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Imaging the Etiology of Apathy, Anxiety, and Depression in Parkinson's Disease: Implication for Treatment

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Abstract Apathy, depression, and anxiety are among the most important non-motor signs of Parkinson's disease (PD). This may be encountered at early stages of illness and represent a major source of burden. Understanding their pathophysiology is a major prerequisite for efficient therapeutic strategies. Anatomical and metabolic imaging studies have enabled a breakthrough by demonstrating that widespread abnormalities within the limbic circuits notably the orbitofrontal and anterior cingulate cortices, amygdala, thalamus, and ventral striatum are involved in the pathophysiology of depression, anxiety, and apathy in PD. Functional imaging has further shown that mesolimbic dopaminergic but also serotonergic lesions play a major role in the mechanisms of these three neuropsychiatric manifestations, which has direct therapeutic implications.

Keywords Apathy · Depression · Anxiety · Limbic system · Dopamine · Serotonin · Brain imaging

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Introduction

Psychiatric symptoms are among the most important non-motor signs in Parkinson's disease (PD). They represent a major source of disability for patients and encompass a large range of heterogeneous manifestations going from depression, anxiety, and apathy to impulse control disorders [1]. Some of these symptoms are induced by dopaminergic medications such as impulse control disorders (ICDs) while others relay on the disease pathophysiology itself [1–3]. Among the latter, apathy, depression, and anxiety are frequently combined and may be encountered at every stages of the disease and even predate the onset of motor symptoms [3].

Understanding the pathophysiology of depression, anxiety, and apathy in PD, in particular the respective role of dopaminergic versus non-dopaminergic denervation, appears crucial to propose tailored medical strategies. To reach this goal, in vivo brain imaging represents a major tool, with the help of magnetic resonance imaging (MRI) morphological imaging tools and functional imaging techniques either by positron emission tomography (PET), single photon emission tomography (SPECT), or functional MRI (fMRI). As shown in this review, these techniques provide an invaluable opportunity to better understand in vivo the neural basis of neuropsychiatric signs in PD.

Anatomical and Metabolic Correlates

Depression and Anxiety

PD-associated depression is linked with many anatomical changes within the limbic system. The temporal cortex, particularly the amygdala and hippocampus, has been shown, in some studies, to be atrophic with negative correlation to

depression severity, which could participate to mood/emotion learning deficits [4–6, 7•, 8, 9]. Furthermore anxiety trait in PD but not its severity is associated with left-sided amygdala atrophy [10•]. Interestingly, PET ^{18}F-fluorodésoxyglucose (FDG) and resting-state MRI reveal that depression severity increases with amygdala metabolism increase [11•, 12]. The amygdala playing a major role in integrating external stimuli and generating emotional responses, this could reflect an excessive and uncontrolled emotion processing in depressed PD patients [12]. In addition, amygdala connectivity with fronto-parietal areas [12] and limbic areas is reduced in depressed PD patients [13].

The role of the orbitofrontal cortex (OFC) in depression and anxiety in PD has also been particularly stressed in many MRI studies showing notably an atrophy of this region proportionally to the severity of depression [5, 6, 14, 15]. In addition, white matter changes within OFC and insular cortex are also observed in depressed PD subjects [16]. Furthermore, [^{18}F]-FDG and $H_2{}^{15}O$ PET studies have disclosed OFC hypometabolism in depressed and "simply dysphoric" PD patients [17, 18]. However, it has to be acknowledged that some fMRI studies have, on the opposite, shown increased resting-state activity in the OFC, which could be interpreted as an abnormally increased top-down control over limbic circuits, leading to abnormal avoidance behavior [19]. Altogether, these data point out the critical role of the OFC in depression in PD, which fits very well with its role in controlling the motivational value-based behaviors and thus their negative emotional states [20].

But, the implication of the prefrontal (PF) cortex in depression associated with PD is not limited to the OFC. Indeed, the severity of depression in PD is also predicted by the variations in the amplitude of low-frequency fluctuations measured by MRI at rest in the dorsolateral prefrontal cortex (DLPFC) and ventro-medial prefrontal cortex (vmPFC). This is of interest with respect to the role of DLPFC in executive functions and response selection and to the one of the vmPFC in providing the contextual value encoding, emotion, and perception processing [21, 22]. The role of PF cortex dysfunction in PD depression has also been underlined in perfusion studies showing reduced left superior and inferior frontal gyrus perfusion in depressed PD [23]. Finally, the reduction of left PF cortex thickness is correlated with the presence and severity of depression in PD [24].

An atrophy of the dorsal anterior cingulate cortex (ACC) in depression in PD has also been demonstrated in depressed and anxious PD patients [4–6, 7•, 8, 14, 15, 25]. This is interesting regarding the role of ACC in motivational processes, conflict monitoring, response initiation, social behaviors, and reward encoding. Therefore, this could explain the reduction of motivation to initiate actions observed in depressed PD subjects. The ventral part of the ACC as well plays an important role in the pathophysiology of depression in PD and a relationship between its activity and metabolism and depression-severity has been found [7•, 19, 26, 27].

Finally, subcortical regions are also implicated in PD depression pathophysiology, in particular the limbic part of the thalamus which has been found to be hypertrophic but also hypoactive during emotion perception [28, 29] as well as the caudate nucleus, which metabolism is diminished in depressed/anxious PD [11•, 17]. Furthermore, white matter abnormalities have been observed in the limbic thalamus, with reduced fractional anisotropy, proportional to depression severity [29].

More recently, a number of MRI connectivity studies have shown widespread alterations of connectivity within cortico-subcortical limbic circuits, which indicates that depression in PD is the consequence, beyond focal abnormalities, to global network dysfunction [12, 13, 19, 30–32]. Some authors point out a possible increased connectivity between limbic regions and a decreased connectivity within cortico-limbic networks which may reflect abnormal top-down control on emotion-related limbic regions [13, 31]. Finally diffusion tensor imaging approach has shown fiber tract disruption in the left hemisphere in depressed PD patients [33].

Apathy

The presence of apathy in PD is associated with several atrophies: an atrophy of the precuneus, which could participate to a lack of insight; an atrophy of the inferior parietal, frontal gyrus, and OFC, possibly responsible for difficulties in integrating information, in attention deficit and in dysexecutive syndrome; and an atrophy of the insula, which could be responsible for a deficit of emotional responsiveness [15, 25].

In addition, OFC metabolism and resting-state activity have been found to be increased in apathetic PD patients [1, 7•, 34, 35]. This could favor an abnormal top-down OFC control and, in turn, an excessive avoidance behavior. The dorsal ACC has also been shown to be atrophic in apathetic PD patients. Concomitantly, its metabolism is increased, possibly reflecting compensatory mechanism [4, 5, 7•, 8, 11•, 15, 25, 34]. Because of the multiple functions of the ACC in emotional self-control, problem solving, error recognition, and adaptive response to changing conditions, its dysfunction could play a major role in the cognitive and emotional components of apathy. A reduction of SMA activity was as well noted in apathy in PD and correlated to its severity. Because of SMA's role in motor programming and execution of intended action sequences, this could participate to the lack of motivation observed in apathetic patients [7•].

Subcortical regions are also involved in apathy, in particular the nucleus accumbens (also called ventral striatum), a region playing a major role in reward processing [20]. Being atrophic and abnormally shaped in apathetic subjects [36•], its hypometabolism is associated with a greater risk of becoming

apathetic after deep brain stimulation [37]. Of note, those PD stimulated patients becoming apathetic exhibit significantly greater metabolism within the cerebellum, brainstem (in particular ventral tegmental area), temporal lobe, insula, amygdala, lentiform nucleus, subgenual anterior cingulate, and inferior frontal gyrus before surgery, suggesting widespread preoperative compensatory mechanisms [38]. Beyond these abnormalities, the presence of apathy in PD is associated with diffuse-reduced functional connectivity within the cortico-subcortical limbic circuitry [39].

Finally, H_2O^{15} PET revealed in apathetic PD patients a blunted response to money in the vmPFC, amygdala, striatum, and midbrain [40], which belong to a neural circuit involved in the representation of the reward prediction of stimuli and actions and the influence of the motivational value (positive or negative) on behavioral choice (approach or avoidance) [41].

Neurotransmission Abnormalities

Depression and Anxiety

Role of Dopaminergic Lesions

SPECT or PET studies are usually performed in PD patients with dopamine D2 receptor tracer such as [^{11}C]-Raclopride [42••], dopamine metabolism marker as [^{18}F]-Dopa [43, 44], dopamine transporter (DAT) ligands such as [99m]Tc-TRODAT-1 [45] or I^{123}-FP-CIT [46–48], or [^{11}C]-RTI32, a dopamine and noradrenalin transporter ligand [49••]. Studies have shown that the presence of depression and anxiety and their severity at various stages of PD are mediated by mesolimbic dopaminergic degeneration. If many studies using DAT ligands have noted a reduction of tracer uptake in depression, it has to be acknowledged that some studies rather found an abnormal increase of DAT tracers binding in depressed or anxious patients, which could suggest an abnormally high dopamine clearance leading to a reduced dopamine tonus [50–52]. Furthermore, a combined PET [^{11}C]-PHNO (a predominant D3-receptor ligand) and [^{11}C]-raclopride (a mixed D2/D3 receptor ligand) study showed an association between lower mood and a greater dopamine D3 vs dopamine D2 receptor alteration in PD, in favor of the crucial role of mesolimbic dopaminergic pathway alteration [53]. Thus, although clarification is necessary regarding the DAT issue, the involvement of the dopaminergic system in depression associated with PD is a clear-cut finding.

Such involvement is further reinforced by pharmacological trials demonstrating a clear improvement of depression by dopamine agonist [54, 55••, 56–60]. Furthermore, in patients experiencing ICDs, the withdrawal of dopamine agonists may result in a "dopamine withdrawal syndrome" characterized notably by anxiety, depression, pain, and fatigue [61•].

Role of Serotonergic Lesions

Despite a large and recent I123-FP-CIT SPECT study finding no association between serotonergic lesions in the raphe nucleus and depression score in early-stage PD patients [62], convergent arguments support the implication of serotonergic alteration in depression in PD. PET studies using [^{11}C]-DASB, a serotonin transporter ligand, have shown increased tracer uptake, which could suggest excessive reuptake of serotonin [63••, 64]. On the other hand, [^{11}C]-DASB binding is reduced in the OFC, caudate, and putamen in non-depressed PD patients [65]. Furthermore, decreased postsynaptic serotonin 5-HT$_{1A}$ receptor density within limbic territories has been demonstrated using PET and [^{18}F]MPPF in depressed PD patients [66]. Further evidence came from the observation that depressive manifestations persist despite the restoration of dopaminergic innervation in grafted PD patients [67]. Very recently, it was demonstrated in de novo PD patients a clear relationship between 5-HT degeneration in widespread limbic regions and the presence of depression, which severity was correlated with subgenual ACC serotonergic denervation [68••]. The involvement of the 5-HT system was further suggested by transcranial sonography revealing that raphe echogenicity is reduced in depressed versus non-depressed PD patients [69, 70]. As for the dopaminergic hypothesis, pharmacological trials using serotonin reuptake inhibitors have also demonstrated improvement of depression in PD reinforcing the "serotonergic hypothesis" of depression in PD [71–77].

Role of Noradrenergic Lesions

One PET imaging study, using [^{11}C]-RTI-32, a dopamine and noradrenalin (NADR) transporter tracer, suggested a link between the presence of depression and the degree of noradrenergic lesions in the locus coeruleus and limbic areas such as the ACC, OFC, and amygdala [46]. However, as said before, the tracer used in this study does not distinguish the respective role of dopaminergic versus noradrenergic dysfunction in depression in PD. In addition, the absence of significant improvement of depression in PD using Atomoxetine, a NADR reuptake inhibitor, reduces the likelihood of an important role of noradrenalin denervation in depression pathophysiology [78].

Role of Cholinergic Lesions

Finally depression in PD also appears to be related to the importance of cholinergic alterations especially when cognitive decline is present [79•]. There is little evidence showing that increasing the level of acetylcholin via anticholinesterase inhibitor could improve depression in PD. However, one study performed in demented PD patients demonstrated

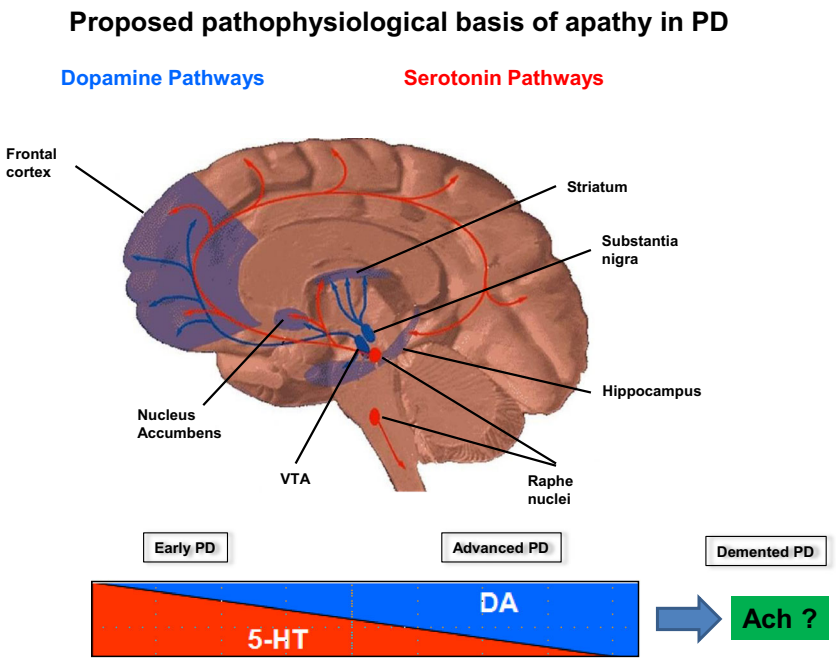


Fig. 1 Schematic representation of serotonergic and dopaminergic pathways. In early-stage PD, serotonergic lesions play a prominent role in the pathophysiology of apathy whereas the role of dopaminergic mesolimbic lesions becomes of greater importance in advanced PD. The role of cholinergic lesions in more advanced and cognitively impaired patients remains unknown

depression improvement with rivastigmine in such PD population [80].

Apathy

The role of mesolimbic dopaminergic denervation in the development of apathy has been particularly highlighted in advanced PD patients. Indeed, using [^{11}C]-Raclopride, it has been shown that the risk of becoming apathetic after deep brain stimulation is greater in PD patients presenting more severe dopaminergic denervation in mesocorticolimbic circuits [42••]. Another PET study using non-specific dopaminergic and noradrenergic [^{11}C]-RTI32 tracer also revealed the involvement of limbic dopaminergic but also possibly noradrenergic lesions in apathy, depression, and anxiety in PD [49••]. In de novo drug-naïve PD patients exhibiting apathy, greater dopaminergic denervation was also found in the right caudate nucleus [81], suggesting that dopaminergic denervation is linked to apathy regardless of disease-stage. The improvement of apathy by dopamine agonist reinforces this dopaminergic hypothesis [82, 83].

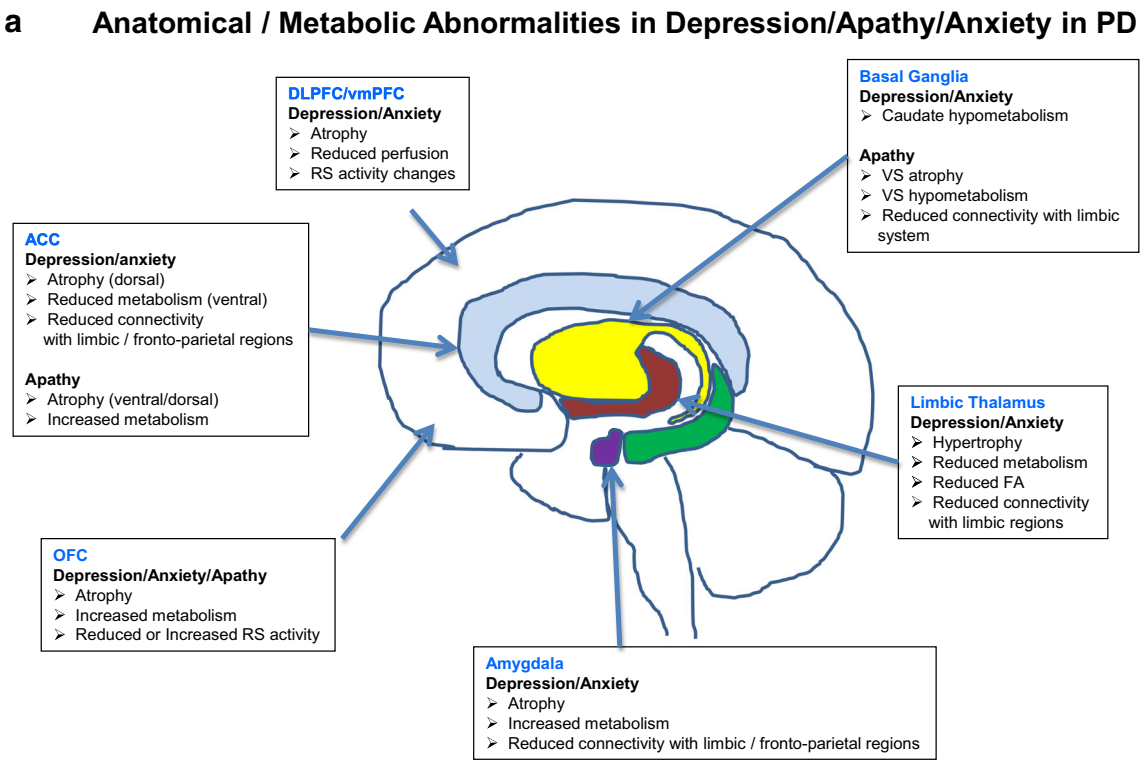
However, recent findings from our group reveal that pathological mechanisms underlying apathy may be different or more complex, depending on the disease-stage (and associated therapy) of PD patients. Indeed, we demonstrated in de novo PD patients a prominent role of serotonergic degeneration, especially within the basal ganglia network, as a key mechanism underlying apathy in early stage PD [68••]. However, the demonstration of an improvement of apathy in PD by selective serotonin reuptake inhibitor remains to be done. Conversely, we found a non-significant trend for greater dopaminergic denervation in both the mesencephalon and the ventral striatum in apathetic but also depressed and anxious patients, in agreement with a recent study showing that dopamine depletion does not contribute to apathy in de novo patients [84]. It has, however, to be acknowledged that this trend for greater limbic dopaminergic denervation in very specific limbic dopaminergic denervation would probably have become significant using a larger group of patients. Nevertheless, we could speculate that the respective role of dopaminergic and serotonergic dysfunction in apathy in PD might differ according to disease stage, the serotonergic system disruption being predominant in early PD, and the dopaminergic one becoming more important later in the disease (Fig. 1). This will need to be firmly demonstrated by "true" longitudinal and multitracer studies but also via local and systemic modulation of serotonergic and dopaminergic systems in the ventral striatum in non-human primates [85•].

And, the story probably does not end here, as Devos et al. (2014) showed in apathetic but depression- and dementia-free PD patients that apathy could be improved by anticholinesterase inhibitor drugs [86•]. Therefore, studying the role of cholinergic tonus in parkinsonian apathy could be of great interest as well.

The most important results are summarized in Fig. 2a, b.

Conclusion

Imaging studies using various approaches have provided important clues for a better understanding of depression, apathy, and anxiety pathophysiology in PD. Widespread dysfunction of the limbic system has been observed as well as complex neurotransmission abnormalities. Things are probably even



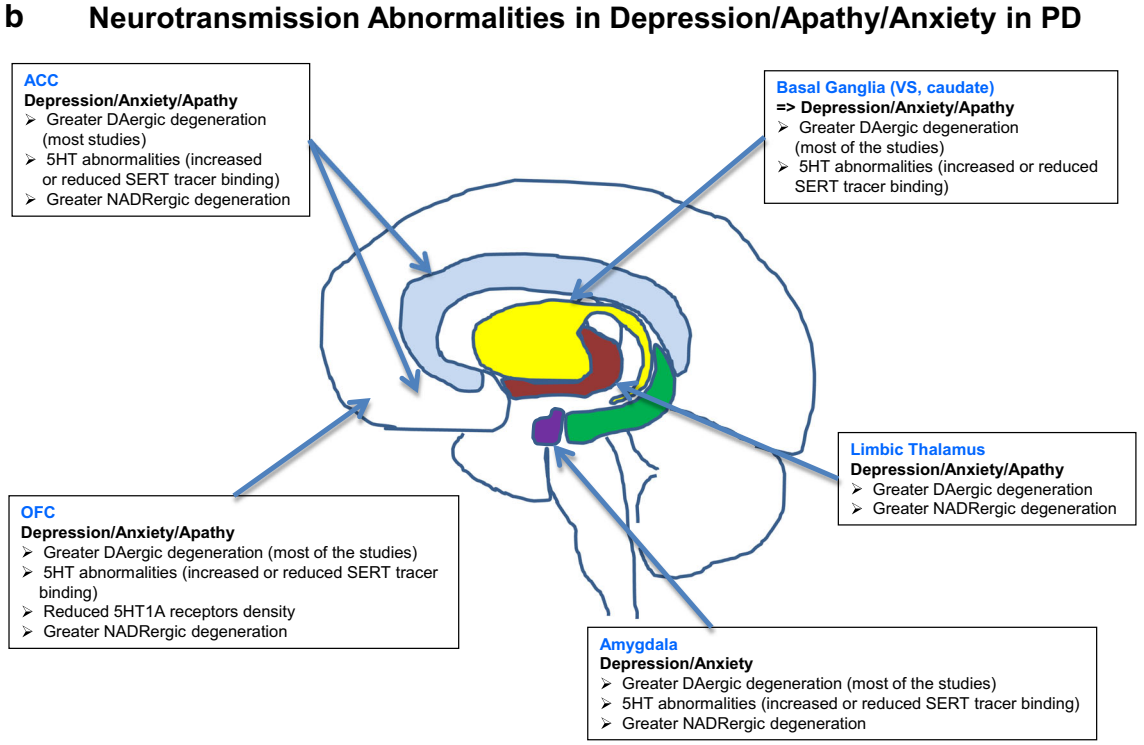


Fig. 2 **a** This schematic representation of the brain illustrates the main anatomical and metabolic abnormalities found in depression, anxiety, and apathy in Parkinson's disease. **b** This schematic representation of the brain illustrates the main neurotransmission abnormalities found in depression, anxiety, and apathy in Parkinson's disease. Abbreviations: *DLPFC* dorsolateral prefrontal cortex, *vmPFC* ventromedial prefrontal cortex, *VS* ventral striatum, *OFC* orbitofrontal cortex, *ACC* anterior cingulate cortex, *RS* resting state, *FA* Fractional anisotropy

more complex when considering that, for a same manifestation, pathophysiology may vary according to disease stage. Therefore, there is a need for multitracer and multimodal imaging studies to gain a more holistic view of the mechanisms of this triad and, in turn, propose new therapeutic avenues depending on the symptomatic and lesion profiles of the patients.

Compliance with Ethical Standards

Conflict of Interest Stephane Thobois reports grants from Fondation pour la Recherche Médicale, France Parkinson, and from Fondation Neurodis and personal fees from UCB, Medtronic, Teva, St Jude, Novartis and Aguettant. Dr. Thobois has received congress fees reimbursement from Abbvie, TEVA and Zambon

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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