The pathobiological basis of depression in Parkinson disease: challenges and outlooks

Kurt A. Jellinger

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Abstract
Depression, with an estimated prevalence of about 40% is a most common neuropsychiatric disorder in Parkinson disease (PD), with a negative impact on quality of life, cognitive impairment and functional disability, yet the underlying neurobiology is poorly understood. Depression in PD (DPD), one of its most common non-motor symptoms, can precede the onset of motor symptoms but can occur at any stage of the disease. Although its diagnosis is based on standard criteria, due to overlap with other symptoms related to PD or to side effects of treatment, depression is frequently underdiagnosed and undertreated. DPD has been related to a variety of pathogenic mechanisms associated with the underlying neurodegenerative process, in particular dysfunction of neurotransmitter systems (dopaminergic, serotonergic and noradrenergic), as well as to disturbances of cortico-limbic, striato-thalamic-prefrontal, mediotemporal-limbic networks, with disruption in the topological organization of functional mood-related, motor and other essential brain network connections due to alterations in the blood–oxygen-level-dependent (BOLD) fluctuations in multiple brain areas. Other hypothetic mechanisms involve neuroinflammation, neuroimmune dysregulation, stress hormones, neurotrophic, toxic or metabolic factors. The pathophysiology and pathogenesis of DPD are multifactorial and complex, and its interactions with genetic factors, age-related changes, cognitive disposition and other co-morbidities awaits further elucidation.

Keywords Parkinson disease · Depression · Neuroimaging · Neuropathology · Brain network disconnections · Neurotransmitter dysfunctions

Abbreviations
6-OHDA 6-Hydroxydopamine
αSyn α-Synuclein
BOLD Blood–oxygen-level-dependent
CI Cognitive impairment
CSVD Cerebral small-vessel disease
DAT Dopamine transporter
DPD Depression in Parkinson disease
FC Functional connectivity
GM Gray matter
LB Lewy body
LC Locus coeruleus
MDD Major depressive disorder
MPTP 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI Magnetic resonance imaging
PD Parkinson disease
RBD REM sleep behavior disorders
SN Substantia nigra
SNc Substantia nigra compacta
VTA Ventral tegmental area
WM White matter

Introduction
Parkinson disease (PD), a progressive multi-organ proteinopathy caused by deposition of misfolded α-synuclein (αSyn) with variegated motor and non-motor symptoms, is clinically characterized by bradykinesia, tremor, rigidity and postural instability (Del Tredici and Braak 2016; Jankovic 2008; Jellinger 2012). Although PD is traditionally defined as a movement disorder, depression is a common neuropsychiatric manifestation, being more prevalent than in any other chronic disabling disease (Aarsland et al. 2011). As one of the most common non-motor symptoms in PD (Aarsland et al. 2011; Tsai and Gopalakrishna 2022) (Zhu et al. 2016a), it contributes significantly to the disease...
burden, severely impacts life quality, cognitive impairment and disability (Barone et al. 2009; Cong et al. 2020; He et al. 2021; Marsh 2013; McKinlay et al. 2008; Menza et al. 2009; Reijnders et al. 2008; Schönenberg et al. 2021; Schrag et al. 2000; Weintraub et al. 2004). Since depression in PD (DPD) is poorly responsive to dopaminergic medication, it may be long-standing (Balestrino and Marín-Martínez-Martin 2017; Rieu et al. 2016). Depression in PD patients was first described by Patrick and Levy (1922). The diagnosis is based on standard criteria (Marsh et al. 2006; Ray and Agarwal 2020), reported in the Diagnostic and Statistical Manual of Mental Disorders (DSM V). These criteria include depressed mood, decreased feelings of pleasure, loss or gain in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy, excessive or inappropriate guilt, decreased ability to think or concentrate, irritability, pessimism about future, and recurrent thoughts of death (American Psychiatric Association 2013). The profile of depressive symptoms in PD differs in some aspects from that in depressed subjects without PD, showing significantly less reported sadness, anhedonia, feelings of guilt and worthlessness, suicidal ideation not being common, while they have more concentration problems than depressed control subjects (Aarsland et al. 2009; Ehrt et al. 2006). Expert opinion and epidemiological, pathophysiological, and therapeutic data favor the hypothesis that DPD is a specific clinical entity (Magnard et al. 2016). Different types and severity of depression are seen in PD patients, including minor and major depression, although some symptoms may not fulfill criteria for major depression disorder (MDD) (Goodarzi et al. 2016; Reijnders et al. 2008). They may manifest in two clinical phenotypes, one "anxious-depressive" and another "depressed" (Brown et al. 2011).

Depression can precede PD onset (Gonera et al. 1997; Nagayama and Kimura 2015; Larsen et al. 2017), appearing five or more years before the onset of motor symptoms (Leentjens et al. 2003; Pont-Sunyer et al. 2015; Schrag et al. 2015; Shibata et al. 2000; Weintraub et al. 2015), premorbid depression being common (Ishihara and Brayne 2006; Wu et al. 2011; Frauscher et al. 2014). The presence of depression in de novo PD often reflects poor motor compensation (Lee et al. 2018), and its severity was greater in non-tremor-dominant de novo patients (Weintraub et al. 2015). Studies demonstrated that neurotoxin-induced PD models may exhibit depression-like behaviors, which sometimes manifest earlier than motor impairments (Mou et al. 2022). However, due to an overlap with other symptoms primarily related to PD or side effects of medication, depression frequently remains unrecognized and undertreated (Laux 2022; Macías-García et al. 2022; Orayj et al. 2021; Politis et al. 2010b; Weintraub et al. 2004).

Prevalence and incidence

The estimated prevalence of DPD ranges from 2.7 to 90% (Timmer et al. 2017), as a result of inconsistent validation, sampling procedures, and disease definitions, but on average is around 40% or 46% (Aarsland et al. 2009, 2011; McDonald et al. 2003; Storch et al. 2008), and its incidence reaches 1.86% per year (Althaus et al. 2008; Cong et al. 2020; Frisina et al. 2009). In a meta-analysis, clinically significant depressive symptoms were present in 35% of PD patients, and MDD in 17% (Reijnders et al. 2008), while a recent meta-analysis found a global frequency of depressive disorders in PD of 30.7%, and a pooled frequency of MDD of 14.0%, mean baseline between PD duration and MDD frequency being positively correlated (Chendo et al. 2020). Incidental depression occurs in about 16% of de novo PD patients previously free of depression, in addition to 13.8% of those suffering from depression at the time of PD diagnosis (Duncan et al. 2014; Ravina et al. 2007), while depression was found in 70% of mid-to-advanced PD outpatients without dementia (Kulisevsky et al. 2008). DPD prevalence is higher than in the general population and may share pathophysiological mechanisms with other psychopathological symptoms (Laux 2022).

In the last time, there is a slight decrease in depression, which could be due to an increase in depression recognition during the prodromal phase of PD (Orayj et al. 2021). On the other hand, a higher prevalence of depression, anxiety, and worries in advanced PD has been observed during the COVID-19 pandemic (Montanaro et al. 2022).

PD-depression and other symptoms

Depression in early PD is regarded a risk factor for worse motor and global prognosis (Bega et al. 2015; Marras et al. 2008; Post et al. 2011), and higher depression scores were found in patients with dyskinesias and/or motor fluctuations (Dissanayaka et al. 2011; Wichowicz et al. 2006), also correlating with bradykinesia (Papapetropoulos et al. 2006; Rojo et al. 2003). On the other hand, a history of depression is a risk factor for developing PD (Aarsland et al. 2011; Bareeqa et al. 2022; Gustafsson et al. 2015; Inoue et al. 2010; Jeong et al. 2021; Leentjens et al. 2003; Nagayama and Kimura 2015; Schuurman et al. 2002; Shen et al. 2013), and neurological symptoms may worsen depression severity in PD (Assogna et al. 2013; Dissanayaka et al. 2011), but depression may also occur after PD onset (DeMarco et al. 2022). DPD is also associated with cognitive impairment (CI) (Fujishiro et al. 2015; Wertzman et al. 1993), and has important impact on autonomic
symptoms in early and middle stages of PD (Sklerov et al. 2022), with greater depression being associated with severe autonomic dysfunction (Matsubara et al. 2018). Non-motor symptoms, poor sleep quality, and cognitive dysfunction are independent predictors of depression (Zhu et al. 2017). Sleep disorders, including REM sleep behavior disorder (RBD) are associated with depression at baseline and longitudinally, which is partially mediated by early autonomic dysfunctions in prodromal PD (Ma et al. 2020).

Depressive symptoms may precede CI in de novo PD patients (Jones et al. 2019), and there is a relationship between early depression with motor worsening and cognitive decline (Fernandez et al. 2009; Ng et al. 2015). That, however, can also be a precursor of depressive symptoms in PD (Han et al. 2021; Petkus et al. 2019; Schroeders et al. 2022). CI and depressive symptoms are associated with increase in the severity of PD, and depressive symptoms are associated with an increase in CI (Sinaeeifar et al. 2021).

PD-depression and sex

There are clinical sex differences in PD: in general, there is a slight male preponderance in incidence and prevalence of PD, starting earlier in males, while women tend to be more prone to develop tremor-dominant PD, show better results for general cognitive abilities, but more pain symptoms and more frequent depression (Georgiev et al. 2017; Nicoletti et al. 2017; Song et al. 2014; Xiao-Ling et al. 2021). Depression and fatigue are the main causes of poorer health-related quality of life in women, even in early disease stages (Balash et al. 2019; Crispino et al. 2020), melancholy featuring prominently females, while apathy and loss of libido features more predominantly affect men (Perrin et al. 2017).

Depression in genetic PD

Depression is frequent in some genetic PD forms, in particular mutations in Parkin, known risk factors for early onset PD, where relatives with compound heterogenous mutations and without diagnosed PD have a higher risk of depression compared to relatives without Parkin mutations (Srivastava et al. 2011). Among subjects with monogenic early onset PD, depression affected 31%, and may precede motor symptoms, which was similar to patients with idiopathic PD (Gaig et al. 2014; Kasten et al. 2010). Carriers with homozygous or compound heterozygous Parkin mutations, compared to those without known causative mutations, had younger ages at onset, longer disease duration, lower Hoehn and Yahr grades, but higher depression index, indicating that the Parkin mutation status might be a good predictor of symptoms of depression without an impact on executive function (Song et al. 2020). Depression and hallucinations were more frequent in carriers of leucine-rich repeat kinase 2 (LRRK2), suggesting the prevalence of a greater involvement of the limbic system in these patients (Belbari et al. 2010), while others did not find such relations in a large study of familial PD (Pankratz et al. 2008). Depression severity in GBA mutation carriers at risk of PD was found to be similar to healthy controls (Simuni et al. 2020), although it increased in GBA mutation carriers at high risk of PD (Beavan et al. 2015). Other studies reported that PD carriers of GBA variants are at high risk for depression and cognitive decline. BDNF (rs6265) and CRY1 (rs2287161) variants have been associated with more depressive symptoms in people with PD (D’Souza and Rajkumar 2020). Five to 25% of PD patients carry GBA gene mutations, and 10–30% of GBA carriers will develop PD by age 80, type 1 Gaucher disease being associated with a higher risk of PD (Nguyen et al. 2019). Progression of microsmia and mild CI is more rapid compared to controls, and those with worse olfaction show more depression (Beavan et al. 2015; Mullin et al. 2019).

In general, the severity of the PD phenotype, showing more severe non-motor symptoms, including depression, is related to the severity of the mutation in the GBA gene (Thaler et al. 2018a).

Overall, these data suggest that depression and PD may share common pathophysiological mechanisms, although these are multifactorial and complex, related to a variety of pathobiological mechanisms associated with the underlying neurodegenerative process of PD (Jankovic and Tan 2020; Prange et al. 2022; Weintraub et al. 2022), the essential ones will be critically reviewed.

Brain structural correlates of DPD

Unlike clinical research and fluid biomarkers, brain imaging studies offer the opportunity to relate neuropsychiatric changes to brain structures. Magnetic resonance imaging (MRI) studies of cognitive healthy persons with depression revealed subtle structural brain changes (gray matter/GM/ volume reductions) in prefrontal, parietal, and temporal regions, including the hippocampus (Ballmaier et al. 2004; Bremner et al. 2000; Pink et al. 2017). Similar changes have been found in patients with mild cognitive impairment (MCI) and concomitant depression (Zheng et al. 2017). Cortical thinning in prefrontal areas in drug-naive PD patients highlights the critical role of those regions in DPD (Luo et al. 2016). Other neuroanatomical correlates of depressive symptoms in de novo PD include decreased bilateral limbic and right amygdala volumes (van Mierlo et al. 2015). Decreased cortical thickness in left precentral and right postcentral gyrus, extending to the middle frontal gyrus,
orbitofrontal region and insula, was seen in DPD (Huang et al. 2016). It was also associated with cortical thinning in left temporal, anterior cingulate, right posterior cingulate and hippocampal cortices as well as thalamus volume shrinking over time, and higher scores of depressive symptoms at baseline correlated with a higher rate of cortical thinning longitudinally (Goto et al. 2018; Hangahan et al. 2017). Precuneus thinning was evident in PD patients with mild-moderate depression in early stages of disease (Zanigni et al. 2017). Others reported smaller amygdala volumes but intact limbic connectivity (Surdhar et al. 2012), and GM decrease in bilateral orbitofrontal, right temporal region and the limbic system (Feldmann et al. 2008). This is consistent with earlier studies demonstrating hypometabolism in the medial frontal, orbitofrontal and anterior cingulate cortex, suggesting that DPD may be associated with dysfunction of the orbital-inferior area of the frontal lobe (Mayberg et al. 1990; Ring et al. 1994).

Generally, the volume of white matter (WM) lesions is greater in PD patients than in healthy controls, but the differences are not significant (Grey et al. 2020). MRI in DPD revealed more severe WM loss in the right frontal lobe including the anterior cingulate bundle and the inferior orbitofrontal region, which is a major site for regulation of mood and activation (Kostic et al. 2010; Kostic and Filippi 2011). Greater WM injury was found in DPD associated with CI and gait disorders (Bohnen and Albin 2011b). A positive correlation with fractional anisotropy in the bilateral inferior fronto-occipital fascicles in early PD but not in middle disease stages suggested that the neural basis of depression might be distinct in different stages of PD (Li et al. 2020a). According to a recent study, depression scores in PD are associated with lower right anterior pulvinar volume and reduced WM tract microstructure across almost all fiber tracts connected to the thalamic subnuclei (Bhome et al. 2022).

Neuroimaging studies in symptomatic Parkin mutation carriers with young onset revealed a reduction of bilateral caudate nuclei volumes compared to those without Parkin mutations. Despite its relatively benign clinical course, carrying the Parkin mutations appeared to be associated with greater atrophy of subcortical structures suggesting divers patterns of subcortical brain changes among different mutation types (Bilgic et al. 2012). Brain sonography studies in Gaucher-related PD showed more frequent SN hyperechogenicity and reduced echogenicity of brainstem raphe than in controls, which was unrelated to type or severity of GBA gene mutations, but correlated with iron-sensitive MRI-T2 hypointensity of SNC. Hyposmia, higher non-motor symptoms score including depression and SN hyperechogenicity were characteristic features of Gaucher disease-related PD (Böttcher et al. 2013). Assessment of cortical thickness and subcortical volumes in a cohort of patients with GBA and LRRK2 related PD revealed lower volumes in bilateral hippocampus, nucleus accumbens, caudate, thalamus, putamen and amygdala compared to unaffected participants. However, no differences in cortical thickness and subcortical volumes were detected within each group based on genetic status, indicating that mutations in the GBA and LRRK2 genes are not important determinants of such lesions, while PD is associated with a general reduction in cortical thickness and subcortical atrophy even in cognitively intact patients (Thaler et al. 2018b).

**Dysfunction of neurotransmitter systems**

Neuroimaging and neuropathological studies have provided insight into important pathobiological mechanisms of DPD, suggesting that it is associated with a more widespread neurodegenerative process, involving subcortical dopaminergic, serotonergic and noradrenergic nuclei and pathways (Maillet et al. 2021; Remy et al. 2005). However, as the loss of neural populations also underlies cognitive impairment, it may be difficult to differentiate the clinical effects of such neurodegeneration in early phases of depression in PD from those of early dementias, although both may occur together (Di Giuda et al. 2012; Jellinger 2022b). Although the diagnosis of PD relies on the effects of dopamine deficiency, it is associated with other neurotransmitter deficits that are causing various motor and non-motor signs and symptoms, e.g., depression (Jones et al. 2019; Schapira et al. 2017).

**Dopaminergic system**

All patients with PD have a moderate to severe loss of dopaminergic neurons in the nigrostriatal pathway. Depressed PD patients showed greater neuron loss and gliosis in substantia nigra compacta (SNC) than non-depressed ones ($p = 0.004$) (Frisina et al. 2009; Paulus and Jellinger 1991). This implicates that the SN as an important modulator area of mood in patient with Lewy body (LB) disorders (Saare et al. 2021), the resting state functional connectivity of midbrain dopaminergic nuclei being important (Wei et al. 2018). Since PD causes depletion of dopaminergic neurons in the SN, depression may be part of the pathophysiological process that leads to PD. Widespread degeneration of dopaminergic terminals in the striatum, particularly in dorsal caudate, is seen in PD patients with both depression and mild cognitive impairment, with relative preservation of the other dopaminergic systems in the brain (Jellinger 2022b).

Dopamine transporter (DAT) availability, providing evidence for anterior presynaptic dopaminergic dysfunction, in the striatum and limbic brain regions (ventral striatum, amygdala, anterior cingulate cortex) is reduced in DPD.
compared to non-depressed PD patients (Remy et al. 2005; Vriend et al. 2014). Decreased DAT correlating with depression severity was found in left anterior putamen (Weintraub et al. 2005), bilateral striatum (Rektorova et al. 2008), and thalamus (Oh et al. 2021). Furthermore, decreased dopaminergic metabolism was demonstrated in bilateral putamen and caudate correlating with DPD severity (Koerts et al. 2007), as well as in non-PD patients with major depression (Meyer et al. 2001). On the contrary, other studies found a significantly higher density of DAT in the bilateral striatum, particularly in the left putamen and right putamen in depressed PD patients in comparison to non-depressed ones, suggesting increased dopaminergic transmission at the synapse (Felicio et al. 2010), or no dopaminergic striatal change related to depression using (18F)FP-CIT PET (Park et al. 2019). It should be considered that DAT imaging provides evidence for presynaptic dopaminergic dysfunction related to DPD either via a reduced availability due to greater degeneration or an increased availability of DAT possibly due to abnormal dopamine clearance (Prange et al. 2022).

Patients with late-onset depression showed abnormal (123)I-iodo-1-flupane SPECT, suggesting that they could be considered at increased risk of PD (Kazmi et al. 2021).

Investigation of neurodegenerative pathology in PD cases in relation to depressive symptoms revealed a significantly higher αSyn burden in SN ($p = 0.006$), ventral tegmental area (VTA) ($p = 0.011$) and nucleus accumbens ($p = 0.0031$), whereas cell density in VTA showed negative correlation with Braak LB stage ($p = 0.026$) and neurofibrillary tangle Braak stage ($p = 0.007$), indicating that dopaminergic αSyn pathology drives depression in PD (Patterson et al. 2019).

A significant relationship was observed for αSyn spread from VTA to caudate, from SN to putamen and from the insula cortex to putamen, suggesting that spread of αSyn from brainstem to the striatum may indicate that not only mesolimbic, but also nigrostriatal dopaminergic circuits are implicated in depression (Alexander et al. 1990; Frisina et al. 2009).

Depressive symptoms were associated with dopamine loss in caudate nucleus, possibly related to degeneration of dopaminergic projections from the VTA, which is consistent with the involvement of cortico-striatal-thalamo-cortical circuits in DPD (Vriend et al. 2014).

Dopaminergic neurons in the ventral tegmental area (VTA) project to the nucleus accumbens, which plays a critical role in the regulation of mood and motivation. A higher level of depressive symptoms was associated with a lower density of tyrosine hydroxylase-immunoreactive neurons in VTA and SN, but not in LC. As a lower neuronal density in VTA was associated with higher density of brainstem LBs, their association with depressive symptoms, was suggested to be in part owing to the lower neuronal density of VTA (Wilson et al. 2013).

Rodent studies have demonstrated that changes within the dopaminergic pathways are associated with depression-like behaviors. They include alterations in the neuroplasticity of medium spiny neurons in the nucleus accumbens, that underlie behavioral despair and social avoidance (Krishnan et al. 2007). Dissociated involvement of the dorsolateral striatum and prefrontal cortex was relevant to depression in 6-hydroxydopamine (6-OHDA)-lesioned rats (Matheus et al. 2016), while unilateral administration of highest doses of 6-OHDA to the rat medial forebrain induced neurochemical and behavioral changes resembling advanced PD with coexisting depression (Kaminska et al. 2017). Dopaminergic lesion in the olfactory bulb involved olfaction and induced depressive-like behaviors in another 6-OHDA model of PD (Ilkiw et al. 2019). Downregulation of astroglial glutamate transporter in the habenula of 6-OHDA rat models may attribute to its downregulation after degeneration of the nigrostriatal pathway, which may be closely associated with DPD (Lyu et al. 2021; Maillet et al. 2016). Unilateral 6-OHDA lesions the SNC in rats involved the presynaptic dopamine D4 receptors in the lateral habenula that are important in the regulation of PD-related depression (Hui et al. 2020).

Serotonergic system

Serotonergic dysfunction is linked to depression in the general population, it is prominent in de novo patients with idiopathic PD (Maillet et al. 2016) and in A53T mutation carriers of the SNCA gene (Wilson et al. 2019), but there is mixed evidence for its involvement in DPD (Remy et al. 2005).

Serotonergic neurons in raphe nuclei as the main source of 5-HT in the brain gradually degenerate as PD pathology progresses (Halliday et al. 1990a; Pasquini et al. 2020). This leads to 5-HT depletion in structures that receive serotonergic projections, such as cortex and basal ganglia (Politis et al. 2010a; Qamhawi et al. 2015). Postmortem and PET studies have confirmed the involvement of the serotonergic system in PD (Buddhala et al. 2015; Huot and Fox 2013; Pagano et al. 2017; Politis and Niccolini 2015). However, other PET studies failed to show any differences between the serotonergic system and neuron loss in the dorsal raphe nuclei between PD patients with and without depression (Fazio et al. 2020; Gallagher and Schrag 2012; Kostic et al. 2010). While some neuroimaging studies point towards alteration of the serotonergic system from the early stages of PD (Ballanger et al. 2012; Boileau et al. 2008; Doder et al. 2003; Pavese et al. 2010; Politis et al. 2010a; Qamhawi et al. 2015), others have not confirmed that (Beucke et al. 2011; Strecker et al. 2011). DPD patients show increased serotonin transporter binding in raphe and limbic regions (Norris et al. 2004), whereas decreased 5-HT1A receptor
densities were seen in limbic regions including insula, hippocampus and orbitofrontal cortex (Ballanger et al. 2012), as well as in posterior cingulated and amygdala-hippocampus complex (Benoit and Robert 2011). Greater serotonergic pathology related to depression was demonstrated across PD stages, underlying the major influence of serotonergic dysfunction in limbic-corticostriatal circuits (Mailet et al. 2021). In murine models of PD, strong stress successfully induced stable depression like symptoms, indicating that 5-HT dysfunction may contribute to depression like symptoms in PD (Wang et al. 2021). However, both in vivo and postmortem studies about the role of the serotonergic system in PD have provided contradictory results (de Natale et al. 2021; Oertel et al. 2019). Either increased or decreased serotonergic markers in striatum and raphe nuclei have been reported (Bédard et al. 2011; Beucke et al. 2011; Buddhala et al. 2015; Halliday et al. 1990a; Huot et al. 2011; Jellinger 1987; Jouts et al. 2015; Kerenyi et al. 2003; Kish et al. 2008; Paulus and Jellinger 1991; Politis et al. 2010b).

Whereas a higher prevalence of pathological features in DPD patients was reported in LC, SNCs and dorsal vagus nerve, suggesting that DPD may be related more to catecholaminergic than serotonergic system dysfunction (Frisina et al. 2009), others showed greater neuron loss and gliosis in the serotonergic dorsal raphe nucleus (Paulus and Jellinger 1991), highlighting its role in the development of depression (Steinbusch et al. 2021). Disruption and/or dysfunction of the 5-HT1A-FGFR1 (fibroblast growth factor receptor 1) heteroreceptor complex, located in the dorsal and median raphe of the brainstem, leads to reduced neuroplasticity and potential atrophy of the raphe-cortical and raphe-striatal 5-HT pathways, and may contribute to the development of MDD (Borrotto-Escuela et al. 2021). In addition to the relevance of the FGFR1-5-HT1A heteroreceptor complex for neuroplasticity and depression (Borrotto-Escuela et al. 2015), striatal 5-HT1A auto- and hetero- receptors may reduce L-DOPA-induced dyskinesia (Meadows et al. 2017), which is not in the focus of this review.

Serotonin 6 receptors in the dorsal hippocampus were shown to regulate depression-like behaviors in unilateral 6-OHDA lesions in Parkinson rats, while there was no change in the density of the glutamate transporter EAAC1/5-HT6 receptor co-expressing neurons in the dorsal hippocampus (Liu et al. 2015). Severely impaired hippocampal neurogenesis was associated with an early serotonergic deficit in an αSyn transgenic rat model of PD (Kohl et al. 2016). Neurochemical studies found that injections of the 5-HT1A receptor-agonist 8-hydroxy-2-(dipropylamino)tetrailin hydrobromide (8-OH-DPAT) into the dorsal hippocampus significantly increased dopamine and 5-HT levels in the medial prefrontal cortex, habenula, ventral hippocampus, and amygdala, suggesting that hippocampal 5-HT1A receptors regulate depression and DPD (Jiang et al. 2020). Strong stress can induce stable depression-like symptoms in subchronic MPTP-PD mice along with highest levels of inflammation enhancement and decrease in expression levels of 5-HT-related genes, suggesting that 5-HT system dysfunctions may contribute to depression-like symptoms in PD (Wang et al. 2021). The adeno-associated virus (AAV5)-induced overexpression of wild-type human αSyn in raphe 5-HT neurons and triggers progressive accumulation, phosphorylation, and aggregation of wild-type human αSyn protein in the 5-HT system, causing axonal impairment in the output brain regions of raphe neurons and deficits in brain-derived neurotrophic factor (BDNF) expression and 5-HT neurotransmission, resulting in a depressive-like phenotype (Miquel-Rio et al. 2022). Recent studies have shown that human αSyn overexpression in mouse serotonergic neurons triggers a depressive-like phenotype, showing that α-synucleinopathy in 5-HT neurons negatively affects brain circuits that control mood and emotions, resembling neuropsychiatric symptoms occurring at the onset of PD (Miquel-Rio et al. 2022).

Noradrenergic system

There is strong evidence for changes in noradrenergic function related to DPD.

The locus coeruleus (LC) is affected in the early stage of PD pathology, which leads to noradrenergic content loss of up to 70% in the brain (Paredes-Rodriguez et al. 2020), resulting in decreased noradrenergic projections to cerebellum, thalamus and motor cortex (Pflü et al. 2012). Imaging studies demonstrated reduction in noradrenergic and dopaminergic innervation in LC, thalamus and limbic regions, and increased neuronal loss and gliosis in LC (Brown et al. 2011; Burn et al. 2012; Frisina et al. 2009). Noradrenergic deficits due to loss of neurons in LC, with reduction of noradrenaline in caudate, putamen and cortical regions (Gibb 1992; Goldstein et al. 2011) are related to depression in early stages of LB disease, since staging of pathology suggests degeneration of the LC before SN degeneration (Vermeiren and De Deyn 2017). Accordingly, non-motor symptoms, such as depression usually correlate with LC related noradrenergic deficiency, consistent with its projection (Oertel et al. 2019). However, the majority of LC neurons can survive the pathological process for many years, in contrast to the abundant early neuronal loss in the SNCs (Beach et al. 2021; Halliday et al. 1990a, b; Hirsch et al. 1988; Oertel et al. 2019), suggesting that clinical features related to LC pathology appear in patients with substantial loss of SNC neurons (Huynh et al. 2021).

The role of cholinergic cortical deficits in PD is well established (Bohnen and Albin 2011a). Interestingly, progression of cholinergic deficit spares the prefrontal cortex in
early PD, and subsequently follows an anterior-to-posterior prefrontal degeneration gradient, which may relate to progressive CI and co-morbid depression (Bohnen et al. 2018). Reduced α4β2*-nicotinic acetylcholine receptor binding in the anterior cingulate and frontoparietal cortex was related to mild cognitive and depressive symptoms in PD (Meyer et al. 2009).

**Combined neurotransmitter deficits**

Both the dorsal raphe nucleus (serotonergic) and LC (noradrenergic) involved in premotor PD stages can lead to depletion of monoaminergic transporter systems in the basal ganglia-cortical loop linked to emotional control. These and changes of precuneal cortex thickness have been associated with depression in early PD (Borgonovo et al. 2017; Zanigni et al. 2017). Higher prevalence of pathological features in depressed vs non-depressed PD patients particularly in the catecholaminergic brain areas, LC (neuronal loss $p = 0.08$; gliosis $p = 0.008$), dorsal raphe nuclei (neuronal loss $p < 0.05$) and SNc (ns), but differences in amygdala and cortical regions suggested that PD is more related to catecholaminergic than to serotonergic dysfunction (Frisina et al. 2009), whereas LBs in the dorsal raphe nuclei in early PD implicated a serotonergic pathology in early PD (Tan et al. 2011), without a prominent role of dopaminergic degeneration (Maillet et al. 2016). PET studies showed elevated serotonin transporter binding in DPD, suggesting an up-regulation in depressed PD patients (Boileau et al. 2009), whereas other studies showed decreased dopamine and noradrenaline innervation in the limbic system in DPD (Remy et al. 2005).

Depression-like behavior has been observed in 6-OHDA-lesioned and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated rodents, and rotenone infusion into the SN of rats was associated with altered dopaminergic and serotonergic transmission (Zhang et al. 2021). Involvement of the dorsal 5-HT1A receptors has been shown to regulate PD-related depression by neurochemical mechanisms including significantly increased serotonin and dopamine levels in the medial prefrontal cortex, lateral habenula, ventral hippocampus and amygdala (Jiang et al. 2020). The lateral habenula was shown as a link between dopaminergic and serotonergic systems contributing to depressive symptoms in PD rats via mediating the effects of dopaminergic neurons in the SN on serotonergic neurons in the raphe nuclei (Luo et al. 2015).

Other studies characterized the concomitant dopaminergic and serotonergic dysfunctions after different durations of PD and the expression and severity of neuropsychiatric signs as follows: both dopaminergic and serotonergic lesions worsen with the duration of PD, spreading from midbrain/subcortical to cortical regions, the severity of depression and apathy appearing primarily related to serotonergic alteration within corticostriatal limbic areas, whereas apathy at PD onset may be associated with more cortical and subcortical dopaminergic and serotonergic disruption (Maillet et al. 2021). Dopaminergic and serotonergic changes progress in a similar way in LRRK2 mutation carriers with manifest PD and those with sporadic PD, while LRRK2 mutation carriers without manifest PD show increased 5-HT transporter binding in striatum and brainstem, possibly reflecting compensatory changes in serotonergic innervation preceding the motor onset of PD (Wile et al. 2017). In preclinical phases of PD, dysfunction of the limbic loop of the basal ganglia and the lateral habenula as well as the network of inter-related dopaminergic, serotonergic and adrenergic systems have been suggested to play a key role for the development of depression (Borgonovo et al. 2017; Wilson et al. 2019). Thus, the role of disordered 5-HT innervation in early PD appears to be rather modest and awaits further full elucidation (Blesa et al. 2022).

In a chronic rotenone model, besides motor deficits, an anxious and depression-like phenotype was associated with neuronal loss, cytoplasmic αSyn accumulation as well as astro- and microglial activation both in SNc and the controlling projections. Occasionally, urocortin-1 (URC-1) immunoreactive neuronal debris was observed in phagocytosing microglia. UCN1 peptide content of viable cells in the Edinger-Westphal nucleus (EW) correlated with dopaminergic SN cell count, while other mood status-related dopaminergic (VTA), serotonergic, dorsal & medial raphe and noradrenergic (LC and A5 area) brainstem centers showed no remarkable morphological changes. These findings suggest that neurodegeneration in the EW contributed to mood-related symptoms in toxic rat models of PD (Ujvári et al. 2022).

**DPD and brain circuit disturbances**

DPD is mediated by dysfunction of multiple brain mechanisms causing functional network disturbances, reinforcing the hypothesis of DPD as a "disconnection syndrome" (Kostic and Filippi 2011). Recent neuroimaging studies have detected impaired deep WM networks associated with clinical motor and non-motor symptoms (Meng et al. 2022), impaired long contact WM fibers integrity being related to DPD (Wu et al. 2018), while other studies did not replicate previous work that found reduced WM integrity in limbic prefrontal regions in DPD (Lacey et al. 2019). Diffuse tensor imaging revealed such changes in the prefronto-limbic/temporal circuitry, mainly in the left hemisphere (Shen et al. 2022; Wu et al. 2018), and impaired frontal and limbic WM integrity, associated with severe depressive symptoms in patients with PD (Li et al. 2020b).
Early microstructural alterations in the medial corticostriatal limbic system in de novo PD patients with apathy and depression extended to the medial frontal, anterior cingulate cortex and subcallosal gyrus, indicating an early disruption of ascending dopaminergic projections and related corticocortical and cortico-subcortical networks (Prange et al. 2019).

Previous studies found WM microstructural changes in the mediodorsal thalamus as possible mechanism of DPD (Li et al. 2010) or increased connectivity between limbic areas and decreased connectivity between cortico-limbic networks which may reflect impaired high-order cortical regulatory effects on the emotion-related limbic areas (Hu et al. 2015a). Abnormal activities and connectivities of the limbic-cortical circuit indicating impaired high-order control of negative mood may be a possible neural mechanism of DPD (Hu et al. 2015b). Impaired resting state functional connectivity between VTA and anterior cingulate cortex was correlated with the severity of depression in PD supporting the role of abnormal neocortical-limbic system in DPD (Wei et al. 2018). PET findings demonstrated the dysfunction of the limbic cortico-basal ganglia circuit—including the orbitofrontal cortex, anterior caudate nucleus and limbic part of basal ganglia—in the pathophysiology of depression, apathy and anxiety (Maillet et al. 2016), which is consistent with the result of previous studies, supporting functional, structural and metabolic abnormalities within this network in DPD (Skidmore et al. 2013; Weintraub et al. 2005). Other connectometry studies showed significant differences in the bilateral uncinate and inferior longitudinal fasciculi, fornices, left fronto-occipital fasciculum, right corticospinal tract, genu of the corpus callosum, and middle cerebellar peduncle. This suggests that the prominent circuits involved in emotion recognition, particularly negative emotions, might be impaired in co-morbid depressive symptoms in PD (Ansari et al. 2019). Furthermore, DPD was associated with dysfunctional connectivity from the medial frontal gyrus and paracentral lobule to the contralateral supplementary motor area (Liao et al. 2020).

Although there is no significant volume change in the amygdala, left amygdala activity increased in DPD patients compared to controls, and decreased functional connectivity between the right amygdala and fronto-parietal areas suggested abnormal amygdala function in DPD (Huang et al. 2015). Other resting-state functional MRI analyses revealed decreased functional connectivity between the anterior cingulate cortex and right temporo-parietal junctions probably associated with emotion-related factors of quality of life in PD patients (Nakano et al. 2021). Depressive symptoms were associated with larger volumes of the left isthmus of the cingulate cortex, which, together with the temporal cortex, is part of the default mode network, and increased activity has been described within this network among patients with depression (Sheline et al. 2009). DPD patients exhibited abnormal functional connectivity within the default mode network (DMN), executive control network (ECN), salience network (SAN), precuneus and sensorimotor network (SMN), as well as between the anterior SAN and bilateral ECN, between posterior SAN and dorsal DMN, between precuneus network and dorsal DMN/SAN/bifrontal ECN. Connectivity within the left hippocampus and dorsal DMN, and the right medial superior frontal gyrus of anterior
SAN was a significant predictor of depression levels in PD patients. This indicates that aberrant intra- and inter-network functional connectivity is involved in several hubs in the large-scale networks which could be a biomarker for distinguishing DPD from non-depressed PD (Liao et al. 2021).

Resting state bidirectional connectivity alterations were observed between emotional and motor networks in DPD in the pathway from bilateral anterior insula and posterior orbital cortices to right basal ganglia (Liang et al. 2016), while others confirmed the involvement of basal ganglia, default mode and left frontoparietal networks and SN in DPD (Wei et al. 2018). There was evidence for clinically relevant microstructural alterations of the anterior insula with loss of interconnecting anterior insular-anterior cingulate cortex in DPD (Jonkman et al. 2021). Brain network analysis revealed a significant hyperconnectivity among the default mode network (left lateral-parietal region), the medial prefrontal and left prefrontal cortex (part of the central executive network), suggesting how the functional connectivity pattern may signal a neural pathway for depression in PD (Alfano et al. 2022).

In de novo PD patients with depression, altered network connection involving the default mode network and cognitive executive network may contribute to depression (Xu et al. 2022b). Likewise, altered neural network connectivity within the ventral attention network in the left middle temporal cortex, the auditory and default mode networks may predict depression in de novo PD (Xu et al. 2022a). Altered functional connectivity of ventral striatal subregions and between ventromedial putamen and left middle occipital gyrus provided new insight into neural mechanisms of depression in early PD (Wang et al. 2022). Recent functional MRI studies characterizing the spontaneous blood–oxygen-level-dependence (BOLD) in the whole brain and multiple brain regions revealed reduction in the resting-state BOLD complexity as an important component in the pathology of DPD (Liu et al. 2022), and a meta-analysis and validation study demonstrated altered BOLD activity in posterior cingulate gyrus, supplementary motor area and cerebellum in DPD compared to non-depressed ones (Su et al. 2022).

With regard to gender differences, altered emotion processing in PD is specific of males that may be related to diminished neural response in putamen and insula, whereas structural MRI found bilateral GM atrophy in female patients (Heller et al. 2018). Sex differences were found in dynamic connectivities in healthy controls but not in PD patients. Available findings suggest that while in healthy controls, sex differences may play a certain role in dynamic connectivity patterns, in PD patients, these effects may be overcome by the neurodegenerative process (Diez-Cirarda et al. 2021).

Imaging genetics analysis to explain the degree if depression in PD tries to identify several brain regions and genes known to be involved in depression, and to explain the degree of depression in PD (Won et al. 2019). fMRI studies in non-manifesting LRRK2 and GBA carriers demonstrated increased task-related activity in the right medial frontal gyrus and reduced activity in left lingual gyrus, while no whole-brain differences were noted between groups (Bregman et al. 2017). Connectome differences were seen between familial and sporadic forms of PD, as indicated by increased activity in the left medial amygdala in familial PD, which showed a distinct functional network between the left medial amygdala and regions related to retrieval of motor information. These data indicate that the medial amygdala might be most vulnerable in both sporadic and familial PD (Tang et al. 2017). Reduced integrity of non-motor networks was detected among non-manifesting carriers of the G2019S mutation in the LRRK2 gene prior to identifiable changes in motor network connectivity, indicating significant non-motor cerebral changes among carriers "at risk" for future development of PD (Jacob et al. 2019).

Other pathogenic factors in DPD

Vascular factors

Whereas vascular risk factors failed to verify the vascular depression hypothesis in PD (Ou et al. 2018), others suggested that co-morbid cerebral small-vessel disease (CSVD), marked by WM hypointensity, number of lacunes and microbleeds, may affect multiple functional domains in PD, including motor, cognitive and emotional impairments (Chen et al. 2021). Many studies have provided evidence that large WM hypointensity volumes, subcortical lacunes and other markers for CSVD are associated with increased risk for depressive symptoms (Geraets et al. 2021; Jellinger 2021, 2022b; Nunes et al. 2022; Wang et al. 2020), since they are disturbing cortico-subcortical neuronal circuits causing microstructural dysfunctions of major brain connections involved in emotion and other important behaviors, thus suggesting an association between CSVD and depression (Empana et al. 2021; Kim and Han 2021; Nunes et al. 2022).

The neurogenesis hypothesis

Degeneration of the midbrain dopaminergic neurons in PD can affect remote regions in the brain that are innervated by the projections of these neurons. The dentate gyrus, a site of continuous production of new neurons in the adult hippocampus, receives dopaminergic inputs from SNc, the depletion of which may directly affect adult hippocampal neurogenesis (Park and Enikolopov 2010).

There is a detrimental synergistic interplay between dopamine depletion and posttranslational modification of αSyn contributing to impairment of adult hippocampal
Neurogenesis (Schlachetzki et al. 2016). Experimental studies have revealed a complex interaction between brain-derived neurotrophic factors (BDNF) and neurotoxins in PD models that result in distinct effects on the catecholaminergic system and hippocampal neurogenesis (Chen et al. 2018). MDD was previously hypothesized to be related to monoaminergic deficiency which leads to reduced levels of monoamines at the synaptic cleft, but more recently, there has been a shift towards the "neurogenesis/neuroplasticity hypothesis of depression". Disruption of hippocampal neurogenesis in depression may be a consequence of neural circuitry impairments, in particular, the entorhinal cortex, which has a regulatory effect on the neural circuitry related to hippocampal function and adult neurogenesis (Kim and Park 2021; Tartt et al. 2022). Neuromodulation and hippocampal neurogenesis that are closely related to dopamine depletion in PD, therefore, may help to elucidate the role of neurogenic-related mechanisms mediating neurotrophic processes, the role of neurogenic effects of the gene SNCA and, possibly, the molecular mechanisms underlying DPD and MDD (Flores et al. 2020). In genetic animal models and human postmortem studies of PD, severely impaired adult neurogenesis has been observed with patients showing hippocampal atrophy. Because adult newborn neurons appear to exert various functions which relate to non-motor symptoms of PD, there might be a close correlation between malfunction of newborn neurons in the adult hippocampus and depressive symptoms, thus presenting a novel framework for targeting adult hippocampal neurogenesis and PD-associated depression (Lim et al. 2018).

SNCA and depression

αSyn overexpression in dopaminergic neurons is not only important for PD, but also for depression, both being correlated with decreased nigral BDNF levels and alterations in proteins involved in synaptic plasticity (Caudal et al. 2015). αSyn interaction with dopamine metabolism (Galvin 2006) and transmission (Phan et al. 2017) may have important implications not only in neuronal loss and motor symptoms (Norris et al. 2004), but also through development of depressive symptoms in LB disease, which suggests that continued progression of symptoms may be underpinned by the neuronal connectivity in the brain and the spread of specific pathologies.

αSyn plays a critical role in neurotransmission, vesicle dynamics, and neuroplasticity. Its overexpression in the hippocampus triggers depressive-like behaviors, leads to synapse loss and microglia-mediated inflammation, thus contributing to the pathogenesis of both PD and depressive disorders (Du et al. 2021). Depression has been shown to affect the metabolism of αSyn, suggesting that depression is not only a prodromal symptom but also a risk factor of PD (Ishiguro et al. 2019). αSyn (SNCA) is not only a hallmark of PD, but SNCA mRNA in peripheral blood cells is increased in MDD and positively correlated with severity of depression (Rotter et al. 2019), which appears important in view of the high co-morbidity of PD with depression. Unfortunately, a preliminary study on the relations between α-synucleinopathy and MDD revealed αSyn pathology in brainstem only in 16.7% of patients with late-life depression, which was comparable to a healthy elderly control population (Jellinger 2009).

Neuroinflammation and immune reactions

The past decade has provided evidence for a significant role of the immune system in PD pathogenesis, either through inflammation or autoimmune response, which may be a cause of, rather than a response to neuronal loss (De Virgilio et al. 2016). An important converging mechanism between MDD and PD appears to be neuroinflammation. Mounting evidence has indicated that broad central and peripheral immune dysfunctions may also contribute to the neurobiology of MDD (Wohleb et al. 2016), and that there is a depression-related disruption in a neuroimmune axis that interfaces the immune system and CNS networks to control behavior and emotion (Hodes et al. 2015). Chronic neuroinflammation is one of the hallmarks of PD pathophysiology (Tansey et al. 2022). Experimental animal models and postmortem studies of human PD patients indicate that activation of glial cells and increase of pro-inflammatory factor levels are common features of the PD brain; indeed, microglia has been shown to play an important role in managing neuronal cell death, neurogenesis and synaptic interaction, besides their involvement in immune-response generating cytokines. The role of neuroinflammation in the emergence of depression is related to dynamic alterations in microglia response to stimulation may have an etiological role in neurodegeneration, in particular in depressive-like disorder.

DPD is accompanied by immune dysregulation, resulting in increased production of proinflammatory cytokines, e.g., interleukin-6 (IL-6), and tumor necrosis factor (TNF-α) in blood and brain (Hodes et al. 2015; Wohleb et al. 2015), the release of which by microglia and activated astrocytes leads to exacerbation of dopaminergic neuron degeneration and other abnormalities in brain function (Tonhajzerova et al. 2020). Furthermore, there is an important interface between peripheral immune cells and brain (Hodes et al. 2015). Clinical studies have shown that elevated levels of TNF-α and IL-6 are observed in the blood of MDD patients (Dowlati et al. 2010; Howren et al. 2009). These changes were associated with significant reduction in connectivity between prefrontal cortex and ventral striatum, which in turn are correlated with anhedonia, a core symptom of depression (Felger et al. 2016). Peripheral immune systems induce
cell-mediated inflammation in PD, highlighting the significant contribution of the immune system in the etiology of PD (Mutoh 2016).

Dysregulation of glial cells results in disruption of homeostasis leading to a chronic, pro-inflammatory, deleterious environment. Peripheral immune cells, in particular T lymphocytes, infiltrate the CNS and accumulate in the SN where they secrete pro-inflammatory cytokines, stimulate surrounding immune cells, and induce dopaminergic neuronal cell death, the pathological hallmarks of PD (Mac-Mahon Copas et al. 2021). Infiltration and accumulation of immune cells from the periphery are detected in and around the affected regions of PD brain. In PD, microglia and astrocytes can be activated by misfolded forms of αSyn protein to release cytokines that interact with multiple processes to produce depressive symptoms, including monoamine transport and availability, hippocampal neurogenesis, and the hypothalamus-pituitary axis. Astrocytes are another major link between PD and depression due to their recognized role in lymphatic clearing mechanisms. Studies suggesting that MDD causes astrocytic destruction or structural atrophy in relevant brain regions suggests the possibility that accumulation of αSyn in specific brain areas is facilitated due to inadequate clearance of these pathogenic protein aggregates. These mechanisms highlight the overlapping pathophysiology of MDD and PD with particular focus on neuroinflammation (Tran et al. 2021). In rodent models, proinflammatory monocytes infiltrate brain regions specifically associated with depression and anxiety (Wohleb et al. 2013), after having been lured in these areas by local increases of chemotactic cytokines and adhesion molecules in endothelium (Torres-Platas et al. 2014). Once inside the brain, infiltrating microglia differentiate into macrophage-derived microglia and produce a local inflammatory response contributing to anxiety-like behavior (Varvel et al. 2012). Increases in peripheral cytokines lead to changes in transcriptome profiles of astrocytes with upregulation of cytokines, chemokines and growth factors (Meeuwsen et al. 2003), which can be directly released into the brain. The loss of complexity in the astrocytic processes could lead to damage in the blood–brain barrier and increased penetration of peripheral substances into the brain. Furthermore, peripheral cytokines and hormones can interface on resident microglia in the CNS to affect depression, as shown from postmortem findings in patients with depression (Steiner et al. 2011). PET studies revealed a greater microglial activation in cortical areas that directly correlated with depression severity (Setiawan et al. 2015). In rodent models of depression, microglia released higher levels of IL-6 and IL-1B (Frank et al. 2007). Cytokines and chemokines can also act directly on neurons to alter plasticity and promote depression-like behaviors (Koo et al. 2010) by directly acting on serotonergic neurons and glutamatergic neurons in frontal cortex and hippocampus to alter synaptic plasticity (Beattie et al. 2002; Garcia-Oscos et al. 2012). The relationship between depression and PD has been investigated in various rodent models, by administration of MPTP in mice causing changes in depression and motor function (Ren et al. 2021) or by rotenone-induced PD in mice, in all of which metformin or fluoxetine showed anti-inflammatory neurogenic and neuroplasticity-inducing effects to improve depressive-like behavior (Ishola et al. 2022; Mendonça et al. 2022; Zhao et al. 2021).

### The gut-brain axis

Gut microbiotic changes that play a crucial role in the bidirectional communication between the gut and the brain (Klann et al. 2022) with a close link between multiple movement disorders and gastrointestinal dysfunction (Talman and Pfeiffer 2022), suggest that the gut microbes may shape neuronal development, modulate neurotransmission and affect behavior, have been associated with the pathomechanism of DPD (Dogra et al. 2022; Mendonça et al. 2020; Moustafa et al. 2021; Socala et al. 2021) (Felice et al. 2016; Jones et al. 2021; Tan et al. 2022; Xie et al. 2022). There is increasing evidence for the highly complex relationship between the gut and the brain in PD, including the potential role of the vagus nerve, αSyn deposition in the enteric nervous system, related to intestinal permeability, autonomic dysfunction, inflammation, neural immune system and the gut microbiome (Nowak et al. 2022; Tan et al. 2022; Tansey et al. 2022; Warnecke et al. 2022). Decreased fecal bacterially produced butyrate is related to epigenetic changes in leucocytes and neurons from PD patients and the severity of depressive symptoms (Xie et al. 2022). Recent studies have detected disturbed lipid metabolism (Dong et al. 2021), and abnormal glycolipid metabolism, fasting plasma glycose levels and motor symptoms being related to depressive symptoms in PD patients (Yao et al. 2022), thus enlarging the pathogenic spectrum of this deleterious co-morbidity to PD (Fig. 1).

### Conclusion and outlook

PD is a common and heterogeneous neurodegenerative disease characterized as a Lewy type α-synucleinopathy that is never restricted to the nigrostriatal system, and has both motor and non-motor manifestations including depression, anxiety and other neuropsychiatric signs and symptoms arising from a diverse neuroanatomical distribution of αSyn aggregates that causes a multitude of degenerative lesions involving a wide variety of nervous systems and networks. Among the non-motor manifestations of PD, depression is particularly important due to its negative impact on the...
course of the disease, its frequent combination with cognitive impairment and functional disability and impact on the quality of life of the patients and caregivers (Mou et al. 2022). The morphological and molecular biochemical basis of depressive symptoms in PD is heterogeneous, and modern neuroimaging, neurochemical and neuropathological studies have provided insight into important pathobiological mechanisms, suggesting that DPD is associated with complex dysfunctions of multiple neurotransmitter nuclei and pathways, in particular widespread degeneration of both the dopaminergic and serotonergic systems, as well as early noradrenergic deficiency due to early degeneration of the LC. Recent advances using functional and structural neuroimaging revealed extensive changes in cerebral GM and WM infrastructures, involving multiple brain areas, causing not only dopaminergic, serotonergic and noradrenergic dysfunctions but widespread disturbances of cortico-limbic, striato-thalamo-prefrontal, mediotemporal-limbic, anterior cingulate- orbitofrontal, and interhemispheric networks, with disruption of functional emotional, behavioral, cognitive and other essential brain circuits. Among the widespread reduced functional connectivities, DPD is particularly related to decreased functional connectivity between the orbitofrontal, hippocampal complex, cingulate, striatum, thalamus and limbic systems, while anxiety, often associated with depression in PD, appears to be related to decreased limbic-dorsolateral prefrontal, orbitofrontal-dorsolateral prefrontal, and sensorimotor-orbitofrontal cortices. These two types of functional dysconnectivity suggest less voluntary and more automatic emotion regulation in PD patients (Dan et al. 2017). In conclusion, modern in vivo imaging studies demonstrated that DPD is mainly underpinned by dysfunction of basal ganglia-cortico-limbic networks and monoaminergic systems, depending on the stage of PD and associated symptoms, including autonomic dysfunctions, CI, and RBD. In particular, the evolution of dopaminergic and serotonergic dysfunction and abnormalities of limbic circuits across time, involving the orbitofrontal and anterior cingulate cortices, ventral striatum, amygdala, thalamus, and other important brain networks, help to delineate the variable expression and severity of depression in patients with preclinical/prodromal, early and advances stages of PD (Prange et al. 2022). A history of depression may also be an increased risk of adverse effects following subthalamic nucleus deep brain stimulation (Kratter et al. 2020).

An essential pathogenic factor of DPD is monoaminergic imbalance and disruption of multiple brain networks related to neurodegeneration of relevant neurotransmitter systems due to aggregation of toxic misfolded αSyn, mitochondrial dysfunction, impairment of protein clearance (associated with deficient ubiquitin-proteasomal and autophagic-lysosomal systems), immunological/neuroinflammatory

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**Fig. 1** Some essential/hypothetical factors influencing the pathogenesis of depression in Parkinson disease (PD)
mechanisms and oxidative stress (Jankovic and Tan 2020; Jellinger and Attems 2015; Jellinger 2022a). A deeper understanding of the pathophysiological processes underlying depressive symptoms in PD, such as the contribution of αSyn "prion-like" progression through the brain, and the impact of other co-morbidities, like immunological/inflammatory or CSVD and Alzheimer-like pathologies in progressed stages of PD, is required to better understanding the relationship between the different forms and degrees of depression in PD and related LB diseases. The prospective assessment and validation of depressive signs and symptoms in PD will be improved by the combined use of clinical standard criteria, neuroimaging and biomarker signatures, making decisions more homogenous, which may be validated by multicentered post-mortem studies of well-characterized, longitudinally followed patients to further elucidate pathophysiological mechanisms of depression and its multifaceted manifestations in PD. Overall, this review emphasizes that increasing understanding of the complex mechanisms in the development of depression may help to implement a roadmap of person-tailored interventions for patients with PD and depression depending on the stage and co-morbid symptoms underlying PD subtypes and their prognosis.

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Conflict of interest The author declares that he has no conflict of interest.

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