

The significant health burden that apathy creates for patients with Parkinson's disease is revealed in the following article by Muhammed and Husain; also highlighted are the difficulties of a therapeutic approach towards tackling a lack of motivation. This is an important issue for clinical neurologists who must be careful not to mistake the characteristics of apathy with those that emerge from neurodegenerative disease, while also tackling its many other diagnostic challenges. Meanwhile, no gold standards have been agreed upon for treatment and caution must be advised to those tasked with treating this poorly understood yet common neuropsychiatric syndrome. This paper explores these themes.

CLINICAL SIGNIFICANCE OF APATHY IN PARKINSON'S DISEASE

Kinan Muhammed, *Masud Husain

Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

**Correspondence to masud.husain@ndcn.ox.ac.uk*

Disclosure: The authors have declared no conflicts of interest.

Received: 14.12.15 **Accepted:** 20.04.16

Citation: EMJ Neurol. 2016;4[1]:56-63.

ABSTRACT

Apathy, or lack of motivation, is increasingly recognised as a major factor affecting quality of life and prognosis in Parkinson's disease (PD). Impacting every stage of the disease, including *de novo* cases, reports have suggested it can affect up to 70% of patients. Despite the pervasiveness of apathy in PD, challenges remain in its detection, clinical assessment, and treatment. Strong overlap with depression and anhedonia can complicate diagnosis, and although common features exist between all of these neuropsychiatric conditions, dissociations may be suggestive of different underlying brain mechanisms. Several lines of evidence have implicated frontostriatal reward and effort-related neural pathways in the genesis of apathy, but the precise processes remain to be fully elucidated. The mainstay of current approaches in the treatment of apathy rely on dopamine replacement, although there is growing evidence that support a potential role for other agents. This paper reviews the current understanding of this important non-motor complication of PD.

Keywords: Apathy, Parkinson's disease (PD), depression, anhedonia, clinical significance, diagnosis, prognosis, mechanisms, treatment, quality of life.

INTRODUCTION

Apathy is a common neuropsychiatric syndrome often characterised by lack of motivation, and is gaining appreciation as a major problem in Parkinson's disease (PD).¹ Its importance has become more apparent over the past two decades as awareness of its clinical impact in

many different neurodegenerative disorders has grown.² As well as being a debilitating non-motor symptom, apathy also poses a significant health burden for patients and their caregivers. It is associated with several adverse outcomes and reduced quality of life,³ yet its underlying mechanisms are poorly understood. This is further complicated by the overlap between apathy and

other neuropsychiatric illnesses, such as depression and anhedonia, which often occur concurrently.⁴ This review will discuss the clinical significance of apathy in PD, focussing on its clinical impact, differentiation from other neuropsychiatric disorders, and potential treatment options. Possible mechanisms of apathy, which may help combat the aforementioned diagnostic challenges, will also be suggested.

EPIDEMIOLOGY

The reported prevalence of apathy in PD ranges from 7–70%.^{5,6} This large variability is a result of the assessment tools used, and also likely reflects the heterogeneity of the PD population. On average ~40% of PD cases,¹ and up to one-quarter of newly diagnosed drug-naïve patients,⁷ are affected. Dividing PD patients further into phenotypic subgroups demonstrates that both tremor-dominant and akinetic-rigid variants of PD suffer

from apathy. The rates however are not equal; akinetic-rigid phenotypes are more strongly affected⁸ and the addition of apathy contributes to poorer patient outcomes normally observed in this subpopulation. Age is also an associated factor: patients with apathy tend to be older,¹ and those given a PD diagnosis at an older age may also have an increased risk of developing the disorder.⁵ Other demographic differences such as gender, disease duration, and Hoehn and Yahr score do not seem to have a definite association, but increased motor-symptom severity is related.¹ Similarly, PD cases with more advanced motor disease progression at 4-year follow-up are also more likely to develop the condition.⁹ Importantly, the evidence suggests that this motor association is not a secondary psychological reaction to the physical disability, but instead is linked to neurodegeneration,¹⁰ implying distinct pathological processes in the development of apathy.

Table 1: Proposed diagnostic criteria for apathy in clinical practice in neurodegenerative disorders.¹⁵

A	Loss of or diminished motivation in comparison to the patient's previous level of functioning and which is not consistent with his/her age or culture. These changes in motivation may be reported by the patient or by the observations of others.	
B	Presence of at least one symptom in at least two of the three following domains for a period of at least 4 weeks and present most of the time.	
Domain B1 (behaviour)	Loss of, or diminished, goal-directed behaviour as evidenced by at least one of the following:	<ul style="list-style-type: none"> • Initiation symptom: loss of self-initiated behaviour (e.g. starting conversation, doing basic tasks of day-to-day living, seeking social activities, communicating choices) • Responsiveness symptom: loss of environment-stimulated behaviour (e.g. responding to conversation, participating in social activities)
Domain B2 (cognition)	Loss of, or diminished, goal-directed cognitive activity as evidenced by at least one of the following:	<ul style="list-style-type: none"> • Initiation symptom: loss of spontaneous ideas and curiosity for routine and new events (e.g. challenging tasks, recent news, social opportunities, personal/family and social affairs) • Responsiveness symptom: loss of environment-stimulated ideas and curiosity for routine and new events (e.g. in the person's residence, neighbourhood, or community)
Domain B3 (emotion)	Loss of, or diminished, emotion as evidenced by at least one of the following:	<ul style="list-style-type: none"> • Initiation symptom: loss of spontaneous emotion, observed or self-reported (e.g. subjective feeling of weak or absent emotions, or observation by others of a blunted affect) • Responsiveness symptom: loss of emotional responsiveness to positive or negative stimuli or events (e.g. observer reports of unchanging affect, or of little emotional reaction to exciting events, personal loss, serious illness, emotion-laden news)
C	These symptoms (A–B) cause clinically significant impairment in personal, social, occupational, or other important areas of functioning.	
D	The symptoms (A–B) are not exclusively explained or due to physical disabilities (e.g. blindness and loss of hearing), motor disabilities, diminished level of consciousness, or the direct physiological effects of a substance (e.g. a non-prescription drug, a medication).	

For a diagnosis of apathy, the patient should fulfil the criteria A, B, C, and D.

Adapted from Mulin et al.¹⁵

CHALLENGES IN DIAGNOSIS

There are many overlapping descriptions of apathy but no clear consensus on an exact definition or formal diagnostic criteria.¹¹ The syndrome is generally defined as a disorder of motivation with central common features. These include a reduction in goal-directed behaviour encompassing cognitive, emotional, and self-initiated motor domains. One challenge that gives rise to the difficulty in its classification is the distinction of apathy as a syndrome in itself or as a symptom of the underlying disease with which it is associated.^{12,13}

In PD, it is often difficult to recognise and distinguish between symptoms of apathy and the phenomenology of the neurodegenerative condition, as there are many features common to PD and apathetic syndromes. For example, indifference and lack of effort caused by apathy can overlap with the masked facial expression and paucity of movement observed in PD.¹⁴ The need for reliable and reproducible criteria is therefore paramount for accurate diagnosis and appropriate treatment. Diagnostic criteria of apathy in Alzheimer's disease (AD) and other neuropsychiatric disorders have been proposed but they have yet to be implemented formally in the current Diagnostic and Statistical Manual of Mental Disorders or International Classification of Disorders classification systems and there are no definite standards for diagnosing apathy specifically in PD.^{11,13,15} The criteria currently suggested for apathy are summarised in [Table 1](#).

DETECTION AND MEASUREMENT OF APATHY

A variety of clinical questionnaires have been designed to assess apathy, but no gold standard has been agreed upon for clinical practice. The Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) attempts to identify apathy in patients through a single questionnaire component, however this should only be considered for screening purposes.¹⁶ More detailed methods for the assessment of apathy in PD take the form of self-reporting clinical questionnaires and semi-structured interviews. Perhaps the most extensively used questionnaire, from a research perspective, is the Lille Apathy Rating Scale,¹⁷ which examines different subdomains and may be the most thorough assessment of apathy in PD.¹⁶

For everyday clinical practice, an abbreviated short form of the Lille Apathy Rating Scale¹⁸ has shown reliability in evaluating apathy in PD; a caregiver version also exists.¹⁹ The Apathy Scale,²⁰ Apathy Evaluation Scale,²¹ and the Apathy Inventory²² have also been validated for use in PD. These instruments, when combined with other objective behavioural measures, give rise to a more accurate and better diagnosis of apathy in PD.

HOW DOES APATHY AFFECT PROGNOSIS?

Mixed opinions exist regarding the clinical impact that apathy has in PD,²³ but overwhelming evidence points towards a negative prognosis. The difficulty lies in attributing causality. Few longitudinal studies have compared the outcomes associated with PD and concurrent apathy directly, but an association with more rapid disease progression and cognitive decline has been suggested in those that have.²⁴ Other cross-sectional studies have found apathy in PD to be associated with a number of adverse outcomes, including communication difficulties,²⁵ increased motor symptoms, and increased physical disability.¹ Perhaps the most significant and consistent finding is the association with cognitive decline in PD.²³ Apathy may in fact herald the onset of dementia²⁶ and therefore represent an important prognostic factor, particularly as dementia increases mortality in PD.²⁷

IMPACT OF APATHY ON QUALITY OF LIFE

The presence of apathy in the elderly correlates with a reduction in satisfaction with life and in general health status.²⁸ This clearly reflects the importance of motivation as well as the negative consequences of its absence. In AD and other dementias, apathy is accompanied by increased functional disability, reduced rehabilitation success, and a larger burden and stress on caregivers.²⁹

Similar findings also hold true in PD, with lower quality of life scores reported in patients who suffer from apathy.^{3,30} Results, however, do vary, and the distinction between the effects of apathy and coexisting neuropsychiatric disorders, such as depression or cognitive impairment, can lead to differences in measured outcomes.³¹ Mood disturbance and apathy together appear to have the greatest negative impact on quality of life.³²

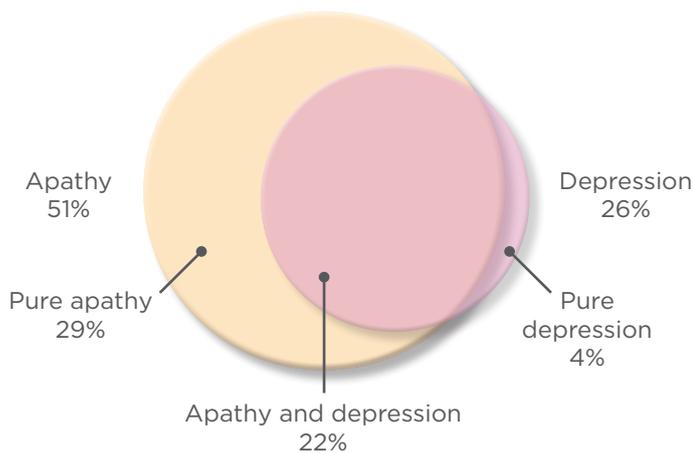


Figure 1: Example of overlap and prevalence of apathy and depression in a cohort of Parkinson's disease patients.

Adapted from Kirsch-Darrow et al.⁴⁰

Indeed, non-motor symptoms in PD are a frequent cause of institutionalisation and increased cost of care.³³ Caregivers are also negatively affected by the presence of apathy in PD. This is apparent in the early stages of the disorder as the care burden becomes significantly greater, even in comparison to other neuropsychiatric illnesses such as depression.³⁴ Activity of daily living scores are also lower, so a functional impact on day-to-day life is also apparent in those suffering from apathy.¹ These reduced activity of daily living scores seem to improve with treatment of apathy in PD, as does the extent of caregiver burden, but quality of life does not recover.³⁵ Consequently, therapies to improve motor function are only one part of restoring quality of life for patients, and neuropsychological disorders like apathy should also be addressed in order to improve outcomes.¹⁴

OVERLAP WITH DEPRESSION AND ANHEDONIA

PD patients can suffer from a large range of neuropsychiatric symptoms. A report suggests that 61% of PD patients have at least one psychiatric symptom, and 45% demonstrate two or more.²⁴ Depression is frequently described, occurring at approximately 2-times the frequency of the general population,³⁶ and also appears to be the most important association with apathy in elderly non-demented PD patients.³¹ Patients suffering with depression often have symptoms of apathy; indeed, loss of motivation forms part of the diagnostic criteria for depression.

Thus, given the strong relationship there has been much debate in the past as to whether apathy is a distinct entity in PD or just a symptom of depression. In a number of other neurological disorders including AD, Huntington's disease, and frontotemporal dementia, apathy is deemed to be a specific neuropsychiatric syndrome, distinct from depression.³⁷

Similarly, consensus is moving toward a distinction between depression and apathy in PD,^{30,38} as approximately half of PD patients with apathy do not suffer from concomitant depression (Figure 1).³⁹ These findings suggest that both disorders are likely to be frequent features of PD, but that they can exist independently of one another.^{4,40} Neuroimaging studies have also revealed differences between apathy and depression.^{41,42} This distinction is important clinically as misdiagnosis can result in inadequate treatment and also worse patient outcomes.^{43,44} Depression and apathy are also strongly associated with fatigue, which is another disabling non-motor symptom in PD.⁴⁵

Anhedonia also has considerable overlap with apathy and is a key component of various neuropsychiatric conditions including depression, where it can be a diagnostic feature. Anhedonia is traditionally defined as reduced ability to experience pleasure⁴⁶ but more recently it has been conceptualised as a disorder that affects motivation mechanisms, including anticipatory 'wanting' (the desire to obtain a reward) and consummatory 'liking' (the satisfaction obtained when consuming a reward).⁴⁷ This can be likened to the desire for food when hungry versus the sensation of satisfaction when you finally eat it, respectively. These components of pleasure may have separate neural pathways. 'Wanting' is associated with frontostriatal dopaminergic circuits, which have also been linked with motivation and apathy,^{48,49} while 'liking' has been associated with the nucleus accumbens, ventral pallidum, and projections to the orbitofrontal cortex (Figure 2).⁵⁰

Although these two systems are interrelated, they are associated with dissociable behavioural features. Some suggest that apathy might be more closely related to the anticipatory, dopamine-responsive component of anhedonia, while the consummatory component is more associated with depression.^{51,52} The similarities between apathy and anhedonia are seemingly

closer than those between apathy and depression; anhedonia accompanies both and might be associated with deficits in 'liking' and 'wanting',⁴ although this is a controversial area. In PD, anhedonia, like apathy, appears to be independent of motor symptoms, has been attributed to frontal lobe dysfunction,⁵³ and is also responsive to PD therapies.⁵⁴

MECHANISMS OF APATHY IN PARKINSON'S DISEASE

Given the heterogeneity of PD and the overlap of apathy with other neuropsychiatric conditions, there is likely to be a range of different underlying mechanisms leading to reduced motivation. It is unlikely that there is one simple cause of apathy; as a result, more targeted and personalised objective methods for the diagnosis and treatment of apathy are needed. Surprisingly, despite the clinical significance, the mechanisms underlying apathy in PD patients are poorly understood. Some theories of goal-directed behaviour conceptualise the processes underpinning motivation as a sequence, starting with the generation of options for behaviour, followed by selection of the goal, initiation or inhibition of an action, and then

subsequent learning from the result.⁵ Dysfunction in any of these components might potentially lead to the manifestations of the different subtypes of apathy. To break down the components further, it is possible that the reduced ability to select goals in apathy is also dependent on several factors. For example, patients might become less sensitive to reward or hypersensitive to effort.⁵⁵ These effects may vary between individuals due to differing levels of neurotransmitter dysfunction or degeneration in different frontostriatal circuits.

Disparities in how frontostriatal brain regions are affected by degenerative processes in PD might lead to different emotional, cognitive, and behavioural manifestations of apathy.⁴⁹ Regions within the limbic system have been most frequently associated with the neural correlates of apathy in PD. Position emission topography (PET) studies suggest a mesolimbic rather than a nigrostriatal cause,⁵⁶ and structural and functional imaging implicate frontal and subcortical brain areas, all of which are linked with reward processing.^{57,58} Other important reward-related areas involved in apathy include the ventral striatum and specifically its frontal connections with dopamine as the principal neurotransmitter.⁴⁹

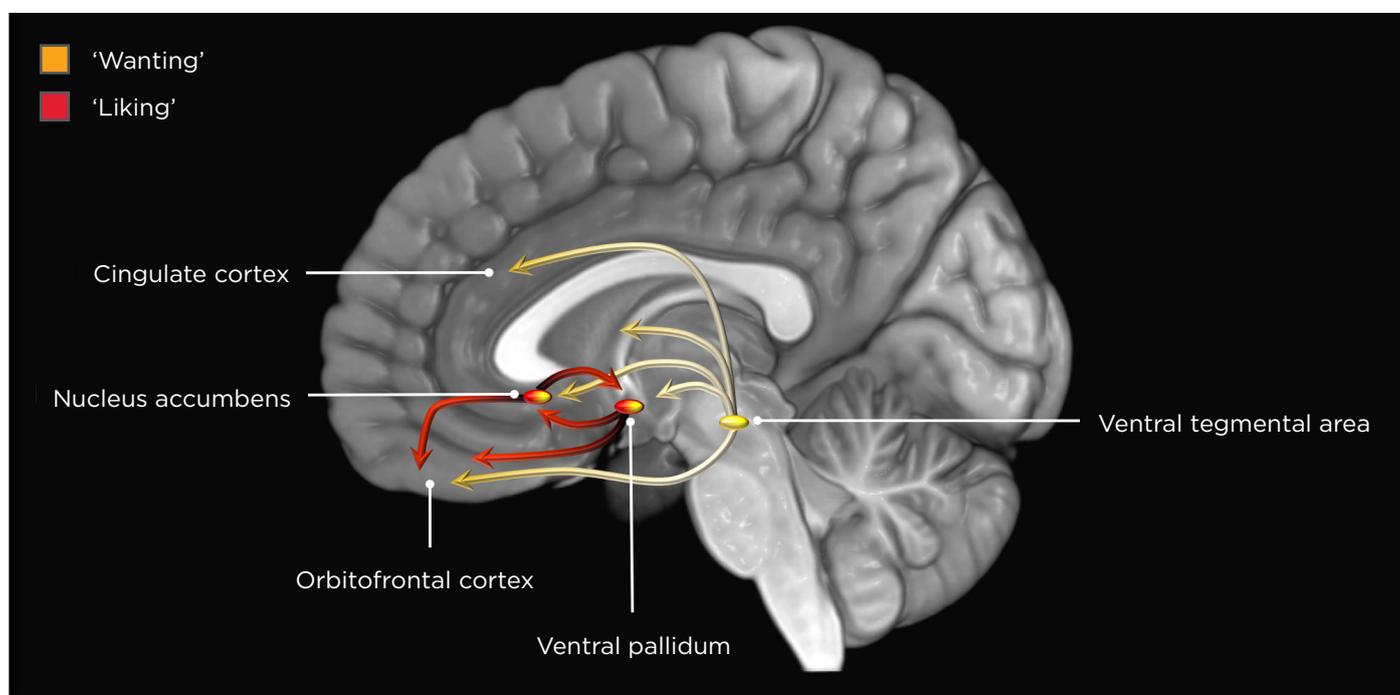


Figure 2: The proposed neural projections involved in the 'wanting' and 'liking' brain circuits, which are implicated in motivation and pleasure.

Hedonic hotspots include the nucleus accumbens and the ventral pallidum, with strong associations to the orbitofrontal brain areas and reward processing areas.

Correspondingly, reward circuits and dopamine dysfunction appear to be key in the development of apathy, as discussed forthwith.

THERAPIES

Given the different domains of apathy and the variety of potential mechanisms contributing to its clinical phenotype, it may be necessary to adopt an individualised, symptom-specific approach in the treatment of each patient.⁵⁹ A variety of pharmacological approaches have been used,⁶⁰ each with varying success, however at present there are no formally approved drugs.⁶¹

The severity of apathy level in PD tends to be lower in patients treated with higher doses of dopaminergic drugs.¹ Dopamine agonists including pramipexole⁶² and piribedil⁶³ can have beneficial effects on apathy, as well as mood, in PD.⁶⁴ Pramipexole can also lead to improvements in associated anhedonia and depression symptoms.⁵⁴ Likewise, the ability of dopamine receptor agonists to improve motivation has been observed in other patients with prefrontal or basal ganglia lesions.⁶⁵ Apathy in PD is not always dopamine responsive; indeed, it has been suggested that there are two types of syndrome: dopamine-sensitive and dopamine-resistant apathy. The former is often reported to occur following deep brain stimulation (DBS) a number of months after dopamine withdrawal following the procedure, and it can be reversed after reintroduction of the medication.^{56,66} Dopamine-resistant apathy, on the other hand, seems to be related to the progression of PD and may be due to structural atrophy in deep brain structures, such as the nucleus accumbens and the caudate nucleus.⁶⁷ Therefore, which class a patient falls into may have significant repercussions on drug responsiveness and subsequent prognosis. Dopamine therapies with reported beneficial effects on apathy include: levodopa,⁶⁸ the dopamine agonists pramipexole,⁶² piribedil,⁶³ ropinirole,⁶⁶ and rotigotine,⁶⁹ and the monoamine oxidase inhibitor rasagiline for patients with early untreated PD.⁷⁰

Although dopamine dysfunction is likely to be contributory it is not necessarily the sole cause. Dysfunction of non-dopaminergic systems has also been shown to predict the development of apathy⁹ and acetylcholine is a possible candidate implicated in the process. A double-blind, placebo-controlled trial studied the cholinesterase inhibitor rivastigmine. The trial included PD

patients suffering from apathy, who were neither depressed nor demented, and yielded marked motivational improvements. This highlights the potential for its use as a therapeutic intervention.³⁵ Other drug therapies such as methylphenidate (which increases brain dopamine and noradrenaline levels) have also been trialled in the treatment of neurological conditions such as AD.⁷¹ Although there have been no controlled studies specific to PD, there is a case report of methylphenidate improving apathy in a PD patient,⁷² as well as a report of a notable improvement in apathy severity from a trial that compared gait hypokinesia and freezing.⁷³

The use of antidepressant therapy in apathy is controversial. There is evidence to suggest that antidepressants can lead to apathy in some individuals,^{44,74} however this may be agent-specific, with selective serotonin reuptake inhibitors faring worse. At the same time, antidepressants with a dopamine component, such as bupropion, have been more effective,⁷⁵ but like most therapies for apathy, further validation is needed.

No firm evidence for DBS as a treatment of apathy has been found. DBS has been reported to lead to apathy directly in some studies⁷⁶ but improve motivation in others,⁷⁷ all with no apparent association to stimulator location.⁷⁸ As previously noted, apathy associated with DBS may be secondary to weaning off of dopamine medication as motor symptoms improve with stimulation. This theory is particularly plausible as apathy is associated with reduced striatal metabolism in PET imaging prior to subthalamic nucleus DBS.⁵⁸

Non-pharmaceutical interventions such as exercise and cognitive training have also been proposed,⁷⁹ but current evidence is limited. Some studies have reported results suggesting that increased physical activity in PD is associated with lower levels of apathy,⁸⁰ however whether this is due to greater motivation to perform activity in the first place remains to be established. Caregivers should be advised to encourage and prompt patients with apathy to engage in tasks and remain active as patients often have little insight into their disorder.

CONCLUSION

Apathy in PD greatly impacts upon the quality of life of patients and their caregivers. Although much headway has been made in recent years, it is a challenging disorder to study and treat.

Associations with other neuropsychiatric conditions make diagnosis difficult and lack of mechanistic understanding has made choosing appropriate therapies a challenge. Although there are positive prospects, more objective assessment methods,

better understanding of underlying mechanisms, and greater rigor in trial design are required to advance the field and improve management of these patients.

Acknowledgements

This work was supported by a Wellcome Trust Clinical Research Training Fellowship to Kinan Muhammed and a Wellcome Trust Principal Research Fellowship to Masud Husain.

REFERENCES

1. den Brok MG et al. Apathy in Parkinson's disease: A systematic review and meta-analysis. *Mov Disord.* 2015;30(6):759-69.
2. Duffy J. Apathy in neurologic disorders. *Curr Psychiatry Rep.* 2000;2(5):434-9.
3. Benito-León J et al. Impact of apathy on health-related quality of life in recently diagnosed Parkinson's disease: The ANIMO study. *Mov Disord.* 2012;27(2):211-8.
4. Kaji Y, Hirata K. Apathy and Anhedonia in Parkinson's Disease. *ISRN Neurol.* 2011;2011:219427.
5. Sinha N et al. Impulsivity and apathy in Parkinson's disease. *J Neuropsychol.* 2013;7(2):255-83.
6. van Reekum R et al. Apathy: why care? *J Neuropsychiatry Clin Neurosci.* 2005;17(1):7-19.
7. Pedersen KF et al. Apathy in drug-naïve patients with incident Parkinson's disease: the Norwegian ParkWest study. *J Neurol.* 2010;257(2):217-23.
8. Moretti R et al. Apathy: A Complex Symptom Specific to the Clinical Pattern of Presentation of Parkinson's Disease? *Am J Alzheimers Dis Other Dement.* 2012;27(3):196-201.
9. Pedersen KF et al. Occurrence and risk factors for apathy in Parkinson disease: a 4-year prospective longitudinal study. *J Neurol Neurosurg Psychiatry.* 2009;80(11):1279-82.
10. Pluck GC, Brown RG. Apathy in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2002;73(6):636-42.
11. Robert P et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. *Eur Psychiatry.* 2009;24(2):98-104.
12. Starkstein SE et al. The nosological position of apathy in clinical practice. *J Neurol Neurosurg Psychiatry.* 2008;79(10):1088-92.
13. Marin RS. Apathy: a neuropsychiatric syndrome. *J Neuropsychiatry Clin Neurosci.* 1991;3(3):243-54.
14. Shulman LM. Apathy in patients with Parkinson's disease. *Int Rev Psychiatry.* 2000;12(4):298-306.
15. Mulin E et al. Diagnostic criteria for apathy in clinical practice. *Int J Geriatr Psychiatry.* 2011;26(2):158-65.
16. Leentjens AF et al. Apathy and anhedonia rating scales in Parkinson's disease: critique and recommendations. *Mov Disord.* 2008;23(14):2004-14.
17. Sockeel P et al. The Lille apathy rating scale (LARS), a new instrument for detecting and quantifying apathy: validation in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2006;77(5):579-84.
18. Dujardin K et al. Assessing apathy in everyday clinical practice with the short-form Lille Apathy Rating Scale. *Mov Disord.* 2013;28(14):2014-9.
19. Dujardin K et al. The Lille Apathy Rating Scale: Validation of a caregiver-based version. *Mov Disord.* 2008;23(6):845-9.
20. Starkstein SE et al. Reliability, validity, and clinical correlates of apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* 1992;4(2):134-9.
21. Marin RS et al. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry Res.* 1991;38(2):143-62.
22. Robert PH et al. The Apathy Inventory: assessment of apathy and awareness in Alzheimer's disease, Parkinson's disease and mild cognitive impairment. *Int J Geriatr Psychiatry.* 2002;17(12):1099-105.
23. Bogart KR. Is apathy a valid and meaningful symptom or syndrome in Parkinson's disease? A critical review. *Health Psychol.* 2011;30(4):386-400.
24. Aarsland D et al. Range of neuropsychiatric disturbances in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 1999;67(4):492-6.
25. McKinlay A et al. A profile of neuropsychiatric problems and their relationship to quality of life for Parkinson's disease patients without dementia. *Parkinsonism Relat Disord.* 2008;14(1):37-42.
26. Dujardin K et al. Apathy may herald cognitive decline and dementia in Parkinson's disease. *Mov Disord.* 2009;24(16):2391-7.
27. Hughes TA et al. Mortality in Parkinson's disease and its association with dementia and depression. *Acta Neurol Scand.* 2004;110(2):118-23.
28. Vallerand RJ et al. Motivation in later life: theory and assessment. *Int J Aging Hum Dev.* 1995;41(3):221-38.
29. Teixeira AL Jr, Caramelli P. Apathy in Alzheimer's disease. *Rev Bras Psiquiatr.* 2006;28(3):238-41.
30. Oguru M et al. Apathy and Depression in Parkinson Disease. *J Geriatr Psychiatry Neurol.* 2010;23(1):35-41.
31. Skorvaneck M et al. Apathy in Elderly Nondemented Patients With Parkinson's Disease: Clinical Determinants and Relationship to Quality of Life. *J Geriatr Psychiatry Neurol.* 2013;26(4):237-43.
32. Martinez-Martin P et al. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov Disord.* 2011;26(3):399-406.
33. Chaudhuri KR et al. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol.* 2006;5(3):235-45.
34. Leiknes I et al. Caregiver distress associated with neuropsychiatric problems in patients with early Parkinson's disease: the Norwegian ParkWest study. *Acta Neurol Scand.* 2010;122(6):418-24.
35. Devos D et al. Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomised clinical trial. *J Neurol Neurosurg Psychiatry.* 2014;85(6):668-74.
36. Lieberman A. Depression in Parkinson's disease -- a review. *Acta Neurol Scand.* 2006;113(1):1-8.
37. Levy ML et al. Apathy Is Not Depression. *J Neuropsychiatry Clin Neurosci.* 1998;10(3):314-9.
38. Kirsch-Darrow L et al. Apathy

- and Depression: Separate Factors in Parkinson's Disease. *J Int Neuropsychol Soc.* 2011;17(6):1058-66.
39. Brown RG, Pluck G. Negative symptoms: The 'pathology' of motivation and goal-directed behaviour. *Trends Neurosci.* 2000;23(9):412-7.
40. Kirsch-Darrow L et al. Dissociating apathy and depression in Parkinson disease. *Neurology.* 2006;67(1):33-8.
41. Hollocks MJ. Differential relationships between apathy and depression with white matter microstructural changes and functional outcomes. *Brain.* 2015;138(Pt12):3803-15.
42. Benoit M. Imaging correlates of apathy and depression in Parkinson's disease. *J Neurol Sci.* 2011;310(1-2):58-60.
43. Drijgers RL et al. Pharmacological Treatment of Apathy in Neurodegenerative Diseases: A Systematic Review. *Dement Geriatr Cogn Disord.* 2009;28(1):13-22.
44. Barnhart WJ et al. SSRI-induced apathy syndrome: a clinical review. *J Psychiatr Pract.* 2004;10(3):196-9.
45. Skorvanek M et al. The associations between fatigue, apathy, and depression in Parkinson's disease. *Acta Neurol Scand.* 2015;131(2):80-7.
46. Fawcett J et al. Assessing Anhedonia in Psychiatric Patients. *Arch Gen Psychiatry.* 1983;40(1):79-84.
47. Rømer Thomsen K et al. Reconceptualizing anhedonia: novel perspectives on balancing the pleasure networks in the human brain. *Front Behav Neurosci.* 2015;9:49.
48. Berridge KC. Motivation concepts in behavioral neuroscience. *Physiol Behav.* 2004;81(2):179-209.
49. Levy R, Dubois B. Apathy and the Functional Anatomy of the Prefrontal Cortex-Basal Ganglia Circuits. *Cereb Cortex.* 2006;16(7):916-28.
50. Berridge KC, Kringelbach ML. Affective neuroscience of pleasure: reward in humans and animals. *Psychopharmacology (Berl).* 2008;199(3):457-80.
51. Loas G et al. Anhedonia in Parkinson's Disease: An Overview. *J Neuropsychiatry Clin Neurosci.* 2012;24(4):444-51.
52. Jordan LL et al. Hedonic and behavioral deficits associated with apathy in Parkinson's disease: Potential treatment implications. *Mov Disord.* 2013;28(9):1301-4.
53. Assogna F et al. Anhedonia in Parkinson's disease: a systematic review of the literature. *Mov Disord.* 2011;26(10):1825-34.
54. Lemke MR et al. Anhedonia, depression, and motor functioning in Parkinson's disease during treatment with pramipexole. *J Neuropsychiatry Clin Neurosci.* 2005;17(2):214-20.
55. Chong TT et al. Dopamine enhances willingness to exert effort for reward in Parkinson's disease. *Cortex.* 2015;69:40-6.
56. Thobois S et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain.* 2010;133(Pt 4):1111-27.
57. Baggio HC et al. Resting-state frontostriatal functional connectivity in Parkinson's disease-related apathy. *Mov Disord.* 2015;30(5):671-9.
58. Robert GH et al. Preoperative factors of apathy in subthalamic stimulated Parkinson disease: A PET study. *Neurology.* 2014;83(18):1620-6.
59. Pagonabarraga J et al. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. *Lancet Neurol.* 2015;14(5):518-31.
60. Chase TN. Apathy in neuropsychiatric disease: diagnosis, pathophysiology, and treatment. *Neurotox Res.* 2011;19(2):266-78.
61. Santangelo G et al. Apathy in Parkinson's disease: diagnosis, neuropsychological correlates, pathophysiology and treatment. *Behav Neurol.* 2013;27(4):501-13.
62. Guttman M, Jaskolka J. The use of pramipexole in Parkinson's disease: are its actions D(3) mediated? *Parkinsonism Relat Disord.* 2011;7(3):231-4.
63. Thobois S et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. *Brain.* 2013;136(Pt 5):1568-77.
64. Castrioto A. Emotional manifestations of PD: Neurobiological basis. *Mov Disord.* 2016. [Epub ahead of print].
65. Adam R et al. Dopamine reverses reward insensitivity in apathy following globus pallidus lesions. *Cortex.* 2013;49(5):1292-303.
66. Czernecki V et al. Apathy following subthalamic stimulation in Parkinson's disease: a dopamine responsive symptom. *Mov Disord.* 2008;23(7):964-9.
67. Carriere N et al. Apathy in Parkinson's disease is associated with nucleus accumbens atrophy: a magnetic resonance imaging shape analysis. *Mov Disord.* 2014;29(7):897-903.
68. Czernecki V et al. Motivation, reward, and Parkinson's disease: Influence of dopatherapy. *Neuropsychologia.* 2002;40(13):2257-67.
69. Ray Chaudhuri K et al. Rotigotine and specific non-motor symptoms of Parkinson's disease: post hoc analysis of RECOVER. *Parkinsonism Relat Disord.* 2013;19(7):660-5.
70. Smith KM. Combined rasagiline and antidepressant use in Parkinson disease in the ADAGIO study: effects on nonmotor symptoms and tolerability. *JAMA Neurol.* 2015;72(1):88-95.
71. Rosenberg PB et al. Safety and efficacy of methylphenidate for apathy in Alzheimer's disease: a randomized, placebo-controlled trial. *J Clin Psychiatry.* 2013;74(8):810-6.
72. Chatterjee A, Fahn S. Methylphenidate treats apathy in Parkinson's disease. *J Neuropsychiatry Clin Neurosci.* 2002;14(4):461-2.
73. Moreau C et al. Methylphenidate for gait hypokinesia and freezing in patients with Parkinson's disease undergoing subthalamic stimulation: a multicentre, parallel, randomised, placebo-controlled trial. *Lancet Neurol.* 2012;11(7):589-96.
74. Wongpakaran N et al. Selective serotonin reuptake inhibitor use associates with apathy among depressed elderly: a case-control study. *Ann Gen Psychiatry.* 2007;6:7.
75. Corcoran C et al. Bupropion in the management of apathy. *J Psychopharmacol.* 2004;18(1):133-5.
76. Drapier D et al. Does subthalamic nucleus stimulation induce apathy in Parkinson's disease? *J Neurol.* 2006;253(8):1083-91.
77. Czernecki V et al. Does bilateral stimulation of the subthalamic nucleus aggravate apathy in Parkinson's disease? *J Neurol Neurosurg Psychiatry.* 2005;76(6):775-9.
78. Kirsch-Darrow L et al. The trajectory of apathy after deep brain stimulation: From pre-surgery to 6 months post-surgery in Parkinson's disease. *Parkinsonism Relat Disord.* 2011;17(3):182-8.
79. Stanton BR, Carson A. Apathy: A practical guide for neurologists. *Pract Neurol.* 2016;16(1):42-7.
80. van der Kolk NM, King LA. Effects of exercise on mobility in people with Parkinson's disease. *Mov Disord.* 2013;28(11):1587-96.