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Review

Molecular Mechanisms and Potential Biomarkers of Neuropsychiatric Disorders in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is the second most common degenerative disease of the central nervous system, characterized by both motor and non-motor disorders. Non-motor disorders include dementia, depression, and anxiety. The prevalence of dementia increases with disease progression, affecting 24–31% of PD patients and up to 75% after 10 years. Furthermore, approximately 50% of PD patients suffer from depression, while anxiety affects around 31% of this population. Molecular factors, including genetic factors, are currently implicated in the manifestation of neuropsychiatric disorders. It is believed that dementia and affective disorders in PD may result from both disturbed homeostasis of proteins such as α-synuclein, amyloid beta, and phosphorylated tau, as well as increased inflammatory processes and impaired neurotransmission. Chronic microglial activation, elevated levels of proinflammatory cytokines, and oxidative stress contribute to the severity of neuroinflammation, which in turn contributes to neuronal dysfunction and synaptic abnormalities. While the effect of pathological proteins in PD primarily involves impairment of dopaminergic neurotransmission, disturbances in the serotonergic, noradrenergic, cholinergic, and glutamatergic systems are also observed. Furthermore, genetic risk factors have been identified in PD patients, including monogenic causes, which are rare in unselected populations. Identifying causative molecular targets in PD is essential for developing therapies for this neurodegenerative disease. In this review, we present current views on the involvement of molecular factors in the development of psychiatric disorders in patients with PD, suggesting that they may have diagnostic and predictive value in the future.

Keywords: molecular factors; dementia; depression; anxiety; Parkinson's disease

1. Introduction

Parkinson's disease (PD) is a complex, progressive neurodegenerative disorder primarily characterized by resting tremor, bradykinesia, rigidity, postural instability [1], and numerous additional motor symptoms (Table 1, Ref. [1–17]). However, beyond these most recognizable motor symptoms, PD, especially in later stages, is frequently associated with a broad spectrum of neuropsychiatric problems, such as depression, anxiety, cognitive impairment, psychosis, mood swings, and apathy [1,18]. These non-motor symptoms (NMS) significantly affect patients' quality of life and may even precede motor manifestations (Table 1). Notably, in some studies, participants reported that non-motor fluctuations caused even greater disability [19]. It may be suggested that neuropsychiatric complications are associated with disease development rather than being mere consequences of disability [20]. Understanding the molecular mechanisms underlying neuropsychiatric symptoms in PD remains an important challenge. Emerging evidence suggests that these manifestations are connected to widespread neurodegenerative changes beyond the dopaminergic system, involving alterations in multiple neurotransmitter systems, neuroinflammatory processes, genetic predispositions, and dysregulated cellular signaling pathways [21,22]. The interaction among these molecular mechanisms may contribute to the heterogeneity of neuropsychiatric phenotypes observed among PD patients.

One of the primary factors associated with neuropsychiatric symptoms in PD is the dysfunction of multiple neurotransmitter systems. It is commonly known that dopaminergic neurodegeneration in the substantia nigra is central to PD pathophysiology [2,22]. In addition, alterations in cholinergic, serotonergic, noradrenergic, γ-aminobutyric acid (GABA), and glutamatergic systems also occur in PD, and thus can play significant roles in the development of psychiatric symptoms (Table 2). For instance, serotonergic deficits in the raphe nuclei are strongly implicated in

Table 1. Summary of motor and non-motor symptoms in Parkinson's disease [1–17].

Motor symptoms	Non-motor symptoms
• Bradykinesia/akinesia • Muscular rigidity • 4–6 Hz resting tremor • Postural instability • Postural deformities (e.g., camptocormia, antecollis, scoliosis) • Gait disturbances • Loss of spontaneous movements (e.g., decreased gesturing, blinking, hypomimia) • Impaired fine motor skills (e.g., micrographia) • Oral motor impairments (disturbed speech, swallowing and saliva control) • Dystonia	• Psychiatric symptoms (depression, anxiety, apathy, cognitive slowing, cognitive deficits, dementia, psychosis, hallucinations) • Sleep disorders • Sensory symptoms and pain (tingling, burning sensations, neuralgic pain) • Olfactory dysfunction • Autonomic dysfunction (excessive sweating, orthostatic hypotension, sexual dysfunction, constipation, urinary incontinence, esophageal dysmotility) • Executive dysfunction, deficits in speech, visuospatial abilities, and memory

Table 2. Neurotransmitter systems dysregulation and neuropsychiatric disorders in Parkinson's disease.

Neurotransmitter system	Dysregulation in Parkinson's disease	Mechanism
Dopamine	↓ downregulated	Degeneration of substantia nigra neurons
Acetylcholine	↓ downregulated	Degeneration of basal forebrain cholinergic neurons
Serotonin	↓ downregulated	Loss of SERT binding in the dorsal raphe nuclei
Noradrenaline	↓ downregulated	Degeneration in locus coeruleus neurons
GABA	↑ upregulated	Increased inhibitory output from globus pallidus internus/striatum
Glutamate	↑ upregulated	Hyperactivity in the subthalamic nucleus and cortex

GABA, γ-aminobutyric acid; SERT, serotonin transporter.

depression and anxiety, whereas cholinergic dysfunction within the basal forebrain has been linked to cognitive impairment in PD. Additionally, disturbances in glutamatergic homeostasis have been associated with impulsive behaviors and psychosis [21,23,24].

Neuroinflammation has also been recognized as an important factor contributing to neuropsychiatric disturbances in PD. Chronic activation of microglia, increased levels of pro-inflammatory cytokines, and oxidative stress influence neuronal dysfunction and synaptic abnormalities, thereby exacerbating both motor symptoms and NMS [25,26]. Elevated inflammatory markers in the cerebrospinal fluid and postmortem brain tissue of PD patients have been correlated with severity of depression and cognitive decline, emphasizing the role of immune dysregulation in the disease's neuropsychiatric manifestations [21,27,28].

Furthermore, genetic predisposition plays a role in the onset of neuropsychiatric symptoms in PD. Nucleotide variants present in genes such as the α-synuclein (*SNCA*) gene, leucine-rich repeat kinase 2 (*LRRK2*), and the glucocerebrosidase beta 1 (*GBA1*) (which are traditionally associated with PD pathogenesis) have been correlated with an increased risk of cognitive impairment, depression, and hallucinations [29]. Additionally, nucleotide variations in genes related to serotonergic and dopaminergic signaling, such as solute carrier family 6 member 4 (*SLC6A4*) and dopamine receptor D2 (*DRD2*), have been associated with mood disorders and psychosis in PD patients [30,31]. Moreover, mitochondrial dysfunction and impaired protein homeostasis have also emerged as significant factors in the development of neuropsychiatric symptoms in PD. Mutations in genes related to mitochondrial maintenance, such as phosphatase and tensin homolog (PTEN)-induced kinase 1 (*PINK1*) and parkin RING-between-RING (RBR E3) ubiquitin protein ligase (*PRKN*), have been implicated in both motor symptoms and NMS [30,32]. Disruptions in autophagy and proteasomal degradation pathways further contribute to the accumulation of misfolded proteins, leading to neuronal stress and synaptic dysfunction, which may contribute to cognitive and affective disturbances in PD [33].

Given the multifactorial and complex nature of neuropsychiatric disorders in PD, a comprehensive understanding of their molecular basis is essential for developing targeted therapeutic strategies. Current pharmacological treatments, including selective serotonin reuptake inhibitors (SSRIs), dopamine agonists, and acetylcholinesterase inhibitors, offer symptomatic relief but often fail to address the pathophysiological causes [34]. Therefore, novel interventions aimed at modulating neuroinflammation, restoring neurotransmitter balance, and preserving mitochondrial function hold promise for improving neuropsychiatric outcomes in PD.

This review provides an in-depth analysis of the molecular mechanisms underlying neuropsychiatric symptoms in PD, highlighting recent advances in our understanding of neurotransmitter dysregulation, neuroinflammation,

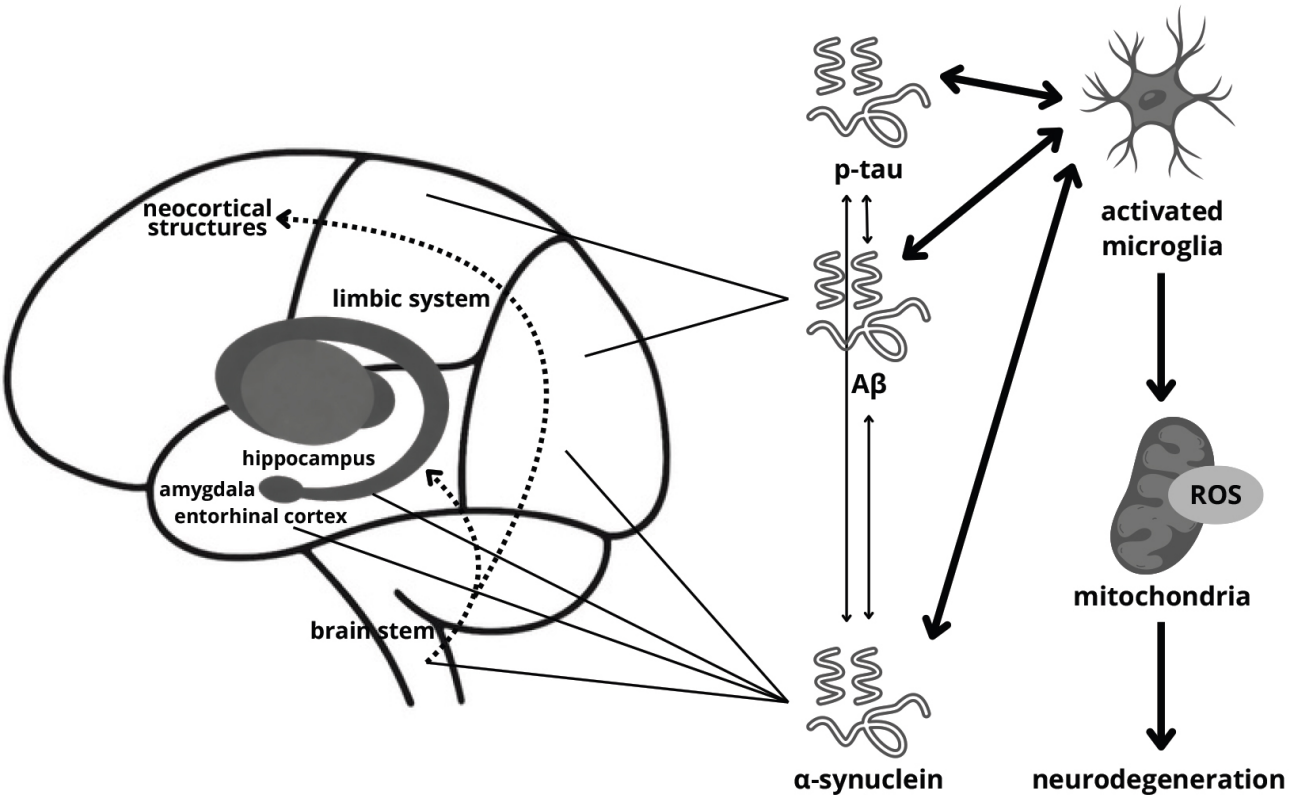

Fig. 1. Probable mechanism of dementia development in Parkinson's disease. ROS, reactive oxygen species; p-tau, phosphorylated tau; Aβ, amyloid beta.

genetic susceptibility, and cellular dysfunction. By elucidating these complex interactions, this review may help pave the way for innovative therapeutic approaches that can improve the quality of life for individuals with PD.

2. Molecular Determinants of Neuropsychiatric Symptoms in Parkinson's Disease

2.1 Dementia

Parkinson's disease dementia (PDD) may develop via various pathophysiological pathways. Proposed mechanisms include protein misfolding, synaptic dysfunction and loss, neurotransmitter activity, microglial and astroglial alterations, adenosine receptor activation, cerebral network disruption, neuroinflammation, aberrant mitochondrial function, and retrograde signaling (Fig. 1) [35,36].

2.1.1 Protein Pathology

The major pathological protein of PD is α-synuclein [37,38]. Evidence indicates that this protein also contributes to PDD development and plays a crucial role in this process [39]. α-synuclein aggregation and Lewy body formation cause neurotoxic effects via mitochondrial dysfunction, synaptic disintegration, prion-like propagation, neuroinflammation, membrane perturbation, or astrocyte and microglial activation [40–42]. Evidence indicates that elevated plasma and cerebrospinal fluid (CSF) levels of α-synuclein correlate with cognitive decline in PD [43,44]. A postmortem investigation revealed that the severity of α-synuclein pathology is significantly elevated in the hippocampus, occipitotemporal, and entorhinal cortex of the PDD brain. Moreover, α-synuclein is a promoting factor of amygdala neuroinflammatory response in PDD [45]. Concomitantly, spreading α-synuclein pathology from the brainstem to neocortical and limbic structures is considered an important sign of emerging PDD. Studies utilizing mouse models of PD confirm the latter finding, showing that α-synuclein fibrils spread to the limbic, cortical, or subcortical regions along with symptoms such as behavioral alterations or memory impairment, depending on α-synuclein injection location [46–49].

Interestingly, studies show that many patients affected by PDD present Alzheimer's disease (AD) pathology—accumulation of amyloid beta (Aβ), tau protein, and neurofibrillary tangles [46]. Nevertheless, the precise influence of Aβ deposition on PDD progression is unclear. Some researchers confirmed an association between Aβ deposition and PD cognitive decline, whereas others did not observe this finding [45,50–52]. Discrepancies between neuropathological and positron emission tomography (PET) analyses may be explained by different Aβ structures. Evidence indicates that Aβ deposits form a diffuse pattern

rather than fibrillar, hindering the binding capabilities of thioflavin ligands in PET imaging. Moreover, some studies have pointed out that the regional presence of Aβ is more important for predicting cognitive decline in PD than whole-brain Aβ analysis [53,54]. Edison *et al.* [55] suggested that persistent microglial activation combined with minor amyloid deposition is linked to decreased glucose metabolism and neuronal loss in PDD. A recent study highlights that severe Aβ accumulation in PD patients promotes disease progression. Furthermore, the cross-seeding of α-synuclein and Aβ may induce each other's aggregation, aggravating the course of the disease [56]. Additionally, another study has shown that PD patients without PDD exhibit a very low prevalence of Aβ in PET imaging [57]. On the other hand, Winer *et al.* [58] concluded that the accumulation of Aβ and tau in PD does not explain the cognitive status of PD patients. Nevertheless, elevated tau deposition is observed in association with increased accumulation of brain Aβ. Conversely, Kotzbauer *et al.* [59] noticed that widespread neocortical tau accumulation was not commonly related to Aβ deposition, suggesting that amyloid pathological processes differ in PDD and AD.

2.1.2 Neuroinflammation

Although pathological proteins are implicated in PDD pathogenesis, growing evidence suggests that additional factors are involved in the development of cognitive decline in PD [60]. A recent study shows that the PDD pathomechanism may include oxidative stress, Toll-like Receptor (TLR) 4/9 activation, impaired DNA binding, and cytosolic DNA sensing. Additionally, aberrant regulation of interferon (IFN) signaling triggers damage to mitochondrial DNA (mtDNA), which spreads in an infectious-like pattern involving extracellular vesicles and Ribosomal Protein S3 (rpS3). Evidence indicates that interferon-beta (IFN-β) loss leads to accumulation of phosphorylated tau (p-tau) tangles, Aβ plaques, and Lewy body-like Aβ+/p-tau+ inclusion bodies, combined with significantly elevated neuronal and glial tumor necrosis factor-α (TNF-α) and neuronal TNF receptor 1 (TNFR1), triggering neuroinflammation and PDD-like manifestations [61]. Ghadery *et al.* [62] observed an interaction between microglial activation and Aβ deposition in cognitive decline among PD patients. Nevertheless, it remains unclear whether amyloid induces neuroinflammation and microglial activation or whether the latter phenomenon serves as a protective measure. Studies showed that increased microglial activation is associated with decreased glucose metabolism, inducing neuronal dysfunction; however, this finding may be observed in PD as well [55,63]. A postmortem investigation showed that activation of microglia and T lymphocyte infiltration is associated with neuroinflammation in the amygdala and substantia nigra in PDD. Moreover, the upregulation of cytokine interleukin-1β (IL-1β) and *TLR* gene expression level in the extra-nigrostriatal regions and substantia nigra contributes to the pro-inflammatory status [45]. Furthermore, elevated pro-inflammatory glia maturation factor associated with glial fibrillary acidic protein (GFAP) reactive astrocytes seems to be another component of neuroinflammation and astrocyte imbalance implicated in PDD pathogenesis [64]. Indeed, significant regional neuroinflammation in the early stage of PD predisposes to PDD development [65]. In contrast, Chai *et al.* [66] analyzed postmortem tissues of PDD patients by measuring a panel of cytokines (IL-13, IL-12p70, IL-10, IL-8, IL-1Ra, IL-1α, fibroblast growth factor 2 (FGF-2), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon-gamma (IFN-γ)) and concluded that there were no significant alterations regarding these molecules, suggesting that neuroinflammation may not be a pivotal component of the pathomechanism of late-stage PDD. On the other hand, mitochondrial dysfunction is another potential feature involved in the pathogenesis of this disorder [67]. Decreased activity of mitochondrial complexes (I, II, III, IV), combined with downregulation of mtDNA, is implicated in PDD etiology [68,69]. Moreover, impaired neuronal IFNβ-IFN-α/β receptor (IFNAR) signaling and elevated protein inhibitor of activated signal transducer and activator of transcription (STAT) 2 (PIAS2) contribute to mitochondrial dyshomeostasis in PDD [70]. Additionally, mitochondrial dysfunction in PD appears to be associated with α-synuclein toxicity, reduced adenosine triphosphate (ATP) production, oxidative stress, synapse dysregulation, and reduction in mitochondrial membrane potential [35,67,71,72].

2.1.3 Neurotransmitter Activity, Synaptic Function

Cognition in PD may also be influenced by neurotransmitter functioning [73,74]. *In vivo* observations indicate that PDD patients exhibit cholinergic and dopaminergic deficit profiles in the brain [75,76]. Similarly, postmortem examinations show decreased choline acetyltransferase (ChAT) activity in PDD [77,78]. Moreover, there is a significant elevation in muscarinic acetylcholine receptors in specific brain regions in PDD [79]. Evidence indicates that serotonin and noradrenaline pathways may also be disturbed, contributing to alterations in neural networks (Table 2) [74,80–82].

Aberrant functioning of synapses and impaired synaptic plasticity are other factors implicated in PDD etiology [83,84]. Synaptic plasticity contributes to neuronal connections, altering the structure of dendritic spines and synapses, axonal modification, and synaptogenesis [85]. Neurotrophins are important molecular mediators of synaptic plasticity and include multiple molecules: immunological factors and biogenic amines described above, as well as growth factors [83,86]. Deregulation of growth factors: epidermal growth factor (EGF), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial-cell-derived neurotrophic factor (GDNF) seems to be a part of PDD pathology related to synaptic dysfunction

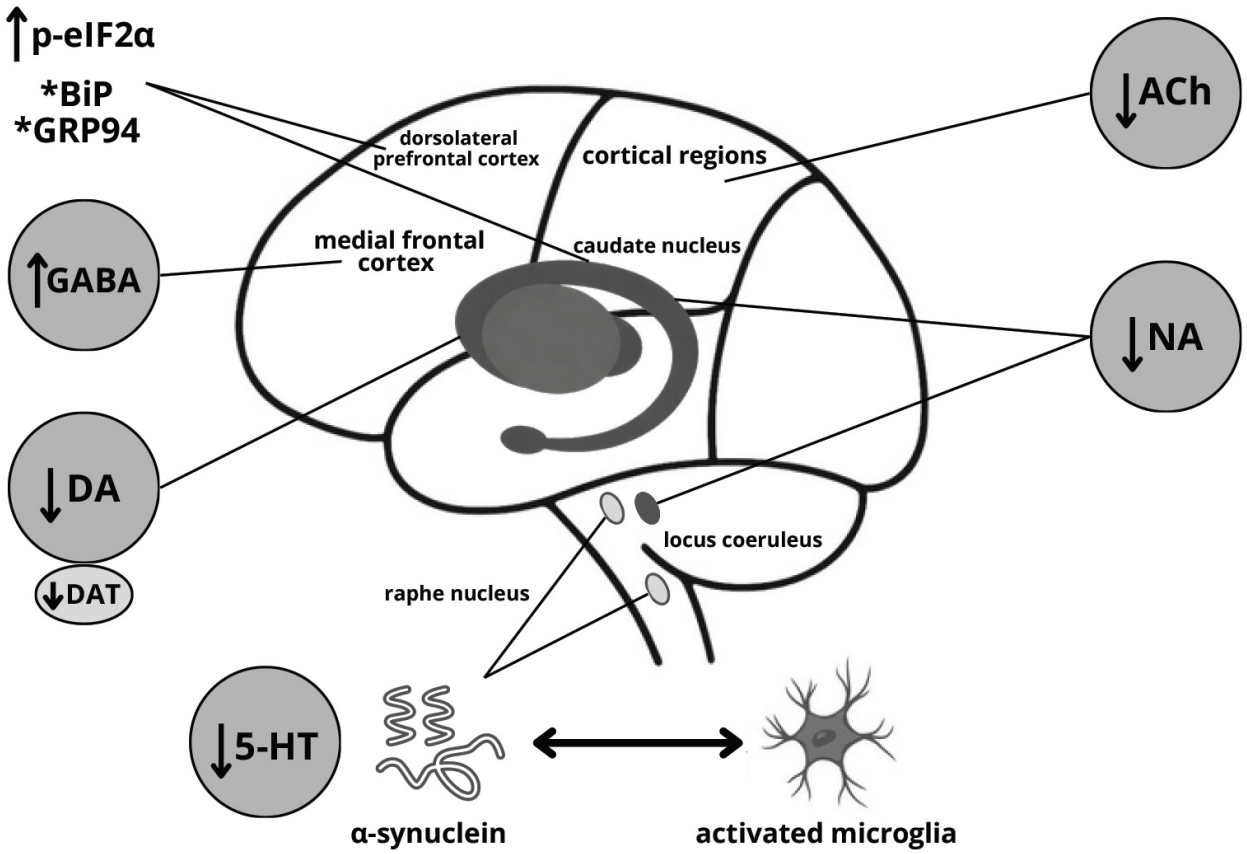

Fig. 2. Probable mechanism of depression development in Parkinson's disease. *levels altered in a region-dependent manner. DA, dopamine; DAT, dopamine transporter; Ach, acetylcholine; NA, noradrenaline; 5-HT, serotonin; p-eIF2α, phosphorylated eukaryotic initiation factor 2 alpha; BiP, 78-kDa glucose-regulated protein; GRP94, 94-kDa glucose-regulated protein.

[83,87–90]. Evidence suggests that synaptic markers such as presynaptic vesicle protein Ras-related protein (Rab3A) and synaptosomal-associated protein, 25 kDa (SNAP25), neurogranin, zinc transporter 3 (ZnT3), postsynaptic density protein 95 (PSD95), synaptopodin, and Dynamin-1 participate in vesicle recycling, vesicle docking, postsynaptic signaling, synaptic release and regulation of divalent zinc cation (Zn^{2+}), regulation of postsynaptic neurotransmitter receptors, cellular scaffolding, neurotransmitter reuptake, or receptor internalization, and play a role in PDD pathogenesis [91–94].

2.2 Affective Disorders

Similarly to PDD, the pathogenesis of affective disorders in PD remains poorly understood [95–97]. Emerging evidence indicates that common pathological mechanisms, including α-synuclein aggregation, neurotransmitter dysregulation, neuroinflammation, and neurotrophic alterations, contribute to both depression and anxiety in PD. These shared as well as disorder-specific pathways are illustrated in Fig. 2 (depression) and Fig. 3 (anxiety), whereas in the following sections, we focus on disorder-specific molecular signatures and their clinical manifestations [98, 99].

2.2.1 Depression

2.2.1.1 Protein Pathology. In addition to its well-established role in motor dysfunction, α-synuclein pathology may also contribute to depressive symptoms in PD, where it is particularly associated with caudate nucleus and prefrontal dysfunction, leading to cognitive bias, impaired reward processing, and low mood (Fig. 2) [100]. Moreover, experimental studies have demonstrated that adeno-associated virus serotype 5 (AAV5)-mediated overexpression of wild-type human α-synuclein in raphe serotonergic neurons leads to progressive accumulation, phosphorylation, and aggregation within the serotonin (5-HT) system. This synucleinopathy results in axonal impairment, reduced BDNF expression, and disrupted serotonergic neurotransmission, ultimately producing a depressive-like phenotype in mice [101]. It is worth noting that α-synuclein aggregation may exacerbate depressive symptoms in PD, while depressive states may further promote α-synuclein aggregation via chronic stress–induced hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, oxidative stress, neuroinflammation, and reduced BDNF signaling, thereby creating a bidirectional pathogenic loop [102].

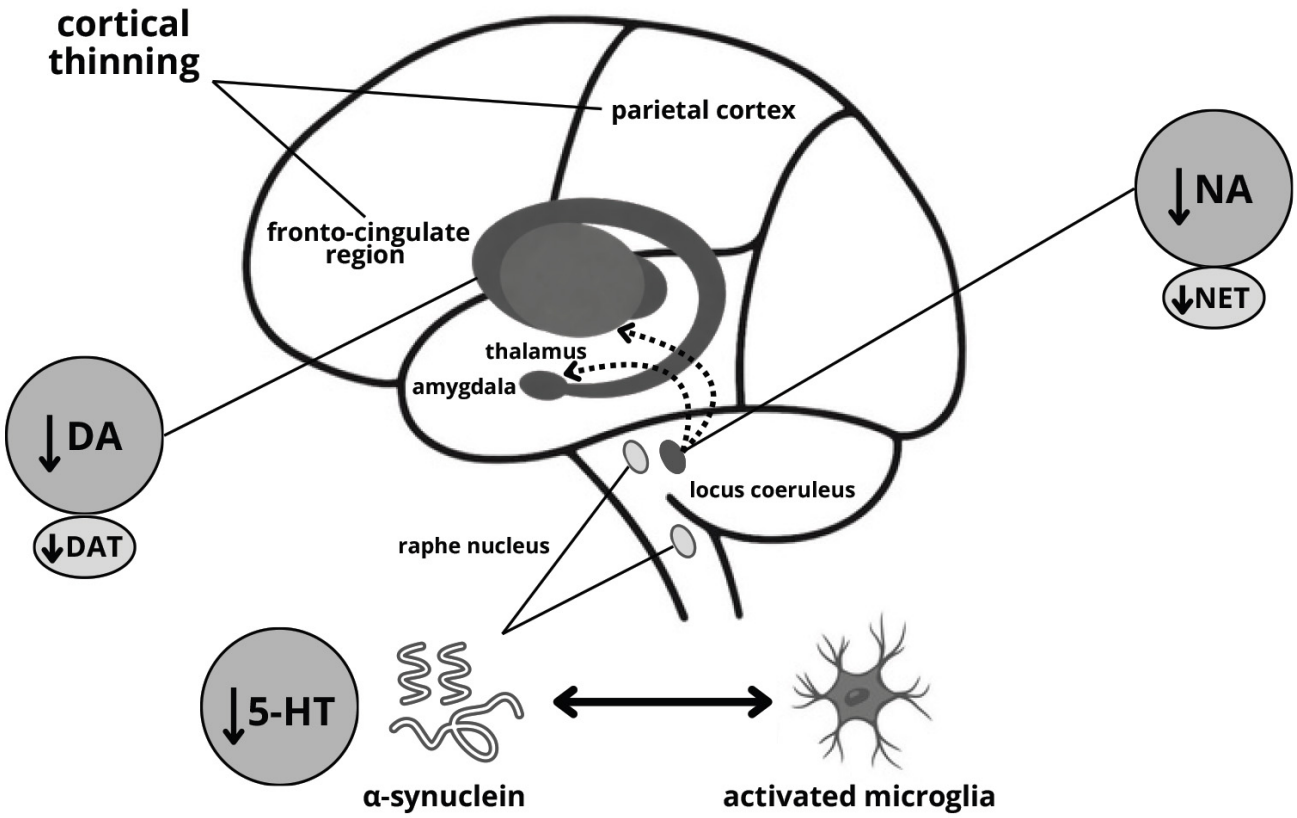

Fig. 3. Probable mechanism of anxiety development in Parkinson's disease. NET, norepinephrine (noradrenaline) transporter.

2.2.1.2 Neuroinflammation. Emerging evidence suggests that neuroinflammation contributes to the development of depressive symptoms in PD and is particularly associated with altered function and connectivity of the posterior cingulate cortex and insula, as well as the amygdala, hippocampus, precuneus, and frontal cortex [103,104]. Recent research shows that PD depression is associated with neuroglial activation-induced dopaminergic neuron apoptosis marked by increased levels of soluble triggering receptor expressed on myeloid cells 2 (sTREM2) and chitinase-3-like protein 1 (YKL-40) in the cerebrospinal fluid [105]. While these findings suggest potential diagnostic and prognostic value, it is important to note that analytical factors such as assay platform, pre-analytical handling of CSF, and inter-laboratory standardization were not fully assessed, and further validation is needed to confirm clinical utility. Moreover, therapeutic approaches in PD models indicate that reducing ionized calcium-binding adapter molecule 1 (IBA-1) and GFAP positive cells, as well as phospho-nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), IL-1α, IL-1β, IL-6, TNF-α, IFN-γ, and inducible nitric oxide synthase (iNOS) levels alleviates depressive symptoms, suggesting the implication of inflammation in PD depression etiology [106–108]. Evidence shows that the reduction of Jagged1, Notch1, Hes1, and Hes5 protein levels, which might influence inflammatory processes, also contributes to a better outcome, implicating that the Notch1 signaling pathway might be involved in PD depression pathomechanism [107–109]. Additionally, another study demonstrated that in PD depression mouse model, neuroinflammatory markers, such as nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain containing 3 (NLRP3), caspase-1, and IL-1β were elevated, expression of purinergic ligand-gated ion channel 7 receptor (P2X7R) of microglia increased, and microglia activated [110]. On the other hand, in PD patients with depression, TNF-α was significantly correlated with depressive symptoms [111]. Bonato *et al*. [112] concluded that alleviation of microglial activation and application of anti-inflammatory effects reduce depressive symptoms in PD depression rat models. Importantly, the neuroinflammatory etiology of depression is similar to PD etiology; concurrent and prodromal depression in PD may play a role in PD development [113].

2.2.1.3 Neurotransmitter Activity, Synaptic Function. Alterations in dopaminergic, serotonergic, cholinergic, and noradrenergic systems are important parts of PD depression etiology. Reports show that PD depression is linked with a specific loss of noradrenaline and dopamine innervation in the limbic system [114]. Moreover, rat models show that presynaptic dopamine receptors participate in PD depression regulation [115]. Dopamine transporter density and availability in PD depression differ in various brain regions

and the results remain inconclusive; however, a decreasing tendency is predominant [116–121]. Concomitantly, Maillet *et al*. [122] showed that serotonergic disruption plays a prominent role in *de novo* PD depression. Moreover, reports indicate that serotonergic dysfunction occurs early in PD development; however, its correlation with NMS is not confirmed [123,124]. Indeed, reports regarding the activity of serotonin receptors are inconclusive; some suggest standard activity in early PD without depression, whereas others dysregulated [125,126]. Politis *et al*. [127] conclude that higher serotonin transporter binding in raphe and limbic structures correlates with depression in PD; however, serotonin receptor density differs between specific brain regions, as another study shows [128]. This complex interplay of serotonergic and dopaminergic systems is further influenced by cholinergic and noradrenergic systems [113,120]. Degeneration of the cholinergic system is associated with PD pathology [129,130]. Evidence shows that cholinergic cortical denervation is also linked with PD depression and tends to be more evident in this disorder [131]. When it comes to the noradrenergic pathway in PD depression, studies show decreased noradrenaline levels, neuronal loss in locus coeruleus, which is a primary source of this neurotransmitter, and loss of noradrenaline innervation in the limbic system [98,114,120,132]. Interestingly, there is also GABAergic dysfunction observed in PD depression, predominantly affecting the medial frontal cortex via elevated GABA+ levels [133]. Furthermore, similarly to PDD, neurotrophic alterations are implicated in the pathophysiology of depression in PD, leading to impaired synaptic plasticity. Emerging evidence demonstrates that BDNF levels decrease in PD depression patients [134–136]. Moreover, a therapeutic activation of the BDNF-involved pathway in a PD depression model alleviated depressive symptoms [137]. However, a meta-analysis shows that PD patients have reduced BDNF levels irrespective of depression status [138], highlighting the need for further research to determine whether BDNF alterations are specifically linked to depressive symptoms or reflect general neurodegenerative processes in PD.

2.2.2 Anxiety

2.2.2.1 Protein Pathology. Accumulation of pathological proteins, particularly α-synuclein, plays a crucial role in the development of anxiety in PD. Within raphe 5-HT neurons, α-synuclein aggregates disrupt axonal projections, promote neuroinflammation and reduce BDNF expression, which is associated with mood disturbances [139]. Clinical observations further support this link: PD patients with anxiety exhibit significantly higher serum levels of hydroxyl radicals (·OH) and TNF-α as well as lower nitric oxide (NO) levels compared with PD patients without anxiety. Moreover, anxiety severity, measured by Hamilton Anxiety Rating Scale, 14-item version (HAMA-14), correlates positively with ·OH and TNF-α in PD patients. Meanwhile, ·OH negatively correlates with Aβ1-42 and TNF-α positively correlates with p-tau [140].

2.2.2.2 Neuroinflammation. Similar inflammatory mediators are implicated in both anxiety and depression; however, in anxiety they tend to promote hyperreactivity of fear-related neural circuits—particularly those involving the locus coeruleus and amygdala—rather than contributing primarily to low mood [140,141]. In animal models, interventions that reduce microglial activation—such as botulinum neurotoxin A or baicalein, which also reduces α-synuclein accumulation—ameliorate anxiety-like behaviors by attenuating pro-inflammatory responses [142].

2.2.2.3 Neurotransmitter Activity, Synaptic Function. Anxiety in PD involves dysfunctions of serotonergic, dopaminergic, and noradrenergic neurotransmission and its neurobiological basis appears to be closely related to fear and stress circuitry. Retrospective studies link anxiety with disease progression and withdrawal of dopaminergic medication, while postmortem analyses show degeneration of the amygdala, a key structure for fear responses that receives mesolimbic dopaminergic input. However, dopaminergic medication does not consistently alleviate anxiety as it does motor symptoms, and anxiety can precede motor deficits by decades, appearing even in medication-naïve patients at diagnosis. These observations suggest that anxiety in PD arises from early alterations in brainstem structures involved in stress responses, including the serotonergic raphe nuclei and noradrenergic locus coeruleus, as well as from alterations in large-scale network connectivity that may involve cognitive circuits before clinical symptom onset. Genetic factors, family history of anxiety, and sex-specific influences further modulate susceptibility. Collectively, this evidence indicates that anxiety in PD reflects complex interactions between multiple neurotransmitter systems and network-level synaptic dysfunction, rather than a single pathway [143]. Neurochemical imaging studies provide further evidence for specific circuit-level alterations. PET using [11C]RTI-32, a marker of dopamine and noradrenaline transporter binding, revealed that anxiety severity in PD patients inversely correlates with transporter availability in the amygdala, locus coeruleus, and thalamus. These findings suggest that loss of dopaminergic and noradrenergic innervation in limbic and brainstem structures contributes directly to anxiety symptoms. Together with serotonergic deficits in the raphe nuclei, these alterations highlight a network-level dysfunction across multiple neurotransmitter systems, including dopamine, noradrenaline, and serotonin, which underlie the synaptic and circuit disruptions responsible for heightened anxiety in PD [100,140,144].

3. Genetic Basis of Neuropsychiatric Disorders in Parkinson's Disease

Symptoms such as depression, anxiety, apathy, psychosis, and cognitive impairment can manifest at any stage of PD and often contribute to greater disability than motor dysfunction [145,146]. While these symptoms arise from complex interactions between neurodegeneration, neurotransmitter imbalances, and environmental factors [147], there is growing evidence that genetic predisposition plays a critical role in their development. Numerous genetic variations influence susceptibility to neuropsychiatric manifestations in PD, either through direct effects on brain function or by modifying the underlying disease pathology [148,149]. It is important to note that rare, highly penetrant mutations, such as those in *SNCA* and *PRKN*, are typically associated with familial or early-onset forms of PD and thus explain neuropsychiatric manifestations only in a small subset of patients. In contrast, sporadic PD, which represents the majority of cases, is influenced by a polygenic risk profile and common genetic variants that modestly affect susceptibility to neuropsychiatric symptoms.

The *SNCA* gene, which encodes α-synuclein, is one of the most significant genetic contributors to PD pathogenesis and is also implicated in neuropsychiatric symptoms [150]. Mutations, duplications, or triplications of *SNCA* lead to abnormal aggregation of α-synuclein, contributing to neuronal dysfunction and cognitive decline [151]. α-Synuclein pathology is particularly associated with executive dysfunction, working memory deficits, and psychotic symptoms, including hallucinations and delusions [152]. One of the most frequently studied point mutations is A53T, in which alanine is replaced by threonine at position 53. This change leads to accelerated aggregation of α-synuclein and a significant increase in neurodegenerative processes [153]. Patients with this mutation often exhibit early dementia and psychotic symptoms, including hallucinations and delusions [154]. The E46K mutation has a similar impact on cognitive functioning, involving the replacement of glutamic acid with lysine at position 46, which causes abnormal interaction of α-synuclein with cell membranes. People with this mutation suffer from severe dementia and recurrent episodes of psychosis, especially visual hallucinations [155]. In addition to point mutations, an important factor influencing the neuropsychiatric symptoms of PD are duplications and triplications of the *SNCA* gene, which lead to the overproduction of α-synuclein and accelerated neurodegeneration. In particular, triplication of this gene is associated with early onset of the disease, rapid progression of dementia, and severe psychiatric symptoms, including depression, anxiety, psychosis, and severe behavioral disorders [156].

Another gene involved in the pathogenesis of PD is the *PRKN* gene. The *PRKN* gene, encoding the Parkin protein, is one of the key genes associated with the autosomal recessive form of early-onset PD (ARJP). Mutations in this gene, including deletions, duplications, and point mutations, lead to dysfunction of the ubiquitin-proteasome system, which results in the accumulation of damaged proteins and intensification of neurodegenerative processes [157]. In addition to motor symptoms, patients with *PRKN* mutations can exhibit neuropsychiatric changes, including depression, apathy, and various degrees of cognitive impairment [158]. One of the mechanisms underlying these symptoms is the role of Parkin in mitochondrial regulation and protection of neurons against oxidative stress [159]. Oxidative stress can lead to damage to brain structures responsible for the control of emotions and executive functions [160].

Beyond individual gene mutations, genome-wide association studies (GWAS) have identified several loci associated with psychiatric symptoms in PD. Many of these genetic risk factors overlap with those implicated in major depressive disorder, schizophrenia, and bipolar disorder, supporting the idea that neuropsychiatric manifestations in PD can share common biological mechanisms with primary psychiatric disorders [161]. For example, polymorphisms in genes regulating serotonin receptors, such as 5-hydroxytryptamine receptor 2A (*HTR2A*), have been linked to increased risk of depression and psychosis in PD [162]. The *HTR2A* gene encodes the serotonin 2A receptor (5-HT2A), which plays a key role in the regulation of serotonergic neurotransmission and is an important factor modulating cognitive functions, mood, and perception [163]. A study has shown that polymorphisms in *HTR2A* may influence the susceptibility to the development of neuropsychiatric disorders in the course of PD [164]. One of the best-studied variants is the rs6311 (–1438G/A) polymorphism in the promoter region of the gene, which may affect the expression level of the 5-HT2A receptor. Carriers of the A allele of this polymorphism are more likely to experience visual hallucinations and other psychotic symptoms in PD, suggesting that increased 5-HT2A receptor expression may lead to hypersensitivity to serotonergic signals and impaired perceptual processing [165,166].

Another gene of interest is the *BDNF* gene, which encodes brain-derived neurotrophic factor, a key regulator of neuronal survival, synaptic plasticity, and emotional stability [167]. Variants in the *BDNF* gene have been associated with depression in PD [134]. Since *BDNF* plays a critical role in maintaining dopaminergic and serotonergic neurotransmission, genetic alterations affecting its expression or function may lead to increased susceptibility to mood disorders and cognitive dysfunction [168,169]. One of the most important polymorphisms in the *BDNF* gene is rs6265 (Val66Met), in which valine (Val) is replaced by methionine (Met) at position 66 of the protein. This change affects BDNF secretion and its transport in the neuron, leading to reduced neurotrophic activity [170]. The Val66Met polymorphism has been associated with a greater risk of depression and severe cognitive deficits in patients with PD [171]. Research indicates that carriers of the Met allele have

a greater tendency to develop mood and anxiety disorders, as well as a worse adaptive capacity of the brain in response to neurodegenerative processes [172].

Apart from the described genes, there are many others, such as leucine-rich repeat kinase 2 (*LRRK2*), vacuolar protein sorting 35 (*VPS35*), ATPase cation transporting 13A2 (*ATP13A2*), microtubule-associated protein tau (*MAPT*), and tyrosine hydroxylase (*TH*), which also play an important role in the pathogenesis of PD, influencing both neurodegenerative processes and the development of neuropsychiatric symptoms. In sporadic PD, these effects are typically mediated by common variants and polygenic risk factors, rather than rare, high-penetrance mutations like those in *SNCA* and *PRKN* genes associated with familial PD. Understanding the genetic basis of neuropsychiatric disorders in PD has significant implications for personalized medicine. Identifying genetic risk factors may allow for early detection of individuals at higher risk of developing psychiatric symptoms.

4. Molecular Diagnostic and Therapeutic Factors for Dementia and Affective Disorders in Parkinson's Disease

A comprehensive understanding of the molecular mechanisms underlying dementia and affective disorders in Parkinson's disease is essential for improving early diagnostic strategies and developing targeted therapeutic interventions.

4.1 Dementia

Alterations in glucose metabolism, which can be assessed using ^{18}F-fluorodeoxyglucose PET (FDG-PET), are indicative of cognitive decline and are widely used to detect functional brain changes in AD [173]. In PD, FDG-PET similarly reveals frontal hypometabolism even in cognitively normal patients, suggesting early functional alterations preceding overt cognitive impairment. In one study, 3 of 29 cognitively normal PD patients and 3 of 17 PD patients with mild cognitive impairment (MCI), who exhibited hypometabolism in the parietal and occipital lobe areas, developed dementia within 3 years of the study. Thus, changes in brain metabolism may be a potential predictor of the onset of dementia in PD patients [174]. Magnetic resonance imaging (MRI) studies indicate structural differences in the brains of patients with PDD and Lewy body dementia (DLB). PDD is characterized by bilateral atrophy of frontal areas, while in DLB, the atrophy involves parietal and occipital areas. In addition, resting state functional MRI (rs-fMRI) indicates in PDD an impaired synchronization of neuronal activity in the frontal lobes, while in DLB it shows impaired neuronal connectivity in the posterior parts of the brain. These findings point to different mechanisms underlying PDD and DLB and may help differentiate between these types of dementia [175]. Other rs-fMRI studies have shown that 22 of 32 patients with PDD have reduced functional connectivity of the mediodorsal thalamus with the posterior cingulate cortex (PCC) compared to cognitively unimpaired PD subjects. This is particularly relevant to cognitive impairment, as the PCC plays a key role in attention, memory and information processing [176]. Inflammatory processes are also involved in the pathogenesis of PDD. They are associated with the activation of microglia and astrocytes, leading to the release of proinflammatory cytokines and chemokines. One of the factors that stimulates their expression is glia maturation factor (GMF). Studies indicate there is increased GMF expression in the substantia nigra as well as increased activation of microglia and astrocytes in PDD patients ($p < 0.05$). This is correlated with the presence of Aβ plaques and neurofibrillary tangles, which underlie the pathogenesis of dementia. GMF is thus an important regulator of the inflammatory response, and its overexpression may drive inflammatory processes, leading to neurodegeneration and ultimately PDD [64]. Reducing GMF expression may therefore represent a potential therapeutic target to reduce inflammation and neurodegeneration. Studies in mouse models of AD have shown reduced production of proinflammatory cytokines and amyloid pathology after reducing GMF expression with anti-GMF antibodies ($p < 0.05$) [177]. Although these biomarkers show promising diagnostic and predictive values for PDD, it is important to emphasize that most findings are based on small, cross-sectional, or single-center cohorts, underscoring the need for well-powered, multicenter, and longitudinal research to validate their clinical relevance.

Current therapeutic approaches in PDD primarily focus on symptomatic relief through cholinesterase inhibitors, N-methyl-D-aspartate (NMDA) receptor antagonists, and emerging combination therapies that target multiple pathways involved in cognitive decline. It has been described that olfactory dysfunction, in the form of hyposmia, can increase the risk of dementia in PD patients [178]. The Donepezil Application for Severe Hyposmic Parkinson's Disease (DASH-PD) study was conducted to investigate the potential of cholinesterase inhibitors (donepezil) to prevent the onset of dementia in PD patients at increased risk of dementia. 4-year donepezil therapy did not affect the risk of developing dementia in PD patients, but had some beneficial effects on general cognitive function compared to placebo [179]. However, another study described the effect of combined therapy with donepezil and Di-Huang-Yi-Zhi (DHYZ), an herbal formula with a potential protective effect against Aβ-induced neurotoxicity [180]. The results indicate that this combined therapy improves cognitive function more effectively than therapy with donepezil alone. The researchers suggest that this may be related to the synergistic amelioration of the cholinergic system between donepezil and DHYZ [181]. A "cocktail therapy" consisting of dl-3n-butylphthalide, oxiracetam, Ginkgo biloba extract and donepezil has also shown therapeutic potential in studies. Like donepezil, dl-3n-butylphthalide and oxirac-

etam help improve cholinergic system function, meanwhile Ginkgo biloba extract promotes the release of neurotrophic factors and neutralizes free radicals. After six months of this therapy, there was an improvement in cognitive function in PDD patients. In addition, the "cocktail therapy" showed better results than therapy with donepezil alone [182]. Furthermore, alterations in the kynurenine pathway (KP), which metabolizes tryptophan into neuroactive metabolites such as quinolinic acid (QA) and kynurenic acid (KYNA), have been linked to neurodegenerative disorders, including PD and AD [183,184]. QA acts as an NMDA receptor agonist, promoting excitotoxicity, oxidative stress, and neuroinflammation, whereas KYNA has neuroprotective properties but can impair cholinergic transmission through nicotinic α7 receptor antagonism. These opposing effects have motivated studies of combined pharmacotherapy with memantine and galantamine to modulate NMDA receptor activity as well as support neuronal function. Memantine, an NMDA receptor antagonist, can reduce QA-induced excitotoxicity, while galantamine, a cholinesterase inhibitor and nicotinic α7 receptor modulator, may counteract KYNA-induced cholinergic deficits. This combined pharmacotherapy produced better results than treatment with memantine alone. It has an effect on both protection against excitotoxicity and improving cholinergic system function. This translates into improved cognitive function in mouse models of PDD and is a worthwhile direction for further research into PDD treatment [185].

4.2 Affective Disorders

The detection of depression and anxiety in PD is particularly challenging due to symptom overlap between affective features and motor or disease-related manifestations, including psychomotor slowing, sleep disturbances, fatigue, and cognitive impairment. Clinical diagnosis is primarily based on structured interviews and validated rating scales, such as the Hamilton Depression Rating Scale (HAMD), the Beck Depression Inventory (BDI) or HAMA-14 [186]. However, no specific biomarker has yet been established for routine clinical use. Emerging evidence indicates that specific inflammatory markers may contribute to the pathophysiology of depression and anxiety in PD. Notably, plasma IL-17A has shown a association with both PD depression in females (rho = 0.075, $p < 0.05$), suggesting a potential role of T helper 17 cells (Th17)-mediated immune responses in modulating neuroinflammation and synaptic function. Moderate correlations have also been reported for soluble IL-2 receptor (sIL-2R) levels in the peripheral blood with depression (r = 0.364, $p = 0.004$) and anxiety (r = 0.452, $p = 0.000$) as well as for serum amyloid A (SAA) levels in the CSF with depression and anxiety ($\beta = 0.313$, $p < 0.001$) which may reflect sustained immune activation and systemic inflammatory burden. In contrast, findings regarding plasma C-reactive protein (CRP), CSF and serum IL-10, IL-6 and TNF-α, as well as CSF monocyte chemoattractant protein-1 (MCP-1), remain inconsistent, indicating that the contribution of peripheral inflammation to PDD is complex and likely involves interactions between immune signaling, neurotransmitter metabolism, and neuroplasticity [187]. Meanwhile, anxiety in PD has been linked to CSF total tau (t-tau) levels, with higher baseline concentrations predicting greater longitudinal increases in anxiety severity over a 4-year follow-up in a study of 252 patients [188]. Moreover, circulating microRNAs (miRs) regulate neuroinflammatory pathways, synaptic plasticity, and neurotrophic signaling, potentially linking molecular dysregulation to the affective symptom burden observed in PD. miR-425 has been found to be significantly downregulated in the serum of patients with PD depression. Receiver operating characteristic (ROC) curve analysis showed an area under the curve (AUC) of 0.867, indicating good diagnostic accuracy. Furthermore, miR-425 levels negatively correlated with the severity of both depression and anxiety ($p < 0.001$) [189]. Additionally, S100A10 protein (p11) has also emerged as a potential molecular link between PD and depression. This protein interacts with serotonin receptors, and its levels are reduced in key mood-related brain regions; notably, postmortem studies have demonstrated decreased p11 expression in the putamen, substantia nigra, and cortex of PD patients, suggesting a contribution to both affective symptoms and cognitive decline. Interestingly, although central p11 levels are reduced in postmortem PD brain regions such as putamen, substantia nigra and cerebral cortex, peripheral p11 expression in specific leukocyte subpopulations from peripheral blood correlates with PD severity and depressive symptoms and shows high diagnostic accuracy (AUC-ROC = 0.97), sensitivity (93%) and specificity (93%), indicating that p11 may represent a promising biomarker reflecting interactions between serotonergic dysfunction, neurodegeneration, and immune mechanisms in PD [190]. Although initial findings suggest potential biomarkers for depression and anxiety in PD, the current evidence is largely derived from small, single-center, or cross-sectional studies. Moreover, peripheral and central inflammatory processes may not fully correspond because of the blood–brain barrier compartmentalization. Larger, multicenter, and longitudinal studies are therefore necessary to validate these results and establish their clinical utility.

Treatment of depression and anxiety in PD currently relies on a combination of pharmacological and non-pharmacological approaches. First-line treatment typically involves SSRIs, including citalopram, sertraline, paroxetine, and fluoxetine, which are widely used because of their favorable safety profile and good tolerability, although evidence from randomized controlled trials (RCTs) shows limited rates of full remission and occasional exacerbation of motor symptoms. On the other hand, serotonin–noradrenaline reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine, which increase both synaptic 5-HT

and noradrenaline, have demonstrated efficacy in reducing mood-related symptoms without worsening motor function. Furthermore, tricyclic antidepressants (TCAs), including desipramine and nortriptyline, may offer stronger antidepressant effects than SSRIs in PD, though their use requires caution due to cardiovascular side effects. In treatment-resistant depression (TRD), monoamine oxidase inhibitors (MAOIs) are used due to their effect not only on 5-HT, noradrenaline, but also dopamine. Selegiline and safinamide can provide both motor and antidepressant benefits, with selective and reversible MAO inhibition offering additional therapeutic potential [191].

Non-pharmacological treatments play a crucial role in managing depression and anxiety in PD, complementing pharmacotherapy and addressing symptoms that may not fully respond to medication. Cognitive-behavioral therapy (CBT) has shown efficacy in reducing affective symptoms in patients with PD, demonstrating sustained improvements in HAMD and HAMA scores following structured CBT interventions [192]. Despite these benefits, access to therapy can be limited by patient mobility and availability of trained clinicians, highlighting the need for tailored, delivery-adapted programs in this population. Interestingly, remote or CBT has also demonstrated positive effects, offering a promising solution to overcome these barriers [193]. Despite CBT, other non-invasive brain stimulation (NIBS) techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have emerged as promising non-pharmacological interventions for cognitive decline and affective symptoms in PD, by modulating cortical excitability, network connectivity, and neuroplasticity. In case of TRD, electroconvulsive therapy (ECT) remains the most effective option, promoting neuroplastic changes via increased BDNF expression, particularly in the hippocampus. Evidence from systematic reviews and meta-analyses shows that ECT improves depressive and motor symptoms without major cognitive worsening, although transient delirium and autonomic complications may occur. Together, NIBS and ECT represent complementary approaches for managing depression in PD, though further research is needed to optimize safety and long-term efficacy [194]. Furthermore, recent studies on fast-acting antidepressants, such as ketamine, suggest that their efficacy may be primarily mediated through modulation of mitochondrial metabolism rather than classical post-synaptic N-methyl-D-aspartate receptor (NMDAr) antagonism [195]. This mechanism could be relevant not only for neuronal mitochondria but also for astrocytic mitochondria, where NMDAr on the inner mitochondrial membrane may play a role [196]. Ketamine is proposed to exert a "preconditioning" effect that enhances mitochondrial function, potentially influencing processes involved in depression, dementia onset, and broader motor and non-motor features of PD [197]. Further research is needed to clarify these mechanisms. Additionally, ketamine has been shown to increase local melatonin production [198], which may contribute to autonomic regulation deficits observed in PD, likely linked to impaired vagal nerve activity [197]. Vagal nerve-mediated anti-inflammatory effects appear to depend on the ability to upregulate melatonin locally, as supported by both clinical [199] and preclinical [200] studies. These findings suggest that gut-mediated melatonergic pathways may be closely involved in PD pathophysiology and its autonomic dysregulation.

Overall, while combined treatment with antidepressants and non-pharmacological approaches continues to form the cornerstone of management, the current therapeutic landscape does not yet fully reflect the complex molecular interplay among proteinopathy, neuroinflammation, and synaptic dysfunction in PD-related depression and anxiety. Future advances in biomarker-guided diagnostics and mechanism-based therapies may enable more personalized and disease-modifying treatment strategies.

5. Future Research Directions: Organoid Models in PD

In recent years, cerebral organoids have become a valuable platform for modeling PD pathomechanisms (Table 3, Ref. [45,47–49,55,61,64,70,78,87,89,101–106,108,109,111–115,119,121–128,131–134,138,147,149,150,152,162,166,167,176,180–192,201]). These three-dimensional models recapitulate human brain architecture and cell interactions, bridging *in vitro* and *in vivo* studies [202–214], and allow investigation of molecular mechanisms and testing of novel treatments [206,207,215–217]. While organoids do not directly replicate dementia or affective disorders, they enable the study of markers associated with cognitive decline, depression, and anxiety in PD. Complete cerebral organoids, as well as region-specific models (e.g., midbrain, striatum), can be generated from patient-derived induced pluripotent stem cells (iPSCs), carrying disease-relevant mutations [115,207,218–221].

Mutations in *SNCA*, including triplication [209–214] and A53T variant [203,206], can be studied in organoid models, as can *PRKN* variants linked to dementia, illustrating astrocytic dysfunction [213]. Organoids also allow exploration of immune system involvement [214,222], metabolic disturbances [221,223], and PD-associated mitochondrial and lysosomal dysfunction due to mutations in *PINK1*, *GBA*, Parkinson disease protein 7 (*DJ1*), and DnaJ homolog subfamily C member 6 (*DNAJC6*) [224–226]. Assembloid models further facilitate investigation of synaptic dysfunction and neurotransmitter imbalances, including serotonin and dopaminergic disturbances relevant to depression and anxiety in PD [202,203,205,227]. Transplantation studies of iPSC-derived midbrain organoids into PD rodent models showed increased dopaminergic neurons and functional improvements, highlighting therapeutic potential [228,229].

Table 3. Summary of studies on neuropsychiatric symptoms in Parkinson's disease.

Symptom	Biomarker	*In vivo* studies	Human studies	*In vitro* studies/organoid studies
Dementia	*SNCA*/α-synuclein	in murine models, A53T BAC-*SNCA* transgenic mice and α-synuclein preformed fibril injections induce memory deficits, impaired behavioral flexibility, hippocampus-dependent learning deterioration, and postsynaptic dysfunction [47–49,147]	in PDD, α-synuclein pathology, including *SNCA* triplication and E46K mutation, promotes neuroinflammation in the amygdala and contributes to early-onset PD with predominant non-motor symptoms such as dementia, depression, psychosis, and behavioral disturbances [45,149,150]	cerebral and midbrain organoids carrying *SNCA* A53T mutation or triplication effectively model α-synuclein propagation and synucleopathy features [181–190]
	PRKN	-	exons 4–6 deletion was associated with dementia [152]	midbrain organoids with *PRKN* mutation modeling astrocytic dysfunction [191]
	Immunologic abnormalities	IFN-β loss promotes PDD-like behavioral abnormalities, induces formation of Aβ plaques and p-tau tangles, increases TNF-α and TNFR1 levels in mice [61]	in PDD, T cell infiltration in the amygdala and substantia nigra and increased microglial activation—negatively correlated with Mini-Mental State Examination scores—indicate region-specific immune involvement [45,55]	stem cell-derived human midbrain organoids offering a platform to study T cell interactions with midbrain neuronal tissue [192]
	GFAP	-	an elevated number of GFAP reactive astrocytes was detected in PDD patients in areas of their brains affected by neurodegeneration [64]	-
	PIAS2	elevated expression of *PIAS2* deteriorated mitochondrial function and caused cognitive impairment in mice [70]	-	-
	cholinergic disturbances	-	in PDD, increased muscarinic acetylcholine receptor density in the occipital lobes and decreased choline acetyltransferase activity are associated with cognitive impairment [78,176]	-
	BDNF	-	*BDNF* Val66Met variant was analyzed regarding cognitive impairment in PD; Val/Val alleles were linked to poorer delayed recall of information [87]	-
	EGF	-	low EGF levels were prognostic of cognitive decline [89]	-
Affective disorders	BDNF	lower BDNF levels in PD patients with depression [131–133,162] *BDNF* valine-to-methionine substitution at codon 66 (Val66Met) genetic variant was associated with a greater risk of depression, anxiety and severe cognitive deficits [166]	activation of the BDNF/TrkB/CREB pathway attenuates depressive-like behaviors in mice, whereas homozygous Val66Met variant carriers show increased anxiety-like behaviors resistant to antidepressants [134,167]	-

Table 3. Continued.

Symptom	Biomarker	*In vivo* studies	Human studies	*In vitro* studies/organoid studies
	dopaminergic disturbances	DA depletion and pre-synaptic D4 receptors play a role in the onset and regulation of PD-related depression in rat models [102]	alterations in dopaminergic and noradrenergic innervation in PD are associated with depression and anxiety, with studies showing region-specific changes in DAT and [11C]RTI-32 binding, including lower DAT availability in limbic and striatal regions correlating with higher affective symptom scores [101,103–106,108]	human midbrain organoids modeling dopaminergic neurons provide a platform to study DA dysfunction, including *PINK1* and *LRRK2* mutation–induced disruptions in the tyrosine hydroxylase–dopamine pathway leading to neuronal death [180–183]
	serotonergic disturbances	-	serotonergic system alterations in PD are linked to depression and anxiety, with PET studies showing both correlations and region-specific changes in SERT availability, while non-depressed patients show no significant differences compared to controls [109,111–115]	-
	cholinergic disturbances	-	depressive symptoms were correlated with cortical cholinergic denervation [119]	-
	GABA disturbances	-	elevated GABA+ levels in the medial frontal cortex of PD patients with depression and anxiety [121]	-
	cortisol	-	elevated cortisol levels in PD patients are associated with both depression and anxiety, and correlate with depression severity following levodopa administration [138,201]	-
	immunologic abnormalities	modulation of microglial and astrocytic activation (IBA-1, GFAP) and pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IFN-γ, iNOS) prevented or alleviated depressive-like behaviors in multiple PD and depression mouse and rat models [123–128]	higher baseline CSF sTREM2 and YKL-40 levels predict faster progression of depression [122] TNF-α correlates with both depression and anxiety; other cytokines (IL-1β, IL-6, IL-10) showed no significant association [127]	-

SNCA, α-synuclein; PRKN, parkin RING-between-RING (RBR E3) ubiquitin protein ligase; PD, Parkinson's disease; PDD, Parkinson's disease dementia; BDNF, brain-derived neurotrophic factor; PET, positron emission tomography; IBA-1, ionized calcium-binding adapter molecule 1; GFAP, glial fibrillary acidic protein; IL, interleukin; iNOS, nitric oxide synthase; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-gamma; IFN-β, interferon-beta; TREM2, triggering receptor expressed on myeloid cells 2; CSF, cerebrospinal fluid; TNFR1, tumor necrosis factor receptor 1; PIAS2, protein inhibitor of activated STAT 2; EGF, epidermal growth factor; BAC, bacterial artificial chromosome; TrkB, tropomyosin receptor kinase B; CREB, cAMP response element-binding protein; PINK1, PTEN-induced kinase 1; LRRK2, leucine-rich repeat kinase 2; sTREM2, soluble triggering receptor expressed on myeloid cells 2; YKL-40, chitinase-3-like protein 1.

Ultimately, the employment of organoids in PD studies holds promise and hopefully will accelerate advancements in our understanding of neuropsychiatric manifestations in PD. They account for a versatile platform for studying molecular intricacies and lay the ground for the development of novel avenues in treatment that would enable personalized therapeutic modalities.

6. Conclusion

Understanding the molecular basis of neuropsychiatric disorders in PD patients, including changes in multiple neurotransmitter systems, neuroinflammatory processes, genetic predispositions, and dysregulated cell signaling pathways, can facilitate accurate diagnosis of PD and enable early pharmacological intervention. Moreover, it should be remembered that the treatment of PD patients should be aimed not only at reducing motor symptoms but also at maintaining good mental performance, including cognitive performance as well as depression and anxiety. Impairment of these functions can affect both the deterioration of the patient's daily functioning and their social or professional life. Due to the high rate of neuropsychiatric disorders in the course of PD and the increasingly longer life of PD patients, the development of sensitive and specific neuropsychological tools for early diagnosis and effective treatment is becoming a significant clinical challenge.

Author Contributions

Writing and literature collection of the manuscript — WO, AF, OK, AS; Writing of the manuscript and design, and draw the figures — BS, OS, JP; Editing and language correction — BS, UG; Conception or design of the work, final manuscript review — PPJ, WK, JD, and UG. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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The authors declare no conflicts of interest. Jolanta Dorszewska is serving as one of the Guest Editors and Editorial Board members of this journal. We declare that Jolanta Dorszewska had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Bettina Platt.

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