CHAPTER NINE

Imaging in Parkinson’s Disease

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Abstract

Parkinson’s disease (PD) is a chronic neurodegenerative disease characterized by the loss of nigrostriatal dopaminergic neurons and aggregation of misfolded α-synuclein in Lewy bodies. The underlying mechanisms of neurodegeneration in PD are still unknown, and there are no disease-modifying treatments to slow the neurodegenerative processes. There is an urgent need to identify biomarkers that are able to monitor disease progression and assess the development and efficacy of novel disease-modifying drugs. Over the past years, neuroimaging techniques such as magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET) have provided important advances in our understanding of PD. MRI provides information about structural and functional organization of the brain, while SPECT and PET can detect molecular changes in the brain. Here, we review the current neuroimaging literature in sporadic and genetic PD, which have contributed to our understanding of the physiopathological mechanisms of the disease.

1. IDIOPATHIC PARKINSON’S DISEASE: INTRODUCTION

Several neuroimaging techniques have been deployed over the past decades, to help understanding the pathophysiology of Parkinson’s disease (PD) and to provide us with biological indicators for early diagnosis and response to treatment (Pagano, Niccolini, Fusar-Poli, & Politis, 2017; Pagano, Niccolini, & Politis, 2016a, 2016b). Neuroimaging techniques such
as magnetic resonance imaging (MRI) have played a critical role in assessing structural and functional changes in the brain, which can be related to the pathophysiology and clinical manifestations of PD. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are molecular noninvasive imaging techniques for the quantitative and qualitative imaging of biological functions (Phelps, 2000). The distribution and kinetic profiles of compounds targeting specific biological molecules in tissue reflect specific biological functions in the living body. Here, we review the findings from neuroimaging studies, which have contributed in the understanding of the pathophysiological mechanisms underlying PD.

1.1 Molecular Imaging

1.1.1 Dopaminergic System

The main pathological hallmark of PD is the progressive loss of dopamine neurons in the substantia nigra pars compacta and the loss of dopaminergic neurotransmission in the denervated areas of the forebrain, above all in the striatum (Jellinger, 1991; Samii, Nutt, & Ransom, 2004). The loss of dopaminergic neurons in PD results in a decrease in the excitatory activity of the D1 direct (striatonigral) pathway and an increase in the inhibitory activity of the D2 indirect (striatopallidal) pathway; this enhances the activity of nigral neurons, resulting in decreased motor response and subsequent manifestation of some classic PD symptoms (Hamani & Lozano, 2003). PET with radioligands targeting presynaptic and postsynaptic dopaminergic markers has been extensively employed to aid with the early diagnosis of PD, track disease progression, and investigate motor and nonmotor correlates of PD (Politis, 2014).

Six selective SPECT radioligands targeting dopamine transporter (DAT), [123I]-β-CIT, [123I]-FP-β-CIT, [123I]-IPT, [123I]-Altropane, [123I]-β-PE2I, and [99Tcm]-TRODAT-1, have been used to assess presynaptic dopamine reuptake availability in PD (Politis, 2014; Roussakis, Piccini, & Politis, 2013). DAT-SPECT is useful for the differential diagnosis between PD and nondegenerative parkinsonism, such as drug-induced parkinsonism, essential tremor (ET), dystonic tremor, or psychogenic parkinsonism. [123I]-FP-CIT DAT-SPECT showed high accuracy in the differential diagnosis of PD vs drug-induced parkinsonism (Cuberas-Borrós et al., 2011; Diaz-Corrales, Sanz-Viedma, Garcia-Solis, Escobar-Delgado, & Mir, 2010; Loberboym et al., 2006). Lower [123I]-FP-CIT binding in the putamen was found in PD patients compared to patients with ET or drug-induced parkinsonism (Cuberas-Borrós et al., 2011).
Dopaminergic degeneration of DAT is an age-related process; however, it is much faster in PD than in physiological aging (Winogrodzka et al., 2001). Pathology and clinical symptoms of PD progress gradually starting as unilateral and progressively affecting both sides (Larsen et al., 2008). DAT-SPECT has been proven to be an objective tool for monitoring PD progression. $^{[123]}$I-$\beta$-CIT, $^{[123]}$I-FP-CIT SPECT, $^{[123]}$I-IPT, and $^{[99mTc]}$TRODAT-1 DAT-SPECT have been used to evaluate disease progression in PD (Marek et al., 2001; Tatsch et al., 1997; Weng et al., 2004; Winogrodzka et al., 2001, 2003). $^{[123]}$I-$\beta$-CIT SPECT have been used in a group of 50 early-stage PD patients showing an average decrease of 8% in the whole striatum (8% in the putamen and 4% in the caudate) at 12-month follow-up (Winogrodzka et al., 2003). Sequential SPECT scans using $^{[123]}$I-$\beta$-CIT demonstrated a decline in striatal uptake of 11.2% per year in PD patients, compared with 0.8% per year in controls (Marek et al., 2001). $^{[123]}$I-FP-CIT SPECT showed consistent results with an annual decrease in striatal binding ratios of 8% (Winogrodzka et al., 2001). Also, $^{[123]}$I-IPT SPECT and $^{[99mTc]}$TRODAT-1 uptake in the striatum showed a progressive decline with the progression of the disease (Tatsch et al., 1997; Weng et al., 2004), and lower striatal uptake correlated with increased motor symptoms severity as measured by the Unified PD Rating Scale part III (UPDRS-III) and Hoehn and Yahr (H&Y) stage (Tatsch et al., 1997; Weng et al., 2004).

There are several PET radioligands available for measuring presynaptic dopaminergic markers such as DAT ($^{[11C]}$CFT, $^{[11C]}$PE2I, $^{[11C]}$RTI32, $^{[11C]}$MP), dopa decarboxylases (DDC; $^{[18F]}$dopa), and vesicular monoamine transporter type 2 (VMAT-2; $^{[11C]}$DBT, $^{[18F]}$DBT), which can be used to provide a measure of integrity of dopaminergic function in PD. $^{[18F]}$dopa PET has shown that early-stage PD patients displayed a rapid progression of dopaminergic denervation in the putamen with a posterior-to-anterior gradient and a side-to-side asymmetry between the less and more affected striatal structures (Hilker, Schweitzer, et al., 2005; Hilker, Thomas, et al., 2005; Nandhagopal et al., 2009). In advanced stages, dopaminergic degeneration becomes slower, and although the gradient is maintained, the degree of asymmetry diminishes (Hilker, Schweitzer, et al., 2005; Hilker, Thomas, et al., 2005; Nandhagopal et al., 2009). The mean annual decline in $^{[18F]}$dopa uptake ranges from 8% to 12% in the putamen and from 4% to 6% in the caudate and it is considerably more than the decline typical of aging (Nurmi et al., 2001; Pavese, Rivero-Bosch, Lewis, Whone, & Brooks, 2011). Moreover, presynaptic dopaminergic
PET imaging has been used to estimate the duration of preclinical PD and it has shown 30%–55% loss of putamen dopaminergic function at the time of symptom onset (de la Fuente-Fernández et al., 2011; Hilker, Schweitzer, et al., 2005; Hilker, Thomas, et al., 2005; Lee, 2000). $[^{11}\text{C}]$DTBZ PET imaging estimated a preclinical state lasting up to 17 years, and $[^{11}\text{C}]$MP PET has shown a period of up to 13 years in patients with PD who were diagnosed at just over 50 years of age. Several studies have shown a correlation between decreased putamen $[^{18}\text{F}]$dopa uptake severity of bradykinesia and rigidity in PD patients (Brooks et al., 2003; Vingerhoets, Schulzer, Calne, & Snow, 1997).

To date, two radioligands, $[^{11}\text{C}]$SCH23390 and $[^{11}\text{C}]$NNC112, have been developed to image dopamine D1 receptors (D1R) (Halldin et al., 1986; Slifstein et al., 2007). $[^{11}\text{C}]$SCH23390 PET has shown no changes in striatal and cortical D1R density in both early-stage de novo (Rinne, Laihinen, et al., 1991; Rinne, Myllykylä, Lönnberg, & Marjamäki, 1991) and levodopa-treated (Ouchi et al., 1999) PD patients. No differences were found in dopamine D1R binding between PD patients with L-dopa-induced dyskinesias (LIDs) and those who were stable responders to levodopa treatment (Turjanski, Lees, & Brooks, 1997). Moreover, executive dysfunction was not associated with striatal and cortical dopamine D1R density as measured by $[^{11}\text{C}]$NNC112 PET, whereas decreases in putamen $[^{18}\text{F}]$dopa uptake predicted performance on executive tasks (Cropley et al., 2008). These findings may be hindered by the lack of specific binding of $[^{11}\text{C}]$SCH23390 and $[^{11}\text{C}]$NNC112 displayed high affinity to the serotoninergic 5-HT$_{2A}$ receptors (Catafau et al., 2010; Ekelund et al., 2007).

PET imaging of dopamine D2 receptor (D2R) expression can be performed by using both dopamine antagonists, such as $[^{11}\text{C}]$raclopride, $[^{11}\text{C}]$NMSP, and $[^{18}\text{F}]$DMFP along with dopamine agonist radioligands ($[^{11}\text{C}]$NPA and $[^{11}\text{C}]$MNPA). Among these radioligands, the most widely used is $[^{11}\text{C}]$raclopride. Increases in D2R availability can occur at the early stages of the disease with reported elevations of $[^{11}\text{C}]$raclopride binding in the putamen of de novo PD patients (Rinne et al., 1993, 1995; Turjanski et al., 1997). Moreover, striatal decreases in $[^{18}\text{F}]$dopa uptake correlated with higher $[^{11}\text{C}]$raclopride binding in early de novo PD patients, suggesting that upregulation of D2R may be a compensatory mechanism in response to synaptic dopamine depletion (Sawle, Playford, Brooks, Quinn, & Frackowiak, 1993). However, as the disease progresses this compensatory upregulation may fail and D2R availability decreases back to normal levels or less in comparison to healthy subjects (Antonini, Schwarz, Oertel, Pogarell, &
Leenders, 1997; Brooks et al., 1992; Dentresangle et al., 1999). Moreover, long-term downregulation of striatal dopamine D2R binding may be induced by chronic dopaminergic therapy (Antonini et al., 1997). D2R availability was reduced by 16% in the caudate of levodopa-treated patients compared to de novo PD patients, and there were no differences in mean caudate and putamen D2R binding between dyskinetic and nondyskinetic PD patients (Turjanski et al., 1997). PET investigations of dopamine D3 receptor (D3R) have also been of current interest because of its potential involvement in psychiatric and motor complications in PD. PET with [11C]PHNO, a radioligand with preferential affinity for D3R over D2R (Rabiner et al., 2009), showed bilaterally decreased [11C]PHNO but not [11C]raclopride binding in the D3-rich ventral striatum, and globus pallidus and [11C]PHNO/[11C]raclopride ratio correlated with motor deficits and depressive symptoms (Boileau et al., 2009). Changes in dopamine receptors are not only restricted to the striatal areas. [11C]raclopride PET showed that D2R binding was significantly reduced in the hypothalamus of PD patients, suggesting a role of hypothalamus in the development of PD nonmotor symptoms (Politis, Piccini, Pavese, Koh, & Brooks, 2008). In advanced PD patients, PET with [11C]FLB457, an extrastriatal D2R radioligand, showed 17%–40% decreases in cortical areas, whereas extrastriatal D2R availability was not significantly different in early PD (Kaasinen et al., 2000). A longitudinal [11C]FLB457 PET study demonstrated 6%–11% annual decline in extrastriatal D2R availability in PD patients (Kaasinen et al., 2003).

[11C]raclopride competes with endogenous dopamine for D2R binding, allowing an indirect measure of synaptic dopamine levels based on changes in D2 receptor availability, and it is estimated that a 10% reduction in D2 receptor binding by 11C-raclopride reflects a fivefold increase in synaptic dopamine levels (Breier et al., 1997). There is a rapid reduction in [11C]raclopride binding following administration of levodopa (Tedroff et al., 1996) or a methamphetamine (Piccini et al., 2003) challenge in PD patients. Following methamphetamine challenge, advanced PD patients could still induce significant endogenous dopamine release in the putamen, which reflected motor symptoms improvement, although dopamine release was significantly smaller than those observed in healthy subjects (Piccini et al., 2003). Altered synaptic dopamine release may play a role in the pathogenesis of motor complications such as LIDs. Using [11C]raclopride PET, it has been demonstrated that 1 h after levodopa administration, dopamine levels in the putamen were three times higher in the group of PD patients with motor fluctuations than PD patients with stable response to levodopa.
(de la Fuente-Fernández, Lim, et al., 2001; de la Fuente-Fernández, Lu, et al., 2001; de la Fuente-Fernández, Ruth, et al., 2001). However, 4 h after levodopa challenge, PD patients with motor fluctuations showed major reductions in putaminal dopamine levels, whereas in PD patients with a stable response to levodopa, putaminal dopamine levels remained unchanged (de la Fuente-Fernández, Lim, et al., 2001; de la Fuente-Fernández, Lu, et al., 2001; de la Fuente-Fernández, Ruth, et al., 2001). These findings suggest that swings in striatal synaptic dopamine levels precede the occurrence of motor fluctuations in PD and that increased dopamine turnover might play a relevant role in levodopa-related motor complications. As the disease advances, PD patients lose their ability to regulate synaptic dopamine levels (de la Fuente-Fernández et al., 2004). Following levodopa administration, mean caudate and putamen $[^{11}C]$raclopride binding were significantly lower compared to baseline and correlated with levodopa-induced improvements in UPDRS-III. Additionally, large putaminal $[^{11}C]$raclopride binding changes were associated with higher dyskinesia scores (Pavese et al., 2006). $[^{11}C]$raclopride PET has been used also to monitor response to transplantation of fetal ventral mesencephalic (fVM) tissue. Transplantation led to a restoration of both basal and drug-induced dopamine release to normal levels (Piccini et al., 1999, 2005; Politis, Loane, Wu, Brooks, & Piccini, 2011; Politis, Oertel, et al., 2011; Politis, Wu, Loane, Kiferle, et al., 2010; Politis, Wu, Loane, Quinn, et al., 2010; Politis, Wu, Loane, Turkheimer, et al., 2010; Politis & Piccini, 2012).

Altered dopamine release appears to play a role in PD impulse control disorders (ICD) and addictive behaviors. Following levodopa challenge, dopamine levels within the ventral striatum were significantly higher in PD patients with dopamine dysregulation syndrome (DDS) compared to those without DDS and correlated in the DDS cohort with them “wanting” but not “liking” the medication even if it produced unpleasant effects (Evans et al., 2006). $[^{11}C]$raclopride PET imaging has suggested that the development of ICDs is related to a drug-induced overstimulation of dopamine release in the ventral striatum (O’Sullivan et al., 2011; Steeves et al., 2009). Although no differences in D2R availability were observed at baseline and following levodopa challenge with neutral cues, PD patients with ICD showed greater decrease in ventral striatal $[^{11}C]$ raclopride binding than those without ICD following exposure to reward-related cues (O’Sullivan et al., 2011). These findings suggest that as a result of neural sensitization in vulnerable individuals, reward-related cues are attributed with pathological incentive salience, leading to compulsive pursuit.
Activation of the nigrostriatal dopaminergic system appears to be relevant in determining placebo effect in PD. In the placebo group, reductions in striatal $[^{11}\mathrm{C}]$raclopride binding were comparable to that observed in PD patients that received a therapeutic dose of apomorphine (de la Fuente-Fernandez, Lim, et al., 2001; de la Fuente-Fernandez, Lu, et al., 2001; de la Fuente-Fernandez, Ruth, et al., 2001). PD patients in the placebo group showed a decrease in $[^{11}\mathrm{C}]$raclopride binding in the ventral striatum after placebo as compared to baseline. However, in contrast to the dorsal striatum, no differences in $[^{11}\mathrm{C}]$raclopride binding were found between patients who experienced the reward and those who did not, suggesting that release of dopamine in the ventral striatum is related to the expectation of reward and not to the reward itself (de la Fuente-Fernandez et al., 2002).

1.1.2 Serotonergic System

Serotonergic system plays an important role in modulating cognition, emotion, and motor behavior and its dysfunction may contribute to the motor and nonmotor symptoms observed in PD (Pagano, Niccolini, Fusar-Poli, et al., 2017; Pagano, Niccolini, & Politis, 2016a, 2016b; Politis & Niccolini, 2015).

PET radioligands tagging serotonin targets have been used to assess the serotonergic system in PD patients (Politis & Niccolini, 2015; Schrag & Politis, 2016). $[^{11}\mathrm{C}]$DASB, which binds to 5-HT transporter (SERT), is the most widely serotonergic radioligand used to image the serotonergic system (Wilson et al., 2000). PET with $[^{11}\mathrm{C}]$DASB has shown global reductions of SERT density at different stages of the PD, which did not correlate with disease duration, motor disability, or chronic exposure to dopamine replacement therapy (Politis, Wu, Loane, Kiferle, et al., 2010; Politis, Wu, Loane, Quinn, et al., 2010; Politis, Wu, Loane, Turkheimer, et al., 2010). The pattern of serotonergic dysfunction in PD is different from that observed for dopaminergic system which greatly affects the posterior putamen (Brooks et al., 1990; Nurmi et al., 2000).

Serotonergic system may play an important role in the development of motor symptoms such as tremor. PET with $[^{11}\mathrm{C}]$WAY100635, a selective marker of 5-HT$_{1A}$ receptors, found that the midbrain raphe 5-HT$_{1A}$ binding was reduced by 27% in PD patients compared to healthy controls and there was a significant correlation between reductions in midbrain raphe 5-HT$_{1A}$ binding and the severity of tremor (Doder, Rabiner, Turjanski, Lees, & Brooks, 2003). PD patients with tremor–dominant phenotype had significant reductions in $[^{11}\mathrm{C}]$DASB binding in caudate, putamen,
raphe nuclei, thalamus, and Brodmann areas 4 and 10 compared with those who had akinetic–rigid PD and with a group of normal controls (Loane et al., 2013). Loss of SERT binding in caudate, putamen, and raphe nuclei in patients with tremor–dominant PD correlated with the severity of postural and action tremor, providing evidence for the role of presynaptic serotonergic terminal dysfunction in the development of tremor in PD (Loane et al., 2013).

Striatal serotonergic neurons are able to take up, convert exogenous levodopa into dopamine, and subsequently release it from the serotonergic terminals (Maeda, Nagata, Yoshida, & Kannari, 2005; Ng, Chase, & Kopin, 1970; Tanaka et al., 1999). This feature is of great interest in advanced stages of PD when the majority of the striatal dopaminergic terminals degenerated, and serotonin terminals might play a role in handling striatal synaptic dopamine concentrations following levodopa treatment. An in vivo [11C]DASB PET study showed that although PD patients with LIDs had no difference in serotonergic terminal density compared with those who had a stable response to levodopa, similar levodopa doses induced markedly higher striatal synaptic dopamine concentrations in PD patients with LIDs compared with those with stable responses to levodopa (Politis, Wu, Loane, Brooks, et al., 2014; Politis, Wu, Loane, Quinn, et al., 2014). When buspirone, a 5–HT1A agonist, was administered before levodopa, it reduced the levodopa–evoked striatal synaptic dopamine increases and attenuated LIDs. Moreover, PD patients with LIDs who exhibited greater decreases in synaptic dopamine after buspirone pretreatment had higher levels of serotonergic terminal functional integrity (Politis, Wu, Loane, Brooks, et al., 2014; Politis, Wu, Loane, Quinn, et al., 2014). When PD patients with LIDs were divided into two groups depending on LIDs severity, buspirone–associated modulation of dopamine levels was greater in PD patients with milder LIDs compared to those with more severe LIDs (Politis, Wu, Loane, Brooks, et al., 2014; Politis, Wu, Loane, Quinn, et al., 2014). Overall, the findings from this study provide the first human evidence for the role of striatal serotonergic terminals in LIDs pathophysiology and support the development of selective 5–HT1A agonists for use as antidyskinetic agents in PD. Serotonin terminals are also involved in graft-induced dyskinesias (GIDs), which are involuntary movements when “off” dopaminergic drugs occurring after transplantation of fVM tissue (Kefalopoulou et al., 2014; Politis, Loane, et al., 2011; Politis, Oertel, et al., 2011; Politis, Wu, Loane, Kiferle, et al., 2010; Politis, Wu, Loane, Quinn, et al., 2010; Politis, Wu, Loane, Turkheimer, et al., 2010). [11C]DASB and [18F]dopa
PET studies have shown that three PD patients who received striatal transplantation with fVM tissue and exhibited GIDs had excessive graft-derived serotonergic innervation and high serotonin-to-dopamine terminal ratio (Politis, Loane, et al., 2011; Politis, Oertel, et al., 2011; Politis, Wu, Loane, Kiferle, et al., 2010; Politis, Wu, Loane, Quinn, et al., 2010; Politis, Wu, Loane, Turkheimer, et al., 2010). Administration of small, repeated doses of buspirone, was able to attenuate GIDs possibly by attenuating the abnormal serotonin terminal–derived dopamine release (Loane & Politis, 2012; Politis, 2010, 2011; Politis, Loane, et al., 2010; Politis, Oertel, et al., 2011; Politis, Wu, Loane, Kiferle, et al., 2010; Politis, Wu, Loane, Quinn, et al., 2010; Politis, Wu, Loane, Turkheimer, et al., 2010).

Serotonergic dysfunction has been implicated also in the pathogenesis of several PD nonmotor symptoms. $^{[11C]}$DASB PET studies have reported relative increases of SERT binding in limbic structures of depressed PD patients (Boileau et al., 2008; Politis, Wu, Loane, Kiferle, et al., 2010; Politis, Wu, Loane, Quinn, et al., 2010; Politis, Wu, Loane, Turkheimer, et al., 2010). Depressed PD patients had significantly increased $^{[11C]}$DASB binding in the amygdala, hypothalamus, caudal raphe nuclei, and posterior cingulate cortex compared to nondepressed PD patients which correlated with the severity of depressive symptoms (Politis, Wu, Loane, Kiferle, et al., 2010; Politis, Wu, Loane, Quinn, et al., 2010; Politis, Wu, Loane, Turkheimer, et al., 2010). These findings provide support for the use of agents acting on SERT for the treatment of PD depression.

SERT dysfunction has been also associated with body mass index (BMI) changes in PD patients (Politis, Loane, et al., 2011; Politis, Oertel, et al., 2011). PD patients with abnormal BMI changes over a 12–month period showed significantly increase of $^{[11C]}$DASB binding in rostral raphe nuclei, hypothalamus, caudate nucleus, and ventral striatum compared to those with no significant weight alterations (Politis, Loane, et al., 2011; Politis, Oertel, et al., 2011). Thus, BMI changes are associated to increased SERT availability in rostral raphe nuclei and its connections to limbic and cognitive areas. Serotonergic dysfunction may have relevance in the development of fatigue symptoms in PD. PD patients with fatigue had 66%–83% significant reductions in $^{[11C]}$DASB binding in the putamen, caudate nucleus, ventral striatum, thalamus, cingulate, and amygdala, compared to the PD patients without fatigue (Pavese, Metta, Bose, Chaudhuri, & Brooks, 2010). Serotonergic system is involved in the regulation of sleep, and its dysfunction could have relevance to the development of sleep problems in PD. Abnormalities in serotonin neurotransmission could be involved in the neural...
mechanisms underlying the development of visual hallucinations and psychosis in PD. PET with [18F]setoperone, a selective 5-HT$_{2A}$ receptor radioligand, showed increased 5-HT$_{2A}$ binding in ventral visual pathway, dorsolateral prefrontal cortex, medial orbitofrontal cortex, and insula of PD patients with visual hallucinations (Ballanger et al., 2010). Moreover, pimavanserin, a selective 5-HT$_{2A}$ antagonist/inverse agonist, has been recently approved by the FDA for treating the delusions and hallucinations associated with psychosis in PD (Cummings et al., 2014). Although transplanted PD patients showed improvement in their motor symptoms, they still suffered from nonmotor symptoms such as depression, fatigue, visual hallucinations, and sleep problems (Politis & Piccini, 2012). [11C]DASB PET indicated decreased SERT binding in raphe nuclei and several brain regions receiving serotonergic projections in these PD patients, suggesting ongoing degeneration of serotonergic neurons despite the surgical-induced improvement in dopaminergic function (Politis & Piccini, 2012).

### 1.1.3 Cholinergic System

Although cholinergic interneurons represent only 1%–2% of the striatal neural population, they play a key role in the functional and structural remodeling of striatocortical circuits by enhancing both dopamine and GABA release and modulating striatal output (Schliebs & Arendt, 2011; Zhou, Wilson, & Dani, 2002). PET with selective radioligands targeting functional components of the cholinergic system, such as acetylcholinesterase (AChE), the nicotinic acetylcholine receptor (nAChR), and the muscarinic acetylcholine receptor (mAChR), has led to significant advances in the understanding of the neurobiology and pathophysiology of PD.

Evidence from postmortem studies indicates that both presynaptic and postsynaptic cholinergic markers are decreased in PD patients with and without dementia (Perry et al., 1993; Quik, Bordia, Forno, & McIntosh, 2004; Rinne, Laihinen, et al., 1991; Rinne, Myllykylä, et al., 1991; Schmaljohann et al., 2006; Shiozaki et al., 1999). Two selective SPECT radioligands, [123I]-QNB and [123I]-5IA, have been used to assess postsynaptic cholinergic system availability of M1 mAChR and $\alpha_4\beta_2$ nAChR, respectively (Colloby et al., 2005; Fujita et al., 2006; Isaias et al., 2014; Lorenz et al., 2014; Oishi et al., 2007). SPECT studies using [123I]-5IA showed in early cognitively normal PD patients significantly higher nAChR density in the putamen, the insular cortex, and the supplementary motor area and lower in the caudate nucleus, the orbitofrontal cortex, and the middle temporal gyrus. Disease duration positively
correlated with nAChR density in the putamen ipsilateral but not contra-
lateral to the clinically most affected side (Isaias et al., 2014). Advanced PD
patients without dementia showed a widespread nAChR decrease, ranging
between 10% and 25%, in cortical and subcortical areas (Fujita et al., 2006;
Lorenz et al., 2014; Oishi et al., 2007), and a significant correlation was
found between cognitive dysfunction and cortical nAChR uptakes (Lorenz et al., 2014).

Two selective AChE radioligands: [11C]PMP and [11C]MP4A have
been used to assess presynaptic cholinergic system integrity in PD patients
(Iyo et al., 1997; Namba et al., 1998). PET studies using [11C]MP4A and
[11C]PMP have demonstrated 11%–12% decreases in cortical and subcortical
AChE activity in PD patients without dementia (Bohlen et al., 2006, 2012;
Gilman et al., 2010; Shimada et al., 2009). Early de novo PD patients also
showed significant 12% AChE losses in the medial occipital cortex,
suggesting that loss of AChE activity occurs even in early stages of the disease
(Shimada et al., 2009). However, differences in AChE activity between early
and advanced PD patients were nonsignificant, suggesting that cholinergic
dysfunction occurs early, but does not progress with the disease (Shimada
et al., 2009). Cortical and thalamic cholinergic denervation as measured
by [11C]PMP PET were associated with increased falls, slower gait speed,
and increased freezing of gait in PD patients, suggesting that cholinergic
degeneration is a major factor leading to impaired postural control and gait
dysfunction in PD (Bohlen et al., 2014, 2013, 2009).

Postsynaptic cholinergic function is also impaired in PD patients. Two
PET studies with [11C]NMPB, a marker for mAChR, demonstrated
increased mAChR levels in the frontal cortex of PD patients which did
not correlate with disease duration, motor, and cognitive symptoms severity
(Asahina et al., 1995, 1998). The increased mAChR availability may repre-
sent denervation hypersensitivity caused by loss of the ascending cholinergic
system in frontal areas.

Two PET studies have studied nAChR availability in PD patients using
[18F]2FA, a radioligand selective for α4β2 nAChR (Kas et al., 2009; Meyer
et al., 2009). Kas and colleagues (2009) found significant reduction in
nAChR in the striatum and substantia nigra of nondemented PD patients,
but no significant correlations were observed between decreased nAChR
availability and disease duration and severity, dopaminergic medication
intake, and [18F]dopa uptake in PD patients. [18F]2FA was decreased in sev-
eral brain regions in PD patients, including the frontoparietal and anterior
cingulate cortices, midbrain, pons, and cerebellum, with the highest reduc-
tion seen in the left parietal cortex (Meyer et al., 2009).
Dysfunction of the ascending cholinergic systems from the basal forebrain and brain stem and the associated loss of cholinergic neurotransmission in the cerebral cortex have been suggested as the underlying substrates of cognitive decline in dementia (Bartus, Dean, Beer, & Lippa, 1982). PET studies using $[^{11}C]$MP4A and $[^{11}C]$PMP have shown 20%–30% decreases in cortical AChE activity in PD with dementia (PDD) and dementia Lewy body (DLB) patients (Bohnen et al., 2006; Hilker, Schweitzer, et al., 2005; Hilker, Thomas, et al., 2005; Klein et al., 2010). Loss of cortical AChE activity as measured by $[^{11}C]$PMP correlated with worse performance in working memory and attention tests in PD patients (Bohnen et al., 2006). Moreover, in PDD patients, decreased striatal $[^{18}F]$dopa uptake correlated with cortical $[^{11}C]$MPA reduction, suggesting that cognitive decline in PD occurs when the disease spreads from nigral neurons to the cortex, leading to a cholinergic dysfunction in this region (Hilker, Schweitzer, et al., 2005; Hilker, Thomas, et al., 2005). Postsynaptic nAChR loss, as measured by $[^{18}F]$2FA PET, also correlated with depression and cognitive decline (Meyer et al., 2009).

With regards to other nonmotor symptoms, cholinergic denervation in neocortical, limbic, and thalamic regions was associated with rapid eye movement (REM) sleep behavior disorder (RBD) in PD (Kotagal et al., 2012).

It has been suggested that abnormal aggregation of α-synuclein in PD initially starts in the autonomic nerve endings of the gastrointestinal mucosa and then spreads in a prion-like fashion via the vagal nerve to the brain stem (Hawkes, Del Tredici, & Braak, 2007). Therefore, parasympathetic nervous system imaging could become an important biomarker for diagnosing prodromal disease. $[^{11}C]$donepezil PET has been recently validated for quantification of AChE density in peripheral organs (Gjerloff et al., 2014). In early-to-moderate stage PD patients, $[^{11}C]$donepezil binding was markedly decreased in the small intestine (−35%) and pancreas (−30%) compared with healthy controls, suggesting that systemic parasympathetic denervation can play a role in the pathogenesis of PD (Gjerloff et al., 2015).

1.1.4 Neuroinflammation

Microglia constitute 10%–20% of glial cells and represent the main form of immune defense in the central nervous system (CNS) (Kreutzberg, 1996). Following CNS injury, microglia become activated overexpress the 18-kDa translocator protein (TSPO) that is involved in the release of proinflammatory cytokines during inflammation and is present at very low levels in the normal healthy CNS (Banati, 2002). The upregulation
of TSPO expression can be detected in vivo with PET and selective radioligands (Fujita et al., 2008; Ikoma et al., 2007; Oh et al., 2011; Owen et al., 2010, 2014; Su & Politis, 2012; Vas et al., 2008), and the most widely used TSPO radioligand to date is \([^{11}C]PK11195\) (Banati et al., 1999, 2000; Chauveau, Boutin, Van Camp, Dollé, & Tavitian, 2008). In early de novo PD patients, \([^{11}C]PK11195\) PET binding in the midbrain contralateral to the clinically affected side was significantly increased compared to a group of healthy controls and increased microglial activation was associated with putamen dopaminergic deficits and increased motor symptom severity (Ouchi et al., 2005). Moderate/advanced levodopa-treated PD patients showed widespread increases in \([^{11}C]PK11195\) binding in the pons, basal ganglia, and frontal and temporal cortical regions, which did not correlate with symptom severity and striatal dopaminergic deficits (Gerhard et al., 2006). Moreover, the levels of microglial activation remained stable over a period of 2 years (Gerhard et al., 2006). \([^{11}C]PK11195\) binding was also increased in the anterior and posterior cingulate, striatum, frontal, temporal, parietal, and occipital cortical regions in PDD patients (Edison et al., 2013) and in the substantia nigra, putamen, and several associative cortices of DLB patients (Iannaccone et al., 2013).

However, evaluation of microglial activation using \([^{11}C]PK11195\) is hampered by unfavorable radioligand characteristics (Chauveau et al., 2008). \([^{11}C]PK11195\) shows high level of nonspecific binding and a poor signal-to-noise ratio (Petit-Taboué et al., 1991), which complicates its quantification; moreover, test–retest data in control subjects showed only moderate intraindividual reproducibility (Jučaitė et al., 2012). Second-generation TSPO radioligands for PET imaging provide a better quantification of microglial activation, although they present three patterns of binding affinity based on genetic polymorphism: high-affinity, mixed-affinity, and low-affinity binders (Owen et al., 2011) which require genotype screening before enrolling the subjects in the study. A recent study using the second-generation TSPO radioligand \([^{18}F]FEPPA\) showed that striatal microglial activation was increased by 16% in both caudate nucleus and putamen of high-affinity binders but not in mixed-affinity binders PD patients compared to the group of healthy controls (Koshimori et al., 2015). The second-generation TSPO radioligand, \([^{11}C]PBR28\), was used to assess the efficacy of AZD3241, a selective and irreversible myeloperoxidase inhibitor, in reducing neuroinflammation in a small cohort of PD patients (Jucaite et al., 2015). This double-blind and placebo-controlled study showed that 8 weeks treatment with AZD3241 was able to decrease
[¹¹C]PBR28 binding across cortical and subcortical brain regions as compared to baseline (Jucaite et al., 2015).

Thus, microglial activation may contribute to the neurodegenerative processes in PD and drugs aiming to decrease neuroinflammation in the brain of PD patients may be aid in slowing down disease progression.

### 1.1.5 Misfolded Proteins

PD is neuropathologically characterized by Lewy body intracellular inclusions that are rich in α-synuclein (Harding & Halliday, 2001). However, extracellular Aβ-amyloid plaques and intracellular tau neurofibrillary tangle are also observed at autopsy in PD, PDD, and DLB patients (Horvath, Herrmann, Burkhard, Bouras, & Kövari, 2013; Jellinger & Attems, 2008; Jellinger, Seppi, Wenning, & Poewe, 2002).

PET studies with the thioflavin derivative ligand [¹¹C]Pittsburgh compound-B (PiB) and related clinically approved radiofluorinated tracers including [¹⁸F]Florbetapir, [¹⁸F]Florbetaben, and [¹⁸F]Flutemetamol have investigated the role of amyloid deposition in PD, PDD, and DLB. Overall these studies found that amyloid deposition tends to be modest in PD with normal cognition occurring in about 0%–13% of PD patients (Edison et al., 2013, 2008; Foster et al., 2010; Gomperts et al., 2012, 2008; Johansson et al., 2008; Jokinen et al., 2010; Maetzler et al., 2009; Petrou et al., 2012). Amyloid burden is generally low in PD subjects with mild cognitive impairment (MCI), and does not distinguish cognitively normal PD patients from PD-MCI (Foster et al., 2010; Gomperts et al., 2012, 2013; Petrou et al., 2012). PDD patients have higher incidence of cortical Aβ-amyloid deposition compared to healthy subjects, PD and PD-MCI, ranging from 0% to 80% (Edison et al., 2013, 2008; Foster et al., 2010; Gomperts et al., 2012, 2008; Jokinen et al., 2010; Maetzler et al., 2009, 2008). Amyloid burden in PDD patients is heterogeneous with cases of PDD, where amyloid deposition overlaps with the levels observed in healthy subjects and in PD patients (Edison et al., 2013, 2008; Foster et al., 2010; Gomperts et al., 2012, 2008; Jokinen et al., 2010; Maetzler et al., 2009, 2008) and other cases of PDD showing elevated cortical amyloid deposition in the Alzheimer’s disease (AD) range (Edison et al., 2013, 2008; Foster et al., 2010; Gomperts et al., 2012; Jokinen et al., 2010; Maetzler et al., 2009, 2008; Shimada et al., 2013). In contrast, amyloid burden is usually elevated in DLB patients compared to healthy subjects and PD patients and the incidence ranges between 33% and 100% (Burke et al., 2011; Claassen, Lowe, Peller, Petersen, & Josephs, 2011; Edison et al.,
Similarly to healthy subjects, apolipoprotein ε4 allele and older age are risk factors for increased cortical amyloid burden in DLB and PDD patients (Gomperts et al., 2012; Maetzler et al., 2009; Rowe et al., 2007). Global amyloid deposition has been associated with worse cognitive performance (Foster et al., 2010; Gomperts et al., 2013; Petrou et al., 2012; Villemagne et al., 2011), and the absence of cortical amyloid deposition was associated with a better response to ACh inhibitors (Burke et al., 2011). The clinical significance of amyloid burden in Lewy bodies diseases is still unclear, but it has been suggested that early and significant cortical amyloid burden may accelerate cognitive decline as a result of synergistic Aβ–α-synuclein neurotoxicity. A longitudinal PET study has shown that nondemented PD patients with higher amyloid burden have baseline progressed to cognitive impairment faster than those with lower amyloid burden over a period of 5 years (Gomperts et al., 2013). Thus, higher amyloid burden in cognitively normal PD patients may predict cognitive decline.

Moreover, postural instability and gait difficulty in PD patients was associated with increased neocortical [11C]PiB retention, suggesting that cortical amyloidopathy may play a role on the etiology of balance and gait impairments (Müller et al., 2013).

A recent PET study using [18F]T807 investigated tau deposition in DLB, PD with and without cognitive impairment (Gomperts et al., 2016). Cortical [18F]T807 uptake was higher in the DLB and PD with cognitive impairment than healthy controls with in low-amyloid pathology, and higher uptake was observed in the inferolateral temporal and parietal/precuneus regions (Gomperts et al., 2016). Tau deposition was more variable in DLB patients and was lower in magnitude and extent in PD with cognitive impairment, whereas PD patients without cognitive impairment showed no evidence for tau deposition (Gomperts et al., 2016). These findings suggest that, beside α-synuclein, also tau pathology may play a role in determining cognitive dysfunction in Lewy body diseases.

1.1.6 Other Systems
1.1.6.1 Glutamate

Increased glutamatergic transmission may play a role in the pathogenesis of LIDs, and a PET study using [11C]CNS51619, a marker of activated NMDA receptors, has shown increased [11C]CNS5161 uptake in caudate, putamen,
and precentral gyrus in PD patients with LIDs in ON condition (Ahmed et al., 2011). However, $^{[11}C]CNS51619$ uptake did not differ between PD patients with LIDs and those with stable response to levodopa when patients were scanned in OFF condition, suggesting that increased glutamatergic transmission may be involved in the development of LIDs (Ahmed et al., 2011).

1.1.6.2 Cannabinoid
Cannabinoid type 1 receptors (CB1Rs) are expressed in the basal ganglia where they regulate intracellular levels of cAMP by interacting with Gi/o and Gs proteins in the direct and indirect pathways, respectively (Glass, Dragunow, & Faull, 1997; Herkenham et al., 1991; Mailleux & Vanderhaeghen, 1992; Martín et al., 2008). A PET study using $^{[18}F]MK-9470$ has shown significant decreases in CB1R levels in the substantia nigra of early de novo and advanced PD patients with and without LIDs (van Laere et al., 2012). However, no differences were found in regional CB1R availability between advanced PD patients with and without LIDs and regional CB1R levels were not associated with LIDs severity (van Laere et al., 2012). Further studies using higher selective CB1R PET radioligands are needed in order to further elucidate the role of these receptors in the pathophysiology of PD.

1.1.6.3 Opioid
All three opioid receptors ($\mu$, $\kappa$, and $\delta$) are involved in regulating dopaminergic signaling in the basal ganglia (Samadi, Bedard, & Rouillard, 2006). Two PET studies using $^{[11}C]diprenorphine$, a nonselective opioid receptor antagonist, have investigated cortical and subcortical opioid receptor availability in PD patients (Burn et al., 1995; Piccini, Weeks, & Brooks, 1997). Burn and colleagues (1995) found no differences in striatal opioid receptor levels between PD patients and healthy controls, whereas mean striatal opioid receptor binding was significant decreased in patients with progressive supranuclear palsy (PSP)–Richardson compared to PD patients and healthy controls. When comparing PD patients with and without LIDs, Piccini and colleagues (1997) found reduced striatal, thalamic, and cingulate and increased prefrontal opioid binding in PD patients with LIDs. However, there were no correlations between $^{[11}C]diprenorphine$ binding and PD severity, disease duration, or duration of levodopa treatment (Piccini et al., 1997). Thus, the role of opioid receptors in the pathophysiology of
PD and its complication remains unclear and further PET studies using more selective opioid radioligands could aid in elucidating the role of the opioid system in PD.

1.1.6.4 Adenosine
Adenosine modulates dopaminergic signaling by acting on A2A adenosine receptors (A2ARs). These receptors are mainly expressed in the striatopallidal medium spiny neurons (indirect pathway) where they stimulate adenylate cyclase and interact with dopamine D2R negatively at the level of second messengers (Fredholm & Svenningsson, 2003). Two PET studies using [11C]TMSX and [11C]SCH442,416, both markers of A2ARs, have shown increased striatal A2ARs in PD patients with LIDs (Mishina et al., 2011; Ramlackhansingh et al., 2011). Moreover, in de novo PD patients, [11C]TMSX binding was significantly decreased in the putamen but not in the caudate on the most affected side and A2ARs availability was increased in the putamen following antiparkinsonian therapy (Mishina et al., 2011). These findings suggest that increased striatal A2AR availability is involved in the pathophysiology of LIDs, and at the early stage of the disease A2AR in the putamen may compensate for the asymmetrical decrease of dopamine.

1.1.6.5 Phosphodiesterases
Phosphodiesterases (PDEs) are intracellular enzyme that modulate the activation of G-proteins through the hydrolysis of cyclic nucleotides, such as cAMP and cGMP, and play an important role in cell signal transduction (Fujishige, Kotera, & Omori, 1999). Among PDEs family, PDE10A is expressed almost exclusively in the striatum (Coskran et al., 2006; Lakics, Karran, & Boess, 2010), where it modulates cAMP/PKA/DARPP-32 signaling cascade thus having a key role in the regulation of striatal output and in promoting neuronal survival (Girault, 2012; Nishi et al., 2008). Using [11C]IMA107 PET, our group has recently investigated PDE10A expression in 24 levodopa-treated moderate to advanced PD patients (Niccolini, Foltynie, et al., 2015; Niccolini, Haider, et al., 2015). PD patients showed lower [11C]IMA107 binding in the caudate, putamen, and pallidum compared to healthy controls. Longer PD duration and higher UPDRS-III motor scores correlated with lower [11C]IMA107 binding in the caudate, putamen, and pallidum (Niccolini, Foltynie, et al., 2015; Niccolini, Haider, et al., 2015). Higher Unified Dyskinesia Rating Scale (UDysRS)
scores in those PD patients with levodopa-induced dyskinesias correlated with lower $[^{11}\text{C}]\text{IMA107}$ binding in the caudate and putamen. These findings provide evidence for the role of PDE10A in the development of PD motor symptoms and complications. Positive evidence on the role of PDE10A in movement disorders comes from recent genetic studies on PDE10A gene mutations (Diggle et al., 2016; Mencacci et al., 2016). Patients with homozygous (Diggle et al., 2016) and heterozygous (Mencacci et al., 2016) PDE10A mutation present with benign childhood-onset chorea that may be followed by adult-onset levodopa-responsive parkinsonism (Mencacci et al., 2016). Moreover, PET molecular studies using $[^{11}\text{C}]\text{IMA107}$, $[^{18}\text{F}]\text{MNI-659}$, and $[^{18}\text{F}]\text{JNJ42259152}$ have shown 30%–70% reduction of striatal PDE10A in Huntington’s disease gene-expansion carriers (HDGECs) (Pagano, Niccolini, Fusar-Poli, et al., 2017; Pagano, Niccolini, & Politis, 2016a, 2016b) spanning from far-onset premanifest stages (Niccolini, Foltynie, et al., 2015; Niccolini, Haider, et al., 2015) to early manifest (Russell et al., 2014, 2016) and advanced (Ahmad et al., 2014) manifest HDGECs. Thus, PDE10A activity is critical for the control of movements and for neuronal survival and could serve as a novel therapeutic target for manipulation with pharmacotherapy in the neuropathological salient circuits, which promote neuronal survival and control of movements.

1.1.6.6 Sigma 1 Receptors

Sigma 1 receptor (S1R) is considered a marker of the mitochondrion-associated endoplasmic reticulum (ER) membrane involved in the regulation mitochondrial activity via $\text{Ca}^{2+}$ influx (Hayashi & Su, 2007). S1R plays a role in a wide variety of cellular functions, including regulation of ion channels, synaptogenesis, and neuronal plasticity (Hayashi & Su, 2007; Renaudo, L’Hoste, Guizouarn, Borgèse, & Soriani, 2007). S1R functions as a molecular chaperone in the ER, which facilitates the proper folding of newly synthesized proteins, but also prevents accumulation of misfolded proteins such as $\alpha$-synuclein, suggesting that S1R plays a key role in cellular survival (Hayashi & Su, 2007). Moreover, preclinical studies have shown that S1R stimulates striatal dopamine synthesis in rats (Booth & Baldessarini, 1991; Chaki, Okuyama, Ogawa, & Tomisawa, 1998). A small PET study using $[^{11}\text{C}]\text{SA4503}$, a S1R agonist, has demonstrated marked decreases of S1R levels in the anterior putamen on the most affected side of in six PD patients providing preliminary evidence for the involvement of S1R in PD (Mishina et al., 2005).
1.2 Magnetic Resonance Imaging

1.2.1 Volumetric MRI

Gray matter (GM) changes have been assessed with voxel-based morphometry and cortical thickness analyses in PD.

Structural MRI studies have mainly focused on regional GM changes associated with cognitive impairment in PD patients. The general consensus suggests widespread cortical atrophy in PDD, although it is less severe compared to AD and DLB (Beyer, Larsen, & Aarsland, 2007; Burton, McKeith, Burn, Williams, & O’Brien, 2004). Cortical atrophy progresses linearly across the cognitive stages in PD and affects temporal, frontal, parietal (Beyer et al., 2007; Burton et al., 2004; Melzer et al., 2012; Pagonabarraga et al., 2013; Tam, Burton, McKeith, Burn, & O’Brien, 2005; Weintraub et al., 2011; Zarei et al., 2013), and less commonly, occipital regions (Burton et al., 2004). Subcortical GM changes can also occur in PDD and affect mainly the hippocampus (Apostolova et al., 2010; Camicioli et al., 2003; Junque et al., 2005; Zarei et al., 2013), thalamus (Burton et al., 2004), putamen (Burton et al., 2004), amygdala (Junque et al., 2005; Zarei et al., 2013), and the caudate (Apostolova et al., 2010; Burton et al., 2004). Regional atrophy in temporal, parietal, and frontal cortices (Melzer et al., 2012; Pagonabarraga et al., 2013; Pereira et al., 2014; Segura et al., 2014; Weintraub et al., 2011) and thalamus (Mak, Bergsland, Dwyer, Zivadinov, & Kandiah, 2014) and hippocampus (Weintraub et al., 2011) has been observed in PD-MCI.

Longitudinal assessment using brain boundary shift integral demonstrated higher rates of global atrophy in PDD (1.12%) compared to non-demented PD patients (0.31%) and control subjects (0.34%) (Burton, McKeith, Burn, & O’Brien, 2005). Additionally, longitudinal analyses of cortical thinning patterns showed that frontal cortical thinning could be a risk factor for the development of PDD (Compta et al., 2013). Non-demented PD patients also presented a more aggressive rate of cortical thinning with a bilateral frontotemporal pattern than healthy subjects (Compta et al., 2013; Ibarretxe-Bilbao et al., 2012; Mak et al., 2015).

Cortical thinning in the parietotemporal association cortex was also associated with longer disease duration, severity of motor symptoms, and in specific with worse bradykinesia and axial motor deficits but not with rigidity and tremor (Lyoo, Ryu, & Lee, 2011). Increased cortical thickness in the right inferior frontal sulcus was observed in PD patients with LIDs supporting the role of the prefrontal cortex in the
pathophysiology of LID (Cerasa, Morelli, et al., 2013). Moreover, early-onset dyskinetic patients showed increased volume in substantia nigra and red nucleus, whereas late-onset dyskinetic patients were characterized by abnormal GM increase in the supplementary motor area (Cerasa, Salsone, et al., 2013).

Mood disorders were also associated with cortical and subcortical changes in PD patients (Carriere et al., 2014; Huang et al., 2016). Surface-based morphometric analysis showed that depressed PD patients had significant cortical thickness in the orbitofrontal regions and insula compared to nondepressed PD patients (Huang et al., 2016), and apathy in PD patients was associated with atrophy of the left nucleus accumbens (Carriere et al., 2014). PD patients who experienced visual hallucinations had significant loss of GM volume in the lingual gyrus and superior parietal lobe compared to healthy controls and PD patients without visual hallucinations (Ramírez-Ruiz et al., 2007). PD patients with probable RBD showed volume loss in the pontomesencephalic tegmentum, medullary reticular formation, hypothalamus, thalamus, putamen, amygdala, and anterior cingulate cortex compared to healthy controls and PD patients without RBD (Boucetta et al., 2016). Structural cortical and subcortical changes in mesocortical and limbic reward-related areas have been observed in PD patients with ICDs. These changes consist in volume loss in nucleus accumbens, caudate, hippocampus, and amygdala (Biundo et al., 2015; Pellicano et al., 2015) as well as increased thickening of anterior cingulate, frontal pole, and orbitofrontal cortices in PD patients with ICDs (Pellicano et al., 2015; Tessitore et al., 2016). These patterns of cortical and subcortical GM changes may be due to maladaptive synaptic plasticity under nonphysiological dopaminergic in patients with a preexisting vulnerability to impulsivity.

1.2.2 Iron Deposition and Neuromelanin
Iron accumulation in the brain can be detected in brain nuclei using sequences sensitive to local magnetic field in homogeneities, such as T2 and T2*, and susceptibility-weighted imaging (SWI) which combines T2* and phase information, increasing the sensitivity to iron (Haacke et al., 2009).

PD patients showed increased iron deposition in the substantia nigra pars compacta, putamen, and globus pallidus (Kosta, Argyropoulou, Markoula, & Konitsiotis, 2006) and substantia nigra pars compacta and red nucleus correlated with higher UPDRS scores (Lewis et al., 2013; Wallis et al., 2008). Over a 3-year follow-up, increased R2* in the substantia nigra correlated
with the worsening of motor symptoms of PD, suggesting that R2* may be a biomarker of disease progression in PD (Ulla et al., 2013). Association between high R2* signal and LIDs has yielded inconsistent results either showing a positive (Bunzeck et al., 2013) or no correlations (Wieler, Gee, & Martin, 2015) between iron deposition and motor complications. Early-onset PD patients showed a higher field-dependent R2 increases in the substantia nigra, putamen, and pallidum, which decreases as the disease progresses, suggesting that dysregulation of iron metabolism occurs in PD (Bartzokis et al., 1999).

SWI studies showed lower levels of phase radians in the substantia nigra pars compacta as well as in the caudate nuclei and red nucleus, with higher phase shift in substantia nigra pars compacta and basal ganglia, were found in PD patients, indicating an increased iron content which correlated with UPDRS scores (Martin-Bastida et al., 2017; Zhang et al., 2009, 2010).

Nigrosomes are small clusters of dopaminergic cells within the substantia nigra exhibiting calbindin D28K negativity on immunohistochemical staining (Damier, Hirsch, Agid, & Graybiel, 1999). Nigrosome-1 is located in the posterior third of the substantia nigra pars compacta and presents high signal on SWI sequences. The healthy nigrosome-1 appears as a “swallow tail” on 3T-SWI sequences, this feature is lost in PD (Blazejewska et al., 2013; Schwarz et al., 2014). Thus, assessing substantia nigra on SWI sequences for the typical “swallow tail” appearance may be an easy applicable 3T MRI diagnostic tool for nigral degeneration in PD.

Neuromelanin is produced by the noradrenergic neurons and is mainly expressed in the neurons of substantia nigra pars compacta, ventral tegmental area, and locus coeruleus (Bazelon, Fenichel, & Randall, 1967). T1-weighted “neuromelanin-sensitive” MRI sequences have been developed to identify and characterize the substantia nigra pars compacta and locus coeruleus in vivo in PD (Ohtsuka et al., 2013; Sasaki et al., 2006). Loss of neuromelanin–related signal intensity in the substantia nigra pars compacta was observed in PD patients and correlated H&Y stages (Kashihara, Shinya, & Higaki, 2011; Matsuura et al., 2013; Schwarz et al., 2011). Additionally, neuromelanin-rich volumes loss follow a specific spatial pattern starting from posterior part of the substantia nigra pars compacta and as the disease progresses, including the anterior part of the substantia nigra pars compacta and locus coeruleus (Schwarz, Xing, Tomar, Bajaj, & Auer, 2016). Neuromelanin–rich volumes loss in the substantia nigra pars compacta significantly correlated with disease severity, as measured by the UPDRS (Schwarz et al., 2016).
1.2.3 Structural Connectivity

Diffusion-weighted imaging and diffusion tensor imaging (DTI) represent advanced morphological approaches useful to detect changes in white matter (WM) integrity (Le Bihan, 2003). The most common finding in many DTI studies was a reduction in fractional anisotropy (FA) in the substantia nigra of PD patients (Chan et al., 2007; Du et al., 2011; Péran et al., 2010; Vaillancourt et al., 2009; Yoshikawa, Nakata, Yamada, & Nakagawa, 2004), and the reduction in FA values in the substantia nigra was inversely correlated with the severity of the clinical symptoms of PD patient (Chan et al., 2007). Extranigral WM changes have been observed in PD patients. Whole-brain DTI approach has detected distinct pattern of microstructural abnormalities in the thalamus, motor, premotor, supplementary motor cortical areas, and somatosensory areas, which correlated with the severity of motor symptoms (Zhan et al., 2012). PD patients with freezing of gait had extensive WM damage in the intrahemispheric cortical areas, motor-related corticofugal, and several basal ganglia WM tracts projecting to motor, sensory, and cognitive frontal regions in the brain (Vercruysse et al., 2015). PD patients with hyposmia or anosmia showed a reduced FA in the WM adjacent to gyrus rectus bilaterally compared to healthy subjects and PD patients without olfactory dysfunction (Ibarretxe-Bilbao et al., 2010). WM tissue loss has been found in cognitive impaired PD patients (Agosta et al., 2014). FA reduction in the bilateral posterior cingulate bundles was found in PDD patients compared with cognitively normal PD patients and significant correlations between these microstructural changes and cognitive parameters were also detected (Matsui et al., 2007). Executive dysfunction, language, and attentional performance in PD were associated with WM abnormalities within frontal connecting tracts (Zheng et al., 2014). Attention domain additionally recruited regions widespread throughout the brain, with the most significant correlation identified in cingulate gyrus, whereas memory impairment mainly involved mean diffusivity alterations within the fornix (Zheng et al., 2014). DTI studies may be useful also in differentiating PD from other atypical parkinsonism such as multiple system atrophy and PSP where WM abnormalities were seen also in the brain stem and cerebellum (Blain et al., 2006; Ito et al., 2007).

1.2.4 Functional Connectivity

Functional connectivity can be assessed with resting-state functional MRI (rs-fMRI), which measure the blood oxygenation level-dependent signal
when subjects are positioned in the scanner in an awake-state without performing any particular task.

Seed-based rs-fMRI studies have shown that advanced PD had reduced functional connectivity between the striatum and several regions, including the thalamus, midbrain, pons, and cerebellum, and the degree of these abnormalities were associated with UPDRS scores (Hacker, Perlmutter, Criswell, Ances, & Snyder, 2012). Changes in functional connectivity with increased functional connectivity in the globus pallidus-cerebello-thalamic circuit were also observed in tremor-dominant PD patients (Helmich, Janssen, Oyen, Bloem, & Toni, 2011). A longitudinal study showed progressive functional connectivity disruption in the posterior cortical areas over a period of 3 years, which correlated with cognitive decline in PD patients (Olde Dubbelink et al., 2014). Several rs-fMRI studies have applied network-based method in PD patients and shown alterations to motor networks (Tessitore et al., 2012). PD patients compared with controls had decreased functional connectivity between posterior putamen with cingulate motor area, postcentral gyrus, and inferior parietal cortex, and increased functional connectivity between anterior putamen and inferior parietal cortex, and in PD patients the precentral gyrus was connected with posterior putamen, while the inferior parietal cortex connected with the anterior putamen (Helmich et al., 2010). These findings suggest that compensatory alterations within the corticostriatal network occur in PD with increased connectivity in the anterior putamen in comparison with the posterior putamen, consistent with the posterior putamen’s earlier and greater dopaminergic dysfunction in PD (Brooks & Pavese, 2011). In addition to striatal network, increased functional connectivity between the subthalamic nucleus and cortex in PD has also been observed (Fernandez-Seara et al., 2015; Kahan et al., 2014). PDD patients showed selective disruption of corticostriatal connectivity (Seibert, Murphy, Kaestner, & Brewer, 2012), specifically, the connectivity of the so-called default mode network, was disrupted in PD patients with cognitive deficits (Disbrow et al., 2014; Gorges et al., 2015). Abnormal prefrontal limbic network connectivity was found in depressed PD patients (Luo et al., 2014; Surdhar et al., 2012), and PD patients with depression showed disrupted functional connectivity between the median cingulate cortex and precuneus, prefrontal cortex, and cerebellum (Hu et al., 2015). Visual hallucinations in PD were associated with functional abnormalities in the occipital corticostriatal network (Meppelink et al., 2009; Yao et al., 2015). Abnormal functional connectivity within
the neural network centered on the inferior frontal cortex was found in PD patients with LIDs (Cerasa et al., 2015; Herz et al., 2015, 2016).

1.2.5 Task-Related Functional MRI

Several task-related fMRI studies have investigated brain activity in patients with PD in order to elucidate pathophysiological mechanisms underlying PD symptoms and complications. The most frequently studied tasks in PD neuroimaging have been motor tasks (finger and hand). Overall these studies showed decreased activation in the right posterior putamen but increased activation in left superior parietal lobule (Herz, Eickhoff, Lokkegaard, & Siebner, 2014). Inconsistent results were yielded by studies investigating functional brain activation in ON vs OFF dopaminergic medication condition. Some studies reported increased and others decreased activation of the presupplementary motor area, putamen, and middle frontal gyrus in PD patients (Herz et al., 2014).

Additional fMRI studies have investigated brain activation using different tasks such as motor or motor sequence learning (Burciu et al., 2015; Gonzalez-Garcia et al., 2011; Herz et al., 2015; Jahanshahi et al., 2010; Ko et al., 2013; Mure et al., 2012; Van Nuenen et al., 2009; Weiss et al., 2015; Wu, Long, et al., 2011; Wu, Wang, et al., 2011), selection (MacDonald et al., 2011), affective face processing (Anders et al., 2012), virtual reality gait (Shine et al., 2013), visuomotor tracking (Palmer, Li, Wang, & McKeown, 2010), and visual tasks that can identify patients with hallucinations (Shine et al., 2014). fMRI studies investigated also the neural visual-cue response in PD with ICD (Loane et al., 2015; Politis et al., 2013). PD patients with hypersexuality following exposure to sexual cues showed significantly increased sexual desire and hedonic responses and enhanced activations in the ventral striatum, and cingulate and orbitofrontal cortices compared with the PD control patients (Politis et al., 2013). When the hypersexuality PD patients were OFF medication, the functional imaging data showed decreases in activation during the presentation of sexual cues relative to rest. These deactivations were not observed when the patients were ON medication, suggesting that dopamine drugs may release inhibition within local neuronal circuits in the cerebral cortex that may contribute to compulsive sexual behavior (Politis et al., 2013). Following drug cue exposure, also PD DDS felt significantly more ON medication and this correlated with significant increases in reward-related regions, suggesting that visual stimuli are sufficient to elicit behavioral response (Loane et al., 2015).
2. CONCLUSIONS AND FUTURE DIRECTIONS

SPECT, PET molecular, and MR imaging have provided a new insight into PD pathophysiology showing that the pathological processes in PD are not only confined within the dopaminergic system as there is a more diffuse pathology involving other, nondopaminergic systems. Among these imaging modalities, PET has the potential to provide a unique tool for the direct evaluation of human in vivo neurochemistry and has become an indispensable part of CNS drug development. Despite the several efforts, a radioligand able to bind to intracellular α-synuclein aggregates has not yet been developed. The development of such biomarker will have widespread application in understanding the pathophysiology, monitoring the progression and response to treatment of PD and other Lewy bodies diseases.

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