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

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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 disorder
SN	Substantia nigra
SNc	Substantia nigra compacta
VTA	Ventral tegmental area
WM	White matter

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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 Martinez-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; Shiba 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; Wertman 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 (Sinaeefar 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 (Belarbi 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; Hanganu 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 (Saari 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 caudate 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 (l8F)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-ioflupane 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 (Maillet 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; Joutsa 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, SNc 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 (Borroto-Escuela et al. 2021). In addition to the relevance of the FGFR1-5-HT1A heteroreceptor complex for neuroplasticity and depression (Borroto-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)tetralin 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 (Pifl 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 SNc (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 DPD 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 DPD (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. 2008), 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 interrelated 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 phagocyting 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 studies suggested that the limbic loop of the basal ganglia and lateral habenula are important for early depression in PD (Borgonovo et al. 2017).

DPD has been associated with disruption in the topological organization of functional brain networks, mainly involving the posterior cingulate gyrus and temporo-occipital cortex as well as the prefrontal-limbic network (Qiu et al. 2021). There is evidence that resting-state functional connectivity within posterior cingulate cortex, insula, and between superior parietal lobule and medial prefrontal cortex characterizes DPD and may distinguish them from non-depressed ones (Lin et al. 2020). Abnormal subcallosal cingulate cortex connectivity was underlying DPD dominated by dysphoric mood (Uhr et al. 2022). The insular networks were severely damaged in depressed PD patients, who further showed decreased functional connectivity in the middle frontal gyrus and inferior parietal lobe, whereas the connectivity between left anterior insula and middle frontal gyrus was positively related with cognitive scale scores. These results suggest that the disrupted connection between the salience and the executive networks may contribute to depression in PD (Huang et al. 2020).

Dysfunction in extensive brain areas was involved in DPD, in particular disturbed connectivity between right middle frontal gyrus, anterior cingulate cortices and cerebellum was found in DPD (Wang et al. 2018), while others reported microstructural alterations in the anterior insula with lower fractional anisotrophy between dorsal and anterior insular cortex subregions that are associated with cognitive and affective impairment in PD (Jonkman et al. 2021). Furthermore, impaired interhemispheric synchrony with decreased connectivity was seen in the bilateral putamen, middle occipital and postcentral gyrus, paracentral lobule and cerebellum in DPD (Zhu et al. 2016b). MRI connectivity studies demonstrated a significant negative correlation between depression scores and quantitative anisotropy (QA) of left cingulum, genu and splenium of the corpus callosum, and anterior and posterior limbs of the right internal capsule (Ghazi Sherbaf et al. 2018). Decreased functional connectivity (FC) within the prefrontal-limbic system and increased FC in the prefrontal cortex and lingual gyrus were seen in DPD (Sheng et al. 2014), while others reported decreased FC in the left posterior cingulate and right superior temporal gyrus, and increased FC in right posterior cingulate cortex (Lou et al. 2015). 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/SMN/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 malformation 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 (MacMahon 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). ln 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 monocytes differentiate into monocyte-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 lL-6 and lL-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 fluoxetin 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

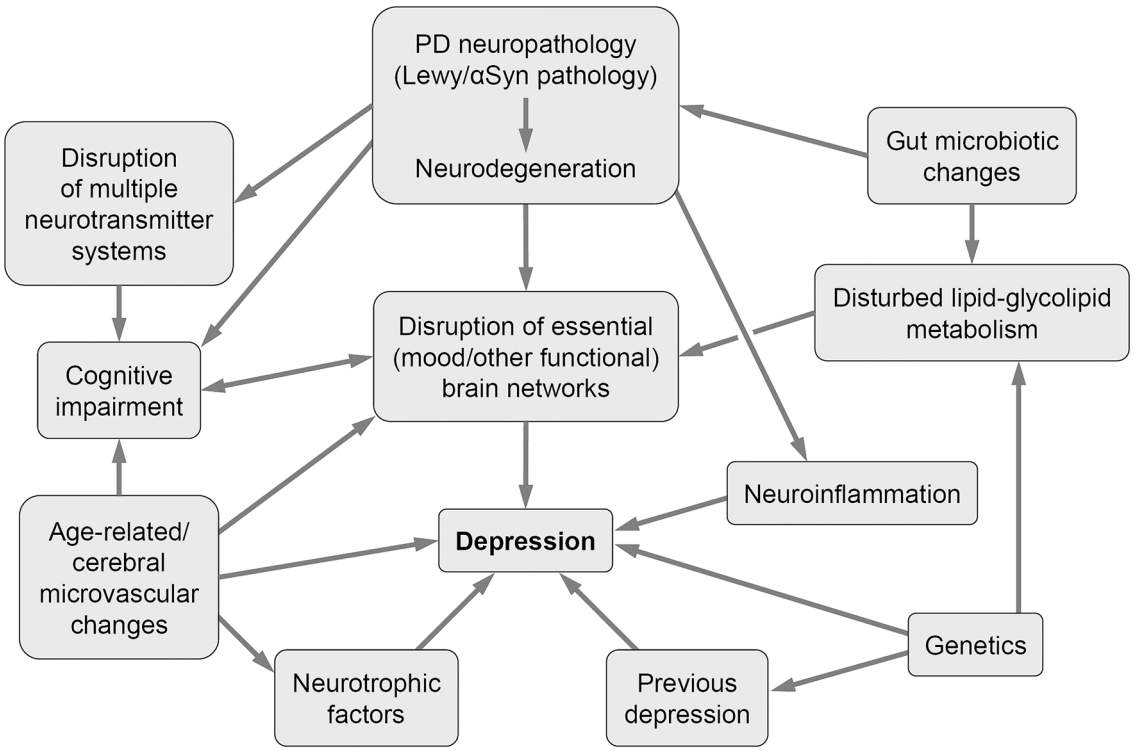

Fig. 1 Some essential/hypothetical factors influencing the pathogenesis of depression in Parkinson disease (PD)

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

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 multifaced 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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Declarations

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

References

Aarsland D, Marsh L, Schrag A (2009) Neuropsychiatric symptoms in Parkinson's disease. Mov Disord 24:2175–2186

Aarsland D, Påhlhagen S, Ballard CG, Ehrt U, Svenningsson P (2011) Depression in Parkinson disease–epidemiology, mechanisms and management. Nat Rev Neurol 8:35–47

Alexander GE, Crutcher MD, DeLong MR (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 85:119–146

Alfano V, Federico G, Mele G, Garramone F, Esposito M, Aiello M, Salvatore M, Cavaliere C (2022) Brain networks involved in depression in patients with frontotemporal dementia and Parkinson's disease: an exploratory resting-state functional connectivity MRI study. Diagnostics (basel) 12:959

Althaus A, Becker OA, Spottke A, Dengler R, Schneider F, Kloss M, Eggert K, Oertel WH, Dillmann U, Herting B, Classen J, Dodel R (2008) Frequency and treatment of depressive symptoms in a Parkinson's disease registry. Parkinsonism Relat Disord 14:626–632

American Psychiatric Association (2013) Diagnostic and statistical manual of mental disorders. American Psychiatric Publishing, Washington, London

Ansari M, Adib Moradi S, Ghazi Sherbaf F, Hedayatnia A, Aarabi MH (2019) Comparison of structural connectivity in Parkinson's disease with depressive symptoms versus non-depressed: a diffusion MRI connectometry study. Int Psychogeriatr 31:5–12

Assogna F, Fagioli S, Cravello L, Meco G, Pierantozzi M, Stefani A, Imperiale F, Caltagirone C, Pontieri FE, Spalletta G (2013) Depressive symptoms in Parkinson's disease and in non-neurological medical illnesses. Neuropsychiatr Dis Treat 9:389–396

Balash Y, Korczyn AD, Migirov AA, Gurevich T (2019) Quality of life in Parkinson's disease: a gender-specific perspective. Acta Neurol Scand 140:17–22

Balestrino R, Martinez-Martin P (2017) Neuropsychiatric symptoms, behavioural disorders, and quality of life in Parkinson's disease. J Neurol Sci 373:173–178

Ballanger B, Klinger H, Eche J, Lerond J, Vallet AE, Le Bars D, Tremblay L, Sgambato-Faure V, Broussolle E, Thobois S (2012) Role of serotonergic 1A receptor dysfunction in depression associated with Parkinson's disease. Mov Disord 27:84–89

Ballmaier M, Kumar A, Thompson PM, Narr KL, Lavretsky H, Estanol L, Deluca H, Toga AW (2004) Localizing gray matter deficits in late-onset depression using computational cortical pattern matching methods. Am J Psychiatry 161:2091–2099

Bareeqa SB, Samar SS, Kamal S, Masood Y, Allahyar ASI, Hayat G (2022) Prodromal depression and subsequent risk of developing Parkinson's disease: a systematic review with meta-analysis. Neurodegener Dis Manag 12:155–164

Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, Bottacchi E, Cannas A, Ceravolo G, Ceravolo R, Cicarelli G, Gaglio RM, Giglia RM, Iemolo F, Manfredi M, Meco G, Nicoletti A, Pederzoli M, Petrone A, Pisani A, Pontieri FE, Quatrale R, Ramat S, Scala R, Volpe G, Zappulla S, Bentivoglio AR, Stocchi F, Trianni G, Dotto PD (2009) The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord 24:1641–1649

Beach TG, Adler CH, Sue LI, Shill HA, Driver-Dunckley E, Mehta SH, Intorcia AJ, Glass MJ, Walker JE, Arce R, Nelson CM, Serrano GE (2021) Vagus nerve and stomach synucleinopathy in Parkinson's disease, incidental Lewy body disease, and normal elderly subjects: evidence against the "body-first" hypothesis. J Parkinsons Dis 11:1833–1843

Beattie EC, Stellwagen D, Morishita W, Bresnahan JC, Ha BK, Von Zastrow M, Beattie MS, Malenka RC (2002) Control of synaptic strength by glial TNFalpha. Science 295:2282–2285

Beavan M, McNeill A, Proukakis C, Hughes DA, Mehta A, Schapira AH (2015) Evolution of prodromal clinical markers of Parkinson disease in a GBA mutation-positive cohort. JAMA Neurol 72:201–208

Bédard C, Wallman MJ, Pourcher E, Gould PV, Parent A, Parent M (2011) Serotonin and dopamine striatal innervation in Parkinson's disease and Huntington's chorea. Parkinsonism Relat Disord 17:593–598

Bega D, Luo S, Fernandez H, Chou K, Aminoff M, Parashos S, Walker H, Russell DS, Christine CW, Dhall R, Singer C, Bodis-Wollner I, Hamill R, Truong D, Mari Z, Glazmann S, Huang M, Houston E, Simuni T (2015) Impact of depression on progression of impairment and disability in early Parkinson's disease. Mov Disord Clin Pract 2:371–378

Belarbi S, Hecham N, Lesage S, Kediha MI, Smail N, Benhassine T, Ysmail-Dahlouk F, Lohman E, Benhabyles B, Hamadouche T, Assami S, Brice A, Tazir M (2010) LRRK2 G2019S mutation in Parkinson's disease: a neuropsychological and neuropsychiatric study in a large Algerian cohort. Parkinsonism Relat Disord 16:676–679

Benoit M, Robert PH (2011) Imaging correlates of apathy and depression in Parkinson's disease. J Neurol Sci 310:58–60
Beucke JC, Plotkin M, Winter C, Endrass T, Amthauer H, Juckel G, Kupsch A (2011) Midbrain serotonin transporters in de novo and L-DOPA-treated patients with early Parkinson's disease—a [123 I]-ADAM SPECT study. Eur J Neurol 18:750–755
Bhome R, Zarkali A, Thomas GEC, Iglesias JE, Cole JH, Weil RS (2022) Thalamic white matter macrostructure and subnuclei volumes in Parkinson's disease depression. NPJ Parkinsons Dis 8:2
Bilgic B, Bayram A, Arslan AB, Hanagasi H, Dursun B, Gurvit H, Emre M, Lohmann E (2012) Differentiating symptomatic Parkin mutations carriers from patients with idiopathic Parkinson's disease: contribution of automated segmentation neuroimaging method. Parkinsonism Relat Disord 18:562–566
Blesa J, Foffani G, Dehay B, Bezard E, Obeso JA (2022) Motor and non-motor circuit disturbances in early Parkinson disease: which happens first? Nat Rev Neurosci 23:115–128
Bohnen NI, Albin RL (2011a) The cholinergic system and Parkinson disease. Behav Brain Res 221:564–573
Bohnen NI, Albin RL (2011b) White matter lesions in Parkinson disease. Nat Rev Neurol 7:229–236
Bohnen N, Muller M, Albin R, Scott P, Frey K, Koeppe R (2018) Progression of regional cortical cholinergic denervation in Parkinson disease: a longitudinal acetycholinesterase 11C-PMP PET study. J Nucl Med 59 suppl 1:630 https://jnm.snmjournals.org/content/659/supplement_631/630
Boileau I, Warsh JJ, Guttman M, Saint-Cyr JA, McCluskey T, Rusjan P, Houle S, Wilson AA, Meyer JH, Kish SJ (2008) Elevated serotonin transporter binding in depressed patients with Parkinson's disease: a preliminary PET study with [11C]DASB. Mov Disord 23:1776–1780
Borgonovo J, Allende-Castro C, Laliena A, Guerrero N, Silva H, Concha ML (2017) Changes in neural circuitry associated with depression at pre-clinical, pre-motor and early motor phases of Parkinson's disease. Parkinsonism Relat Disord 35:17–24
Borroto-Escuela DO, Pérez-Alea M, Narvaez M, Tarakanov AO, Mudó G, Jiménez-Beristain A, Agnati LF, Ciruela F, Belluardo N, Fuxe K (2015) Enhancement of the FGFR1 signaling in the FGFR1-5-HT1A heteroreceptor complex in midbrain raphe 5-HT neuron systems. Relevance for neuroplasticity and depression. Biochem Biophys Res Commun 463:180–186
Borroto-Escuela DO, Ambrogini P, Chruscicka B, Lindskog M, Crespo-Ramirez M, Hernández-Mondragón JC, Perez de la Mora M, Schellekens H, Fuxe K (2021) The role of central serotonin neurons and 5-HT heteroreceptor complexes in the pathophysiology of depression: a historical perspective and future prospects. Int J Mol Sci 22:1927
Böttcher T, Rolfs A, Meyer B, Grossmann A, Berg D, Kropp P, Benecke R, Walter U (2013) Clinical, genetic, and brain sonographic features related to Parkinson's disease in Gaucher disease. J Neurol 260:2523–2531
Bregman N, Thaler A, Mirelman A, Helmich RC, Gurevich T, Orr-Urtreger A, Marder K, Bressman S, Bloem BR, Giladi N (2017) A cognitive fMRI study in non-manifesting LRRK2 and GBA carriers. Brain Struct Funct 222:1207–1218
Bremner JD, Narayan M, Anderson ER, Staib LH, Miller HL, Charney DS (2000) Hippocampal volume reduction in major depression. Am J Psychiatry 157:115–118
Brown RG, Landau S, Hindle JV, Playfer J, Samuel M, Wilson KC, Hurt CS, Anderson RJ, Carnell J, Dickinson L, Gibson G, van Schaick R, Sellwood K, Thomas BA, Burn DJ (2011) Depression and anxiety related subtypes in Parkinson's disease. J Neurol Neurosurg Psychiatry 82:803–809
Buddhala C, Loftin SK, Kuley BM, Cairns NJ, Campbell MC, Perlmutter JS, Kotzbauer PT (2015) Dopaminergic, serotonergic, and noradrenergic deficits in Parkinson disease. Ann Clin Transl Neurol 2:949–959
Burn DJ, Landau S, Hindle JV, Samuel M, Wilson KC, Hurt CS, Brown RG (2012) Parkinson's disease motor subtypes and mood. Mov Disord 27:379–386
Caudal D, Alvarsson A, Björklund A, Svenningsson P (2015) Depressive-like phenotype induced by AAV-mediated overexpression of human α-synuclein in midbrain dopaminergic neurons. Exp Neurol 273:243–252
Chen JF, Wang M, Zhuang YH, Behnisch T (2018) Intracerebroventricularly-administered 1-methyl-4-phenylpyridinium ion and brain-derived neurotrophic factor affect catecholaminergic nerve terminals and neurogenesis in the hippocampus, striatum and substantia Nigra. Neural Regen Res 13:717–726
Chen H, Wan H, Zhang M, Liu G, Wang X, Wang Z, Ma H, Pan Y, Feng T, Wang Y (2021) Cerebral small vessel disease may worsen motor function, cognition, and mood in Parkinson's disease. Parkinsonism Relat Disord 83:86–92
Chendo I, Silva C, Duarte GS, Prada L, Vian J, Quintão A, Voon V, Ferreira JJ (2020) Frequency of depressive disorders in Parkinson's disease: a systematic review and meta-analysis. J Parkinsons Dis 12:1409–1418
Cong S, Xiang C, Zhang S, Zhang T, Wang H (2020) Prevalence and clinical aspects of depression in Parkinson's disease: a systematic review and metaâ€'analysis of 129 studies. Neurosci Biobehav Rev 141:104749
Crispino P, Gino M, Barbagelata E, Ciarambino T, Politi C, Ambrosino I, Ragusa R, Marranzano M, Biondi A, Vacante M (2020) Gender differences and quality of life in Parkinson's disease. Int J Environ Res Public Health 18:198
Dan R, Ružicka F, Bezdicek O, Ružicka E, Roth J, Vymazal J, Goelman G, Jech R (2017) Separate neural representations of depression, anxiety and apathy in Parkinson's disease. Sci Rep 7:12164
de Natale ER, Wilson H, Politis M (2021) Serotonergic imaging in Parkinson's disease. Prog Brain Res 261:303–338
De Virgilio A, Greco A, Fabbrini G, Inghilleri M, Rizzo MI, Gallo A, Conte M, Rosato C, Ciniglio Appiani M, de Vincentiis M (2016) Parkinson's disease: autoimmunity and neuroinflammation. Autoimmun Rev 15:1005–1011
Del Tredici K, Braak H (2016) Review: Sporadic Parkinson's disease: development and distribution of alpha-synuclein pathology. Neuropathol Appl Neurobiol 42:33–50
DeMarco EC, Zhang Z, Al-Hakeem H, Hinyard L (2022) Depression after Parkinson's disease: treated differently or not at all? J Geriatr Psychiatry Neurol. https://doi.org/10.1177/08919887221090217
Di Giuda D, Camardese G, Bentivoglio AR, Cocciolillo F, Guidubaldi A, Pucci L, Bruno I, Janiri L, Giordano A, Fasano A (2012) Dopaminergic dysfunction and psychiatric symptoms in movement disorders: a 123I-FP-CIT SPECT study. Eur J Nucl Med Mol Imaging 39:1937–1948
Diez-Cirarda M, Gabilondo I, Ibarretxe-Bilbao N, Gómez-Esteban JC, Kim J, Lucas-Jiménez O, Del Pino R, Peña J, Ojeda N, Mihaescu A, Valli M, Acera MA, Cabrera-Zubizarreta A, Gómez-Beldarrain MA, Strafella AP (2021) Contributions of sex, depression, and cognition on brain connectivity dynamics in Parkinson's disease. NPJ Parkinsons Dis 7:117
Dissanayaka NN, Sellbach A, Silburn PA, O'Sullivan JD, Marsh R, Mellick GD (2011) Factors associated with depression in Parkinson's disease. J Affect Disord 132:82–88
Doder M, Rabiner EA, Turjanski N, Lees AJ, Brooks DJ (2003) Tremor in Parkinson's disease and serotonergic dysfunction: an 11C-WAY 100635 PET study. Neurology 60:601–605
Dogra N, Mani RJ, Katare DP (2022) The gut-brain axis: two ways signaling in Parkinson's disease. Cell Mol Neurobiol 42:315–332

Dong MX, Wei YD, Hu L (2021) The disturbance of lipid metabolism is correlated with neuropsychiatric symptoms in patients with Parkinson's disease. Chem Phys Lipids 239:105112

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL (2010) A meta-analysis of cytokines in major depression. Biol Psychiatry 67:446–457

D'Souza T, Rajkumar AP (2020) Systematic review of genetic variants associated with cognitive impairment and depressive symptoms in Parkinson's disease. Acta Neuropsychiatr 32:10–22

Du T, Li G, Luo H, Pan Y, Xu Q, Ma K (2021) Hippocampal alpha-synuclein mediates depressive-like behaviors. Brain Behav Immun 95:226–237

Duncan GW, Khoo TK, Yarnall AJ, O'Brien JT, Coleman SY, Brooks DJ, Barker RA, Burn DJ (2014) Health-related quality of life in early Parkinson's disease: the impact of nonmotor symptoms. Mov Disord 29:195–202

Ehrt U, Brønnick K, Leentjens AF, Larsen JP, Aarsland D (2006) Depressive symptom profile in Parkinson's disease: a comparison with depression in elderly patients without Parkinson's disease. Int J Geriatr Psychiatry 21:252–258

Empana JP, Boutouyrie P, Lemogne C, Jouven X, van Sloten TT (2021) Microvascular contribution to late-onset depression: mechanisms, current evidence, association with other brain diseases, and therapeutic perspectives. Biol Psychiatry 90:214–225

Fazio P, Ferreira D, Svenningsson P, Halldin C, Farde L, Westman E, Varrone A (2020) High-resolution PET imaging reveals subtle impairment of the serotonin transporter in an early non-depressed Parkinson's disease cohort. Eur J Nucl Med Mol Imaging 47:2407–2416

Feldmann A, Illes Z, Kosztolanyi P, Illes E, Mike A, Kover F, Balas I, Kovacs N, Nagy F (2008) Morphometric changes of gray matter in Parkinson's disease with depression: a voxel-based morphometry study. Mov Disord 23:42–46

Felger JC, Li Z, Haroon E, Woolwine BJ, Jung MY, Hu X, Miller AH (2016) Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol Psychiatry 21:1358–1365

Felice VD, Quigley EM, Sullivan AM, O'Keeffe GW, O'Mahony SM (2016) Microbiota-gut-brain signalling in Parkinson's disease: implications for non-motor symptoms. Parkinsonism Relat Disord 27:1–8

Felicio AC, Moriyama TS, Godeiro-Junior C, Shih MC, Hoexter MQ, Borges V, Silva SM, Amaro-Junior E, Andrade LA, Ferraz HB, Bressan RA (2010) Higher dopamine transporter density in Parkinson's disease patients with depression. Psychopharmacology 211:27–31

Fernandez HH, See RH, Gary MF, Bowers D, Rodriguez RL, Ct J, Okun MS (2009) Depressive symptoms in Parkinson disease correlate with impaired global and specific cognitive performance. J Geriatr Psychiatry Neurol 22:223–227

Flores AD, Yu WS, Fung ML, Lim LW (2020) Neuromodulation and hippocampal neurogenesis in depression: a scoping review. Brain Res Bull 188:92–107

Frank MG, Baratta MV, Sprunger DB, Watkins LR, Maier SF (2007) Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS pro-inflammatory cytokine responses. Brain Behav Immun 21:47–59

Frauscher B, Jennum P, Ju YE, Postuma RB, Arnulf I, Cochen De Cock V, Dauvilliers Y, Fantini ML, Ferini-Strambi L, Gabelia D, Iranzo A, Leu-Semenescu S, Mitterling T, Miyamoto M, Miyamoto T, Montplaisir JY, Oertel W, Pelletier A, Prunetti P, Puligheddu M, Santamaria J, Sonka K, Unger M, Wolfson C, Zucconi M, Terzaghi M, Högl B, Mayer G, Manni R (2014) Comorbidity and medication in REM sleep behavior disorder: a multicenter case-control study. Neurology 82:1076–1079

Frisina PG, Haroutunian V, Libow LS (2009) The neuropathological basis for depression in Parkinson's disease. Parkinsonism Relat Disord 15:144–148

Fujishiro H, Nakamura S, Sato K, Iseki E (2015) Prodromal dementia with Lewy bodies. Geriatr Gerontol Int 15:817–826

Gaig C, Vilas D, Infante J, Sierra M, García-Gorostiaga I, Buongiorno M, Ezquerra M, Martí MJ, Valldeoriola F, Aguilar M, Calopa M, Hernandez-Vara J, Tolosa E (2014) Nonmotor symptoms in LRRK2 G2019S associated Parkinson's disease. PLoS ONE 9:e108982

Gallagher DA, Schrag A (2012) Psychosis, apathy, depression and anxiety in Parkinson's disease. Neurobiol Dis 46:581–589

Galvin JE (2006) Interaction of alpha-synuclein and dopamine metabolites in the pathogenesis of Parkinson's disease: a case for the selective vulnerability of the substantia nigra. Acta Neuropathol 112:115–126

Garcia-Oscos F, Salgado H, Hall S, Thomas F, Farmer GE, Bermeo J, Galindo LC, Ramirez RD, D'Mello S, Rose-John S, Atzori M (2012) The stress-induced cytokine interleukin-6 decreases the inhibition/excitation ratio in the rat temporal cortex via trans-signaling. Biol Psychiatry 71:574–582

Georgiev D, Hamberg K, Hariz M, Forsgren L, Hariz GM (2017) Gender differences in Parkinson's disease: a clinical perspective. Acta Neurol Scand 136:570–584

Geraets AFJ, Schram MT, Jansen JFA, Koster A, Dagnelie PC, van Greevenbroek MMJ, Stehouwer CDA, Verhey FRJ, Köhler S (2021) The relation of depression with structural brain abnormalities and cognitive functioning: the Maastricht study. Psychol Med. https://doi.org/10.1017/S0033291721000222

Ghazi Sherbaf F, Same K, Aarabi MH (2018) High angular resolution diffusion imaging correlates of depression in Parkinson's disease: a connectometry study. Acta Neurol Belg 118:573–579

Gibb WR (1992) Neuropathology of Parkinson's disease and related syndromes. Neurol Clin 10:361–376

Goldstein DS, Sullivan P, Holmes C, Kopin IJ, Basile MJ, Mash DC (2011) Catechols in post-mortem brain of patients with Parkinson disease. Eur J Neurol 18:703–710

Gonera EG, van't Hof M, Berger HJ, van Weel C, Horstink MW (1997) Symptoms and duration of the prodromal phase in Parkinson's disease. Mov Disord 12:871–876

Goodarzi Z, Mrklas KJ, Roberts DJ, Jette N, Pringsheim T, Holroyd-Leduc J (2016) Detecting depression in Parkinson disease: a systematic review and meta-analysis. Neurology 87:426–437

Goto M, Kamagata K, Hatano T, Hattori N, Abe O, Aoki S, Hori M, Gomi T (2018) Depressive symptoms in Parkinson's disease are related to decreased left hippocampal volume: correlation with the 15-item shortened version of the Geriatric Depression Scale. Acta Radiol 59:341–345

Grey MT, Mitterová K, Gajdoš M, Uher R, Klobušiaková P, Rektorová I, Rektor I (2020) Differential spatial distribution of white matter lesions in Parkinson's and Alzheimer's diseases and cognitive sequelae. J Neural Transm (vienna) 129:1023–1030

Gustafsson H, Nordström A, Nordström P (2015) Depression and subsequent risk of Parkinson disease: a nationwide cohort study. Neurology 84:2422–2429

Halliday GM, Blumbergs PC, Cotton RG, Blessing WW, Geffen LB (1990a) Loss of brainstem serotonin- and substance P-containing neurons in Parkinson's disease. Brain Res 510:104–107

Halliday GM, Li YW, Blumbergs PC, Joh TH, Cotton RG, Howe PR, Blessing WW, Geffen LB (1990b) Neuropathology of immunohistochemically identified brainstem neurons in Parkinson's disease. Ann Neurol 27:373–385

Han LL, Wang L, Xu ZH, Liang XN, Zhang MW, Fan Y, Sun YM, Liu FT, Yu WB, Tang YL (2021) Disease progression in Parkinson's disease patients with subjective cognitive complaint. Ann Clin Transl Neurol 8:2096–2104

Hanganu A, Bruneau MA, Degroot C, Bedetti C, Mejia-Constain B, Lafontaine AL, Chouinard S, Monchi O (2017) Depressive symptoms in Parkinson's disease correlate with cortical atrophy over time. Brain Cogn 111:127–133

He Y, Tian Y, Han H, Cui J, Ge X, Qin Y, Luo Y, Bai W, Yu H (2021) The path linking disease severity and cognitive function with quality of life in Parkinson's disease: the mediating effect of activities of daily living and depression. Health Qual Life Outcomes 19:92

Heller J, Mirzazade S, Romanzetti S, Habel U, Derntl B, Freitag NM, Schulz JB, Dogan I, Reetz K (2018) Impact of gender and genetics on emotion processing in Parkinson's disease—a multimodal study. Neuroimage Clin 18:305–314

Hirsch E, Graybiel AM, Agid YA (1988) Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. Nature 334:345–348

Hodes GE, Kana V, Menard C, Merad M, Russo SJ (2015) Neuroimmune mechanisms of depression. Nat Neurosci 18:1386–1393

Howren MB, Lamkin DM, Suls J (2009) Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom Med 71:171–186

Hu X, Song X, Li E, Liu J, Yuan Y, Liu W, Liu Y (2015a) Altered resting-state brain activity and connectivity in depressed Parkinson's disease. PLoS ONE 10:e0131133

Hu X, Song X, Yuan Y, Li E, Liu J, Liu W, Liu Y (2015b) Abnormal functional connectivity of the amygdala is associated with depression in Parkinson's disease. Mov Disord 30:238–244

Huang P, Xuan M, Gu Q, Yu X, Xu X, Luo W, Zhang M (2015) Abnormal amygdala function in Parkinson's disease patients and its relationship to depression. J Affect Disord 183:263–268

Huang P, Lou Y, Xuan M, Gu Q, Guan X, Xu X, Song Z, Luo W, Zhang M (2016) Cortical abnormalities in Parkinson's disease patients and relationship to depression: a surface-based morphometry study. Psychiatry Res Neuroimaging 250:24–28

Huang P, Guan X, Guo T, Zeng Q, Xuan M, Gu Q, Xu X, Zhou C, Wu J, Zhang M (2020) Damaged insula network contributes to depression in Parkinson's disease. Front Psychiatry 11:119

Hui Y, Du C, Xu T, Zhang Q, Tan H, Liu J (2020) Dopamine D(4) receptors in the lateral habenula regulate depression-related behaviors via a pre-synaptic mechanism in experimental Parkinson's disease. Neurochem Int 140:104844

Huot P, Fox SH (2013) The serotonergic system in motor and nonmotor manifestations of Parkinson's disease. Exp Brain Res 230:463–476

Huot P, Fox SH, Brotchie JM (2011) The serotonergic system in Parkinson's disease. Prog Neurobiol 95:163–212

Huynh B, Fu Y, Kirik D, Shine JM, Halliday GM (2021) Comparison of locus coeruleus pathology with nigral and forebrain pathology in Parkinson's disease. Mov Disord 36:2085–2093

Ilkiw JL, Kmita LC, Targa ADS, Noseda ACD, Rodrigues LS, Dorieux FWC, Fagotti J, Dos Santos P, Lima MMS (2019) Dopaminergic lesion in the olfactory bulb restores olfaction and induces depressive-like behaviors in a 6-OHDA model of Parkinson's disease. Mol Neurobiol 56:1082–1095

Inoue T, Kitagawa M, Tanaka T, Nakagawa S, Koyama T (2010) Depression and major depressive disorder in patients with Parkinson's disease. Mov Disord 25:44–49

Ishiguro M, Baba H, Maeshima H, Shimano T, Inoue M, Ichikawa T, Yasuda S, Shukuzawa H, Suzuki T, Arai H (2019) Increased serum levels of α-synuclein in patients with major depressive disorder. Am J Geriatr Psychiatry 27:280–286

Ishihara L, Brayne C (2006) A systematic review of depression and mental illness preceding Parkinson's disease. Acta Neurol Scand 113:211–220

Ishola IO, Awogbindin IO, Olubodun-Obadun TG, Oluwafemi OA, Onuelu JE, Adeyemi OO (2022) Morin ameliorates rotenone-induced Parkinson disease in mice through antioxidation and anti-neuroinflammation: gut-brain axis involvement. Brain Res 1789:147958

Jacob Y, Rosenberg-Katz K, Gurevich T, Helmich RC, Bloem BR, Orr-Urtreger A, Giladi N, Mirelman A, Hendler T, Thaler A (2019) Network abnormalities among non-manifesting Parkinson disease related LRRK2 mutation carriers. Hum Brain Mapp 40:2546–2555

Jankovic J (2008) Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry 79:368–376

Jankovic J, Tan EK (2020) Parkinson's disease: etiopathogenesis and treatment. J Neurol Neurosurg Psychiatry 91:795–808

Jellinger K (1987) Quantitative changes in some subcortical nuclei in aging, Alzheimer's disease and Parkinson's disease. Neurobiol Aging 8:556–561

Jellinger KA (2009) Lewy body/alpha-synucleinopathy in schizophrenia and depression: a preliminary neuropathological study. Acta Neuropathol 117:423–427

Jellinger KA (2012) Neuropathology of sporadic Parkinson's disease: evaluation and changes of concepts. Mov Disord 27:8–30

Jellinger KA (2021) Pathomechanisms of vascular depression in older adults. Int J Mol Sci 23:308

Jellinger KA (2022a) Morphological basis of Parkinson disease-associated cognitive impairment: an update. J Neural Transm (vienna) 129:977–999

Jellinger KA (2022b) The enigma of vascular depression in old age: a critical update. J Neural Transm (vienna) 129:961–976

Jellinger KA, Attems J (2015) Challenges of multimorbidity of the aging brain: a critical update. J Neural Transm 122:505–521

Jeong W, Kim H, Joo JH, Jang SI, Park EC (2021) Association between depression and risk of Parkinson's disease in South Korean adults. J Affect Disord 292:75–80

Jiang YF, Liu J, Yang J, Guo Y, Hu W, Zhang J, La XM, Xie W, Wang HS, Zhang L (2020) Involvement of the dorsal hippocampus 5-HT1A receptors in the regulation of depressive-like behaviors in hemiparkinsonian rats. Neuropsychobiology 79:198–207

Jones JD, Kurniadi NE, Kuhn TP, Szymkowicz SM, Bunch J, Rahmani E (2019) Depressive symptoms precede cognitive impairment in de novo Parkinson's disease patients: Analysis of the PPMI cohort. Neuropsychology 33:1111–1120

Jones JD, Dominguez B, Bunch J, Uribe C, Valenzuela Y, Jacobs JP (2021) A bidirectional relationship between anxiety, depression and gastrointestinal symptoms in Parkinson's disease. Clin Park Relat Disord 5:100104

Jonkman LE, Fathy YY, Berendse HW, Schoonheim MM, van de Berg WDJ (2021) Structural network topology and microstructural alterations of the anterior insula associate with cognitive and affective impairment in Parkinson's disease. Sci Rep 11:16021

Joutsa J, Johansson J, Seppänen M, Noponen T, Kaasinen V (2015) Dorsal-to-ventral shift in midbrain dopaminergic projections and increased thalamic/raphe serotonergic function in early Parkinson disease. J Nucl Med 56:1036–1041

Kaminska K, Lenda T, Konieczny J, Czarnecka A, Lorenc-Koci E (2017) Depressive-like neurochemical and behavioral markers of Parkinson's disease after 6-OHDA administered unilaterally to the rat medial forebrain bundle. Pharmacol Rep 69:985–994

Kasten M, Kertelge L, Brüggemann N, van der Vegt J, Schmidt A, Tadic V, Buhmann C, Steinlechner S, Behrens MI, Ramirez A, Binkofski F, Siebner H, Raspe H, Hagenah J, Lencer R, Klein C (2010) Nonmotor symptoms in genetic Parkinson disease. Arch Neurol 67:670–676

Kazmi H, Walker Z, Booij J, Khan F, Shah S, Sudre CH, Buckman JEJ, Schrag AE (2021) Late onset depression: dopaminergic deficit and clinical features of prodromal Parkinson's disease: a cross-sectional study. J Neurol Neurosurg Psychiatry 92:158–164

Kerenyi L, Ricaurte GA, Schretlen DJ, McCann U, Varga J, Mathews WB, Ravert HT, Dannals RF, Hilton J, Wong DF, Szabo Z (2003) Positron emission tomography of striatal serotonin transporters in Parkinson disease. Arch Neurol 60:1223–1229

Kim YK, Han KM (2021) Neural substrates for late-life depression: A selective review of structural neuroimaging studies. Prog Neuropsychopharmacol Biol Psychiatry 104:110010

Kim IB, Park SC (2021) The entorhinal cortex and adult neurogenesis in major depression. Int J Mol Sci 22:11725

Kish SJ, Tong J, Hornykiewicz O, Rajput A, Chang LJ, Guttman M, Furukawa Y (2008) Preferential loss of serotonin markers in caudate versus putamen in Parkinson's disease. Brain 131:120–131

Klann EM, Dissanayake U, Gurrala A, Farrer M, Shukla AW, Ramirez-Zamora A, Mai V, Vedam-Mai V (2022) The gut-brain axis and its relation to Parkinson's disease: a review. Front Aging Neurosci 13:782082

Koerts J, Leenders KL, Koning M, Portman AT, van Beilen M (2007) Striatal dopaminergic activity (FDOPA-PET) associated with cognitive items of a depression scale (MADRS) in Parkinson's disease. Eur J Neurosci 25:3132–3136

Kohl Z, Ben Abdallah N, Vogelgsang J, Tischer L, Deusser J, Amato D, Anderson S, Müller CP, Riess O, Masliah E, Nuber S, Winkler J (2016) Severely impaired hippocampal neurogenesis associates with an early serotonergic deficit in a BAC α-synuclein transgenic rat model of Parkinson's disease. Neurobiol Dis 85:206–217

Koo JW, Russo SJ, Ferguson D, Nestler EJ, Duman RS (2010) Nuclear factor-kappaB is a critical mediator of stress-impaired neurogenesis and depressive behavior. Proc Natl Acad Sci U S A 107:2669–2674

Kostic VS, Filippi M (2011) Neuroanatomical correlates of depression and apathy in Parkinson's disease: magnetic resonance imaging studies. J Neurol Sci 310:61–63

Kostic VS, Agosta F, Petrovic I, Galantucci S, Spica V, Jecmenica-Lukic M, Filippi M (2010) Regional patterns of brain tissue loss associated with depression in Parkinson disease. Neurology 75:857–863

Kratter IH, Jorge A, Feyder MT, Whiteman AC, Chang YF, Henry LC, Karp JF, Richardson RM (2020) Depression history modulates effects of subthalamic nucleus topography on neuropsychological outcomes of deep brain stimulation for Parkinson's disease. Transl Psychiatry 12:213

Krishnan V, Han MH, Graham DL, Berton O, Renthal W, Russo SJ, Laplant Q, Graham A, Lutter M, Lagace DC, Ghose S, Reister R, Tannous P, Green TA, Neve RL, Chakravarty S, Kumar A, Eisch AJ, Self DW, Lee FS, Tamminga CA, Cooper DC, Gershenfeld HK, Nestler EJ (2007) Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. Cell 131:391–404

Kulisevsky J, Pagonabarraga J, Pascual-Sedano B, García-Sánchez C, Gironell A (2008) Prevalence and correlates of neuropsychiatric symptoms in Parkinson's disease without dementia. Mov Disord 23:1889–1896

Lacey C, Ohlhauser L, Gawryluk JR (2019) Microstructural white matter characteristics in Parkinson's disease with depression: a diffusion tensor imaging replication study. Front Neurol 10:884

Larsen JP, Dalen I, Pedersen KF, Tysnes OB (2017) The natural history of depressive symptoms in patients with incident Parkinson's disease: a prospective cohort study. J Neurol 264:2401–2408

Laux G (2022) Parkinson and depression: review and outlook. J Neural Transm (vienna) 129:601–608

Lee Y, Oh JS, Chung SJ, Lee JJ, Moon H, Lee PH, Kim JS, Sohn YH (2018) The presence of depression in de novo Parkinson's disease reflects poor motor compensation. PLoS ONE 13:e0203303

Leentjens AF, Van den Akker M, Metsemakers JF, Lousberg R, Verhey FR (2003) Higher incidence of depression preceding the onset of Parkinson's disease: a register study. Mov Disord 18:414–418

Li W, Liu J, Skidmore F, Liu Y, Tian J, Li K (2010) White matter microstructure changes in the thalamus in Parkinson disease with depression: a diffusion tensor MR imaging study. AJNR Am J Neuroradiol 31:1861–1866

Li Y, Huang P, Guo T, Guan X, Gao T, Sheng W, Zhou C, Wu J, Song Z, Xuan M, Gu Q, Xu X, Yang Y, Zhang M (2020a) Brain structural correlates of depressive symptoms in Parkinson's disease patients at different disease stage. Psychiatry Res Neuroimaging 296:111029

Li Z, Liu W, Xiao C, Wang X, Zhang X, Yu M, Hu X, Qian L (2020b) Abnormal white matter microstructures in Parkinson's disease and comorbid depression: a whole-brain diffusion tensor imaging study. Neurosci Lett 735:135238

Liang P, Deshpande G, Zhao S, Liu J, Hu X, Li K (2016) Altered directional connectivity between emotion network and motor network in Parkinson's disease with depression. Medicine (baltimore) 95:e4222

Liao H, Fan J, Shen Q, Cai S, Wang M, Wang C, Zhang H, Liu J, Zhu X, Tan C (2020) Alterations of interhemispheric functional connectivity in Parkinson's disease with depression: a resting-state functional MRI study. Front Hum Neurosci 14:193

Liao H, Cai S, Shen Q, Fan J, Wang T, Zi Y, Mao Z, Situ W, Liu J, Zou T, Yi J, Zhu X, Tan C (2021) Networks are associated with depression in patients with Parkinson's disease: a resting-state imaging study. Front Neurosci 14:573538

Lim J, Bang Y, Choi HJ (2018) Abnormal hippocampal neurogenesis in Parkinson's disease: relevance to a new therapeutic target for depression with Parkinson's disease. Arch Pharm Res 41:943–954

Lin H, Cai X, Zhang D, Liu J, Na P, Li W (2020) Functional connectivity markers of depression in advanced Parkinson's disease. Neuroimage Clin 25:102130

Liu KC, Li JY, Tan HH, Du CX, Xie W, Zhang YM, Ma WL, Zhang L (2015) Serotonin-6 receptors in the dorsal hippocampus regulate depressive-like behaviors in unilateral 6-hydroxydopamine-lesioned Parkinson's rats. Neuropharmacology 95:290–298

Liu Z, Su D, Ma L, Chen H, Fang J, Ma H, Zhou J, Feng T (2022) The altered multiscale dynamics of spontaneous brain activity in depression with Parkinson's disease. Neurol Sci 43:4211–4219

Lou Y, Huang P, Li D, Cen Z, Wang B, Gao J, Xuan M, Yu H, Zhang M, Luo W (2015) Altered brain network centrality in depressed Parkinson's disease patients. Mov Disord 30:1777–1784

Luo XF, Zhang BL, Li JC, Yang YY, Sun YF, Zhao H (2015) Lateral habenula as a link between dopaminergic and serotonergic systems contributes to depressive symptoms in Parkinson's disease. Brain Res Bull 110:40–46

Luo C, Song W, Chen Q, Yang J, Gong Q, Shang HF (2016) Cortical thinning in drug-naive Parkinson's disease patients with depression. J Neurol 263:2114–2119

Lyu S, Guo Y, Zhang L, Tang G, Li R, Yang J, Gao S, Li W, Liu J (2021) Downregulation of astroglial glutamate transporter GLT-1 in the lateral habenula is associated with depressive-like behaviors in a rat model of Parkinson's disease. Neuropharmacology 196:108691

Ma J, Dou K, Liu R, Liao Y, Yuan Z, Xie A (2020) Associations of sleep disorders with depressive symptoms in early and prodromal Parkinson's disease. Front Aging Neurosci 14:898149

Macías-García P, Rashid-López R, Cruz-Gómez ÁJ, Lozano-Soto E, Sanmartino F, Espinosa-Rosso R, González-Rosa JJ (2022) Neuropsychiatric symptoms in clinically defined Parkinson's disease: an updated review of literature. Behav Neurol 2022:1213393

MacMahon Copas AN, McComish SF, Fletcher JM, Caldwell MA (2021) The pathogenesis of Parkinson's disease: a complex

interplay between astrocytes, microglia, and T lymphocytes? Front Neurol 12:666737
Magnard R, Vachez Y, Carcenac C, Krack P, David O, Savasta M, Boulet S, Carnicella S (2016) What can rodent models tell us about apathy and associated neuropsychiatric symptoms in Parkinson's disease? Transl Psychiatry 6:e753
Maillet A, Krack P, Lhommée E, Météreau E, Klinger H, Favre E, Le Bars D, Schmitt E, Bichon A, Pelissier P, Fraix V, Castrioto A, Sgambato-Faure V, Broussolle E, Tremblay L, Thobois S (2016) The prominent role of serotonergic degeneration in apathy, anxiety and depression in de novo Parkinson's disease. Brain 139:2486–2502
Maillet A, Météreau E, Tremblay L, Favre E, Klinger H, Lhommée E, Le Bars D, Castrioto A, Prange S, Sgambato V, Broussolle E, Krack P, Thobois S (2021) Serotonergic and dopaminergic lesions underlying parkinsonian neuropsychiatric signs. Mov Disord 36:2888–2900
Marras C, McDermott MP, Rochon PA, Tanner CM, Naglie G, Lang AE (2008) Predictors of deterioration in health-related quality of life in Parkinson's disease: results from the DATATOP trial. Mov Disord 23:653–659 (**quiz 776**)
Marsh L (2013) Depression and Parkinson's disease: current knowledge. Curr Neurol Neurosci Rep 13:409
Marsh L, McDonald WM, Cummings J, Ravina B (2006) Provisional diagnostic criteria for depression in Parkinson's disease: report of an NINDS/NIMH Work Group. Mov Disord 21:148–158
Matheus FC, Rial D, Real JI, Lemos C, Takahashi RN, Bertoglio LJ, Cunha RA, Prediger RD (2016) Temporal dissociation of striatum and prefrontal cortex uncouples anhedonia and defense behaviors relevant to depression in 6-OHDA-lesioned rats. Mol Neurobiol 53:3891–3899
Matsubara T, Suzuki K, Fujita H, Watanabe Y, Sakuramoto H, Matsubara M, Hirata K (2018) Autonomic symptoms correlate with non-autonomic non-motor symptoms and sleep problems in patients with Parkinson's disease. Eur Neurol 80:193–199
Mayberg HS, Starkstein SE, Sadzot B, Preziosi T, Andrezejewski PL, Dannals RF, Wagner HN Jr, Robinson RG (1990) Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. Ann Neurol 28:57–64
McDonald WM, Richard IH, DeLong MR (2003) Prevalence, etiology, and treatment of depression in Parkinson's disease. Biol Psychiatry 54:363–375
McKinlay A, Grace RC, Dalrymple-Alford JC, Anderson T, Fink J, Roger D (2008) A profile of neuropsychiatric problems and their relationship to quality of life for Parkinson's disease patients without dementia. Parkinsonism Relat Disord 14:37–42
Meadows SM, Chambers NE, Conti MM, Bossert SC, Tasber C, Sheena E, Varney M, Newman-Tancredi A, Bishop C (2017) Characterizing the differential roles of striatal 5-HT(1A) auto- and hetero-receptors in the reduction of l-DOPA-induced dyskinesia. Exp Neurol 292:168–178
Meeuwsen S, Persoon-Deen C, Bsibsi M, Ravid R, van Noort JM (2003) Cytokine, chemokine and growth factor gene profiling of cultured human astrocytes after exposure to proinflammatory stimuli. Glia 43:243–253
Mendonça IP, Duarte-Silva E, Chaves-Filho AJM, Andrade da Costa B, Peixoto CA (2020) Neurobiological findings underlying depressive behavior in Parkinson's disease: a review. Int Immunopharmacol 83:106434
Mendonça IP, Paiva IHR, Duarte-Silva EP, Melo MG, Silva RSD, Oliveira WH, Costa BLDSAD, Peixoto CA (2022) Metformin and fluoxetine improve depressive-like behavior in a murine model of Parkinson's disease through the modulation of neuroinflammation, neurogenesis and neuroplasticity. Int Immunopharmacol 102:108415
Meng L, Wang H, Zou T, Wang X, Chen H, Xie F, Li R (2022) Attenuated brain white matter functional network interactions in Parkinson's disease. Hum Brain Mapp 43:4567–4579
Menza M, Dobkin RD, Marin H, Mark MH, Gara M, Buyske S, Bienfait K, Dicke A (2009) The impact of treatment of depression on quality of life, disability and relapse in patients with Parkinson's disease. Mov Disord 24:1325–1332
Meyer JH, Krüger S, Wilson AA, Christensen BK, Goulding VS, Schaffer A, Minifie C, Houle S, Hussey D, Kennedy SH (2001) Lower dopamine transporter binding potential in striatum during depression. NeuroReport 12:4121–4125
Meyer PM, Strecker K, Kendziorra K, Becker G, Hesse S, Woelpl D, Hensel A, Patt M, Sorger D, Wegner F, Lobsien D, Barthel H, Brust P, Gertz HJ, Sabri O, Schwarz J (2009) Reduced alpha4beta2*-nicotinic acetylcholine receptor binding and its relationship to mild cognitive and depressive symptoms in Parkinson disease. Arch Gen Psychiatry 66:866–877
Miquel-Rio L, Alarcón-Arís D, Torres-López M, Cóppola-Segovia V, Pavia-Collado R, Paz V, Ruiz-Bronchal E, Campa L, Casal C, Montefeltro A, Vila M, Artigas F, Revilla R, Bortolozzi A (2022) Human α-synuclein overexpression in mouse serotonin neurons triggers a depressive-like phenotype. Rescue by oligonucleotide therapy. Transl Psychiatry 12:79
Montanaro E, Artusi CA, Rosano C, Boschetto C, Imbalzano G, Romagnolo A, Bozzali M, Rizzone MG, Zibetti M, Lopiano L (2022) Anxiety, depression, and worries in advanced Parkinson disease during COVID-19 pandemic. Neurol Sci 43:341–348
Mou YK, Guan LN, Yao XY, Wang JH, Song XY, Ji YQ, Ren C, Wei SZ (2022) Application of neurotoxin-induced animal models in the study of Parkinson's disease-related depression: profile and proposal. Front Aging Neurosci 14:890512
Moustafa SA, Mohamed S, Dawood A, Azar J, Elmorsy E, Rizk NAM, Salama M (2021) Gut brain axis: an insight into microbiota role in Parkinson's disease. Metab Brain Dis 36:1545–1557
Mullin S, Beavan M, Bestwick J, McNeill A, Proukakis C, Cox T, Hughes D, Mehta A, Zetterberg H, Schapira AHV (2019) Evolution and clustering of prodromal parkinsonian features in GBA1 carriers. Mov Disord 34:1365–1373
Mutoh T (2016) Current understanding of immunopathogenesis of Parkinson's disease (Editorial). Austin J Clin Neurol 3:1097
Nagayama H, Kimura K (2015) Depression preceding Parkinson's disease onset. Austin Alzheimers J Parkinsons Dis 2:1023; https://austinpublishinggroup.com/aapd/fulltext/aapd-v1022-id1023.php
Nakano T, Kajiyama Y, Revankar GS, Hashimoto R, Watanabe Y, Kishima H, Ikeda M, Mihara M, Mochizuki H, Hattori N (2021) Neural networks associated with quality of life in patients with Parkinson's disease. Parkinsonism Relat Disord 89:6–12
Ng A, Chander RJ, Tan LC, Kandiah N (2015) Influence of depression in mild Parkinson's disease on longitudinal motor and cognitive function. Parkinsonism Relat Disord 21:1056–1060
Nguyen Y, Stirnemann J, Belmatoug N (2019) Gaucher disease: a review. Rev Med Interne 40:313–322
Nicoletti A, Vasta R, Mostile G, Nicoletti G, Arabia G, Iliceto G, Lamberti P, Marconi R, Morgante L, Barone P, Quattrone A, Zappia M (2017) Gender effect on non-motor symptoms in Parkinson's disease: are men more at risk? Parkinsonism Relat Disord 35:69–74
Norris EH, Giasson BI, Lee VM (2004) Alpha-synuclein: normal function and role in neurodegenerative diseases. Curr Top Dev Biol 60:17–54
Nowak JM, Kopczynski M, Friedman A, Koziorowski D, Figura M (2022) Microbiota dysbiosis in Parkinson disease—in search of a biomarker. Biomedicines 10:2057
Nunes PV, Suemoto CK, Rodriguez RD, Leite REP, Nascimento C, Pasqualucci CA, Nitrini R, Jacob-Filho W, Grinberg LT, Lafer

B (2022) Neuropathology of depression in non-demented older adults: a large postmortem study of 741 individuals. Neurobiol Aging 117:107–116

Oertel WH, Henrich MT, Janzen A, Geibl FF (2019) The locus coeruleus: another vulnerability target in Parkinson's disease. Mov Disord 34:1423–1429

Oh YS, Kim JH, Yoo SW, Hwang EJ, Lyoo CH, Lee KS, Kim JS (2021) Neuropsychiatric symptoms and striatal monoamine availability in early Parkinson's disease without dementia. Neurol Sci 42:711–718

Orayj K, Almeleebia T, Vigneshwaran E, Alshahrani S, Alavudeen SS, Alghamdi W (2021) Trend of recognizing depression symptoms and antidepressants use in newly diagnosed Parkinson's disease: population-based study. Brain Behav 11:e2228

Ou R, Wei Q, Hou Y, Yuan X, Song W, Cao B, Liu H, Zhang L, Chen Y, Shang H (2018) Vascular risk factors and depression in Parkinson's disease. Eur J Neurol 25:637–643

Pagano G, Niccolini F, Fusar-Poli P, Politis M (2017) Serotonin transporter in Parkinson's disease: a meta-analysis of PET studies. Ann Neurol 81:171–180

Pankratz N, Marder KS, Halter CA, Rudolph A, Shults CW, Nichols WC, Foroud T (2008) Clinical correlates of depressive symptoms in familial Parkinson's disease. Mov Disord 23:2216–2223

Papapetropoulos S, Ellul J, Argyriou AA, Chroni E, Lekka NP (2006) The effect of depression on motor function and disease severity of Parkinson's disease. Clin Neurol Neurosurg 108:465–469

Paredes-Rodriguez E, Vegas-Suarez S, Morera-Herreras T, De Deurwaerdere P, Miguelez C (2020) The noradrenergic system in Parkinson's disease. Front Pharmacol 11:435

Park JH, Enikolopov G (2010) Transient elevation of adult hippocampal neurogenesis after dopamine depletion. Exp Neurol 222:267–276

Park SB, Kwon KY, Lee JY, Im K, Sunwoo JS, Lee KB, Roh H, Ahn MY, Park S, Kim SJ, Oh JS, Kim JS (2019) Lack of association between dopamine transporter loss and non-motor symptoms in patients with Parkinson's disease: a detailed PET analysis of 12 striatal subregions. Neurol Sci 40:311–317

Pasquini J, Ceravolo R, Brooks DJ, Bonuccelli U, Pavese N (2020) Progressive loss of raphe nuclei serotonin transporter in early Parkinson's disease: a longitudinal (123)I-FP-CIT SPECT study. Parkinsonism Relat Disord 77:170–175

Patrick HT, Levy DM (1922) Parkinson's disease: a clinical study of 146 cases. Arch Neurol Psychiatry 7:711–720

Patterson L, Rushton SP, Attems J, Thomas AJ, Morris CM (2019) Degeneration of dopaminergic circuitry influences depressive symptoms in Lewy body disorders. Brain Pathol 29:544–557

Paulus W, Jellinger K (1991) The neuropathologic basis of different clinical subgroups of Parkinson's disease. J Neuropathol Exp Neurol 50:743–755

Pavese N, Metta V, Bose SK, Chaudhuri KR, Brooks DJ (2010) Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction. Brain 133:3434–3443

Perrin AJ, Nosova E, Co K, Book A, Iu O, Silva V, Thompson C, McKeown MJ, Stoessl AJ, Farrer MJ, Appel-Cresswell S (2017) Gender differences in Parkinson's disease depression. Parkinsonism Relat Disord 36:93–97

Petkus AJ, Filoteo JV, Schiehser DM, Gomez ME, Petzinger G (2019) Worse cognitive performance predicts increased anxiety and depressive symptoms in patients with Parkinson's disease: a bidirectional analysis. Neuropsychology 33:35–46

Phan JA, Stokholm K, Zareba-Paslawska J, Jakobsen S, Vang K, Gjedde A, Landau AM, Romero-Ramos M (2017) Early synaptic dysfunction induced by a-synuclein in a rat model of Parkinson's disease. Sci Rep 7:6363

Pifl C, Kish SJ, Hornykiewicz O (2012) Thalamic noradrenaline in Parkinson's disease: deficits suggest role in motor and non-motor symptoms. Mov Disord 27:1618–1624

Pink A, Przybelski SA, Krell-Roesch J, Stokin GB, Roberts RO, Mielke MM, Knopman DS, Jack CR, Petersen RC, Geda YE (2017) Cortical thickness and depressive symptoms in cognitively normal individuals: the Mayo Clinic Study of Aging. J Alzheimers Dis 58:1273–1281

Politis M, Niccolini F (2015) Serotonin in Parkinson's disease. Behav Brain Res 277:136–145

Politis M, Wu K, Loane C, Kiferle L, Molloy S, Brooks DJ, Piccini P (2010a) Staging of serotonergic dysfunction in Parkinson's disease: an in vivo 11C-DASB PET study. Neurobiol Dis 40:216–221

Politis M, Wu K, Loane C, Turkheimer FE, Molloy S, Brooks DJ, Piccini P (2010b) Depressive symptoms in PD correlate with higher 5-HTT binding in raphe and limbic structures. Neurology 75:1920–1927

Pont-Sunyer C, Hotter A, Gaig C, Seppi K, Compta Y, Katzenschlager R, Mas N, Hofeneder D, Brücke T, Bayés A, Wenzel K, Infante J, Zach H, Pirker W, Posada IJ, Álvarez R, Ispierto L, De Fàbregues O, Callén A, Palasí A, Aguilar M, Martí MJ, Valldeoriola F, Salamero M, Poewe W, Tolosa E (2015) The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). Mov Disord 30:229–237

Post B, Muslimovic D, van Geloven N, Speelman JD, Schmand B, de Haan RJ (2011) Progression and prognostic factors of motor impairment, disability and quality of life in newly diagnosed Parkinson's disease. Mov Disord 26:449–456

Prange S, Metereau E, Maillet A, Lhommée E, Klinger H, Pelissier P, Ibarrola D, Heckemann RA, Castrioto A, Tremblay L, Sgambato V, Broussolle E, Krack P, Thobois S (2019) Early limbic microstructural alterations in apathy and depression in de novo Parkinson's disease. Mov Disord 34:1644–1654

Prange S, Klinger H, Laurencin C, Danaila T, Thobois S (2022) Depression in patients with Parkinson's disease: current understanding of its neurobiology and implications for treatment. Drugs Aging 39:417–439

Qamhawi Z, Towey D, Shah B, Pagano G, Seibyl J, Marek K, Borghammer P, Brooks DJ, Pavese N (2015) Clinical correlates of raphe serotonergic dysfunction in early Parkinson's disease. Brain 138:2964–2973

Qiu YH, Huang ZH, Gao YY, Feng SJ, Huang B, Wang WY, Xu QH, Zhao JH, Zhang YH, Wang LM, Nie K, Wang LJ (2021) Alterations in intrinsic functional networks in Parkinson's disease patients with depression: a resting-state functional magnetic resonance imaging study. CNS Neurosci Ther 27:289–298

Ravina B, Camicioli R, Como PG, Marsh L, Jankovic J, Weintraub D, Elm J (2007) The impact of depressive symptoms in early Parkinson disease. Neurology 69:342–347

Ray S, Agarwal P (2020) Depression and anxiety in Parkinson disease. Clin Geriatr Med 36:93–104

Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF (2008) A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord 23:183–189 (**quiz 313**)

Rektorova I, Srovnalova H, Kubikova R, Prasek J (2008) Striatal dopamine transporter imaging correlates with depressive symptoms and tower of London task performance in Parkinson's disease. Mov Disord 23:1580–1587

Remy P, Doder M, Lees A, Turjanski N, Brooks D (2005) Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain 128:1314–1322

Ren C, Li LX, Dong AQ, Zhang YT, Hu H, Mao CJ, Wang F, Liu CF (2021) Depression induced by chronic unpredictable mild stress increases susceptibility to Parkinson's disease in mice via neuroinflammation mediated by P2X7 receptor. ACS Chem Neurosci 12:1262–1272

Rieu I, Houeto JL, Pereira B, De Chazeron I, Bichon A, Chéreau I, Ulla M, Brefel-Courbon C, Ory-Magne F, Dujardin K, Tison F, Krack

P, Durif F (2016) Impact of mood and behavioral disorders on quality of life in Parkinson's disease. J Parkinsons Dis 6:267–277
Ring HA, Bench CJ, Trimble MR, Brooks DJ, Frackowiak RS, Dolan RJ (1994) Depression in Parkinson's disease. A positron emission study. Br J Psychiatry 165:333–339
Rojo A, Aguilar M, Garolera MT, Cubo E, Navas I, Quintana S (2003) Depression in Parkinson's disease: clinical correlates and outcome. Parkinsonism Relat Disord 10:23–28
Rotter A, Lenz B, Pitsch R, Richter-Schmidinger T, Kornhuber J, Rhein C (2019) Alpha-synuclein RNA expression is increased in major depression. Int J Mol Sci 20:2029
Saari L, Heiskanen L, Gardberg M, Kaasinen V (2021) Depression and nigral neuron density in Lewy body spectrum diseases. Ann Neurol 89:1046–1050
Schapira AHV, Chaudhuri KR, Jenner P (2017) Non-motor features of Parkinson disease. Nat Rev Neurosci 18:435–450
Schlachetzki JC, Grimm T, Schlachetzki Z, Ben Abdallah NM, Ettle B, Vöhringer P, Ferger B, Winner B, Nuber S, Winkler J (2016) Dopaminergic lesioning impairs adult hippocampal neurogenesis by distinct modification of a-synuclein. J Neurosci Res 94:62–73
Schönenberg A, Zipprich HM, Teschner U, Grosskreutz J, Witte OW, Prell T (2021) Impact of subthreshold depression on health-related quality of life in patients with Parkinson's disease based on cognitive status. Health Qual Life Outcomes 19:107
Schrag A, Jahanshahi M, Quinn N (2000) What contributes to quality of life in patients with Parkinson's disease? J Neurol Neurosurg Psychiatry 69:308–312
Schrag A, Horsfall L, Walters K, Noyce A, Petersen I (2015) Prediagnostic presentations of Parkinson's disease in primary care: a case–control study. Lancet Neurol 14:57–64
Schroeders U, Zimmermann J, Wicke T, Schaumburg M, Lang E, Trenkwalder C, Mollenhauer B (2022) Dynamic interplay of cognitive functioning and depressive symptoms in patients with Parkinson's disease. Neuropsychology 36:266–278
Schuurman AG, van den Akker M, Ensinck KT, Metsemakers JF, Knottnerus JA, Leentjens AF, Buntinx F (2002) Increased risk of Parkinson's disease after depression: a retrospective cohort study. Neurology 58:1501–1504
Setiawan E, Wilson AA, Mizrahi R, Rusjan PM, Miler L, Rajkowska G, Suridjan I, Kennedy JL, Rekkas PV, Houle S, Meyer JH (2015) Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. JAMA Psychiat 72:268–275
Sheline YI, Barch DM, Price JL, Rundle MM, Vaishnavi SN, Snyder AZ, Mintun MA, Wang S, Coalson RS, Raichle ME (2009) The default mode network and self-referential processes in depression. Proc Natl Acad Sci U S A 106:1942–1947
Shen CC, Tsai SJ, Perng CL, Kuo BI, Yang AC (2013) Risk of Parkinson disease after depression: a nationwide population-based study. Neurology 81:1538–1544
Shen Q, Liu Y, Guo J, Zhang H, Xiang Y, Liao H, Cai S, Zhou B, Wang M, Liu S, Yi J, Zhang Z, Tan C (2022) Impaired white matter microstructure associated with severe depressive symptoms in patients with PD. Brain Imaging Behav 16:169–175
Sheng K, Fang W, Su M, Li R, Zou D, Han Y, Wang X, Cheng O (2014) Altered spontaneous brain activity in patients with Parkinson's disease accompanied by depressive symptoms, as revealed by regional homogeneity and functional connectivity in the prefrontal-limbic system. PLoS ONE 9:e84705
Shiba M, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, Schaid DJ, Rocca WA (2000) Anxiety disorders and depressive disorders preceding Parkinson's disease: a case–control study. Mov Disord 15:669–677
Simuni T, Uribe L, Cho HR, Caspell-Garcia C, Coffey CS, Siderowf A, Trojanowski JQ, Shaw LM, Seibyl J, Singleton A, Toga AW, Galasko D, Foroud T, Tosun D, Poston K, Weintraub D, Mollenhauer B, Tanner CM, Kieburtz K, Chahine LM, Reimer A, Hutten SJ, Bressman S, Marek K (2020) Clinical and dopamine transporter imaging characteristics of non-manifest LRRK2 and GBA mutation carriers in the Parkinson's Progression Markers Initiative (PPMI): a cross-sectional study. Lancet Neurol 19:71–80
Sinaeefar MJ, Saadat P, Hamidia A, Hosseini SR (2021) Evaluation of the cognitive impairments and depressive symptoms in patients with Parkinson's disease: a case-control study from Iran. Clin Neurol Neurosurg 203:106549
Skidmore FM, Yang M, Baxter L, von Deneen K, Collingwood J, He G, Tandon R, Korenkevych D, Savenkov A, Heilman KM, Gold M, Liu Y (2013) Apathy, depression, and motor symptoms have distinct and separable resting activity patterns in idiopathic Parkinson disease. Neuroimage 81:484–495
Sklerov M, Browner N, Dayan E, Rubinow D, Frohlich F (2022) Autonomic and depression symptoms in Parkinson's disease: clinical evidence for overlapping physiology. J Parkinsons Dis 12:1059–1067
Socala K, Doboszewska U, Szopa A, Serefko A, Wlodarczyk M, Zielinska A, Poleszak E, Fichna J, Wlaz P (2021) The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. Pharmacol Res 172:105840
Song Y, Gu Z, An J, Chan P (2014) Gender differences on motor and non-motor symptoms of de novo patients with early Parkinson's disease. Neurol Sci 35:1991–1996
Song J, Shen B, Yang YJ, Liu FT, Zhao J, Tang YL, Chen C, Ding ZT, An Y, Wu JJ, Sun YM, Wang J (2020) Non-motor symptoms in Parkinson's disease patients with parkin mutations: more depression and less executive dysfunction. J Mol Neurosci 70:246–253
Srivastava A, Tang MX, Mejia-Santana H, Rosado L, Louis ED, Caccappolo E, Comella C, Colcher A, Siderowf A, Jennings D, Nance M, Bressman S, Scott WK, Tanner C, Mickel S, Andrews H, Waters C, Fahn S, Cote L, Frucht S, Ford B, Alcalay RN, Ross B, Orbe Reilly M, Rezak M, Novak K, Friedman JH, Pfeiffer RD, Marsh L, Hiner B, Merle D, Ottman R, Clark LN, Marder K (2011) The relation between depression and parkin genotype: the CORE-PD study. Parkinsonism Relat Disord 17:740–744
Steinbusch HWM, Dolatkhah MA, Hopkins DA (2021) Anatomical and neurochemical organization of the serotonergic system in the mammalian brain and in particular the involvement of the dorsal raphe nucleus in relation to neurological diseases. Prog Brain Res 261:41–81
Steiner J, Walter M, Gos T, Guillemin GJ, Bernstein HG, Sarnyai Z, Mawrin C, Brisch R, Bielau H, Meyer ZU, Schwabedissen L, Bogerts B, Myint AM (2011) Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? J Neuroinflamm 8:94
Storch A, Ebersbach G, Fuchs G, Jost WH, Odin P, Reifschneider G, Bauer M (2008) Depression in Parkinson's disease. Part 1: epidemiology, signs and symptoms, pathophysiology and diagnosis. Fortschr Neurol Psychiatr 76:715–724
Strecker K, Wegner F, Hesse S, Becker GA, Patt M, Meyer PM, Lobsien D, Schwarz J, Sabri O (2011) Preserved serotonin transporter binding in de novo Parkinson's disease: negative correlation with the dopamine transporter. J Neurol 258:19–26
Su D, Cui Y, Liu Z, Chen H, Fang J, Ma H, Zhou J, Feng T (2022) Altered brain activity in depression of Parkinson's disease: a meta-analysis and validation study. Front Aging Neurosci 14:806054
Surdhar I, Gee M, Bouchard T, Coupland N, Malykhin N, Camicioli R (2012) Intact limbic-prefrontal connections and reduced amygdala volumes in Parkinson's disease with mild depressive symptoms. Parkinsonism Relat Disord 18:809–813

Talman LS, Pfeiffer RF (2022) Movement disorders and the gut: a review. Mov Disord Clin Pract 9:418–428
Tan SK, Hartung H, Sharp T, Temel Y (2011) Serotonin-dependent depression in Parkinson's disease: a role for the subthalamic nucleus? Neuropharmacology 61:387–399
Tan AH, Lim SY, Lang AE (2022) The microbiome-gut-brain axis in Parkinson disease—from basic research to the clinic. Nat Rev Neurol 18:476–495
Tang Y, Xiao X, Xie H, Wan CM, Meng L, Liu ZH, Liao WH, Tang BS, Guo JF (2017) Altered functional brain connectomes between sporadic and familial Parkinson's patients. Front Neuroanat 11:99
Tansey MG, Wallings RL, Houser MC, Herrick MK, Keating CE, Joers V (2022) Inflammation and immune dysfunction in Parkinson disease. Nat Rev Immunol. https://doi.org/10.1038/s41577-022-00684-6
Tartt AN, Mariani MB, Hen R, Mann JJ, Boldrini M (2022) Dysregulation of adult hippocampal neuroplasticity in major depression: pathogenesis and therapeutic implications. Mol Psychiatry 27:2689–2699
Thaler A, Bregman N, Gurevich T, Shiner T, Dror Y, Zmira O, Gan-Or Z, Bar-Shira A, Gana-Weisz M, Orr-Urtreger A, Giladi N, Mirelman A (2018a) Parkinson's disease phenotype is influenced by the severity of the mutations in the GBA gene. Parkinsonism Relat Disord 55:45–49
Thaler A, Kliper E, Maidan I, Herman T, Rosenberg-Katz K, Bregman N, Gurevich T, Shiner T, Hausdorff JM, Orr-Urtreger A, Giladi N, Mirelman A (2018b) Cerebral imaging markers of GBA and lRRK2 related Parkinson's disease and their first-degree unaffected relatives. Brain Topogr 31:1029–1036
Timmer MHM, van Beek M, Bloem BR, Esselink RAJ (2017) What a neurologist should know about depression in Parkinson's disease. Pract Neurol 17:359–368
Tonhajzerova I, Sekaninova N, Bona Olexova L, Visnovcova Z (2020) Novel insight into neuroimmune regulatory mechanisms and biomarkers linking major depression and vascular diseases: the dilemma continues. Int J Mol Sci 21:2317
Torres-Platas SG, Cruceanu C, Chen GG, Turecki G, Mechawar N (2014) Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. Brain Behav Immun 42:50–59
Tran AA, De Smet M, Grant GD, Khoo TK, Pountney DL (2021) Investigating the convergent mechanisms between major depressive disorder and Parkinson's disease. Complex Psychiatry 6:47–61
Tsai P, Gopalakrishna G (2022) Mood disorders in Parkinson's disease. In: Gálvez-Jiménez N, Korczyn A, Lugo-Sanchez R (eds) Non-motor Parkinson's disease. Cambridge University Press, Cambridge, pp 91–98. https://doi.org/10.1017/9781009039291.9781009039010
Uhr L, Tsolaki E, Pouratian N (2022) Diffusion tensor imaging correlates of depressive symptoms in Parkinson disease. J Comp Neurol 530:1729–1738
Ujvári B, Pytel B, Márton Z, Bognár M, Kovács LÁ, Farkas J, Gaszner T, Berta G, Kecskés A, Kormos V, Farkas B, Füredi N, Gaszner B (2022) Neurodegeneration in the centrally-projecting Edinger-Westphal nucleus contributes to the non-motor symptoms of Parkinson's disease in the rat. J Neuroinflamm 19:31
van Mierlo TJ, Chung C, Foncke EM, Berendse HW, van den Heuvel OA (2015) Depressive symptoms in Parkinson's disease are related to decreased hippocampus and amygdala volume. Mov Disord 30:245–252
Varvel NH, Grathwohl SA, Baumann F, Liebig C, Bosch A, Brawek B, Thal DR, Charo IF, Heppner FL, Aguzzi A, Garaschuk O, Ransohoff RM, Jucker M (2012) Microglial repopulation model reveals a robust homeostatic process for replacing CNS myeloid cells. Proc Natl Acad Sci U S A 109:18150–18155
Vermeiren Y, De Deyn PP (2017) Targeting the norepinephrinergic system in Parkinson's disease and related disorders: the locus coeruleus story. Neurochem Int 102:22–32
Vriend C, Raijmakers P, Veltman DJ, van Dijk KD, van der Werf YD, Foncke EM, Smit JH, Berendse HW, van den Heuvel OA (2014) Depressive symptoms in Parkinson's disease are related to reduced [123I]FP-CIT binding in the caudate nucleus. J Neurol Neurosurg Psychiatry 85:159–164
Wang H, Chen H, Wu J, Tao L, Pang Y, Gu M, Lv F, Luo T, Cheng O, Sheng K, Luo J, Hu Y, Fang W (2018) Altered resting-state voxel-level whole-brain functional connectivity in depressed Parkinson's disease. Parkinsonism Relat Disord 50:74–80
Wang J, Lyu H, Chen J, Lin S, Zheng H, Li J, Kong F, Gao J, Yu H, Hu Y, Guo Z (2020) Cortical alterations are associated with depression in subcortical vascular mild cognitive impairment revealed by surface-based morphometry. J Alzheimers Dis 78:673–681
Wang X, Xu J, Wang Q, Ding D, Wu L, Li Y, Wu C, Meng H (2021) Chronic stress induced depressive-like behaviors in a classical murine model of Parkinson's disease. Behav Brain Res 399:112816
Wang H, Xu J, Yu M, Ma X, Li Y, Pan C, Ren J, Liu W (2022) Altered functional connectivity of ventral striatum subregions in de-novo Parkinson's disease with depression. Neuroscience 491:13–22
Warnecke T, Schäfer KH, Claus I, Del Tredici K, Jost WH (2022) Gastrointestinal involvement in Parkinson's disease: pathophysiology, diagnosis, and management. NPJ Parkinsons Dis 8:31
Wei L, Hu X, Yuan Y, Liu W, Chen H (2018) Abnormal ventral tegmental area-anterior cingulate cortex connectivity in Parkinson's disease with depression. Behav Brain Res 347:132–139
Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB (2004) Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. J Am Geriatr Soc 52:784–788
Weintraub D, Newberg AB, Cary MS, Siderowf AD, Moberg PJ, Kleiner-Fisman G, Duda JE, Stern MB, Mozley D, Katz IR (2005) Striatal dopamine transporter imaging correlates with anxiety and depression symptoms in Parkinson's disease. J Nucl Med 46:227–232
Weintraub D, Simuni T, Caspell-Garcia C, Coffey C, Lasch S, Siderowf A, Aarsland D, Barone P, Burn D, Chahine LM, Eberling J, Espay AJ, Foster ED, Leverenz JB, Litvan I, Richard I, Troyer MD, Hawkins KA (2015) Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. Mov Disord 30:919–927
Weintraub D, Aarsland D, Chaudhuri KR, Dobkin RD, Leentjens AF, Rodriguez-Violante M, Schrag A (2022) The neuropsychiatry of Parkinson's disease: advances and challenges. Lancet Neurol 21:89–102
Wertman E, Speedie L, Shemesh Z, Gilon D, Raphael M, Stessman J (1993) Cognitive disturbances in parkinsonian patients with depression. Neuropsychiatry, Neuropsychol Behav Neurol 6:31–37; https://journals.lww.com/cogbehavneurol/Abstract/1993/01000/Cognitive_Disturbances_in_Parkinsonian_Patients.01005.aspx
Wichowicz HM, Slawek J, Derejko M, Cubala WJ (2006) Factors associated with depression in Parkinson's disease: a cross-sectional study in a Polish population. Eur Psychiatry 21:516–520
Wile DJ, Agarwal PA, Schulzer M, Mak E, Dinelle K, Shahinfard E, Vafai N, Hasegawa K, Zhang J, McKenzie J, Neilson N, Strongosky A, Uitti RJ, Guttman M, Zabetian CP, Ding YS, Adam M, Aasly J, Wszolek ZK, Farrer M, Sossi V, Stoessl AJ (2017) Serotonin and dopamine transporter PET changes in the premotor phase of LRRK2 parkinsonism: cross-sectional studies. Lancet Neurol 16:351–359
Wilson RS, Nag S, Boyle PA, Hizel LP, Yu L, Buchman AS, Shah RC, Schneider JA, Arnold SE, Bennett DA (2013) Brainstem

aminergic nuclei and late-life depressive symptoms. JAMA Psychiat 70:1320–1328
Wilson H, Dervenoulas G, Pagano G, Koros C, Yousaf T, Picillo M, Polychronis S, Simitsi A, Giordano B, Chappell Z, Corcoran B, Stamelou M, Gunn RN, Pellecchia MT, Rabiner EA, Barone P, Stefanis L, Politis M (2019) Serotonergic pathology and disease burden in the premotor and motor phase of A53T α-synuclein parkinsonism: a cross-sectional study. Lancet Neurol 18:748–759
Wohleb ES, Powell ND, Godbout JP, Sheridan JF (2013) Stress-induced recruitment of bone marrow-derived monocytes to the brain promotes anxiety-like behavior. J Neurosci 33:13820–13833
Wohleb ES, McKim DB, Sheridan JF, Godbout JP (2015) Monocyte trafficking to the brain with stress and inflammation: a novel axis of immune-to-brain communication that influences mood and behavior. Front Neurosci 8:447
Wohleb ES, Franklin T, Iwata M, Duman RS (2016) Integrating neuroimmune systems in the neurobiology of depression. Nat Rev Neurosci 17:497–511
Won JH, Kim M, Park BY, Youn J, Park H (2019) Effectiveness of imaging genetics analysis to explain degree of depression in Parkinson's disease. PLoS ONE 14:e0211699
Wu Y, Le W, Jankovic J (2011) Preclinical biomarkers of Parkinson disease. Arch Neurol 68:22–30
Wu JY, Zhang Y, Wu WB, Hu G, Xu Y (2018) Impaired long contact white matter fibers integrity is related to depression in Parkinson's disease. CNS Neurosci Ther 24:108–114
Xiao-Ling Q, Yin-Zhen D, Xue-Kui L, Xue L, Gang C, Zai-Li L, Dian-Shuai G (2021) Gender was associated with depression but not with gastrointestinal dysfunction in patients with Parkinson's disease. Parkinsons Dis 2021:3118948
Xie A, Ensink E, Li P, Gordevicius J, Marshall LL, George S, Pospisilik JA, Aho VTE, Houser MC, Pereira PAB, Rudi K, Paulin L, Tansey MG, Auvinen P, Brundin P, Brundin L, Labrie V, Scheperjans F (2022) Bacterial butyrate in Parkinson's disease is linked to epigenetic changes and depressive symptoms. Mov Disord 37:1644–1653
Xu J, Chen Y, Wang H, Li Y, Li L, Ren J, Sun Y, Liu W (2022a) Altered neural network connectivity predicts depression in de novo Parkinson's disease. Front Neurosci 16:828651
Xu J, Yu M, Wang H, Li Y, Li L, Ren J, Pan C, Liu W (2022b) Altered dynamic functional connectivity in de novo Parkinson's disease patients with depression. Front Aging Neurosci 13:789785
Yao C, Niu L, Fu Y, Zhu X, Yang J, Zhao P, Sun X, Ma Y, Li S, Li J (2022) Cognition, motor symptoms, and glycolipid metabolism in Parkinson's disease with depressive symptoms. J Neural Transm (vienna) 129:563–573
Zanigni S, Sambati L, Evangelisti S, Testa C, Calandra-Buonaura G, Manners DN, Terlizzi R, Poda R, Oppi F, Lodi R, Cortelli P, Tonon C (2017) Precuneal thickness and depression in Parkinson disease. Neurodegener Dis 17:97–102
Zhang X, Cao X, Xue C, Zheng J, Zhang S, Huang Q, Liu W (2021) Aberrant functional connectivity and activity in Parkinson's disease and comorbidity with depression based on radiomic analysis. Brain Behav 11:e02103
Zhao X, Kong D, Zhou Q, Wei G, Song J, Liang Y, Du G (2021) Baicalein alleviates depression-like behavior in rotenone- induced Parkinson's disease model in mice through activating the BDNF/TrkB/CREB pathway. Biomed Pharmacother 140:111556
Zheng LJ, Yang GF, Zhang XY, Wang YF, Liu Y, Zheng G, Lu GM, Zhang LJ, Han Y (2017) Altered amygdala and hippocampus effective connectivity in mild cognitive impairment patients with depression: a resting-state functional MR imaging study with granger causality analysis. Oncotarget 8:25021–25031
Zhu K, van Hilten JJ, Marinus J (2016a) Associated and predictive factors of depressive symptoms in patients with Parkinson's disease. J Neurol 263:1215–1225
Zhu Y, Song X, Xu M, Hu X, Li E, Liu J, Yuan Y, Gao JH, Liu W (2016b) Impaired interhemispheric synchrony in Parkinson's disease with depression. Sci Rep 6:27477
Zhu J, Lu L, Pan Y, Shen B, Xu S, Hou Y, Zhang X, Zhang L (2017) Depression and associated factors in nondemented Chinese patients with Parkinson's disease. Clin Neurol Neurosurg 163:142–148