, my wife pushes me all the time."

Wife: "If I don't insist on him taking a shower in the morning, he won't take it and will not get dressed...he will just walk around in his pyjamas."

Question: "So, you have to push him?"

Wife: "I try not to."

Question: "Could you describe his behaviour working with computers?"

Wife: "He was like a conductor of an orchestra with the computer. All the computers [that] wouldn't work, he would take them apart into little pieces and rebuild again, and then they worked again. And he did that right up to just before surgery. It took him longer, but he still did it. It would take a long time, and he would struggle with his tremor to get the bits in or call me to help him, but he would do it. Now he doesn't have any interest to open a computer."

Question: "For lack of interest?"

Wife: "No interest at all. Completely."

Question: "Not related to the shaking or the lack of dexterity?"

Wife: "No, he doesn't shake any more. Physically everything has improved a million times. This makes it also difficult to be the caregiver, because you don't understand. He got everything but he is not making the most of it."

Question: "And that tends to upset you?"

Wife: "Oh yes!"

The patient was put back on his preoperative dose of the dopamine agonist drug pramipexole and 3 months later sent an email reporting that he had enjoyed travelling to the Antarctic, which he had dreamt of for years. "I am pleased to report that with the changes in medication, the depression I suffered with disappeared very quickly. Now, I manage to help my wife again with her work and set up a computer from its basic components."

neurons.⁵⁸ The isolated postoperative apathy that occurs with chronic STN-DBS during the first postoperative year in relatively young levodopa-sensitive patients with Parkinson's disease, with predominant degeneration of midbrain dopaminergic neurons in the substantia nigra and ventral tegmental area (but without much cortical synucleinopathy), can be seen as a model of fairly pure dopamine-dependent apathy. This model points to the importance of dopamine in both cognitive and emotional aspects of motivated human behaviour and provides a rationale for dopaminergic treatment in the management of apathy in Parkinson's disease without dementia. Modulation of the mesocorticolimbic networks by dopaminergic drugs (especially dopamine D2 and D3 receptor agonists) with relatively high affinity for the

mesolimbic system¹¹⁹ is also implicated in the appetitive drive to perform pleasurable activities (eg, creativity or hobbies),^{120,121} which can lead (at extreme levels) to behavioural addictions and impulse control disorders.^{88,89,122} Decrease of dopaminergic agonists in the context of STN-DBS, or a switch to non-pulsatile treatment with levodopa, results in disappearance of the increased drive for artistic creativity^{120,121} and the emergence of severe apathy.¹²⁰ This process can at least partly be reversed after a careful titration of the dose of the dopamine agonist.¹²⁰ Prospective systematic assessment⁹¹ of behaviours before and after STN-DBS in Parkinson's disease has shown that these observations apply not only to creativity and hobbies, but also to the full range of motivated human behaviours.

Diagnosis of apathy in Parkinson's disease

Reported frequencies of apathy range from 15% to 70% in studies of Parkinson's disease.^{46,47,49,60} These differences seem to depend on disease severity and on the diagnostic approach used—ie, whether the diagnosis was established according to cutoff scores on rating scales, instruments rated by caregivers, or clinical diagnostic criteria. Accurate diagnosis is difficult in view of the multidimensional and subjective nature of apathy, as is the development of instruments or criteria that are operative enough to be generalisable between physicians and research groups.

The development of specific scales for apathy has been one of the most important advances in recognition of this issue, both in clinical practice and in research. A task force commissioned by the International Parkinson and Movement Disorder Society reviewed the clinimetric properties of apathy in Parkinson's disease samples.⁶⁹ On the basis of the use of available scales in research studies, use beyond original developers (ie, by research groups different from those who designed and validated the scale), successful clinimetric properties, and existence of cutoff scores for screening apathy in Parkinson's disease, only the Starkstein Apathy Scale (SAS)⁶⁰ was classified as "recommended" by the task force. Although the Unified Parkinson's Disease Rating Scale (UPDRS) apathy item also met criteria to be classified as recommended, the task force concluded that the UPDRS should be considered for screening purposes only. Scales that met criteria to be classified but were not recommended were the Apathy Evaluation Scale,¹ the Lille Apathy Rating Scale (LARS),¹²³ and item 7 in the Neuropsychiatric Inventory.¹²⁴ The LARS has since been used in Parkinson's disease by research groups different from those who designed and validated the scale,¹²⁵ so this scale would now meet criteria for recommendation. The LARS, based on Marin's original conceptualisation,¹ provides an overall apathy score and four composite subscores that assess relevant subdimensions of apathy: intellectual curiosity, action initiation, emotion, and self-awareness.

Overall, the task force deemed that the absence of widely accepted diagnostic criteria for apathy hampers the development of valid assessment scales—a major barrier to the study of apathy across different neuropsychiatric disorders, and its relation to depression and dementia.⁶⁹ As evidence is now emerging that some forms of pharmacotherapy could be beneficial for motivational symptoms, widely accepted criteria would also be crucial for the registration of new drugs for the specific treatment of apathy.⁶⁹

With regard to diagnostic criteria, only two studies have published formal validations of clinical criteria specific to Parkinson's disease¹²⁶ or criteria applicable to Alzheimer's disease and other neuropsychiatric disorders.^{127,128} Specific clinical criteria for apathy in Parkinson's disease proposed by Starkstein and colleagues¹²⁶ are based on diminished motivation relative to

the patient's previous level of motivation, and require the presence of at least one symptom belonging to each of the following domains: diminished goal-directed behaviour, diminished goal-directed cognition, or diminished emotional response to positive or negative events. In a sample of 164 patients with Parkinson's disease, 53 (32%) met criteria for apathy. In view of the demographic and clinical features of this sample—a mean age of 68 years, mean Mini Mental State Examination of 24·2, and 87 (53%) of 164 patients with a Hoehn and Yahr score of III or more—this frequency seems lower than expected, which could be ascribed to the restrictive requirement of the patient needing to present at least one symptom from each domain.

Robert and colleagues¹²⁸ proposed diagnostic criteria for apathy to be applied in Alzheimer's disease and other neuropsychiatric disorders.¹²⁸ The authors also proposed three symptomatic domains that cover behavioural, cognitive, and emotional aspects of apathy, but are less restrictive for the final diagnosis of apathy (at least one symptom from two of these three domains). When these criteria were applied in a sample of 122 patients with Parkinson's disease, frequency was also low. In a sample with a mean age of 64·0 years and 8·5 years of disease duration, the frequency of apathy was 17% (21 of 122), also lower than expected compared with the frequency of apathetic symptoms in similar samples that used less restrictive scales, such as the Neuropsychiatric Inventory and the Non-Motor Symptoms Scale.^{43,46,129}

Although previous diagnostic criteria^{127,128} cover the most important subdimensions of apathy, the abstract nature of the items included might restrict their application in daily clinical practice. An additional limitation is the lack of items that relate apathetic symptoms to their possible cause: reward deficiency syndrome, depression or emotional distress, or cognitive impairment.

To overcome these limitations, we propose less restrictive and clinically more operative criteria for the diagnosis of apathy, based on a checklist of symptoms directly related to diminished motivation, irrespective of its cause. If the patient manifests apathetic symptoms, two additional checklists of symptoms could suggest an association of diminished motivation with (1) sadness and emotional symptoms of depression, or (2) symptoms suggestive of cognitive impairment. When depressive and cognitive symptoms are absent, a diagnosis of apathy associated with reward deficiency syndrome could be established (panel 3).

Treatment of apathy in Parkinson's disease

Pharmacological interventions with cholinesterase inhibitors, dopaminergic drugs (including methylphenidate), and antidepressants have been investigated to improve apathy in Parkinson's disease. To test the efficacy of pharmacological interventions in Parkinson's

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Panel 3: Proposed clinical diagnostic criteria for apathy

The following proposed criteria represent the views of the authors. They are intended to guide clinicians in making a diagnosis of apathy and in identifying appropriate treatments. Previous diagnostic criteria for apathy have been published.^{127,128} If a patient satisfies the criteria for A only, a diagnosis of isolated apathy (apathy associated with reward deficiency syndrome) is established. If the patient satisfies criteria for A plus B, a diagnosis of apathy associated with depression is established. If the patient satisfies criteria for A plus C, a diagnosis of apathy associated with cognitive impairment is established.

A Apathy

Three or more of the following symptoms, present for most of the time for a period of at least 4 weeks. Symptoms must have an effect on activities of daily living (personal, social, occupational):

- Reduced initiative, with observable decrease in self-generated activities or interests.
- Decrease in spontaneous or environment-induced ideas or curiosity.
- Difficulty maintaining self-initiated purposeful behaviours, or activities initiated by external stimulation (other people, external events).
- Difficulty engaging or participating in cognitively demanding situations.
- Blunted affect or emotional indifference, with reduced emotional responsiveness or reactivity to positive or negative events.
- Decrease in affectionate behaviour.
- Lack of concern about personal problems.

If the patient satisfies criteria for a diagnosis of apathy, the presence of depressive or cognitive symptoms will help to identify the underlying mechanism of apathetic symptoms.

B Apathy associated with depression (A plus B)

Three or more of the following symptoms, present for most of the time for a period of at least 4 weeks. Symptoms must cause clinically significant impairment:

- Sadness.
- Feelings of guilt.
- Negative thoughts and feelings towards self or others.
- Helplessness.
- Hopelessness or pessimism.
- Self-criticism and negative thoughts about the future.
- Suicidal ideation.

C Apathy associated with cognitive impairment (A plus C)

Three or more of the following symptoms, present most of the time for a period of at least 4 weeks. Symptoms must cause clinically significant impairment:

- Difficulty managing money.
- Difficulty planning or organising daily activities, or keeping track of bills, mail, or appointments.
- Difficulty knowing the day, month, or year.
- Recent memory impairment (eg, forgetting recent episodic verbal or visual information, or difficulty remembering recently learned information).
- Difficulty following a conversation among several people.
- Difficulty understanding or remembering what is read (eg, in books, magazines, or newspapers).
- Difficulty maintaining attention or concentration.

Exclusion criteria

The symptoms of apathy are better explained by diminished level of consciousness, physical disability (eg, loss of sight or hearing), motor disability, or the direct physiological effects of a substance (eg, a drug of abuse or a medication).

disease, two randomised trials with apathy as the primary outcome have been done. In a double-blind, placebo-controlled study¹³⁰ of 31 patients with Parkinson's disease with moderate to severe apathy without dementia and depression, a significant improvement in the LARS was reported after 6 months of treatment with rivastigmine at 9.5 mg/day (adjusted effect size -0.9 ; $p=0.031$) (Level B, one Class I study according to evidence based medicine assessment).

An exploratory study¹⁰⁹ showed that the dopamine D2 and D3 receptor agonist piribedil significantly improved apathy as assessed using the SAS score (>14) in 37 patients with Parkinson's disease presenting apathy after STN-DBS. In this 12 week prospective, placebo-controlled, randomised, double-blinded trial,¹⁰⁹ the SAS score was reduced by 34.6% in the piribedil group ($n=19$) compared with 3.2% in the placebo group ($n=18$; $p=0.015$) (Level B, one Class I study). In an open-label study,¹⁰⁸ the dopamine D2 and D3 receptor agonist ropinirole proved to be efficacious in eight patients with apathy after STN-DBS, as shown by substantial decreases

in SAS scores after 6 months of treatment. The average score on the SAS decreased from 21.4 (SD 4.0) to 9.9 (SD 6.1) after ropinirole—ie, an improvement of 54% (SD 24%; range 0–78%). Also in open-label studies,^{87,131} and using non-specific scales for apathy, pramipexole and rotigotine have led to significant improvements in the UPDRS-I motivational items ($p<0.001$) and the Non-Motor Symptoms Scale ($p=0.0003$) (Level C, one Class II and two Class III studies).

Improvement of parkinsonian apathy with the dopaminergic drug methylphenidate has been reported in early Parkinson's disease in a case report¹³² (Level U). In another study,¹³³ administration of high doses of methylphenidate for 3 months was associated with significant reductions in apathy ($p=0.03$), measured using the LARS, in a subgroup of seven patients with advanced-stage Parkinson's disease undergoing STN-DBS. The study,¹³³ however, was not specifically designed to assess apathy (Level U). These few findings in Parkinson's disease are in line with double-blind, placebo-controlled studies^{134–136} in Alzheimer's disease

that have shown mild but significant improvement of apathy and attention with methylphenidate 20 mg/day. Methylphenidate is known to enhance mesolimbic dopaminergic stimulation by inhibition of the dopamine transporter. In the pre-levodopa era, intravenous and oral administration of methylphenidate produced a lightening of mood and euphoria in patients with Parkinson's disease.¹³⁷ In this randomised crossover trial,¹³⁷ 6 of 12 patients were reported to feel better with methylphenidate treatment. These beneficial effects were not derived from improvement in parkinsonian motor features, but from a subjective increase in energy and improvement in their mood.¹³⁷ Notably, patients with Parkinson's disease with major depression showed less sensitivity to the euphoric effects of methylphenidate than did those with Parkinson's disease without major depression or healthy controls.¹³⁸

The use of antidepressants for apathy in Parkinson's disease is controversial. Single cases^{9,139} of postoperative parkinsonian apathy after STN-DBS have been reported to be resistant to antidepressive treatment with selective serotonin reuptake inhibitors, combined serotonin–noradrenaline reuptake inhibitors, or amitriptyline, but responsive to dopaminergic treatment. In non-operated patients, selective serotonin reuptake inhibitors have even been reported to increase apathy in Parkinson's disease,¹⁴⁰ and in elderly people with depression,¹⁴¹ whereas the noradrenaline–dopamine reuptake inhibitor bupropion was reported to improve motivation¹⁴² (Level U).

Apathy in the wider context of neurodegenerative diseases

Apathy is recognised at present as one of the most prevalent neuropsychiatric symptoms in various neurodegenerative diseases. In Alzheimer's disease, apathy is present in 20–25% of patients in the early stages, with up to 80% of patients developing it during the course of the disease.^{78,143,144} Prevalence of apathy is substantially higher in neurodegenerative diseases with more prominent involvement of the prefrontal cortex and caudate nuclei: it is present in 60–90% of patients with progressive supranuclear palsy, 75–95% of patients with frontotemporal dementia, and 55–90% of patients with Huntington's disease.^{145–148} In these diseases, apathy is one of the first neuropsychiatric symptoms to appear, is predictive of disease onset,^{149,150} and is more clearly distinguished from depression than it is in Parkinson's disease.^{151–153}

A consideration of the multidimensional nature of apathy, as presented in this Review, would be useful in understanding the major components of apathy in each of these neurodegenerative diseases. Is apathy in Alzheimer's disease related more to global cognitive deterioration? Is apathy in Huntington's disease or frontotemporal dementia associated mainly with emotional indifference? Is apathy in progressive supranuclear palsy linked to auto-activation deficits?

Finding answers to these questions would help to establish the neurobiological bases of apathy in these disorders and could guide an individualised approach to treatment.

Conclusions and future directions

A range of cognitive and emotional disturbances might lead to impairments of human motivation and decreased self-generated purposeful behaviours. The normal maintenance of spontaneous mental activity, the capacity to associate emotions with complex stimuli, and the adequate expression of these emotions depends on the integrity of cortical and subcortical structures that link the medial and lateral prefrontal cortex with the limbic system. Selective lesions of these structures, including the amygdala and the ventral striatum and its main connection through the anterior cingulate cortex, have been associated with the acute appearance of severe auto-activation deficits. These descriptions have led to the present clinical idea of apathy as a behavioural disorder with reduced motivation, manifesting as a decrease in goal-oriented behaviours with both cognitive and emotional aspects.¹² Neuroimaging studies in neurodegenerative diseases have linked the state of cognitive inertia, characteristic of apathy, to decreased activity in a network that encompasses the dorsolateral prefrontal cortex, lateral aspects of the caudate nucleus and putamen, anterior cingulate cortex, and posterior parietal cortex.^{33,79–82}

We have focused on Parkinson's disease as a model to study motivated behaviours, in which the symptoms of apathy are associated with deficits in dopaminergic innervation from the mesolimbic and mesocortical pathways. Patients with Parkinson's disease who are exposed to non-physiological dopaminergic stimulation are at high risk of developing a range of behavioural addictions or impulse control disorders.^{88,89,91,122,154} By contrast, patients are at risk of developing apathy—an

Search strategy and selection criteria

We comprehensively searched PubMed for papers published in English between Jan 1, 1970, and Dec 31, 2014, with the general search term "apathy", combined with more specific search terms related to other motivational symptoms, including "abulia", "akinetic-mutism", "bradyphrenia", "auto-activation deficit", "athymhormia", "akinesia", and terms related to the key components of this Review, including "neurodegenerative", "Parkinson's disease", "imaging", "deep brain stimulation", "depression", "acetylcholinesterase", "dopamine agonist", and "methylphenidate". We checked references from identified papers and included them if they were deemed to be appropriate, relevant, and scientifically important. We considered articles in other languages if cited in a selected English language paper. We also searched references from our own files.

opposite motivational state—in untreated de-novo Parkinson's disease,¹⁵⁵ in more advanced stages of Parkinson's disease during non-motor off-periods,^{91,92} in parallel with progressive cognitive deterioration, or in the context of a rapid decrease in dopaminergic drugs after deep brain stimulation, leading to a hypodopaminergic withdrawal syndrome or Parkinson's disease-related apathy.^{83,90,91,93} Impairments of motivation therefore appear in Parkinson's disease as a continuum of abnormal behaviours that range from the syndrome of apathy to impulse control disorders and other behavioural addictions.

Two double-blind, placebo-controlled studies^{109,130} have shown promising results with drugs that either enhance acetylcholine (rivastigmine) or stimulate dopamine D2 or D3 receptors (piribedil) for the treatment of apathy in patients with Parkinson's disease without dementia and depression. Preliminary results suggest that methylphenidate (which reinforces mesocorticolimbic stimulation by selective inhibition of mesocorticolimbic dopamine reuptake) might be a useful drug to reduce apathy in Parkinson's disease and Alzheimer's disease.^{133,134} Antidepressants have been investigated in studies of neurodegenerative disorders that were either open label or in which apathy was not the main outcome variable, so further studies are needed. Altogether, good rationale exists for the use of dopaminergic drugs to improve the emotional and behavioural aspects of motivation, and for cholinesterase inhibitors to treat the cognitive aspects of apathy.^{156,157}

Contributors

JP, JK, APS, and PK prepared the first draft of the text, tables, and figures, contributed to the discussion, and critically edited the Review.

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The authors declare no competing interests with respect to the content of this Review. JP has received honoraria for lecturing or consultation from Boehringer Ingelheim, UCB, Allergan, Ipsen, and Lundbeck. JK has received honoraria for lecturing or consultation from the Michael J Fox Foundation, Merck Serono, AbbVie, Boehringer Ingelheim, UCB, Zambon, MSD, Italfarmaco, General Electric, and Lundbeck. PK has received research support from Orkyn, Novartis, UCB, Medtronic, LVL, Boston Scientific, and St Jude, and honoraria for lecturing or consultation from the Movement Disorder Society, Lundbeck, Boehringer Ingelheim, Novartis, UCB, Medtronic, Orkyn, Abbott, Orion, TEVA, and Boston Scientific. APS declares no competing interests.

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