



Article
scientifique

Revue de la
littérature

2016

Published
version

Open
Access

This is the published version of the publication, made available in accordance with the publisher's policy.

Emotional manifestations of PD: Neurobiological basis

Castrioto, Anna; Thobois, Stephane; Carnicella, Sebastien; Maillet, Audrey; Krack, Paul

How to cite

CASTRIOTO, Anna et al. Emotional manifestations of PD: Neurobiological basis. In: Movement disorders, 2016, vol. 31, n° 8, p. 1103–1113. doi: 10.1002/mds.26587

This publication URL: <https://archive-ouverte.unige.ch//unige:95963>

Publication DOI: [10.1002/mds.26587](https://doi.org/10.1002/mds.26587)

Emotional Manifestations of PD: Neurobiological Basis



Anna Castrioto, MD, PhD,^{1,2,3} Stéphane Thobois, MD, PhD,^{4,5} Sebastien Carnicella, PhD,^{1,2} Audrey Maillet, PhD,⁴ and Paul Krack, MD, PhD^{1,2,3*}

¹Univ. Grenoble Alpes, Grenoble Institut des Neurosciences, GIN, Grenoble, France

²Inserm, U1216, Grenoble, France

³Movement Disorders Unit, Neurology Department, CHU de Grenoble, Grenoble, France

⁴CNRS, UMR 5229, Centre de Neurosciences Cognitives, Bron, France

⁵Hospices Civils de Lyon, Hôpital Neurologique, Neurologie C; Université Lyon I, Faculté de Médecine et de Maïeutique Lyon Sud Charles Mérieux, Lyon, France

ABSTRACT: Neuropsychiatric symptoms are common and disabling in PD. Their neurobiological bases are complex, partly because of the disease itself and partly because of the dopaminergic treatment. The aim of this review is to focus on the emotional manifestations stemming from the neurodegenerative process itself. We focus on depression, anxiety, apathy, and fatigue, which can all be part of the clinical spectrum of premotor disease and may be improved or masked by medications targeting parkinsonian motor signs or psychiatric symptoms as the disease progresses. Findings from clinical, neuroimaging, and animal studies are reviewed, showing a major contribution of the dopaminergic system to the pathophysiology of these disabling symptoms. Degeneration of noradrenergic and sero-

tonergic projection systems also has an impact on psychiatric symptoms of PD. The available literature is reviewed, but at present there is a lack of studies that would allow disentangling the separate contribution of each of the monoaminergic systems. The use of a pragmatic classification of all these symptoms under the umbrella of hypodopaminergic behavioral syndrome seems clinically useful, as it emphasizes the crucial, although not exclusive, nature of their dopaminergic neurobiological basis, which has important implications in the clinical management of PD. © 2016 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; dopamine; apathy; depression; anxiety

Psychiatric symptoms are so common in Parkinson's disease (PD) that it has been defined as a neuropsychiatric disorder.¹ Neuropsychiatric symptoms, that is, emotional and cognitive symptoms, constitute a major source of disability and can be socially disruptive.²⁻⁴ Some of these symptoms are a side effect of dopaminergic treatment (behavioral and dopaminergic replacement treatment addiction, nocturnal hyperactivity, hypomania, and punning).³⁻⁵ Others, like apa-

thy, depression, and anxiety, seem more related to the disease itself, already presenting in the early stages of the disease and potentially preceding the first motor symptoms. As such, apathy, depression, and anxiety might at least in part be associated with insufficient dopaminergic drive.⁴⁻⁸ Fluctuating patients might experience apathy, depression, and anxiety in the off-periods, with euphoria, well-being, self-confidence, and hypomania characterizing the on-drug condition.⁹ The management of neuropsychiatric symptoms remains a challenge, also because it is not always easy to weight the relative contribution of medications, disease, and emotional response. The neurobiological bases of these symptoms are complex and not yet fully understood. The relative contribution of dopaminergic deficit and of other nondopaminergic systems is still under investigation. The objective of this review is to focus on the neuropsychiatric symptoms, which are most likely related to the disease itself, and to analyze

*Correspondence to: Paul Krack, Movement Disorders Unit, Psychiatry and Neurology Department, CHU Grenoble, 38043 Grenoble Cedex 9, France, E-mail: Paul.Krack@ujf-grenoble.fr

Relevant conflicts of interest/financial disclosures: none.

Funding agencies: none.

Received: 16 October 2015; Revised: 22 January 2016; Accepted: 24 January 2016

Published online 4 April 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.26587

the literature relating to their underlying mechanisms. We will therefore largely leave aside symptoms secondary to dopaminergic replacement treatment except when discussing neurodegeneration as part of the risk factors for developing iatrogenic behavioral complications. From a clinical point of view, patients with drug-naïve de novo PD represent an interesting model that allows the investigation of symptoms related to the disease itself. Yet there are only a few studies on drug-naïve de novo PD, and they carry the risk of including patients who will eventually develop an atypical parkinsonian syndrome. We will also report evidence based on human imaging studies and on animal models, which contribute to a better understanding of the mechanisms of the neurobiological basis of emotional manifestations in PD, as surrogates to the still-too-rare neuropathological-clinical correlation studies.¹⁰

Depression and Anxiety

Clinical Findings

Depression and anxiety are not only pervasive symptoms of PD,^{11,12} but they may also precede the onset of motor symptoms by several years.¹²⁻²² In a recent large epidemiological case-control study, depression and anxiety were found to be more frequent in PD patients up to 5 years before motor onset.¹⁷ A previous case-control study suggested that anxiety could be more strongly associated with PD and could precede motor onset by as much as 20 years.¹⁴ A recent study assessing populations at risk for PD, such as *LRRK2* G2019S mutation carriers, supported this strong association, finding higher trait anxiety in G2019S carriers than in noncarriers.²² The risk of developing PD was found to be greater in a population with anxiety and correlated with severity of anxiety.²³ Another recent case-control study, involving untreated PD patients, showed that of the nonmotor symptoms, depressed mood was already more frequent than anxiety 2 and even 10 years before motor onset.²¹ Once motor symptoms develop, both anxiety and depression remain more frequent in PD patients than in controls.^{18,19}

It has been shown that in PD, anxiety and depression can either coexist or be present independently, suggesting that they are separate entities.^{11,24} In addition to actual depression and anxiety, patients may also experience acute mood fluctuations, with feelings of depression and anxiety as medication wears off.^{9,25,26} This suggests that the role of the dopaminergic system is critical. Besides generalized anxiety and anxiety related to fluctuations, specific phobias, panic disorder, and social phobia have been reported to be more frequent in PD than in the general population.^{12,27} Disease severity and fluctuations have been found to be risk factors for anxiety disorders.^{12,27}

From a neuropathological point of view, besides dopaminergic denervation, the involvement of the locus coeruleus and the raphe nuclei (ie, the noradrenergic and serotonergic system, respectively) from the early stages of Braak's classification can explain why depression and anxiety are frequent early nonmotor signs.^{10,28}

Recognizing and treating depression and anxiety is important, as they have a negative impact on functioning.^{29,30} To optimize their management, it is important to distinguish between 2 phenomena, chronic depression and/or anxiety and psychic fluctuations, because the neurobiology of the chronic psychiatric symptoms might be more complex than that of symptoms fluctuating with the sole dopaminergic treatment.

Only a few studies on management of depression and anxiety in de novo PD are available so far, suggesting a possible role of the dopaminergic system.^{18,31,32} Analysis of depression in the ADAGIO study³² suggested that rasagiline compared with placebo was associated with less depression, even after controlling for improvement of motor impairment. Studies in treated PD have shown that dopamine agonists improve mood, too,³³⁻³⁶ supporting the important role of the dopaminergic system in depression. Depressive symptoms in PD have been found to be associated with lower doses of dopamine agonists.¹⁶ Similarly, the MAO-B inhibitors rasagiline and selegiline have been shown to improve depression compared with placebo.^{37,38} Anxiety has also been found to respond to dopaminergic therapy.³⁹ Moreover, depressed mood and anxiety experienced in the off-medication phase during nonmotor fluctuations are also improved by dopaminergic medication.²⁵

Several controlled and uncontrolled studies have suggested that antidepressant treatment causes some improvement in depressed mood, although not consistently,⁴⁰⁻⁴⁸ pointing toward potential additional involvement of the serotonergic and/or noradrenergic systems. In a small open-label study, PD patients with depression were treated with pramipexole or sertraline.⁴⁶ Depression improved in both groups, but the percentage of patients with full recovery was higher in the pramipexole group than in the sertraline group (60% vs 27%). When comparing selective serotonin uptake inhibitors with nonselective serotonin uptake inhibitors or a tricyclic antidepressants, the response to the latter seems to be faster, although their use is limited by their side effects.^{41-45,48} A placebo-controlled study on atomoxetine, a selective noradrenaline reuptake inhibitor, for depressed PD patients, showed a trend toward greater improvement with atomoxetine.⁴⁹ All these findings highlight a possible role of the noradrenergic system in depression.⁵⁰

Although there are no randomized, controlled studies about the effects of antidepressant drugs on anxiety,

studies on depression have shown that noradrenergic and serotonergic antidepressants also have a positive effect on anxiety.^{41,43,48} Although a randomized, controlled study comparing paroxetine and nortriptyline showed superiority of nortriptyline in alleviating anxiety and depression,⁴³ another randomized, controlled study comparing desipramine and citalopram found improvement with both treatments.⁴⁸ A placebo-controlled study reported a suggestion of effectiveness of atomoxetine in PD.⁴⁹ These findings support a role for both serotonergic and noradrenergic system in the neurobiology of anxiety in PD.

Anatomical and Metabolic Correlates

Many anatomical changes in the brain have been observed in PD-associated depression. The temporal cortex, particularly the amygdala and hippocampus, is atrophic, and this could explain mood/emotion learning deficits.⁵¹⁻⁵⁶ The role of the orbitofrontal cortex (OFC) has also been highlighted by MRI studies that showed atrophy of this region correlating with severity of depression in PD.^{52,53,57} Furthermore, [¹⁸F]-FDG and H₂¹⁵O PET studies have revealed hypometabolism of the OFC in both depressed and “simply dysphoric” PD patients.^{58,59} However, the pattern of abnormalities of OFC activity remains the subject of debate. Some fMRI studies have yielded results to the contrary, with increased resting-state activity of the OFC. This could be interpreted as an abnormally increased top-down control over limbic circuits, leading to abnormal avoidance behavior.⁶⁰

Depression scores in PD are predicted by the variations in the amplitude of low-frequency fluctuations measured by MRI at rest in the dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex (vmPFC). This is interesting in relation to the role of DLPFC in executive functions and response selection and to the role of the vmPFC in providing the contextual value of reward, emotion, and perception processing.⁶¹

Finally, atrophy of the dorsal anterior cingulate cortex (ACC), which plays an important role in motivation, conflict monitoring, response initiation, social behaviors, and reward encoding, has also been found in depressed PD patients.^{51-55,57,62} This could participate in the reduction of initiative and motivation to initiate actions observed in depressed PD subjects. The ventral part of the ACC also plays a prominent role in the pathophysiology of depression in PD, and a relationship between its activity and metabolism and depression severity has been noted.^{54,60,63,64}

Amygdala dysfunction also plays a role in the pathophysiology of depression in PD, with increased activity and reduced connectivity with frontoparietal areas.⁶⁵ Finally, subcortical regions are also involved in PD depression, in particular, the limbic part of the

thalamus, which has been found to be atrophic and hypoactive during emotional perception.^{66,67}

More recently, a number of MRI connectivity studies have revealed widespread reduction of connectivity in cortico-subcortical limbic circuits and increased connectivity between certain specific limbic areas such as the amygdala, limbic thalamus, and temporal cortex in depressed PD subjects. This indicates that depression in PD is linked not only to focal abnormalities, but also to global dysfunction in interaction between areas.^{60,68,69} Some authors point out a possible increase in connectivity between limbic regions and a decrease in connectivity in corticolimbic networks, which may reflect abnormal top-down control on emotion-related limbic regions.⁶⁹

Neurotransmitter Abnormalities

Role of Dopaminergic Lesions

Degeneration of mesocorticolimbic dopaminergic projections to the ACC, OFC, ventral striatum, and thalamus appears to be one of the key mechanisms responsible for depression in PD. This has been demonstrated by several SPECT or PET studies using the dopamine D2 receptor antagonist [¹¹C]-raclopride,⁷⁰ [¹⁸F]-dopa,^{71,72} dopamine transporter (DAT) ligands [99m]Tc-TRODAT-1⁷³ or I¹²³-FP-CIT,⁷⁴ or [¹¹C]-RTI32 a ligand to both DAT and noradrenalin transporter.⁷⁵ However, DAT imaging studies have sometimes yielded conflicting results. Indeed, some have revealed a reduction in DAT binding in depressed PD patients, which is an argument in favor of greater dopaminergic degeneration. However, other studies have found quite the opposite and suggest that abnormally high dopamine clearance results in reduced dopamine tonus.^{76,77} Clarification is necessary, but overall, involvement of the dopaminergic system in depression associated with PD is a clear-cut finding. In particular, the involvement of the mesolimbic dopaminergic pathway was neatly highlighted by a combined PET [¹¹C]-PHNO (a predominant D3-receptor ligand) and [¹¹C]-raclopride (a mixed D2/D3 receptor ligand) study showing an association between lower mood and a greater dopamine D3 versus dopamine D2 receptor alteration in PD.⁷⁹ Involvement of the dopaminergic system has also been demonstrated in anxiety, indicating the existence of a common mechanism.^{70,73,74}

Role of Serotonergic Lesions

The serotonergic system is altered in PD, notably in limbic areas such as the medial temporal cortex and frontal regions, and in the raphe and hippocampus independently of the presence of depression as shown by PET imaging studies using [¹¹C]WAY100635, a 5-HT_{1A} receptor antagonist^{80,81} or I¹²³-FP-CIT.⁸² PET studies using [¹¹C]-DASB, a serotonin transporter

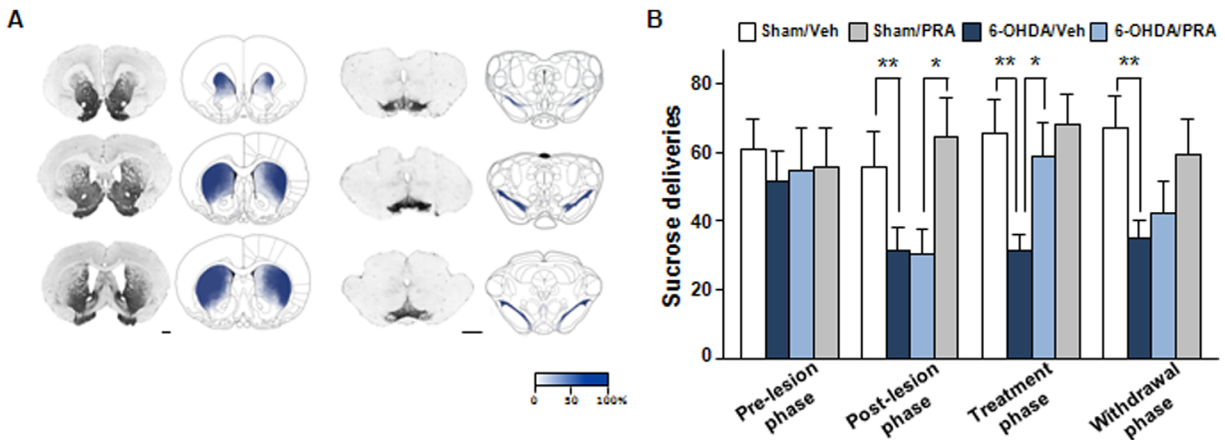


FIG. 1. Bilateral and partial substantia nigra pars compacta (SNc) dopaminergic lesions induce motivational deficits that are reversed by pramipexole. (A) Stereotaxic infusion of 6-OHDA leads to a loss of dopaminergic innervation in the dorsal striatum, mainly in its lateral part. Representative photomicrographs of coronal sections stained for tyrosine hydroxylase (TH) in striatal (1.7 to 0.7 mm anterior to bregma) and mesencephalic (-5 to -5.8 mm anterior to bregma) regions according to the stereotaxic atlas of Paxinos and Watson, 1998. Bar = 1 mm. The intensity of the gradient of color (white to blue) in schematic sections corresponds to the measured dopaminergic lesioned area. The highest intensity of blue color (100%) indicates that all animals had lesions in the corresponding area, whereas the lowest color intensity (white, 0%) corresponds to a nonlesioned or denervated area. (B) SNc dopaminergic lesions, which do not induce bradykinesia, greatly reduce operant sucrose self-administration (postlesion phase), a deficit corrected by chronic administration of low doses of pramipexole 0.2 mg/kg intraperitoneally (treatment phase). This beneficial effect of pramipexole disappears when the treatment is interrupted (withdrawal phase). Data are represented as mean number of sucrose deliveries \pm SEM. Data for each phase were sampled from the last 6 operant sessions. Adapted from Drui et al, 2014, and Favier et al, 2014. PRA, pramipexole.

ligand, in PD patients who are depressed have shown increased binding of the transporter, which could suggest excessive reuptake of serotonin.^{83,84} Furthermore, decreased postsynaptic serotonin 1A receptor density within limbic territories has been demonstrated using PET and [¹⁸F]MPPF, a selective serotonin 1A receptor antagonist, in depressed PD patients.⁸⁵ This supports the role of serotonergic system dysfunction in the pathophysiology of depression in PD and fits well with neuropathological data.⁸⁶ Further evidence has come from the observation, in grafted PD patients, that after the restoration of dopaminergic innervation, the persistence of depressive manifestations were related to greater serotonergic lesions.⁸⁷ This remains the subject of debate and a large and recent I¹²³-FP-CIT SPECT study found no association between serotonergic lesions in the raphe nucleus and depression score in early-stage PD patients.⁸² However, these last results should be interpreted carefully, as this study only analyzed correlations between depression score and I¹²³-FP-CIT binding and did not include patients with clinically defined depression. This may suggest that the involvement of the serotonergic system in the pathophysiology of depression in PD could be different according to the stage of the disease and more prominent when disease progresses.

Role of Noradrenergic Lesions

Only 1 PET imaging study has reported a link between the presence of depression and the degree of noradrenergic lesions in the locus coeruleus and limbic areas such as the anterior cingulate cortex, amygdala,

and ventral striatum.⁷⁵ However, it has to be acknowledged that the tracer used in this study (¹¹C-RTI-32) is a marker of both dopamine and noradrenalin transporter and not specific to the noradrenergic system.

Animal Studies

Lesion-based rodent models have recently afforded interesting insight into the pathophysiology of depression and anxiety in PD.⁸⁸⁻⁹⁰ Several studies have used bilateral and partial dopaminergic lesions of the nigrostriatal system (Fig. 1) to avoid causing motor impairment so severe that it would preclude any nonmotor behavioral evaluation. Such bilateral and partial dopaminergic lesions induced anxiety- and depression-related behaviors in lesioned rats.⁸⁸⁻⁹⁰ Very recently, a depression-like phenotype was also observed in an α -synuclein-based rodent model.⁹¹ Interestingly, these behavioral deficits are corrected by dopaminergic medication, notably D2/D3 receptor agonists such as pramipexole.^{88,89} This confirms the role of dopamine dysfunction in PD-related affective disorders and highlights the predictive value of such rodent models in the study of nonmotor, behavioral PD symptoms. In contrast to human functional imaging studies, these preclinical data rather point toward involvement of the nigrostriatal dopaminergic system.⁷³ However, regarding the relative anatomofunctional organization of the ascending dopamine pathways,⁹² further investigation is needed to determine their exact contribution to the development of depression in PD. Some animal-based research data suggest that, in addition to the

dopaminergic system, the serotonergic system is also involved, and this corresponds to clinical findings on human patients. Indeed, affective-related behaviors in rats were seen to occur only when unilateral dopamine lesions were combined with serotonergic and/or noradrenergic depletion.⁹³ In a recent study, 6-hydroxydopamine (6-OHDA)-lesioned and sham-injected rats underwent 2 PET scans, one for the dopaminergic and the other for the serotonergic system. Findings reveal that 6-OHDA rats present an altered serotonergic system, which correlates with the severity of depression.⁹⁴ As 6-OHDA has highly selective toxicity for dopamine neurons, these findings suggest strong interactions between dopamine and serotonergic systems. Moreover, anxiety- and depression-related behaviors induced by partial and bilateral dopamine lesions can be reversed by selective serotonergic reuptake inhibitors,^{88,89} suggesting a complex interaction between these 2 monoaminergic systems.

Apathy and Fatigue

Clinical Findings

Apathy is one of the most common and disabling neuropsychiatric symptoms in PD.^{95,96} It can be defined as lack of motivation, resulting in decreased goal-directed behaviors, and variably decreased interests and emotions. An emotional and a cognitive dimension can be recognized in apathy.⁹⁶ Its prevalence in PD ranges from 15% to 70% depending on disease severity and on the diagnostic tool used.^{95,96} Apathy can present in isolation or in association with depressed mood or cognitive decline. It is one of the most frequent symptoms in untreated *de novo* PD.^{18,19,95,97-102} One case-control study has shown that it can precede disease onset.²¹ Several studies in early PD have shown that apathy correlates with more severe motor impairment, suggesting an underlying common mechanism such as dopaminergic denervation.^{95,97,99}

Apathy has been reported to improve with levodopa,¹⁰³ and dopamine agonists in treated PD patients^{35,36,104,105} and with the MAO inhibitor rasagiline in early untreated PD.³²

More evidence of the dopaminergic nature of apathy comes from experience with patients operated on with STN DBS. A recent study used experimental pharmacological management, reducing levodopa therapy as much as possible and completely stopping dopamine agonists after surgery.⁷⁰ Half the patients on STN DBS managed with such drastic withdrawal of dopaminergic treatment developed apathy during the first year after surgery. Half the apathetic patients also developed depression. Apathy in this population was improved by treatment with pramipexole, a D2-D3 dopamine agonist, in a randomized placebo-controlled trial.¹⁰⁵ Although postoperative apathy had been

attributed to STN DBS by itself in the literature, the authors took the reversibility of apathy after reintroduction of a dopamine agonist as proof that postoperative apathy in patients with STN DBS is indeed related to withdrawal of dopaminergic treatment in the same way that dopamine agonist withdrawal syndrome has been described in parallel in patients with rapid decrease in dopamine agonists.¹⁰⁶ In a randomized study comparing subthalamic stimulation with best medical treatment, avoiding marked postoperative reduction of dopaminergic medication, no difference in apathy was found between the 2 groups.¹⁰⁷ This provides further support for the idea that postoperative apathy can be managed by optimal drug management and is the consequence of excessive withdrawal of dopaminergic treatment and not of stimulation *per se*. It should be noted that it is important to detect and treat the appearance of postoperative apathy as it can nullify the benefits of motor improvement for quality of life (QOL).¹⁰⁸ Although apathy responds to dopaminergic treatment, there are no systematic studies showing improvement of apathy with antidepressant treatment. Single case reports, however, have described good response of apathy to dopaminergic treatment after ineffective trials with serotonergic and noradrenergic antidepressant treatment, pointing to a major role of dopamine as the key neurotransmitter in motivational deficit.^{96,109}

In a double-blind, placebo-controlled study in PD patients with moderate to severe apathy without dementia and depression, significant improvement of apathy was reported following treatment with rivastigmine, suggesting that cholinergic denervation may also participate in parkinsonian apathy.¹¹⁰

In advanced PD, apathy may be associated with dementia. The diffuse cortical synucleinopathy of advanced PD corresponding to Braak stages IV and V¹¹¹ can by itself explain apathy.⁹⁶ In this case it is no longer possible to reverse apathy by dopaminergic replacement therapies. The management of apathy with dopaminergic drugs therefore should also take into account the presence or absence of cognitive deterioration.

Interestingly, it was recently shown that in *de novo* PD, after adjustment for confounding factors such as cognitive impairment or motor severity, apathy correlated strongly with fatigue and anhedonia, which is impaired ability to experience pleasure.⁹⁵ Fatigue is one of the most common premotor symptoms in PD.¹⁷ The association between apathy and fatigue has also been observed in PD patients undergoing treatment.¹¹² The neurobiological bases of fatigue are still unclear, and its management remains unsatisfactory. A subjective complaint of fatigue may express different underlying disorders such as somnolence, motor fatigability, or lack of motivation. Several studies have suggested

improvement in fatigue with dopamine agonists,^{18,35,36,113} levodopa,¹¹⁴ and the MAO inhibitor rasagiline.³² Analysis of neuropsychiatric signs in the Parkinson's Progressive Markers Initiative, a prospective longitudinal study following early untreated PD patients and healthy controls, revealed improvement in fatigue with dopaminergic treatment.⁹⁶ However, most available data come from studies that did not assess fatigue as a primary end point and that did not use fatigue scales. Interestingly, a recent pilot double-blind, placebo-controlled study specifically designed to assess fatigue found improvement of fatigue in the rasagiline group compared with the placebo group, supporting implication of the dopaminergic system.¹¹⁵ Further studies are needed to confirm this role. The association of apathy and fatigue deserves further investigation. In our experience most apathetic patients do not have spontaneous complaints besides fatigue.¹⁸ Apathy can easily remain undetected during neurological evaluation, unless specifically screened for. In our view, the association between apathy and fatigue therefore might be particularly interesting, as fatigue could represent a “red flag” for apathy.

Anatomical and Metabolic Correlates

MRI studies involving apathetic PD patients have shown atrophy of the precuneus, possibly responsible for a lack of insight about the inferior parietal and frontal gyrus and possibly involved in difficulties in integrating information in attention deficit and in dys-executive syndrome and of the insula, which could lead to a loss of emotional responsiveness.⁶²

Abnormal increased activity of the OFC has also been found using PET [¹⁸F]-FDG or resting-state fMRI.^{54,116-118} This could explain excessive top-down OFC control of limbic circuits and, in turn, abnormal avoidance behavior. In addition, the degree of apathy correlates with variations in amplitude of low-frequency fluctuations of the OFC, again pointing to the key role played by this area.⁵⁴

Although apathy in PD is associated with dorsal ACC atrophy, metabolism in this area is increased, possibly to compensate.^{51,52,54,55,62,116,118} ACC dysfunction appears to be crucial in any explanation of the cognitive and emotional aspects of apathy because of the role this area plays in emotional self-control, problem solving, error recognition, and adaptive response to changing conditions.

The SMA is also involved. SMA activity is diminished in apathetic PD patients and predicts the severity of apathy. Because of the SMA's role in motor programming and execution of intended action sequences, this could explain the lack of motivation.⁵⁴

Subcortical regions are also involved in apathy, in particular, the nucleus accumbens, which has been shown to be atrophic and abnormally shaped in apa-

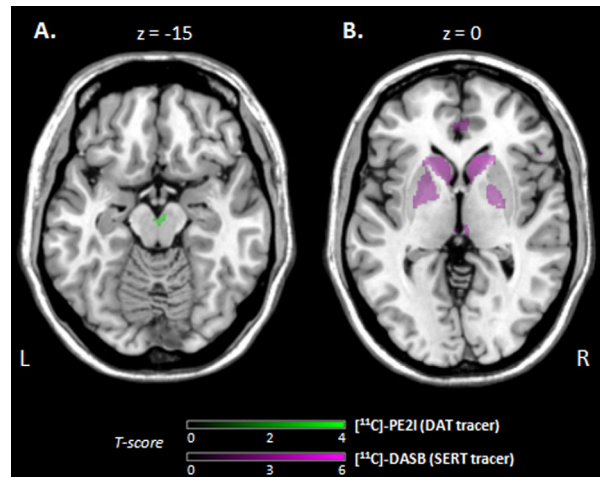


FIG. 2. (A) PET study with [¹¹C]-PE2I (green), a dopamine transporter ligand, used as a measure of dopamine depletion, and (B) [¹¹C]-DASB (purple), a serotonin transporter ligand, used as measure of serotonin depletion, demonstrating a link between the severity of apathy (assessed using the Lille Apathy Rating Scale) and a combined dopaminergic (SN-VTA) and serotonergic depletion (caudate, putamen, and pallidum) within basal ganglia in a cohort of drug-naïve de novo PD patients suffering from or not suffering from apathy (results come from a voxel-based regression analysis performed using SPM8 software). Axial views were superimposed on a brain MRI at a $P < 0.005$ uncorrected.¹²⁶

thetic subjects.¹¹⁹ Another recent study found that hypometabolism of the ventral striatum is associated with the risk of becoming apathetic after STN stimulation in PD, pointing, again, to the importance of this region, which plays a major role in reward processes.¹²⁰

More recently, apathetic PD patients were seen to have reduced functional connectivity between areas of cortico-subcortical limbic circuitry,¹²¹ stressing the presence of global dysfunction across a large network. Detailed analysis of the existing literature on apathy related to brain lesions has shown that different neural networks subserve emotional-affective, cognitive, and autoactivation aspects of apathy.⁹⁶

Neurotransmission Abnormalities

Thanks to PET imaging studies using [¹¹C]-raclopride, the role of dopaminergic denervation now appears very clearly as a key factor in explaining the development of apathy in PD. The presence of more diffuse and more severe dopaminergic denervation in mesocorticolimbic circuits in PD patients is associated with greater risk of developing apathy after STN stimulation.⁷⁰ Another PET study using [¹¹C]-RTI32, a ligand for both DAT and the noradrenalin transporter, also revealed the involvement of limbic dopaminergic but also noradrenergic lesions in apathy and in depression and anxiety.⁷⁵ The role of dopaminergic denervation in the occurrence of apathy was also demonstrated using several dopaminergic PET tracers in MPTP monkey models.^{122,123} Recently, in de novo drug-naïve PD patients exhibiting apathy, greater dopaminergic denervation was found in the right caudate nucleus,¹²⁴

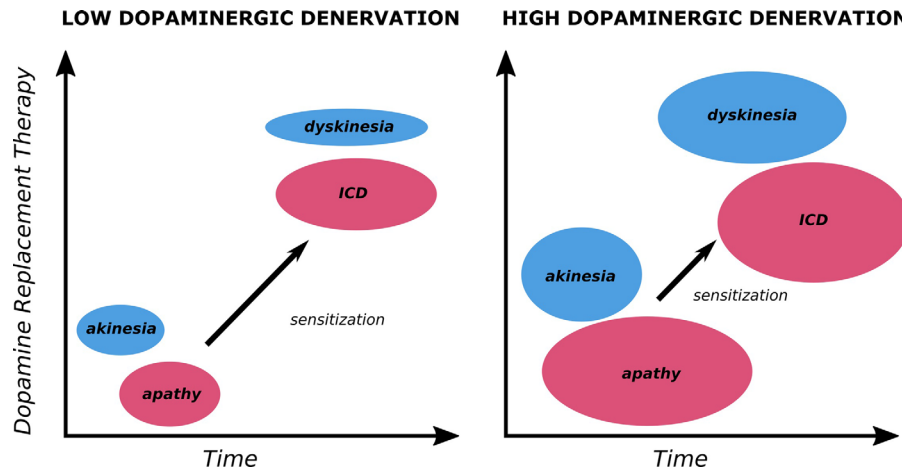


FIG. 3. Apathy and impulse control disorders (ICDs), like akinesia and dyskinesia, lie at the opposite ends of a spectrum of dopaminergic tone. Dopaminergic pulsatile treatment induces sensitization of the ventral limbic striatum and of the motor dorsal striatum. Such sensitization leads to a shift, from a behavioral point of view, from apathy to ICDs and, from a motor point of view, from akinesia to dyskinesia. Higher degrees of dopaminergic denervation are associated with more severe apathy and akinesia and, once dopaminergic treatment is started, reduce the threshold to the development of ICDs and dyskinesia, as shown in the graph on the right. Dopamine agonists with a selective affinity for D3 receptors have more powerful psychotropic than motor effects, leading to ICDs in the absence of dyskinesia. ICD, Impulse Control disorders.

suggesting that dopaminergic denervation is linked to apathy regardless of disease stage. Moreover, recent and unpublished findings of our group suggest that combined dopaminergic and serotonergic degeneration, especially within the basal ganglia network, could be a key mechanism underlying apathy in de novo PD patients. Therefore, such results suggest that the pathogenesis of this symptom is complex and is not exclusively linked to dopaminergic disruption (Fig. 2).¹²⁵

Animal Studies

Although there are fewer studies than on depression and anxiety, preclinical studies also support the involvement of dopamine in the pathophysiology of apathy and anhedonia.⁷³ As mentioned previously,^{122,123} diffuse DA lesions in MPTP monkey models lead to a reduction in goal-directed behavior and behavioral activities that resembles apathy (see also reference 126). In addition, partial and bilateral DA lesions of the nigrostriatal system of rats induce strong motivational deficits that can be reversed by DA agonists^{89,127,128} (Fig. 1). Bilateral loss of dopaminergic denervation can also lead to anhedonia-like behavior in mice and rats.⁸⁸⁻⁹⁰ Again, these studies do not make it clear whether apathy intrinsically results from the loss of dopamine in the nigrostriatal system or from the diffusion to the ventral tegmental area.

Hypodopaminergic Behavioral Syndrome

Depression, anxiety, and apathy can be defined as a hypodopaminergic syndrome that can precede motor onset and develop over the course of the disease (Fig. 3).

They may be associated with other nonmotor symptoms such as fatigue.

Apathy occurring during premotor PD can account for the typical premorbid parkinsonian personality^{129,130} of reduced sensation seeking, reduced smoking, and lower alcohol and caffeine intake. Apathy can be seen as the nonmotor emotional counterpart of akinesia. The neurobiological basis of depression and anxiety seems more complex than the purely dopaminergic basis. Dopaminergic sensitization in the motor loop induces the development of dyskinesia. In the same way, sensitization of the limbic and cognitive loops explains the switch from hypodopaminergic symptoms to a hyperdopaminergic behavioral syndrome (behavioral and dopaminergic replacement treatment addiction, nocturnal hyperactivity, hypomania, and punding)^{5,6,8} (Video), as well as changes in the personality traits of PD patients. In the early levodopa era, Oliver Sacks had already described a shift induced by dopaminergic medication from apathy to an opposite behavioral state that he proposed to call a “hyperpathy” to summarize what today would rather be defined as hyperdopaminergic behaviours (Fig. 4).¹³¹

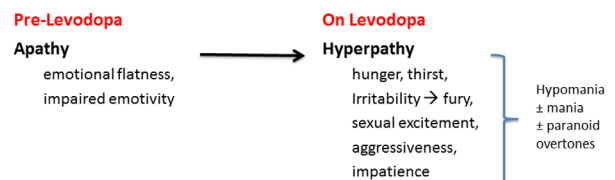


FIG. 4. Oliver Sacks already described a shift induced by dopaminergic medication from apathy to an opposite behavioral state that he proposed to call a “hyperpathy.” Adapted from Oliver Sacks’s notes from the time he was writing *Awakenings*, from Sacks O. *On the Move: A Life*. New York: Alfred A Knopf, a Division of Penguin Random House LLC; 2015.

The severity of the clinical hypodopaminergic syndrome, which reflects the extent of the dopaminergic lesion, seems to be the main risk factor for developing hyperdopaminergic behavioral complications and non-motor psychic fluctuations while on dopaminergic treatment.^{7,70,132} The pulsatility of dopaminergic treatment, selective D3-receptor stimulation, and duration of treatment are the main risk factors of pharmacological management to develop such behavioral complications (Fig. 3).^{7,132-136}

In conclusion, apathy, anxiety, depression, and fatigue can all be classified under the umbrella of hypodopaminergic syndrome. This is a pragmatic oversimplification, as dopamine is the main, but not the only, neurotransmitter involved. The concept of hypodopaminergia is useful, though, in the clinical management of PD patients, as all these symptoms can be improved with dopaminergic medication. It is important to detect the symptoms of hypodopaminergia, as they have a major impact on QOL.^{29,108} Symptoms can be improved with a positive effect on patients' QOL. However, their presence requires careful treatment strategies because hypodopaminergic symptoms might represent a risk factor for developing impulse control disorders, behavioral addictions, and dopamine dysregulation syndrome.⁷ In our view, this strategy should not be applied only after sensitization has taken place and the patient has already developed pathological hyperdopaminergic behavioral disorder, but should be started early on, as soon as patients start developing changes in behavior with hyperdopaminergic symptoms that do not correspond to psychiatric disease, to prevent excessive sensitization and severe pathology. Possible strategies should rely on highly fractionated low doses of L-dopa, associated with MAO-I and COMT-I, which have longer-lasting effects than L-dopa in isolation individually adapted doses of D3 receptor agonists not exceeding the threshold for clinical signs of hyperdopaminergic behavior and combination with nondopaminergic or with dopamine-sparing drugs whenever useful.⁷ ■

Acknowledgments: The work shown in Figure 1 was supported by the Institut National de la Santé et de la Recherche, Fondation Neurodis et Association France Parkinson. The work shown in Figure 2 was supported by the Agence Nationale de la Recherche, the Fondation pour la Recherche Médicale, the France Parkinson Association, the Federation Française pour le Groupement des Parkinsoniens, and UCB Pharma, as well as the Hospices Civils de Lyon.

References

1. Agid Y, Arnulf I, Bejjani P, et al. Parkinson's disease is a neuropsychiatric disorder. *Adv Neurol* 2003;91:365-370.
2. Aarsland D, Marsh L, Schrag A. Neuropsychiatric symptoms in Parkinson's disease. *Mov Disord* 2009;24:2175-2186.
3. Evans AH, Okai D, Lim S, et al. Scales to assess impulsive and compulsive behaviors in Parkinson's disease: critique and recommendations. *Mov Disord in press*.

4. Rieu I, Martinez-Martin P, Pereira B, et al. International validation of a behavioral scale in Parkinson's disease without dementia. *Mov Disord* 2015;30:705-713.
5. Weintraub D, David AS, Evans AH, Grant JE, Stacy M. Clinical spectrum of impulse control disorders in Parkinson's disease. *Mov Disord* 2015;30:121-127.
6. Ardouin C, Chereau I, Llorca PM, et al. [Assessment of hyper- and hypodopaminergic behaviors in Parkinson's disease]. *Rev Neurol (Paris)* 2009;165:845-856.
7. Sierra M, Carnicella S, Strafella AP, et al. Apathy and Impulse Control Disorders: Yin & Yang of Dopamine Dependent Behaviors. *J Parkinsons Dis* 2015;5:625-636.
8. Voon V, Mehta AR, Hallett M. Impulse control disorders in Parkinson's disease: recent advances. *Curr Opin Neurol* 2011;24:324-330.
9. Witjas T, Kaphan E, Azulay JP, et al. Nonmotor fluctuations in Parkinson's disease: frequent and disabling. *Neurology* 2002;59:408-413.
10. Halliday GM, Leverenz JB, Schneider JS, Adler CH. The neurobiological basis of cognitive impairment in Parkinson's disease. *Mov Disord* 2014;29:634-650.
11. Brown RG, Landau S, Hindle JV, et al. Depression and anxiety related subtypes in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2011;82:803-809.
12. Dissanayaka NN, Sellbach A, Matheson S, et al. Anxiety disorders in Parkinson's disease: prevalence and risk factors. *Mov Disord* 2010;25:838-845.
13. Gonera EG, van't Hof M, Berger HJ, van Weel C, Horstink MW. Symptoms and duration of the prodromal phase in Parkinson's disease. *Mov Disord* 1997;12:871-876.
14. Shiba M, Bower JH, Maraganore DM, et al. Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. *Mov Disord* 2000;15:669-677.
15. Jacob EL, Gatto NM, Thompson A, Bordelon Y, Ritz B. Occurrence of depression and anxiety prior to Parkinson's disease. *Parkinsonism Relat Disord* 2010;16:576-581.
16. Negre-Page L, Grandjean H, Lapeyre-Mestre M, et al. Anxious and depressive symptoms in Parkinson's disease: the French cross-sectional DoPaMiP study. *Mov Disord* 2010;25:157-166.
17. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. *Lancet Neurol* 2015;14:57-64.
18. de la Riva P, Smith K, Xie SX, Weintraub D. Course of psychiatric symptoms and global cognition in early Parkinson disease. *Neurology* 2014;83:1096-1103.
19. Weintraub D, Simuni T, Caspell-Garcia C, et al. Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. *Mov Disord* 2015;30:919-927.
20. Zis P, Martinez-Martin P, Sauerbier A, et al. Non-motor symptoms burden in treated and untreated early Parkinson's disease patients: argument for non-motor subtypes. *Eur J Neurol* 2015; 22:1145-1150.
21. Pont-Sunyer C, Hotter A, Gaig C, et al. The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). *Mov Disord* 2015;30:229-237.
22. Mirelman A, Alcalay RN, Saunders-Pullman R, et al. Nonmotor symptoms in healthy Ashkenazi Jewish carriers of the G2019S mutation in the LRRK2 gene. *Mov Disord* 2015;30:981-986.
23. Lin CH, Lin JW, Liu YC, Chang CH, Wu RM. Risk of Parkinson's disease following anxiety disorders: a nationwide population-based cohort study. *Eur J Neurol* 2015;22:1280-1287.
24. Burn DJ, Landau S, Hindle JV, et al. Parkinson's disease motor subtypes and mood. *Mov Disord* 2012;27:379-386.
25. Maricle RA, Nutt JG, Valentine RJ, Carter JH. Dose-response relationship of levodopa with mood and anxiety in fluctuating Parkinson's disease: a double-blind, placebo-controlled study. *Neurology* 1995;45:1757-1760.
26. Maricle RA, Valentine RJ, Carter J, Nutt JG. Mood response to levodopa infusion in early Parkinson's disease. *Neurology* 1998; 50:1890-1892.
27. Pontone GM, Williams JR, Anderson KE, et al. Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. *Mov Disord* 2009;24:1333-1338.

28. Dickson DW, Fujishiro H, Orr C, et al. Neuropathology of non-motor features of Parkinson disease. *Parkinsonism Relat Disord* 2009;15(Suppl 3):S1-S5.
29. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson's disease? *J Neurol Neurosurg Psychiatry* 2000;69:308-312.
30. Pontone GM, Bakker CC, Chen S, et al. The longitudinal impact of depression on disability in Parkinson disease. *Int J Geriatr Psychiatry* 2015 [Epub ahead of print].
31. Spalletta G, Robinson RG, Cravello L, et al. The early course of affective and cognitive symptoms in de novo patients with Parkinson's disease. *J Neurol* 2014;261:1126-1132.
32. Smith KM, Eyal E, Weintraub D. Combined rasagiline and antidepressant use in Parkinson disease in the ADAGIO study: effects on nonmotor symptoms and tolerability. *JAMA Neurol* 2015;72:88-95.
33. Rektorova I, Rektor I, Bares M, et al. Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. *Eur J Neurol* 2003;10:399-406.
34. Barone P, Poewe W, Albrecht S, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2010;9:573-580.
35. Ray Chaudhuri K, Martinez-Martin P, Antonini A, et al. Rotigotine and specific non-motor symptoms of Parkinson's disease: post hoc analysis of RECOVER. *Parkinsonism Relat Disord* 2013;19:660-665.
36. Antonini A, Bauer L, Dohin E, et al. Effects of rotigotine transdermal patch in patients with Parkinson's disease presenting with non-motor symptoms - results of a double-blind, randomized, placebo-controlled trial. *Eur J Neurol* 2015;22:1400-1407.
37. Korchounov A, Winter Y, Rossy W. Combined beneficial effect of rasagiline on motor function and depression in de novo PD. *Clin Neuropharmacol* 2012;35:121-124.
38. Group. PS. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. 1993;328:176-183.
39. Kulisevsky J, Pascual-Sedano B, Barbanj M, Gironell A, Pagonabarraga J, Garcia-Sanchez C. Acute effects of immediate and controlled-release levodopa on mood in Parkinson's disease: A double-blind study. *Mov Disord* 2007;22:62-67.
40. Rocha FL, Murad MG, Stumpf BP, Hara C, Fuzikawa C. Antidepressants for depression in Parkinson's disease: systematic review and meta-analysis. *J Psychopharmacol* 2013;27:417-423.
41. Troeung L, Egan SJ, Gasson N. A meta-analysis of randomised placebo-controlled treatment trials for depression and anxiety in Parkinson's disease. *PLoS One* 2013;8:e79510.
42. Bomasang-Layno E, Fadlon I, Murray AN, Himelhoch S. Antidepressive treatments for Parkinson's disease: A systematic review and meta-analysis. *Parkinsonism Relat Disord* 2015;21:833-842; discussion 833.
43. Menza M, Dobkin RD, Marin H, et al. A controlled trial of antidepressants in patients with Parkinson disease and depression. *Neurology* 2009;72:886-892.
44. Richard IH, McDermott MP, Kurlan R, et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. *Neurology* 2012;78:1229-1236.
45. Antonini A, Tesi S, Zecchinelli A, et al. Randomized study of sertraline and low-dose amitriptyline in patients with Parkinson's disease and depression: effect on quality of life. *Mov Disord* 2006;21:1119-1122.
46. Barone P, Scarzella L, Marconi R, et al. Pramipexole versus sertraline in the treatment of depression in Parkinson's disease: a national multicenter parallel-group randomized study. *J Neurol* 2006;253:601-607.
47. Ceravolo R, Nuti A, Piccinni A, et al. Paroxetine in Parkinson's disease: effects on motor and depressive symptoms. *Neurology* 2000;55:1216-1218.
48. Devos D, Dujardin K, Poirat I, et al. Comparison of desipramine and citalopram treatments for depression in Parkinson's disease: a double-blind, randomized, placebo-controlled study. *Mov Disord* 2008;23:850-857.
49. Weintraub D, Mavandadi S, Mamikonyan E, et al. Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. *Neurology* 2010;75:448-455.
50. Espay AJ, LeWitt PA, Kaufmann H. Norepinephrine deficiency in Parkinson's disease: the case for noradrenergic enhancement. *Mov Disord* 2014;29:1710-1719.
51. Matsui H, Nishinaka K, Oda M, et al. Depression in Parkinson's disease. Diffusion tensor imaging study. *J Neurol* 2007;254:1170-1173.
52. Feldmann A, Illes Z, Kosztolanyi P, et al. Morphometric changes of gray matter in Parkinson's disease with depression: a voxel-based morphometry study. *Mov Disord* 2008;23:42-46.
53. Kostic VS, Agosta F, Petrovic I, et al. Regional patterns of brain tissue loss associated with depression in Parkinson disease. *Neurology* 2010;75:857-863.
54. Skidmore FM, Yang M, Baxter L, et al. Apathy, depression, and motor symptoms have distinct and separable resting activity patterns in idiopathic Parkinson disease. *Neuroimage* 2013;81:484-495.
55. Surdhar I, Gee M, Bouchard T, Coupland N, Malykhin N, Camicioli R. Intact limbic-prefrontal connections and reduced amygdala volumes in Parkinson's disease with mild depressive symptoms. *Parkinsonism Relat Disord* 2012;18:809-813.
56. van Mierlo TJ, Chung C, Foncke EM, Berendse HW, van den Heuvel OA. Depressive symptoms in Parkinson's disease are related to decreased hippocampus and amygdala volume. *Mov Disord* 2015;30:245-252.
57. O'Callaghan C, Shine JM, Lewis SJ, Hornberger M. Neuropsychiatric symptoms in Parkinson's disease: fronto-striatal atrophy contributions. *Parkinsonism Relat Disord* 2014;20:867-872.
58. Mayberg HS, Starkstein SE, Sadzot B, et al. Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. *Ann Neurol* 1990;28:57-64.
59. Mentis MJ, McIntosh AR, Perrine K, et al. Relationships among the metabolic patterns that correlate with mnemonic, visuospatial, and mood symptoms in Parkinson's disease. *Am J Psychiatry* 2002;159:746-754.
60. Luo C, Chen Q, Song W, et al. Resting-state fMRI study on drug-naive patients with Parkinson's disease and with depression. *J Neurol Neurosurg Psychiatry* 2014;85:675-683.
61. Wen X, Wu X, Liu J, Li K, Yao L. Abnormal baseline brain activity in non-depressed Parkinson's disease and depressed Parkinson's disease: a resting-state functional magnetic resonance imaging study. *PLoS One* 2013;8:e63691.
62. Reijnders JS, Scholtissen B, Weber WE, Aalten P, Verhey FR, Leentjens AF. Neuroanatomical correlates of apathy in Parkinson's disease: A magnetic resonance imaging study using voxel-based morphometry. *Mov Disord* 2010;25:2318-2325.
63. Mayberg HS, Liotti M, Brannan SK, et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry* 1999;156:675-682.
64. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. *Neuron* 2005;45:651-660.
65. Huang P, Xuan M, Gu Q, et al. Abnormal amygdala function in Parkinson's disease patients and its relationship to depression. *J Affect Disord* 2015;183:263-268.
66. Cardoso EF, Maia FM, Fregni F, et al. Depression in Parkinson's disease: convergence from voxel-based morphometry and functional magnetic resonance imaging in the limbic thalamus. *Neuroimage* 2009;47:467-472.
67. Li W, Liu J, Skidmore F, Liu Y, Tian J, Li K. White matter microstructure changes in the thalamus in Parkinson disease with depression: A diffusion tensor MR imaging study. *AJNR Am J Neuroradiol* 2010;31:1861-1866.
68. Sheng K, Fang W, Su M, et al. Altered spontaneous brain activity in patients with Parkinson's disease accompanied by depressive symptoms, as revealed by regional homogeneity and functional connectivity in the prefrontal-limbic system. *PLoS One* 2014;9:e84705.
69. Hu X, Song X, Yuan Y, et al. Abnormal functional connectivity of the amygdala is associated with depression in Parkinson's disease. *Mov Disord* 2015;30:238-244.
70. Thobois S, Ardouin C, Lhommee E, et al. Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease:

- predictors and underlying mesolimbic denervation. *Brain* 2010;133:1111-1127.
71. Broussolle E, Dentresangle C, Landais P, et al. The relation of putamen and caudate nucleus 18F-Dopa uptake to motor and cognitive performances in Parkinson's disease. *J Neurol Sci* 1999;166:141-151.
 72. Koerts J, Leenders KL, Koning M, Portman AT, van Beilen M. Striatal dopaminergic activity (FDOPA-PET) associated with cognitive items of a depression scale (MADRS) in Parkinson's disease. *Eur J Neurosci* 2007;25:3132-3136.
 73. Weintraub D, Newberg AB, Cary MS, et al. Striatal dopamine transporter imaging correlates with anxiety and depression symptoms in Parkinson's disease. *J Nucl Med* 2005;46:227-232.
 74. Erro R, Pappata S, Amboni M, et al. Anxiety is associated with striatal dopamine transporter availability in newly diagnosed untreated Parkinson's disease patients. *Parkinsonism Relat Disord* 2012;18:1034-1038.
 75. Remy P, Doder M, Lees A, Turjanski N, Brooks D. Depression in Parkinson's disease: loss of dopamine and noradrenergic innervation in the limbic system. *Brain* 2005;128:1314-1322.
 76. Felicio AC, Moriyama TS, Godeiro-Junior C, et al. Higher dopamine transporter density in Parkinson's disease patients with depression. *Psychopharmacology (Berl)* 2010;211:27-31.
 77. Moriyama TS, Felicio AC, Chagas MH, et al. Increased dopamine transporter density in Parkinson's disease patients with social anxiety disorder. *J Neurol Sci* 2011;310:53-57.
 78. Ceravolo R, Frosini D, Poletti M, et al. Mild affective symptoms in de novo Parkinson's disease patients: relationship with dopaminergic dysfunction. *Eur J Neurol* 2013;20:480-485.
 79. Boileau I, Guttman M, Rusjan P, et al. Decreased binding of the D3 dopamine receptor-preferring ligand [11C](+)-PHNO in drug-naive Parkinson's disease. *Brain* 2009;132:1366-1375.
 80. Drevets WC, Frank E, Price JC, et al. PET imaging of serotonin 1A receptor binding in depression. *Biol Psychiatry* 1999;46:1375-1387.
 81. Savitz J, Lucki I, Drevets WC. 5-HT(1A) receptor function in major depressive disorder. *Prog Neurobiol* 2009;88:17-31.
 82. Qamhawi Z, Towey D, Shah B, et al. Clinical correlates of raphe serotonergic dysfunction in early Parkinson's disease. *Brain* 2015;138:2964-2973.
 83. Boileau I, Warsh JJ, Guttman M, et al. Elevated serotonin transporter binding in depressed patients with Parkinson's disease: a preliminary PET study with [11C]DASB. *Mov Disord* 2008;23:1776-1780.
 84. Politis M, Wu K, Loane C, et al. Depressive symptoms in PD correlate with higher 5-HTT binding in raphe and limbic structures. *Neurology* 2010;75:1920-1927.
 85. Ballanger B, Klinger H, Eche J, et al. Role of serotonergic 1A receptor dysfunction in depression associated with Parkinson's disease. *Mov Disord* 2012;27:84-89.
 86. Fox SH, Chuang R, Brotchie JM. Serotonin and Parkinson's disease: On movement, mood, and madness. *Mov Disord* 2009;24:1255-1266.
 87. Politis M, Wu K, Loane C, et al. Serotonin neuron loss and non-motor symptoms continue in Parkinson's patients treated with dopamine grafts. *Sci Transl Med* 2012;4:128ra141.
 88. Bonito-Oliva A, Masini D, Fisone G. A mouse model of non-motor symptoms in Parkinson's disease: focus on pharmacological interventions targeting affective dysfunctions. *Front Behav Neurosci* 2014;8:290.
 89. Drui G, Carnicella S, Carcenac C, et al. Loss of dopaminergic nigrostriatal neurons accounts for the motivational and affective deficits in Parkinson's disease. *Mol Psychiatry* 2014;19:358-367.
 90. Tadaiesky MT, Dombrowski PA, Figueiredo CP, Cargnin-Ferreira E, Da Cunha C, Takahashi RN. Emotional, cognitive and neurochemical alterations in a premotor stage model of Parkinson's disease. *Neuroscience* 2008;156:830-840.
 91. Caudal D, Alvarsson A, Bjorklund A, Svenningsson P. Depressive-like phenotype induced by AAV-mediated overexpression of human alpha-synuclein in midbrain dopaminergic neurons. *Exp Neurol* 2015;273:243-252.
 92. Bjorklund A, Dunnett SB. Dopamine neuron systems in the brain: an update. *Trends Neurosci* 2007;30:194-202.
 93. Delaville C, Chetrit J, Abdallah K, et al. Emerging dysfunctions consequent to combined monoaminergic depletions in Parkinsonism. *Neurobiol Dis* 2012;45:763-773.
 94. Lee M, Ryu YH, Cho WG, et al. Relationship between dopamine deficit and the expression of depressive behavior resulted from alteration of serotonin system. *Synapse* 2015;69:453-460.
 95. Dujardin K, Langlois C, Plomhause L, et al. Apathy in untreated early-stage Parkinson disease: relationship with other non-motor symptoms. *Mov Disord* 2014;29:1796-1801.
 96. Pagonabarraga J, Kulisevsky J, Strafella AP, Krack P. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. *Lancet Neurol* 2015;14:518-531.
 97. Cubo E, Benito-Leon J, Coronell C, Armesto D. Clinical correlates of apathy in patients recently diagnosed with Parkinson's disease: the ANIMO study. *Neuroepidemiology* 2012;38:48-55.
 98. den Brok MG, van Dalen JW, van Gool WA, Moll van Charante EP, de Bie RM, Richard E. Apathy in Parkinson's disease: A systematic review and meta-analysis. *Mov Disord* 2015;30:759-769.
 99. Pedersen KF, Alves G, Bronnick K, Aarsland D, Tysnes OB, Larsen JP. Apathy in drug-naive patients with incident Parkinson's disease: the Norwegian ParkWest study. *J Neurol* 2010;257:217-223.
 100. Santangelo G, Barone P, Cuoco S, et al. Apathy in untreated, de novo patients with Parkinson's disease: validation study of Apathy Evaluation Scale. *J Neurol* 2014;261:2319-2328.
 101. Santangelo G, Vitale C, Trojano L, et al. Relationship between apathy and cognitive dysfunctions in de novo untreated Parkinson's disease: a prospective longitudinal study. *Eur J Neurol* 2015;22:253-260.
 102. Skorvanek M, Gdovinova Z, Rosenberger J, et al. The associations between fatigue, apathy, and depression in Parkinson's disease. *Acta Neurol Scand* 2015;131:80-87.
 103. Czernecki V, Pillon B, Houeto JL, Pochon JB, Levy R, Dubois B. Motivation, reward, and Parkinson's disease: influence of dopaminergic therapy. *Neuropsychologia* 2002;40:2257-2267.
 104. Czernecki V, Schupbach M, Yaici S, et al. Apathy following subthalamic stimulation in Parkinson disease: a dopamine responsive symptom. *Mov Disord* 2008;23:964-969.
 105. Thobois S, Lhomme E, Klinger H, et al. Parkinsonian apathy responds to dopaminergic stimulation of D2/D3 receptors with piribedil. *Brain* 2013;136:1568-1577.
 106. Nirenberg MJ. Dopamine agonist withdrawal syndrome and non-motor symptoms after Parkinson's disease surgery. *Brain* 2010;133:e155; author reply e156.
 107. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med* 2013;368:610-622.
 108. Martinez-Fernandez R, Pelissier P, Quesada JL, et al. Postoperative apathy can neutralise benefits in quality of life after subthalamic stimulation for Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2016;87(3):311-318.
 109. Funkiewiez A, Ardouin C, Krack P, et al. Acute psychotropic effects of bilateral subthalamic nucleus stimulation and levodopa in Parkinson's disease. *Mov Disord* 2003;18:524-530.
 110. Devos D, Moreau C, Maltete 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;85:668-674.
 111. Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197-211.
 112. Hagell P, Brundin L. Towards an understanding of fatigue in Parkinson disease. *J Neurol Neurosurg Psychiatry* 2009;80:489-492.
 113. Morita A, Okuma Y, Kamei S, et al. Pramipexole reduces the prevalence of fatigue in patients with Parkinson's disease. *Intern Med* 2011;50:2163-2168.
 114. Schifitto G, Friedman JH, Oakes D, et al. Fatigue in levodopa-naive subjects with Parkinson disease. *Neurology* 2008;71:481-485.
 115. Lim TT, Kluger BM, Rodriguez RL, et al. Rasagiline for the symptomatic treatment of fatigue in Parkinson's disease. *Mov Disord* 2015;30:1825-1829.

116. Le Jeune F, Drapier D, Bourguignon A, et al. Subthalamic nucleus stimulation in Parkinson disease induces apathy: a PET study. *Neurology* 2009;73:1746-1751.
117. Robert G, Le Jeune F, Lozachmeur C, et al. Apathy in patients with Parkinson disease without dementia or depression: a PET study. *Neurology* 2012;79:1155-1160.
118. Huang C, Ravdin LD, Nirenberg MJ, et al. Neuroimaging markers of motor and nonmotor features of Parkinson's disease: an 18f fluorodeoxyglucose positron emission computed tomography study. *Dement Geriatr Cogn Disord* 2013;35:183-196.
119. Carriere N, Besson P, Dujardin K, et al. Apathy in Parkinson's disease is associated with nucleus accumbens atrophy: a magnetic resonance imaging shape analysis. *Mov Disord* 2014;29:897-903.
120. Robert GH, Le Jeune F, Lozachmeur C, et al. Preoperative factors of apathy in subthalamic stimulated Parkinson disease: a PET study. *Neurology* 2014;83:1620-1626.
121. Baggio HC, Segura B, Garrido-Millan JL, et al. Resting-state frontostriatal functional connectivity in Parkinson's disease-related apathy. *Mov Disord* 2015;30:671-679.
122. Brown CA, Campbell MC, Karimi M, et al. Dopamine pathway loss in nucleus accumbens and ventral tegmental area predicts apathetic behavior in MPTP-lesioned monkeys. *Exp Neurol* 2012; 236:190-197.
123. Tian L, Xia Y, Flores HP, Campbell MC, Moerlein SM, Perlmutter JS. Neuroimaging Analysis of the Dopamine Basis for Apathetic Behaviors in an MPTP-Lesioned Primate Model. *PLoS One* 2015;10:e0132064.
124. Santangelo G, Vitale C, Picillo M, et al. Apathy and striatal dopamine transporter levels in de-novo, untreated Parkinson's disease patients. *Parkinsonism Relat Disord* 2015;21:489-493.
125. Thobois S, Mailliet A, Metereau E, et al. Motor and nonmotor symptoms in drug-naive de novo Parkinsonian patients and their relationship to dopaminergic and serotonergic lesions. *Mov Disord* 2015;30 S25-S25
126. Visanji NP, Gomez-Ramirez J, Johnston TH, et al. Pharmacological characterization of psychosis-like behavior in the MPTP-lesioned nonhuman primate model of Parkinson's disease. *Mov Disord* 2006;21:1879-1891.
127. Carnicella S, Drui G, Boulet S, et al. Implication of dopamine D3 receptor activation in the reversion of Parkinson's disease-related motivational deficits. *Transl Psychiatry* 2014;4:e401.
128. Favier M, Duran T, Carcenac C, Drui G, Savasta M, Carnicella S. Pramipexole reverses Parkinson's disease-related motivational deficits in rats. *Mov Disord* 2014;29:912-920.
129. Evans AH, Lawrence AD, Potts J, et al. Relationship between impulsive sensation seeking traits, smoking, alcohol and caffeine intake, and Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2006;77:317-321.
130. Moccia M, Erro R, Picillo M, et al. Quitting smoking: an early non-motor feature of Parkinson's disease? *Parkinsonism Relat Disord* 2015;21:216-220.
131. Sacks O. *On the Move. A Life.* New York: Knopf AA; 2015.
132. Engeln M, Fasano S, Ahmed SH, et al. Levodopa gains psychostimulant-like properties after nigral dopaminergic loss. *Ann Neurol* 2013;74:140-144.
133. Bordet R, Ridray S, Carboni S, Diaz J, Sokoloff P, Schwartz JC. Induction of dopamine D3 receptor expression as a mechanism of behavioral sensitization to levodopa. *Proc Natl Acad Sci U S A* 1997;94:3363-3367.
134. Evans AH, Lawrence AD, Lees AJ. Changes in psychomotor effects of L-dopa and methylphenidate after sustained dopaminergic therapy in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2009;80:267-272.
135. Napier TC, Corvol JC, Grace AA, et al. Linking neuroscience with modern concepts of impulse control disorders in Parkinson's disease. *Mov Disord* 2015;30:141-149.
136. Lodge DJ, Grace AA. Amphetamine activation of hippocampal drive of mesolimbic dopamine neurons: a mechanism of behavioral sensitization. *J Neurosci* 2008;28:7876-7882.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site