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DOI:

[10.1016/bs.im.2018.08.002](https://doi.org/10.1016/bs.im.2018.08.002)

Document Version

Peer reviewed version

[Link to publication record in King's Research Portal](#)

Citation for published version (APA):

Pagano, G., & Politis, M. (2018). Molecular Imaging of the Serotonergic System in Parkinson's Disease. *International Review of Neurobiology*. <https://doi.org/10.1016/bs.im.2018.08.002>

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Molecular Imaging of the serotonergic system in Parkinson's disease

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Abstract (words): 195

Word count: 8,441

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1. ABSTRACT

In the last decades, the main focus of molecular imaging of Parkinson's disease has been on non-dopaminergic systems involved in the disease alongside the pathognomonic dopaminergic changes. Molecular imaging can detect, *in vivo*, both presynaptic and postsynaptic serotonergic changes in the brain and has played a key role in elucidating the pathophysiology of the serotonergic system in Parkinson's disease. Alterations in the serotonergic system may happen very early in the course of the disease and have shown a leading role in the development of tremor and dyskinesias, and in several non-motor symptoms, including sleep, cognitive and neuropsychiatric disturbances. These studies increasingly recognize that the regional topography of serotonergic brain areas associates with specific dysfunctions. In parallel with this trend, more recent molecular serotonergic imaging approaches are investigating serotonergic modulatory treatment and their contributions to the improvement of cognitive functions. In this review, we discussed *post-mortem*, preclinical and imaging evidence of serotonergic system changes in Parkinson's disease, and described how disease-specific serotonergic changes are relevant for motor and non-motor symptoms and complications. Future directions of serotonergic imaging have been also described alongside with the novel findings on the role of serotonergic system in asymptomatic LRRK2 carriers.

Key words

Serotonin; Parkinson's disease; Sleep; Depression; Cognition; DASB; Tremor; Dyskinesias.

2. INTRODUCTION

Parkinson's disease (PD) is one of the most common neurodegenerative diseases and is characterized by cardinal motor symptoms, including tremor, bradykinesia, and rigidity (Pagano, Ferrara, Brooks, & Pavese, 2016; Pagano, Polychronis, et al., 2018), mainly due to a deficit of dopaminergic terminals. PD patients also experience a plethora of non-motor symptoms, including sleep problems (Pagano, Molloy, et al., 2016; H. Wilson, Giordano, Turkheimer, Chaudhuri, & Politis, 2018; Yousaf, Pagano, Niccolini, & Politis, 2018a, 2018b), depression (Politis, Wu, Loane, Turkheimer, et al., 2010), chronic fatigue (Pavese, Metta, Bose, Chaudhuri, & Brooks, 2010), weight loss (Politis, Loane, Wu, Brooks, & Piccini, 2011), constipation (Pagano, Tan, Haider, Bautista, & Tagliati, 2015; Pagano, Yousaf, et al., 2018), urinary dysfunction (Pagano, Niccolini, Yousaf, et al., 2017), cognitive (Niccolini et al., 2017; Schulz, Pagano, Fernandez Bonfante, Wilson, & Politis, 2018) and neuropsychiatric disturbances (Maillet et al., 2016; Politis, Wu, Loane, Turkheimer, et al., 2010; Schrag & Politis, 2016). The development of non-motor symptoms is mainly due to the dysfunction of non-dopaminergic terminals (Qamhawi et al., 2015).

The pathognomonic diagnostic feature of PD is a loss of dopaminergic neurons in the substantia nigra pars compacta (Jellinger, 1991) and the main pathological process is the accumulation of Lewy body pathology. However, Lewy body pathology is not confined to the dopaminergic system but involves also the serotonergic, cholinergic and noradrenergic systems (Buddhala et al., 2015; Kish, 2003). According to the Braak's staging theory of PD, pathological processes begin early in the serotonergic raphe nuclei, prior to the onset of motor symptoms, and precede damage of the substantia nigra (Braak et al., 2003). Furthermore, *post-mortem* studies (Buddhala

et al., 2015; Kish et al., 2008), have shown that the serotonergic system is damaged in PD, with loss of synaptic terminals in serotonin-containing neurons including the raphe nuclei (Paulus & Jellinger, 1991).

Serotonin, also called 5-hydroxytryptamine (5-HT), is one of the most widely distributed and the serotonergic system virtually innervates all brain areas (Fox, Chuang, & Brotchie, 2009). This diversity of function is manifested by the large number and wide distribution of 5-HT receptors (Fox et al., 2009). To date, there are 14 distinct subtypes of the 5-HT receptor, with many more isoforms; this large number has been suggested to reflect the fact that the 5-HT system is one of the oldest neurotransmitter systems in evolutionary terms and has thus had the longest to diversify (Fox et al., 2009).

Positron emission tomography (PET) molecular imaging is a powerful analytical method to detect *in vivo* changes in the brain (Pagano, Niccolini, & Politis, 2016; Pagano, Yousaf, & Politis, 2017; Politis & Niccolini, 2015; Politis, Pagano, & Niccolini, 2017; Roy, Niccolini, Pagano, & Politis, 2016). PET used together with specific serotonin radioligands has played a key role in elucidating the pathophysiology of serotonergic system in PD (Pagano, Niccolini, Fusar-Poli, & Politis, 2017; Pagano, Niccolini, & Politis, 2017).

In this review, we will discuss *post-mortem*, preclinical and imaging evidence suggesting serotonergic system changes in PD. We will also review molecular serotonergic imaging studies in PD and discuss how disease-specific serotonergic changes are relevant for motor and non-motor symptoms and motor complications. Finally, we will discuss novel findings on the role of

the serotonergic system in familial PD, focusing on asymptomatic carriers of the leucine-rich kinase 2 (LRRK2) gene mutation.

3. MOLECULAR IMAGING TECHNIQUES TO STUDY SEROTONERGIC SYSTEM CHANGES IN PARKINSON'S DISEASE

Molecular imaging ligands have been developed for PET to allow *in vivo* visualization of presynaptic 5-HT transporter (SERT) and post-synaptic serotonergic receptors targets. Figure 1 provides an overview of the major serotonergic imaging ligands currently available for studies in humans.

**** Insert Figure 1 ****

The first PET tracer developed to image the SERT levels was the [¹¹C]McN5652 (Suehiro, Scheffel, Ravert, Dannals, & Wagner, 1993; Szabo et al., 1995; Szabo et al., 2002; Szabo et al., 1999). [¹¹C]McN5652 has a relatively high specificity and selectivity for the SERT (Szabo et al., 1999), with a tracer distribution that correlates well with the known distribution of the SERT in humans, and yields a reliable assessment of SERT binding with a documented loss of 5-HT innervation (McCann, Szabo, Scheffel, Dannals, & Ricaurte, 1998; Scheffel et al., 1998). Kerenyi and colleagues employed [¹¹C]McN5652 to study the serotonergic system in PD (Kerenyi et al., 2003). The [¹¹C]McN5652 binding was quantified with the (apparent) total distribution volume that was derived from a 1-compartment, 3-parameter model (Szabo et al., 1999). The distribution volume of specific binding was calculated as $(DV_{total} - DV_{cer})/DV_{cer}$, where DV_{cer} is the radioligand distribution volume in the cerebellum (Frey et al., 1996). They evaluated 13 patients

with idiopathic PD compared to 13 normal controls by using [^{11}C]McN5652 PET to assess the SERT availability, [^{11}C]WIN35428 PET to assess the dopamine transporter (DAT) and [^{15}O]H $_2$ O PET to assess the blood flow (Kerenyi et al., 2003). Binding of [^{11}C]McN5652 was reduced in the caudate and the putamen of PD patients along with the expected reductions in striatal [^{11}C]WIN35428 binding. The distribution volume of the cerebellum, used to assess non-specific binding of [^{11}C]McN5652, was not statistically different between controls and PD patients, with no significant covariance effect of age. Unlike [^{11}C]WIN35428, [^{11}C]McN5652 binding was not disproportionately reduced in striatal nuclei contralateral to the more affected side of the body among PD patients with asymmetric tremor or rigidity. A trend for reduced [^{11}C]McN5652 binding in the thalamus was also observed. There were no reductions in regional cerebral blood flow or the sizes of the regions of interest, brain atrophy, or partial volume effects. Reductions in [^{11}C]McN5652 binding correlated with ratings of UPDRS-III disease staging. However, despite these promising findings, in regions with moderate-to-low SERT density, the quantification of [^{11}C]McN5652 is not so reliable due to high non-specific binding and [^{11}C]McN5652 scans required long imaging sessions in order to acquire accurate SERT measures (Frankle et al., 2004).

To overcome the limitations of the first generation PET ligand for SERT, a tracer called [^{11}C]-3-Amino-4-(2-dimethylaminomethylphenylsulfaryl)-benzonitrile ([^{11}C]DASB) was developed (A. A. Wilson et al., 2000). [^{11}C]DASB is a second generation PET ligand with higher selectivity for the SERT (compared to [^{11}C]McN5652, [^{11}C]DASB is three orders of magnitude more selective for SERT than for DAT or noradrenaline transporter) (Hummerich et al., 2004; A. A. Wilson et al., 2000; A. A. Wilson, Jin, Garcia, DaSilva, & Houle, 2001), and higher specific-to-nonspecific binding ratios (Frankle et al., 2004). Recently, the different approaches used for the quantification

of cerebral SERT binding using the tracer [^{11}C]DASB have been reviewed (Norgaard et al., 2018). One-hundred and five original research articles published by 21 different PET centers have used [^{11}C]DASB PET imaging, showing reliable results when a given preprocessing pipeline was applied (Norgaard et al., 2018).

Over the past years [^{11}C]DASB PET studies have demonstrated SERT changes in patients with PD (Pagano, Niccolini, Fusar-Poli, et al., 2017), which were associated with the development of tremor, dyskinesias, and non-motor symptoms such as depression, weight changes and fatigue. [^{11}C]DASB PET has been also employed to investigate associations between SERT changes and olfactory dysfunction, rapid eye movement sleep behavior disorder, and sleep-disordered breathing in PD without significant correlations (Pagano, Niccolini, Fusar-Poli, et al., 2017). [^{11}C]DASB binding in early PD patients has been reported either reduced or within normal levels (Pagano, Niccolini, Fusar-Poli, et al., 2017). Only studies in PD depression demonstrated relative increased [^{11}C]DASB binding in patients with PD depression compared to non-depressed PD patients (Pagano, Niccolini, Fusar-Poli, et al., 2017).

We recently systematically reviewed all [^{11}C]DASB PET studies in PD (Pagano, Niccolini, Fusar-Poli, et al., 2017). The serotonergic system was investigated in 234 PD patients across 20 PET studies. PD patients showed a reduction of serotonergic terminals in the raphe nuclei, thalamus, hypothalamus, ventral striatum, caudate and putamen, which correlated with the duration of the disease.

PET imaging has also been employed to assess 5-HT receptors *in vivo*. [¹⁸F]MPPF for 5-HT_{1A}, [¹⁸F]setoperone for 5-HT_{2A}, and [¹¹C]AZ10419369 for 5-HT_{1B} receptors are some of the examples of selective PET tracers available for studying the serotonin system in the human brain (Ballanger et al., 2012; Ballanger et al., 2010; Costes et al., 2007; Varnas et al., 2011). 5-HT receptors are a group of G protein-coupled receptor and ligand-gated ion channels expressed in the brain and in the peripheral nervous systems (Beliveau et al., 2017). 5-HT receptors are activated by the neurotransmitter 5-HT and involved in both excitatory and inhibitory neurotransmission. The main role of the 5-HT receptors is to modulate the release of other neurotransmitters, including glutamate, GABA, dopamine, noradrenaline, and acetylcholine and, thus, influencing several processes, including aggression, anxiety, appetite, cognition, learning, memory, mood, nausea, sleep, and thermoregulation. They are targets of a variety of pharmaceutical and recreational drugs, including antidepressants, antipsychotics, anorectics, antiemetics, gastroprokinetic agents, antimigraine agents, hallucinogens, and entactogens (Johnston, Lu, & Rudd, 2014). There are several PET ligands that can bind to 5-HT receptors, as indicated in Table 1.

** Insert Table 1 **

4. SEROTONERGIC SYSTEM CHANGES IN PARKINSON'S DISEASE

The vast majority of 5-HT producing-cells are located in a group of nuclei in the brainstem defined as the raphe. The raphe nuclei are subdivided on the basis of their distribution and main projections into two groups: the rostral raphe with major projections to the forebrain innervating the striatum and the limbic system (hypothalamus, amygdala, cingulum, the medial cerebral cortex and part of the hippocampus), and the caudal raphe with major projections to the caudal brainstem and to the spinal cord (Hornung, 2003). Several functions have been attributed to the serotonergic system including cognition, emotion and motor behavior; thus, altered serotonergic neurotransmission may contribute to the motor and non-motor features commonly associated with PD (Politis & Niccolini, 2015; Politis et al., 2017). Evidence from animal and human studies has suggested that striatal serotonergic terminals may contribute in the development of LIDs by promoting a non-physiological release of dopamine (Pagano, Niccolini, & Politis, 2017; Politis & Niccolini, 2015; Politis et al., 2017; Politis et al., 2014).

4.1. Post-mortem studies

In early *post-mortem* studies of patients with PD, depletion of 5-HT in the caudate as well as hypothalamus and frontal cortex was reported, although not to the same degree as dopamine loss (Hartmann, 2004). A recent pathological study has confirmed some of these findings, showing preferential loss of 5-HT in the caudate compared with the putamen, but with relatively less loss of 5-HT (66%) than dopamine (98%) (Kish et al., 2008). The common link between neurodegeneration in the serotonergic system may be the presence of Lewy bodies, which stresses their importance in PD pathogenesis and explains the high prevalence of depression (Politis, Wu, Loane, Turkheimer, et al., 2010), dementia (Kotagal, Spino, Bohnen, Koeppe, & Albin, 2018),

and sleep disorders in PD (H. Wilson et al., 2018). According to Braak's staging, the pathological process in PD occurs in a gradual ascending fashion, starting from the olfactory nucleus and the medulla in presymptomatic stages and spreading to the pons and midbrain later (Braak et al., 2003). In Braak stage 2, Lewy body and Lewy neurite deposition occurs within the median raphe nuclei containing the serotonergic neurons of the caudal brainstem (Braak et al., 2003). These data suggest that caudal brainstem serotonergic neurons are affected before dopaminergic midbrain neurons while in the midbrain the two systems should be affected simultaneously.

4.2. Preclinical studies

Experimental studies have demonstrated a key role of the serotonergic system in the development of LIDs and of non-motor symptoms, including sleep-related disturbances. In preclinical models of PD induced by 6-hydroxy (6-OH) dopamine, the number of striatal serotonin terminals has been associated with both striatal dopamine peaks and abnormal involuntary movements (AIMs) scores (Gil, Park, Lee, Minn, & Koh, 2011). In addition, it has been demonstrated that dopamine release from serotonergic terminals is ectopic in terms of both subcellular release sites and anatomical distribution. The lesion induced by 6-OH dopamine is associated with a large increase in dopamine levels after levodopa administration in several brain areas, including the hippocampus and prefrontal cortex, richly innervated by serotonergic pathways. These increases are totally abolished by a complete lesion of serotonin neurons (Navailles, Bioulac, Gross, & De Deurwaerdere, 2010). The AIMs are alleviated by removing striatal serotonin afferents (Carta, Carlsson, Kirik, & Bjorklund, 2007) and by blocking serotonergic transmission with 5-HT_{1A} and 5-HT_{1B} agonists (Bezard et al., 2013; Eskow, Gupta, Alam, Park, & Bishop, 2007; Munoz et al., 2009; Munoz et al., 2008). However, low doses of 5-HT_{1A} and 5-HT_{1B} agonists are able to

suppress only the mild levodopa-induced AIMs, but they do not reduce the moderate-severe apomorphine-induced AIMs (Munoz et al., 2009). These findings confirm that the activation of pre-synaptic receptors account for the effect of combined low doses of 5-HT_{1A} and 5-HT_{1B} agonists on mild dyskinesias, whereas other mechanisms may explain the more severe apomorphine-induced AIMs. These results have been confirmed in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) monkey models of PD (Bezard et al., 2013; Rylander et al., 2010). MPTP monkeys show increased serotonergic terminals in the striatum (Rylander et al., 2010) and a positive anti-dyskinetic effect of 5-HT_{1A} and 5-HT_{1B} agonist anpirtoline (Bezard et al., 2013). This evidence further confirms an abnormal sprouting of serotonin terminals in PD, suggesting a key role of serotonergic system in the development of LIDs.

In terms of non-motor symptoms, the lesion of raphe nuclei is associated with lower brain levels of serotonin and the development of reduction of sleep in experimental models (Jouvet, 1972). In experimental studies with sleep deprivation, it has been found a reduction of the SERT (by using [¹¹C]DASB PET) in the anterior olfactory nucleus and substantia nigra in rats that have been deprived of sleep when compared to control rats without sleep deprivation (Hipolide et al., 2005).

4.3.Imaging studies

Over the past years [¹¹C]DASB PET studies have demonstrated SERT changes in patients with PD. Staging of SERT dysfunction in PD patients has shown reductions of [¹¹C]DASB binding in the caudate, thalamus, hypothalamus, and anterior cingulate cortex in early PD patients followed by additional [¹¹C]DASB binding reductions in the putamen, insula, posterior cingulate cortex,

and prefrontal cortex in patients with established PD (Politis, Wu, Loane, Kiferle, et al., 2010). Advanced PD patients showed further [^{11}C]DASB binding reductions in the ventral striatum, raphe nuclei and amygdala. A recent meta-analysis of [^{11}C]DASB PET imaging studies have shown that PD patients have a reduction of serotonergic terminals in the raphe nuclei, thalamus, hypothalamus, ventral striatum, caudate and putamen, which correlates with the duration of the disease (Pagano, Niccolini, Fusar-Poli, et al., 2017). This suggests that the progressive loss of synaptic terminals in PD affects the serotonergic system and is not only confined to the dopaminergic terminals. However, PD patients who experienced LIDs showed preserved serotonergic terminals compared to PD patients with stable response to levodopa. These findings indicate that although serotonergic system progressively degenerates in PD disease, those who develop LIDs have an aberrant spreading of serotonergic terminals or a faster degeneration of dopaminergic than serotonergic terminals. Several imaging studies have been performed aiming to understand the how disease-specific serotonergic changes are relevant for motor and non-motor symptoms and complications. These studies are described below in each specific paragraph.

5. SEROTONERGIC SYSTEM CHANGES AND MOTOR SYMPTOMS IN PARKINSON'S DISEASE

The development of tremor in PD has been speculated to be underlined by non-dopaminergic mechanisms due to the fluctuating response of this symptom to dopaminergic supplementation and the lack of correlations with dopaminergic molecular imaging markers. PET studies with [^{11}C]DASB have shown reduced binding in the caudate, putamen, raphe nuclei and thalamus of tremor-dominant PD patients when compared with those who had akinetic-rigid phenotype, and a correlation between [^{11}C]DASB binding in the caudate, putamen and raphe nuclei and tremor

scores (Loane et al., 2013). Serotonergic pathology has also been associated with the development of the motor complications LIDs and graft-induced dyskinesias (GIDs) (Pagano, Niccolini, & Politis, 2017). Parkinson's patients who experienced LIDs and GIDs have an aberrant spreading of serotonergic terminals, which lead to an increased serotonergic/dopaminergic terminals ratio within the putamen. Serotonergic terminals convert exogenous levodopa into dopamine in a non-physiological manner and release an abnormal amount of dopamine without an auto-regulatory feedback. This results in higher swings in synaptic levels of dopamine, which leads to the development of LIDs and GIDs. The modulation of serotonergic terminals with 5-HT_{1A} and 5-HT_{1B} receptors agonists partially reduced these motor complications. However, other systems also play a role in the development of these motor complications (Pagano, Niccolini, & Politis, 2017).

5.1.Tremor

Tremor is considered one of the diagnostic feature of PD, but also the most difficult to diagnose. Although is usually asymmetric and mainly present on the most affected side of the body during rest, it can also be seen on the “wrong side” of the body (contralateral to the side of more severe bradykinesia) and “in action” often with a short pause in the transition from rest to posture. This has been called re-emergent tremor but also other type of tremors are present in PD. Some patients show a distinct postural tremor clearly different from re-emergent tremor based either on the frequency (which is often faster than resting tremor) or the lack of tremor at rest. Another postural tremor can be essential tremor, and there is an increased incidence of PD in patients with essential tremor. It also can be dystonic tremor, and this might even look similar to classic tremor and has been suggested that the scans without evidence of dopamine deficiency patients have dystonic

tremor (Taylor et al., 2016). Additionally, a patient can have an exaggerated physiological tremor. However, the so-called “re-emergent tremor” is currently considered a variant of resting tremor and should be differentiated from the postural tremor typically observed in patients with essential tremor and from the physiological tremor typically observed in the elderly (Belvisi et al., 2017). Considering its complexity, it is easy to understand why tremor is one of the most challenging symptoms to manage in clinic, with a poor and unpredictable response to treatment compared to bradykinesia and rigidity (Koller & Hubble, 1990). Evidence from PET and SPECT molecular imaging studies have shown that dopamine transporter is less affected in tremor-dominant compared with akinetic-rigid patients and that tremor does not correlate with dopamine transporter levels, assessed with [^{123}I]FP-CIT SPECT (Asenbaum et al., 1998), dopamine terminal capacity, assessed with [^{18}F]FDOPA PET (Brooks et al., 1992), nor dopamine D2 receptor availability, assessed with [^{11}C]raclopride PET (Pavese et al., 2006), which suggests that this symptom could be associated with non-dopaminergic mechanisms.

PET imaging studies have been performed in PD patients with tremor using [^{11}C]WAY100635 (Doder et al., 2003), a selective marker of 5-HT_{1A} receptors, and [^{11}C]DASB (Loane et al., 2013), a selective marker of SERT levels. In the first study, they found in 26 PD patients compared to 8 healthy controls that midbrain raphe 5-HT_{1A} binding was reduced by 27% in PD patients and there was a correlation between reductions in midbrain raphe 5-HT_{1A} binding and the severity of resting tremor (Doder et al., 2003). In the second study, we found in 12 patients with tremor dominant PD, compared to 12 with akinetic-rigid PD, and 12 healthy controls, that SERT was reduced by 30% in the caudate, putamen, raphe nuclei, thalamus, and Brodmann areas 4 and 10 in patients with tremor-dominant PD and there was a correlation between reductions in caudate,

putamen, and raphe nuclei [^{11}C]DASB binding and the severity of postural and action tremor. It is important to underline that the scale used to quantify the tremor (MDS-UPDRS) cannot differentiate between postural and “re-emergent tremor”, thus, it is possible to speculate that the findings of the [^{11}C]DASB study could actually show a correlation between SERT and this specific form of resting tremor, in line with the findings of [^{11}C]WAY100635 study. However, in the [^{11}C]DASB study, no correlations were found between SERT levels and tremor at-rest scores, which further confirms the complexity of tremor in PD suggesting that more than one mechanisms is involved in the development of this symptom.

5.2. Dyskinesias

Levodopa induces sharp increases in striatal dopamine levels, which are particularly elevated in PD patients who experience LIDs (Pagano, Niccolini, Fusar-Poli, et al., 2017). However, a moderate-to-severe loss of dopaminergic terminals in the dorsal putamen is a necessary condition for the development of LIDs, This is associated with the inability of remaining dopaminergic terminals to remove the released dopamine and to store it into the pre-synaptic vesicles. In these circumstances, the same amount of levodopa administered induces higher release of dopamine in the extracellular space (augmented dopamine percent change from basal levels) (Lindgren, Andersson, Lagerkvist, Nissbrandt, & Cenci, 2010). This results in higher swings in synaptic levels of dopamine and pulsatile stimulation of postsynaptic receptors located on striatal projection neurons (Pagano, Niccolini, Fusar-Poli, et al., 2017). At the same time, in absence of enough intact dopaminergic terminals, exogenous levodopa is metabolized in other terminals expressing the enzyme aromatic L-amino acid decarboxylase, such as serotonergic, which do not possess the molecular machinery to properly control the release of dopamine (Carta, Carlsson,

Munoz, Kirik, & Bjorklund, 2010). Since serotonergic neurons lack of an auto-regulatory feedback of dopamine release, serotonergic terminals will release dopamine in a non-physiological manner. This results in higher swings in synaptic levels of dopamine and pulsatile stimulation of post-synaptic receptors located on striatal projection neurons (Carta & Bezard, 2011).

Four [^{11}C]DASB PET studies have been performed in PD patients, investigating the LIDs. In the first PET study (Politis et al., 2014), we compared PD patients with LIDs to those with stable response to levodopa in term of serotonergic terminals density and striatal dopamine release. We measured serotonergic terminals by using [^{11}C]DASB PET imaging and dopamine release by using [^{11}C]raclopride PET, a D2 receptor antagonist radioligand which competes with endogenous dopamine for D2 receptor binding. Changes in D2 receptor availability, as reduction of baseline [^{11}C]raclopride levels after levodopa administration, allows an indirect measure of synaptic dopamine release. PD patients with LIDs showed increased dopamine release after the administration of levodopa compared to those with stable response to levodopa, with a relative preservation of serotonergic terminals in the putamen (Politis et al., 2014). Oral administration prior to levodopa of the 5-HT_{1A} receptor agonist buspirone, a pre-synaptic modulator of serotonergic system, reduced levodopa-evoked striatal synaptic dopamine release and attenuated LIDs (Politis et al., 2014). To note, among patients with LIDs, the antidyskinetic effect of buspirone was greater in those with higher levels of serotonergic terminals, who also exhibited a greater decrease in dopamine release after buspirone pretreatment (Politis et al., 2014). We also divided the patients with LIDs into two groups based on the severity of LIDs severity (milder versus severe forms). We found that buspirone-associated modulation of dopamine levels was

greater in patients with milder LIDs compared to those with more severe LIDs (Politis et al., 2014). This suggests that in PD patients who experiences more severe LIDs, higher doses or stronger 5-HT_{1A} agonists are needed to achieve similar suppression of LIDs. Another possibility, however, is that other downstream mechanisms, such as glutamatergic overactivity, could play a more dominant role in generating severe dyskinesias, and therefore the combined use of an 5-HT_{1A} agonist and an NMDA antagonist may be needed. This is in line with the preclinical experimental evidence previously described (Munoz et al., 2009), in which 5-HT_{1A} and 5-HT_{1B} agonists were able to suppress the mild levodopa-induced AIMs, but not to reduce the moderate-severe apomorphine-induced AIMs (Munoz et al., 2009). Overall the findings from this study provide the first human evidence and indicate that striatal serotonergic terminals contribute to LIDs pathophysiology *via* aberrant processing of exogenous levodopa and release of dopamine as false neuro-transmitter in the denervated striatum of PD patients with LIDs. The results also support the development of selective 5-HT_{1A} receptor agonists for use as antidyskinetic agents. We then investigated the role of serotonergic innervation of the globus pallidus in the development of dyskinesias (Smith et al., 2015). We measured the density of serotonergic terminals and the striatal dopamine release in the globus pallidus of PD patients with LIDs compared to those with stable response to levodopa by using [¹¹C]DASB PET and [¹¹C]raclopride challenge, respectively. PD patients with LIDs showed preserved serotonergic terminals in the globus pallidus, with a level similar to healthy controls. Higher density of serotonin terminals in the globus pallidus correlated with a greater amount of dopamine released and greater severity of LIDs. This indicates that either the serotonin terminal function in the globus pallidus in patients with LIDs is spared or, that an adaptive terminal sprouting of remaining serotonergic projections occurs not only in the putamen but also in the globus pallidus. Taking together this finding

(preserved serotonergic terminals in the globus pallidus) and the previous one (preserved serotonergic terminals in the putamen), we suggest that the imbalance caused by a normalization of serotonin terminals in the dopamine-denervated striatum creates increased dopamine release after levodopa administration, resulting in an increased negative input to the globus pallidus neurons controlling thalamic output. Greater LIDs might be the results of increased dopamine release at presynaptic dopaminergic receptors located at the synapses of striato-pallidal GABAergic neurons in the globus pallidus. These neurons control the projection neurons to the thalamus and thereby the thalamic output. By over-inhibition of these neurons, the dysregulated basal ganglia output then results in LIDs. This is in line with the preclinical evidence of a profound suppression of globus pallidus output activity in monkeys experiencing LIDs (Papa, Desimone, Fiorani, & Oldfield, 1999). In the third study (Roussakis, Politis, Towey, & Piccini, 2016), we investigated the interaction between serotonergic and dopaminergic terminals in the development of LIDs. We measured the density of serotonergic and dopaminergic terminals in the striatum of PD patients with LIDs and of patients with stable response to levodopa by using [^{11}C]DASB PET and [^{123}I]FP-CIT SPECT, respectively. We found that higher putaminal serotonergic-to-dopaminergic terminals ratio correlate with longer disease duration in PD patients, indicating that, as PD progresses, the ratio between serotonergic and dopaminergic terminals becomes higher, as reflected by the higher [^{11}C]DASB PET to [^{123}I]FP-CIT SPECT binding ratio. This might be due to a faster progression of dopaminergic terminals compared to serotonergic ones, or to an aberrant sprouting of serotonergic innervation in the patients who will experience LIDs, as previously demonstrated in animal studies (Carta et al., 2007; Carta et al., 2010). In parallel, a fourth PET study from another team, has also shown that, compared to non-dyskinetic patients, PD patients with LIDs had a higher striatal serotonergic to dopaminergic terminals availability, as reflected

by the higher [^{11}C]DASB to [^{18}F]FP-CIT PET binding ratio, with no difference in striatal dopaminergic terminals (Lee et al., 2015).

Overall these findings suggest that when the dopaminergic innervation in the striatum is critically low, the serotonergic system plays an important role in development of LIDs (Figure 2). These findings support the role of serotonergic terminals in the aberrant release of striatal dopamine and in promoting the development of LIDs in patients with PD.

**** Insert Figure 2 ****

Another troublesome involuntary movement associated with serotonergic system is the GIDs. Transplantation with foetal ventral mesencephalic tissue aimed to restore the dopaminergic terminals in advanced cases of Parkinson's disease. This treatment showed tremendous efficacy in some patients with remarkable improvement of motor symptoms but some of them developed GIDs, a complication similar to LIDs but presents in 'off' their dopaminergic treatment (Freed et al., 1992; Freed et al., 1990; Hagell et al., 2002; Levivier et al., 1997; Lindvall et al., 1990; Lindvall et al., 1992; Ma et al., 2002; Olanow et al., 2009; Peschanski et al., 1994; Widner et al., 1992). Graft tissue contained a varied proportion of non-dopaminergic cells including serotonergic neurons. Thus, striatal graft tissue containing high levels of serotonin neurons leads to mishandling of striatal dopamine levels resulting in the occurrence of GIDs (Politis, 2010; Politis, Oertel, et al., 2011; Politis, Wu, Loane, Quinn, et al., 2010). We have demonstrated that the same serotonergic mechanisms, such as excessive striatal serotonergic innervation and high serotonin to dopamine striatal terminal ratio, are pivotal in the development of GIDs in

Parkinson's patients who underwent striatal transplantation with foetal ventral mesencephalic tissue (Politis, 2010; Politis, Oertel, et al., 2011; Politis, Wu, Loane, Quinn, et al., 2010). We evaluated the density of serotonergic terminals, by using [^{11}C]DASB PET imaging, and the presynaptic dopaminergic amino acid aromatic decarboxylase terminals' activity, by using [^{18}F]DOPA PET imaging, in three Parkinson's patients who received striatal transplantation with foetal ventral mesencephalic tissue and exhibited GIDs. All three patients showed an excessive graft-derived serotonergic innervation (Politis, Wu, Loane, Quinn, et al., 2010) and high serotonin to dopamine terminal ratio (Politis, Oertel, et al., 2011). Furthermore, administration of small, repeated doses of 5-HT_{1A} receptor agonist buspirone, was able to attenuate graft-induced dyskinesias possibly by attenuating the abnormal serotonin terminal-derived dopamine release. These findings support the involvement of the serotonergic system in the development of GIDs and indicate that a 'close-to-normal' striatal serotonin/dopamine ratio in the transplanted foetal ventral mesencephalic tissue should be necessary to avoid the development of GIDs.

6. SEROTONERGIC SYSTEM CHANGES AND NON-MOTOR SYMPTOMS IN PARKINSON'S DISEASE

6.1. Sleep disturbances

Approximately two-third of PD patients develop sleep-related problems in the course of the disease (Goetz, Wu, Curgian, & Leurgans, 2005). They include rapid eye movement (REM) behavior disorder (RBD), insomnia, sleep apnoea, restless leg syndrome, sleep attacks and excessive daytime sleepiness (EDS) (Yousaf et al., 2018a, 2018b). Serotonergic system has a key role in the regulation of sleep patterns and the damage of raphe's serotonergic neurons and projections is relevant in the development of sleep-related problems in PD. Preclinical data have

shown that a damage of raphe nuclei is associated with the onset of sleep problems (Jouvet, 1972) and in experimental studies with sleep deprivation, by using [^{11}C]DASB PET, it has been found a reduction in the anterior olfactory nucleus and substantia nigra in rats that have been deprived of sleep when compared to control rats without sleep deprivation (Hipolide et al., 2005). In humans, the use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression is commonly associated with the development of sleep alterations (Rush et al., 1998), which further confirms the theory that serotonergic system is relevant for the development of sleep disturbances.

Sleep-related problems in PD might both have a presynaptic and a postsynaptic component. By using [^{11}C]DASB PET imaging, we recently demonstrated that sleep dysfunction in PD is associated with reduced SERT in the midbrain raphe, basal ganglia and hypothalamus (H. Wilson et al., 2018). Compared to healthy controls, PD patients with sleep dysfunction had a 32–49% reduction of SERT, while PD without sleep dysfunction had only 14–25%. The reduction was higher in serotonergic raphe nuclei and their related projections (hypothalamus, thalamus and striatum) and correlated with greater severity of sleep symptoms (assessed with Parkinson Disease Sleep Scale). By using [^{18}F]altanserin PET imaging, it has been shown that a single night of sleep deprivation induces an increase in cortical 5-HT $_2\text{A}$ receptors (medial inferior frontal gyrus, insula, anterior cingulate, parietal, sensorimotoric, and ventrolateral prefrontal cortices) in healthy volunteers. This confirms a role for the serotonergic dysfunction in the onset of insomnia. However, the involvement of serotonergic system might not be homogenous across all sleep-related disorders. In PD patients with sleep apnea, the levels of SERT in the raphe, measured by using [^{11}C]DASB PET, were not associated with the severity (Lelieveld et al., 2012). In PD

patients with RBD, it has been shown no changes in SERT levels but a reduction in brain cholinergic activity (Kotagal, Albin, et al., 2012), with lower thalamic, limbic cortex and neocortical [^{11}C]PMP PET binding in PD patients with RBD compared to PD patients without RBD. Cholinergic changes, especially in brainstem and subcortical circuits, may contribute to this parasomnia.

6.2. Depression

Approximately 50% of PD patients develop mood disturbances in the course of the disease (Zhuo et al., 2017). Monoaminergic neurotransmitter changes, in particular 5-HT, play a key role in the development of depression (Remy, Doder, Lees, Turjanski, & Brooks, 2005) and represent the major pharmacological target to treat this disorder (Weintraub et al., 2005). Imaging studies in patients with major depression (Cannon et al., 2007) and with bipolar (Cannon et al., 2006; Cannon et al., 2007) disorder have shown an increased [^{11}C]DASB binding in the insula, thalamus and striatum compared to healthy controls, suggesting that increased SERT density could account for symptoms of depression by leading to increased clearance of serotonin from the synapse. However, the serotonergic component of depression in PD might involve both presynaptic and postsynaptic terminal dysfunction. Compared to PD patients without depression, PD patients with depression showed a reduction in CSF 5-hydroxyindoleacetic acid levels, the principal metabolite of 5-HT (Mayeux et al., 1986). In PET studies using [^{11}C]DASB, PD patients with depression have reported relative increases of SERT binding in limbic structures compared to non-depressed PD patients (Boileau et al., 2008; Politis, Wu, Loane, Turkheimer, et al., 2010). The increase was greater in the dorsolateral (37%) and prefrontal (68%) cortices and correlated with depressive symptoms (assessed by the Hamilton Depression Rating Scale) (Boileau et al., 2008). We also

demonstrated an increase in subcortical SERT levels, in the amygdala, hypothalamus, raphe nuclei, and posterior cingulate cortex in PD patients with depressive symptoms compared to matched-PD patients without depression. This increase in [^{11}C]DASB binding was indeed correlated with depressive symptoms (as assessed by Beck Depression Inventory-II and Hamilton Depression Rating Scale) (Politis, Wu, Loane, Turkheimer, et al., 2010). In the limbic regions of depressed PD patients, it has also been found a decrease in 5-HT_{1A} receptors by using [^{18}F]MPPF PET imaging (Ballanger et al., 2012), which is in agreement with *post-mortem* evidence (Sharp et al., 2008) and support the hypothesis that there is also a postsynaptic in the development of depression in PD (Ballanger et al., 2012).

Overall, these findings suggest that in PD, as in major and bipolar depression, an excessive 5-HT clearance by SERT induces a reduced extracellular concentration of 5-HT leading to the development of depressive symptoms. However, the prevalence of depression in PD is higher compared to non-PD population and this could be explained by the concurrent decrease in 5-HT_{1A} receptors and loss of serotonergic terminals in limbic regions. Thus, depression in PD could be the result of a combined effect of serotonergic terminal loss, inappropriate upregulation of SERT and reduced postsynaptic efficacy of the already depleted 5-HT. However, it should be noted that the pathophysiology of depression is complex and involves changes in multiple circuits and neurotransmitters beyond the serotonergic system likely in a dynamic and interactive way.

6.3. Fatigue

Approximately 75% of PD patients reported that fatigue affects their quality of life and often goes undetected, due to an uncertain pathological basis and lack of specific treatment (Chaudhuri &

Behan, 2000). Fatigue can be secondary to depression and anxiety due to the association between PD disability and this symptom fatigue. This suggests that the serotonergic system could be also implicated in development of fatigue in PD (Hagell & Brundin, 2009).

A study using combined [^{18}F]DOPA and [^{11}C]DASB PET investigated the role of 5-HT in PD patients with fatigue (Pavese et al., 2010). Seven PD patients with fatigue and eight PD patients without fatigue, matched for age, disease duration and severity, daily intake of levodopa equivalent units, and with no history of depression or sleep disturbance, were compared using a region of interest analytical approach. PD patients with fatigue had about 70% reductions in [^{11}C]DASB binding in the putamen, caudate nucleus, ventral striatum, thalamus, cingulate and amygdala, compared to the PD patients without fatigue, but striatal [^{18}F]DOPA uptake was similar (Pavese et al., 2010). This observation suggests that the presynaptic component of serotonergic system plays a significant role in fatigue in PD. However, further research using other ligands, such as postsynaptic 5-HT receptors tracer, is needed to further investigate this area.

6.4. Weight loss

Approximately half of the PD patients develop weight loss over the course of the disease (Beyer, Palarino, Michalek, Busenbark, & Koller, 1995). Several mechanisms have been suggested to explain this loss of weight, including changes in energy expenditure, perturbation of homeostatic control, and eating behaviors (Kistner, Lhomme, & Krack, 2014). The main risks factors identified are the progression of the disease, the age of onset, and the level of disabilities (Uc et al., 2006), but the precise mechanisms involved in the development of weight loss are not fully understood. Serotonergic projections to the hypothalamus may influence homeostatic metabolic

regulation and weight loss can be secondary to the damage of serotonergic system. Serotonergic neurons also express considerable amounts of orexin receptor and dense orexin fiber projections (Eriksson, Sergeeva, Haas, & Selbach, 2010) and 5-HT plays a role in eating behavior. On the other hand, the diet can also influence 5-HT. The main precursor of 5-HT biosynthesis in the brain is the essential amino acid tryptophan. Carbohydrates intake induces an increase of insulin that enhances cerebral uptake of tryptophan, thus, increasing 5-HT biosynthesis (Wurtman & Wurtman, 1996). This explains the craving for carbohydrates of people with depression, due to their 5-HT-mediated positive effect on mood (Wurtman & Wurtman, 1996). Alterations of the serotonergic system in PD may explain the pronounced preference for carbohydrates and the increased intake of chocolate in this population (Wolz et al., 2009). Moreover, it has been described an abnormal regulation of growth hormone secretion by the serotonin receptors in response to receptor agonists in early drug-naïve PD patients compared to healthy controls (Volpi et al., 1997). These findings suggest that the 5-HT may be involved in weight changes observed in PD. We evaluated with [^{11}C]DASB PET the relationship between body mass index (BMI) changes and serotonergic dysfunction in PD (Politis, Loane, et al., 2011). PD patients with abnormal BMI changes over a 12-month period showed significantly increase of [^{11}C]DASB binding in rostral raphe nuclei, hypothalamus, caudate nucleus and ventral striatum compared to cases with no significant BMI alterations. BMI gainers showed an increase in [^{11}C]DASB binding in anterior cingulate cortex, which is a central region modulating hunger (Politis, Loane, et al., 2011). Therefore, BMI changes seem to be related to relatively raised SERT availability in rostral raphe nuclei and its connections to limbic and cognitive areas.

6.5.Cognitive disturbances

About 80% of PD patients develop cognitive disturbances in the course of the disease {Aarsland, 2010 #5680}. We demonstrated a key role of cholinergic nucleus basalis of Meynert in the initiation of the process (Schulz et al., 2018), but several components are needed in the development of dementia. Misfolded proteins, including α -synucleinopathy, β -amyloidopathy, tauopathy, are considered *primum movens* in the development of neuronal and synaptic dysfunctions, that leads to reduced glucose metabolic and cerebral blood flow, and impairment of brain network connectivity (Kalia, 2017). The presence of β -amyloid plaques has been associated with dementia in *post-mortem* PD studies (Kotzbauer et al., 2012). *In vivo* β -amyloid plaques in PD have been associated with more severe cognitive impairment (Shah et al., 2016). Experimental evidence suggests that $A\beta$ production is modulated by synaptic activity and by activation of specific neurotransmitter receptors, including serotonin receptors (Shen et al., 2011). Preclinical studies suggest that augmentation of serotonergic neurotransmission by SSRIs can reduce extracellular cerebral $A\beta$ deposition and plaque burden (Cirrito et al., 2011). 5-HT and SSRIs can stimulate G-protein-coupled receptors and induce the cleavage of Amyloid Precursor Protein by α -secretase, leading to a reduction in $A\beta_{1-42}$ generation and reduced plaque formation (Cirrito et al., 2011). SSRIs may also promote the efflux of $A\beta_{1-42}$ from the brain to the bloodstream. A small study performed in 13 PD patients using [^{11}C]DASB PET showed an inverse correlations between [^{11}C]DASB and Pittsburgh compound B distribution volume ratios in the neocortex and striatum (Kotagal, Bohnen, et al., 2012). These findings have been confirmed recently in a bigger population, for the neocortex but not for the striatum (Kotagal et al., 2018). In the same study, it has been demonstrated that the use of SSRIs for at least 6 months was associated with a lower level of CSF $A\beta_{1-42}$ and with lower risk of cognitive decline (Kotagal et al., 2018). This confirms the hypothesis that that serotonergic terminals are important in the

clearance of A β and indirectly to the development of cognitive impairment. The relationship between serotonergic system and accumulation of misfolded proteins open to a fascinating hypothesis on its potential connection with the deposition of Lewy bodies. However, to test this hypothesis *in vivo*, it will be necessary to have, alongside with [^{11}C]DASB, a α -synuclein PET tracer which is currently unavailable.

A postsynaptic component of cognitive disturbances can also be speculated in PD. Twelve control subjects and 12 PD patients were examined with PET using the 5-HT $_{1B}$ -radioligand [^{11}C]AZ10419369. In PD patients, 5-HT $_{1B}$ -receptor availability in the right orbitofrontal cortex was lower than in control subjects. Lower 5-HT $_{1B}$ -receptor availability correlated with older age in the right temporal cortex in control subjects and for the right midbrain and left parahippocampal gyrus in PD patients (Varrone et al., 2014). PD patients showed also lower measures of semantic and episodic memory, as well as creative ability, compared with control subjects. Greater creative ability correlated with 5-HT $_{1B}$ receptor availability in grey matter, and in PD patients between scores of Beck Depression Inventory-II and creative ability (Varrone et al., 2015).

6.6.Neuropsychiatric disturbances

In addition to depression, several neuropsychiatric disturbances are common in PD, including apathy, visual hallucinations and psychosis. Apathy is characterized by a diminished goal-oriented behavior, and reduction in emotional expression (Starkstein, 2012). About one third of PD patients develop apathy in the course of the disease, although it is often confused with dementia or depression, of which it can also be an integral part (Pagonabarraga, Kulisevsky, Strafella, & Krack, 2015). In PD patients, the main mechanism identified in the development of

apathy is dopaminergic (Wen, Chan, Tan, & Tan, 2016), although recently a presynaptic serotonergic component has been described (Maillet et al., 2016). In this study, [^{11}C]DASB and [^{11}C]PE2I PET were used in 15 apathetic and 15 non-apathetic early drug-naïve PD patients. PD patients with apathy showed a 21-58% [^{11}C]DASB binding reduction in the striatum compared to PD patients without apathy, with similar [^{11}C]PE2I binding. Lower [^{11}C]DASB binding in the caudate and in the orbitofrontal cortex correlated with the severity of apathy (Maillet et al., 2016). Interestingly, in this population with early disease, there was a more pronounced reduction in serotonergic than in dopamine terminals in those with apathy, thus challenging the concept of predominantly dopaminergic involvement in early disease stages (Schrug & Politis, 2016). These findings may also change the treatment of apathy in PD, options for which are current limited, and medications that act on serotonergic targets may assume a major role in the next future.

About 50% of PD patients experiences visual hallucinations (Williams & Lees, 2005). A PET study with [^{18}F]setoperone, a selective 5-HT_{2A} receptor radioligand, showed that PD patients with visual hallucination have an increased 5-HT_{2A} binding in ventral visual pathway, dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula (Ballanger et al., 2010). These findings suggested that abnormalities in serotonin neurotransmission could be involved in the neural mechanisms underlying the development of visual hallucinations that is associated with PD, and support the use of selective 5-HT_{2A} receptor antagonists in the treatment of visual hallucinations in PD (Ballanger et al., 2010).

Psychosis may occur in more than 40% of PD patients leading to increased nursing home placements, and higher rates of morbidity (Marsh et al., 2004). The treatment of psychosis in PD

is complicated by the D2 antagonist effect of typical and atypical antipsychotics, which may worsen motor and cognitive PD symptoms (Ffytche et al., 2017). There is evidence suggesting that the serotonergic system maybe involved in the pathophysiology of psychosis in PD (Ffytche et al., 2017; Zahodne & Fernandez, 2008). Pimvanserin is a selective 5-HT_{2A} antagonist/inverse agonist that showed to be efficacious on psychotic-like behavioral deficits in a 6-week, randomised, double-blind, placebo-controlled phase 3 study (Cummings et al., 2014). These findings confirm a key role of serotonergic system in the development of psychosis in PD.

7. SEROTONERGIC SYSTEM CHANGES IN ASYMPTOMATIC LRRK2 CARRIERS: COMPENSATION, OR DIFFERENT PATHOLOGY?

Mutations in LRRK2 are associated with the highest genetic attributable risk factor for familial and idiopathic forms PD (Kalia et al., 2015). The clinical features of manifesting LRRK2 mutation carriers are generally indistinguishable from those of patients with idiopathic PD but the non-motor features of LRRK2 PD may be less prominent, include better olfactory performance, and less cognitive decline, compared to idiopathic PD (Healy et al., 2008). A recent dopaminergic and serotonergic PET imaging study in LRRK2 mutation carriers with and without manifest PD have been performed, who they assessed in parallel with a cohort of individuals with idiopathic PD and healthy controls (Wile et al., 2017). LRRK2 mutation carriers with manifest PD and idiopathic PD patients showed a reduction in dopaminergic [¹⁸F]DOPA and [¹¹C]DTBZ binding in the striatum, whereas LRRK2 mutation carriers without manifest disease were largely unaffected. However, several LRRK2 mutation carriers without manifest PD showed reduction

of DAT, assessed with [^{11}C]d-threo-methylphenidate PET scans. Interestingly, LRRK2 mutation carriers without manifest PD showed an increase in [^{11}C]DASB binding in the hypothalamus, striatum, and brainstem in comparison with all other study populations. LRRK2 mutation carriers with manifest PD and individuals with idiopathic PD showed a similar reduced expression of striatal [^{11}C]DASB binding (Wile et al., 2017). These findings challenge the classic pathological interpretation of disease progression. If the midbrain raphe nucleus is affected in a presymptomatic stage according to Braak, and LRRK2 pathological features are similar to those seen in idiopathic PD, serotonergic PET would have shown decreases rather than increases. As described above, serotonergic PET studies in idiopathic PD have shown a progressive and non-linear loss of serotonergic terminals (Politis, Wu, Loane, Kiferle, et al., 2010). Only two PET studies have reported relative increases in the expression of [^{11}C]DASB in the hypothalamus, striatum, and brainstem in idiopathic PD patients with depressive symptoms (Boileau et al., 2008; Politis, Wu, Loane, Turkheimer, et al., 2010) and weight changes (Politis, Loane, et al., 2011) compared with individuals with idiopathic PD but without depressive symptoms and weight changes (but not with healthy controls). This finding suggests that elevated expression of serotonin transporters was probably a concurrent occurrence with serotonergic terminal loss in the individuals with idiopathic PD (Politis, 2017). Unfortunately, data for depression were reported in only five LRRK2 mutation carriers without manifest PD who were assessed with the self-reported Beck Depression Inventory, with no data related to weight changes or other non-motor symptoms, therefore limiting interpretation. Moreover, expression of serotonin transporters in LRRK2 mutation carriers without manifest PD was increased, compared with healthy controls, which might indicate serotonergic terminals affected by Parkinson's pathology (Wile et al., 2017). In such a scenario, upregulation of serotonin transporters might be secondary to decreases in

synaptic serotonin levels and, therefore, indirect PET measures of synaptic serotonin release could help elucidate mechanisms in LRRK2 mutation carriers without manifest PD. However, to better understand these findings, additional studies are needed in a larger cohort of LRRK2 mutation carriers without manifest PD, including thorough clinical assessments for depression, weight changes, and other non-motor symptoms, and perhaps longitudinal observations to elucidate molecular changes over time and their associations with clinical symptoms.

8. CONCLUSIONS AND FUTURE DIRECTIONS

The serotonergic system is emerging as a dynamic player within not only motor and non-motor symptoms but also on the development and progression of the disease. The regional cerebral biodistribution of serotonergic nerve terminals in the brain can be associated with specific biological dysfunctions. Reduced raphe-thalamic serotonergic activity associates with the presence of tremors in PD. Abnormal serotonergic sprouting in the striatum is one of the determinants of LIDs and GIDs. Limbic serotonergic changes are an important determinant of sleep and neuropsychiatric-related disorders. Serotonergic system seems central in the clearance of misfolded proteins, in particular A β deposition, with dramatic implication for the development of cognitive impairments. However, serotonergic functions extend well beyond current understanding. Whilst a plethora of symptoms has now been associated with serotonergic dysfunction, there are as yet no treatments that specifically target these deficits in PD. Future studies should additionally explore the involvement of other 5-HT receptors in the development of motor and non-motor symptoms and complications. PET with [^{11}C]Cimbi-36, a 5HT $_2\text{AR}$ agonist, has shown higher sensitivity for changes in synaptic serotonin levels compared to other

5HT PET ligands, and may eventually allow indirect measures of serotonin release in health and parkinsonism (Yang et al., 2017). Emerging evidence of serotonergic changes in asymptomatic LRRK2 mutation carriers may be cardinal in the identification of the earliest changes involved in the development of PD. In fact, although some risk factors (i.e. rapid eye movement sleep behavior disorder, anosmia, and constipation) have been suggested for development of idiopathic PD, people with these symptoms, who might be considered as having prodromal idiopathic PD, provide limited possibilities to study premotor pathology because not all people at risk will eventually develop PD, and observation of such individuals needs very long follow-up periods. Studies in genetic populations without manifest PD, such as the asymptomatic LRRK2 mutation carriers, provide a good opportunity to understand the mechanisms underlying the premotor stages of PD. Advances in PET will allow novel investigations of molecular pathology *in vivo* (tau, synaptic and mitochondria pathology) and these studies will be important for understanding premotor stages and progression of PD. Such studies might also be expanded to include carriers of the rarer—but more penetrant—autosomal dominant mutation in the gene encoding α -synuclein (*SNCA*), which is directly implicated in Lewy body pathology and in PD susceptibility (Politis, 2017).

9. ACKNOWLEDGMENT

Dr Gennaro Pagano reports personal fees from UCB, outside the submitted; and Research Grant funding from Michael J. Fox Foundation and Edmond and Lily Safra Foundation. Member of Editorial Boards: Frontiers in Neurology.

Professor Marios Politis reports personal fees from Abbvie, other from Piramal Imaging, from

Alliance Medical, other from UCB, outside the submitted work; and Research Grant funding from Michael J. Fox Foundation, Edmond and Lily Safra Foundation, Parkinson's UK, Alzheimer's Research UK, CHDI Foundation, Medical Research Council. Member of Editorial Boards: Nature Parkinson's Journal, Movement Disorders Journal, Frontiers in Neurology.

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Figure captions

Figure 1. Serotonergic nerve terminal figure illustrating presynaptic and postsynaptic molecular serotonergic imaging targets. Abbreviations: SERT = Serotonin Transporter; 5HT-R = 5-hydroxytryptamine Receptor.

Figure 2. Summed [^{11}C]DASB PET images coregistered and fused with 3T MRI images at the level of the dorsal basal ganglia for a healthy subject with normal dopaminergic and serotonergic innervation (A); a Parkinson's patient (57 years old, disease duration 52 months, MDS-UPDRS-III of 28) with stable response to levodopa with loss of serotonergic and dopaminergic innervation (B); and a Parkinson's patient (56 years old, disease duration 58 months, MDS-UPDRS-III of 33) who experiences levodopa-induced dyskinesia with a loss of dopaminergic innervation but preserved serotonergic innervation (C).

Table 1. Overview of serotonin receptors and PET radioligands

Overview of serotonin receptors						
Receptor	Receptor Sub-type	PET Ligand	Used in PD	Function	Agonists	Antagonists
5-HT ₁	5-HT _{1A}	[¹¹ C]WAY100635, [¹⁸ F]MPPF, [¹¹ C]CUMI-101	Doder et al. found in 26 PD patients compared to 8 healthy controls that midbrain raphe [¹¹ C]WAY100635 binding was reduced by 27% in PD patients and there was a significant correlation between reductions in midbrain raphe [¹¹ C]WAY100635 binding and the severity of resting tremor (Doder et al., 2003). Compared with controls, nondepressed parkinsonian patients presented reduced [¹⁸ F]MPPF uptake bilaterally in the inferior frontal cortex as well as in the right ventral striatum and insula. Compared with controls, [¹⁸ F]MPPF uptake was decreased in depressed parkinsonian patients in the left dorsal anterior cingulate and orbitofrontal cortices, in the right hippocampic region, and in the temporal cortex (Ballanger et al. 2012).	Addiction, Aggression, Anxiety, Appetite, Autoreceptor, Blood Pressure, Cardiovascular Function, Emesis, Heart Rate, Impulsivity, Memory, Mood, Nausea, Nociception, Erection, Pupil Dilation, Respiration, Sexual Behavior, Sleep, Sociability, Thermoregulation and Vasoconstriction	Selective (for 5-HT _{1A} over other 5-HT receptors) Vilazodone (Viibryd), F-15,599 (research compound, highly potent and selective for 5-HT _{1A}), Flesinoxan (potent, EC ₅₀ = 24 nM), Gepirone (partial agonist, Ki = 70 nM), Haloperidol, Ipsapirone (partial agonist, Ki = 12.1 nM), Quetiapine, Trazodone, Yohimbine (unselective partial agonist), Tansospirone (potent and selective partial agonist) Nonselective 5-CT (potent - Ki = 250±50 pM), 8-OH-DPAT (potent), Aripiprazole (atypical antipsychotic), Asenapine (atypical antipsychotic), Buspirone (partial agonist), Vortioxetine (high-efficacy partial agonist), Ziprasidone (Partial agonist, Ki = 3.4 nM), Methylphenidate (weak agonist)	BMY 7378, Cyanopindolol, Iodocyanopindolol, Lecozotan, Methiothepin, Methysergide, NAN-190, Nebivolol, Nefazodone, WAY-100,135, WAY-100,635, Mefway

5-HT _{1B}	[¹¹ C]AZ10419369, [¹¹ C]P943	<p>Twelve control subjects and 12 PD patients were examined with PET using the 5-HT_{1B}-radioligand [¹¹C]AZ10419369. In PD patients, 5-HT_{1B}-receptor availability in the right orbitofrontal cortex was lower than in control subjects. Lower 5-HT_{1B}-receptor availability correlated with older age in the right temporal cortex in control subjects and for the right midbrain and left parahippocampal gyrus in PD patients (Varrone et al. 2014). PD patients showed also lower measures of semantic and episodic memory, as well as creative ability, compared with control subjects. Greater creative ability correlated with 5-HT_{1B} receptor availability in grey matter, and in PD patients between scores of Beck Depression Inventory-II and creative ability (Varrone et al. 2015).</p>	Addiction, Aggression, Anxiety, Autoreceptor, Learning, Locomotion, Memory, Mood, Erection, Sexual Behavior, Vasoconstriction	5-CT, CGS-12066A, CP-93,129, CP-94,253, Dihydroergotamine, Eltoprazine, Ergotamine, Methysergide, RU 24969, TFMPP, Triptans (antimigraine), Zolmitriptan, Eletriptan, Sumatriptan, Vortioxetine (partial agonist, Ki = 33 nM)	Alprenolol, AR-A000002, Asenapine, Cyanopindolol, GR-127,935, Iodocyanopindolol, Isamoltane, Metergoline, Methiothepin, Oxprenolol, Pindolol, Propranolol, SB-216,641, Yohimbine
5-HT _{1D}	[¹¹ C]P943	No studies in PD patients.	Anxiety, Autoreceptor, Locomotion, Vasoconstriction	5-CT, CP-135,807, Dihydroergotamine, Ergotamine, Methysergide, Triptans (antimigraine), Almotriptan, Eletriptan, Frovatriptan, Naratriptan, Rizatriptan, Sumatriptan, Zolmitriptan, Yohimbine	BRL-15572, GR-127,935, Ketanserin, Metergoline, Methiothepin, Rauwolscine, Ritanserin, Vortioxetine (Ki = 54 nM), Ziprasidone
5-HT _{1E}	Under development	No studies in PD patients.	Unknown	BRL-54443	Unknown
5-HT _{1F}	Under development	No studies in PD patients.	Migrane	BRL-54443, Lasmiditan, LY-334,370, Naratriptan, Eletriptan	Unknown

5-HT ₂	5-HT _{2A}	[¹¹ C]MDL100907, [¹⁸ F]altanserin, [¹⁸ F]setoperone, [¹¹ C]Cimbi-36, [¹¹ C]N-methylspiperone	Patients having PD with visual hallucinations demonstrate increased [¹⁸ F]setoperone 5-HT _{2A} receptor availability in the ventral visual pathway (including the bilateral inferooccipital gyrus, right fusiform gyrus, and inferotemporal cortex) as well as the bilateral dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula (Ballanger et al. 2010)	Addiction (potentially modulating), Anxiety, Appetite, Cognition, Imagination, Learning, Memory, Mood, Perception, Sexual Behavior, Sleep, Thermoregulation, Vasoconstriction	25I-NBOMe (Full agonist), 2C-B, 5-MeO-DMT, BZP, Bufotenin, DMT, DOM, Ergonovine, Lisuride, LSD, Mescaline, Myristicin, PNU-22394 (Partial agonist), Psilocin, Psilocybin, TFMPP (partial agonist or antagonist)	Atypical antipsychotics Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole, Asenapine, Amitriptyline, Clomipramine, Cyproheptadine, Eplivanserin, Etoperidone, Haloperidol, Hydroxyzine, Iloperidone, Ketanserin (antihypertensive), Methysergide, Mianserin, Mirtazapine, Nefazodone, Pimavanserin, Pizotifen, Ritanserin, Trazodone, Yohimbine
	5-HT _{2B}	Under development	No studies in PD patients.	Anxiety, Appetite, Cardiovascular Function, Gut Motility, Sleep, Vasoconstriction	BW-723C86, Fenfluramine, MDMA, Norfenfluramine, PNU-22394, (Partial agonist), Ro60-0175, Methylphenidate (weak agonist)	Agomelatine, Asenapine, BZP, Ketanserin, Methysergide, Ritanserin, RS-127,445, Tegaserod, Yohimbine
	5-HT _{2C}	[¹⁸ F]fluorophenethoxy)pyrimidine	No studies in PD patients.	Addiction. (potentially modulating), Anxiety, Appetite, Gut Motility, Heteroreceptor for	A-372,159, AL-38022A, Aripiprazole, Ergonovine, Lorcaserin, PNU-22394 (Full agonist), Ro60-0175, TFMPP, Trazodone, (hypnotic), YM-348	Agomelatine (antidepressant), Amitriptyline, Asenapine, Clomipramine, Clozapine,

				norepinephrine and dopamine, Locomotion, Mood, Erection, Sexual Behavior, Sleep, Thermoregulation, Vasoconstriction		(antipsychotic), Cyproheptadine, Dimebolin, Eltoprazine, Etoperidone, Fluoxetine, Haloperidol, Iloperidone, Ketanserin, (antihypertensive), Lisuride, Methysergide, Mianserin, Mirtazapine, Nefazodone, Olanzapine, Paroxetine, Quetiapine, Risperidone, Ritanserin, Tramadol, Trazodone, Ziprasidone
5-HT ₃	/	[¹¹ C]MDL72222, [¹¹ C]YM060, [¹¹ C]Y-25130, [¹¹ C]KF17643, [¹¹ C]S21007, [¹⁸ F]MR18445, [¹¹ C]NMQ	No studies in PD patients.	Addiction, Anxiety, Emesis, Gut Motility, Learning, Memory, Nausea	2-Methyl-5-HT, BZP, Quipazine, RS-56812	Alosetron, Several antiemetics, Dolasetron, Ondansetron, Granisetron, Tropisetron, Clozapine, Memantine, Metoclopramide, Mianserin, Mirtazapine, Olanzapine, Quetiapine, Vortioxetine (Ki = 3.7 nM)
5-HT ₄	/	[¹¹ C]SB207145, [¹²³ I]SB207710	No studies in PD patients.	Anxiety, Appetite, Gut Motility, Learning,	5-MT, BIMU-8, Cinitapride, Cisapride (gastroprokinetic), Dazopride, Metoclopramide,	L-Lysine, Piboserod

				Memory, Mood, Respiration	Mosapride, Prucalopride, RS-67333, Renzapride, Tegaserod, Zacopride	
5-HT ₅	5-HT _{5A}	Under development	No studies in PD patients.	Autoreceptor, Locomotion, Sleep	5-CT, Ergotamine, Valerenic Acid (partial agonist)	Asenapine, Dimebolin, Methiothepin, Ritanserin, SB-699,551, SB-699,551-A
	5-HT _{5B}	Under development	No studies in PD patients.	Unclear	Unclear	Unclear
5-HT ₆	/	[¹¹ C]GSK215083, [¹¹ C]GSK224558, [¹⁸ F]12ST05	No studies in PD patients.	Anxiety, Cognition, Learning, Memory, Mood	EMD-386,088, EMDT	Amitriptyline, Aripiprazole, Asenapine, Clomipramine, Clozapine, Dimebolin, EGIS-12233, Haloperidol, Iloperidone, MS-245, Olanzapine, Ro04-6790, SB-258,585, SB-271,046, SB-357,134, SB-399,885
5-HT ₇	/	[¹⁸ F]2FP3, [¹¹ C]DR4446	No studies in PD patients.	Anxiety, Autoreceptor, Memory, Mood, Respiration, Sleep, Thermoregulation, Vasoconstriction	5-CT, 8-OH-DPAT, Aripiprazole (weak partial agonist), AS-19, E-55888, RA-7	Amitriptyline, Asenapine, Clomipramine, Clozapine, EGIS-12233, Haloperidol, Iloperidone, Imipramine, Ketanserin, Mirtazapine, Olanzapine, Ritanserin, Risperidone, SB-269,970, Vortioxetine (K _i = 19 nM)

EC₅₀ = Half maximal effective concentration; k_i = Inhibition constant.