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Review Article

Pathology of behavior in PD: What is known and what is not?

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ABSTRACT

Abnormal behavior in Parkinson's disease (PD) stems from a complex orchestration of impaired neural networks that result from PD-related neurodegeneration across multiple levels. Typically, cellular and tissue abnormalities generate neurochemical changes and disrupt specific regions of the brain, in turn creating impaired neural circuits and dysfunctional global networks. The objective of this chapter is to provide an overview of the array of pathological changes that have been linked to different behavioral symptoms of PD such as depression, anxiety, apathy, fatigue, impulse control disorders, psychosis, sleep disorders and dementia.

Contents

1. Overview of pathology in PD

The pathology underlying Parkinson's disease is not fully understood. Whilst the Braak staging model has attempted to describe the progression of Lewy body pathology [1], the precise interplay between structural and functional changes across multiple neurotransmitter pathways and inter-related networks leads to a complex array of clinical features. These dysfunctional global networks [2] manifest with a wide range of abnormal behaviors in Parkinson's disease (PD) that often co-exist and impact negatively on quality of life. The objective of this chapter is to provide an overview of the current state of knowledge

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regarding the pathological changes that have been linked to behavioral abnormalities in PD.

2. Pathological mechanisms underlying behaviors in PD

2.1. Neuropsychiatric symptoms

Certain neuropsychiatric symptoms can present at different stages of the disease and thus may reflect distinct mechanisms manifesting with the same clinical presentation. For example, a number of epidemiological studies have highlighted the onset of late life mood disorder, typically anxiety or depression as a prodromal 'risk factor' for the development of PD [3–7]. By way of contrast, some patients can experience anxiety and depression as part of a 'wearing off' phenomenon [8,9]. This implies that disparate mechanisms such as the prodromal loss of serotonergic/noradrenergic cells in the brainstem can cause similar clinical features to those presumably arising from a relatively hypo-dopaminergic state [10,11]. Furthermore, such neuropathological contributions may coexist and PET studies in patients with established PD have demonstrated the potential relationship between affective symptoms and brainstem serotonergic levels [12,13]. Thus, behavioral symptoms are likely to represent a breadth of structural and functional neuropathology, which may also be impacted by other factors within individuals such as genetic influences and medications. Whilst trends have suggested that certain genetic polymorphisms (e.g. LRRK2) might also be associated with neuropsychiatric symptoms (i.e. anxiety and depression) [14–17], there has been no conclusive genetic correlations with visual hallucinations in PD [18]. Additionally, the development of cognitive decline and dementia has been linked with the tau (MAPT) inversion polymorphism [19], however associations between dementia and the APOE4 allele, and LRRK2 gene remain controversial [14,20]. In the following sections, we will provide a summary based on evidence from the current literature and attempt to describe the hierarchical mechanisms that underlie neuropsychiatric behaviors.

2.1.1. Depression and anxiety

A seven-fold loss of nigral neurons has been found in post-mortem brains from depressed PD patients compared to non-depressed PD patients [21]. In addition, many studies have found strong associations between depressive and anxiety symptoms and the decreased binding to dopamine transporters in the striatum [22–27]. Thus, dysregulation of frontostriatal and mesocorticolimbic dopaminergic circuits have been suggested to play a key role in depression and anxiety in PD [22,28,29]. However, in parallel greater pathology has also been suggested in the serotonergic raphe nucleus [30,31], as well as the noradrenergic locus coeruleus [1,21], which both heavily innervate corticolimbic regions involved in integrating anxious responses and emotional states [32]. Although limited research has examined this at the microscopic level, studies have reported evidence for the increased binding of serotonin transporters and reduced postsynaptic serotonin 1A receptor density within limbic regions in depressed PD patients [33–35]. Furthermore, PD patients who carried the short allele for the serotonin transporter scored significantly higher on anxiety scales than non-carriers [36]. In addition, an increased incidence of anxiety and depression has also been correlated with lower dopamine/noradrenaline transporter binding in the locus coeruleus in PD [24]. Interestingly, research studying de novo PD patients (i.e. those who have not begun dopaminergic therapy) has highlighted that treatment and/or disease progression may exacerbate the disruption of non-dopaminergic pathways [37,38]. This work has suggested that serotonergic and noradrenergic neurons might act as surrogates for the dopaminergic system, by taking up exogenous levodopa and converting it to dopamine and then releasing it, at the expense of its normal function [39–41]. This notion suggests that chronic levodopa treatment may interact with non-dopaminergic systems, creating a paucity of serotonin and noradrenaline which in turn may contribute to depression and anxiety in PD.

Reflecting the disruption of dopaminergic, serotonergic and noradrenergic circuits in PD patients with depression and/or anxiety, it is not surprising that gray matter atrophy [28,42–45] as well as white matter reductions [46–48] have also been found across limbic areas (e.g. orbitofrontal cortex, prefrontal cortex, cingulate cortex, temporal lobe, thalamus, hippocampus and amygdala). Furthermore, metabolic changes, such as reductions in cerebral blood flow have been noted in frontal and anterior cingulate regions [49] as well as increased metabolism within the amygdala [50].

From a neural network perspective, reduced functional connectivity has been reported within the corticolimbic network in depressed PD patients, whereas increased functional connectivity has been noted within their limbic system [29,51,52]. It has been proposed that such a pattern of disturbances may reflect an abnormal top-down control of emotional processing [53]. Unfortunately, much of the research to date has primarily investigated depression in PD with less work on anxiety. Future research is therefore needed to fully understand the synergies and differences in pathology that exist between anxiety and depression, as well as trying to further understand whether their pathophysiological mechanisms change in response to treatment or in relation to the progression of other symptoms such as dementia.

2.1.2. Apathy and fatigue

Whilst some researchers have argued that apathy can be explained by diffuse cortical Lewy bodies as a result of the advanced stages in PD [54], it is more widely accepted that apathy can early in disease progression. In this circumstance researchers have proposed that apathy might be primarily associated with low dopaminergic tone in both the striatum and prefrontal cortex [10,55]. In support of the latter, greater dopaminergic denervation has been shown in de novo PD patients with apathy [56] and mesolimbic dopaminergic denervation has also been linked with developing apathy in PD [55]. Additionally, gray matter atrophy in the prefrontal, parietal and cingulate cortices has been associated with higher levels of apathy [57] and the nucleus accumbens has been shown to be atrophic in apathetic PD patients [58]. It should be noted that these findings have not been identified consistently and other studies comparing PD groups based on high and low apathy scores have failed to find any gray matter density differences [59]. More research is needed in this area to fully understand the underlying mechanisms of motivation and how PD pathology might disrupt these networks in patients with apathy.

There is growing evidence that a strong relationship exists between apathy and dementia in PD. Apathy is more common in PDD patients [60] and represents an independent neuropsychiatric profile of PDD, separate from mood, agitation and psychosis [61]. Even a caregivers' report of patients' apathy has been suggested to determine those at risk for subsequently developing dementia in PD [62]. Executive dysfunction has also been found to be worse in PD patients with apathy [63,64]. Notably, a recent study also suggested that fatigue might be related to executive dysfunction, since motor performance worsened over time in PD patients with fatigue during an attention-demanding externally cued task, compared to PD without fatigue, whilst deterioration of performance was not seen in either group in the un-cued motor task [65].

The neural underpinnings of fatigue are also unclear. A strong association has been made between apathy and fatigue [29], and both symptoms have been hypothesized to share a common pathology within the basal ganglia-limbic dopaminergic system [54,66]. In support of this, fatigue has been shown to significantly improve with dopaminergic replacement therapy (i.e. rosagiline or dopamine agonists), although these improvements remains clinically [67]. Fatigue has also been associated with abnormal blood flow in the putamen and supplementary motor area, suggesting that abnormalities in the basal ganglia pathways may cause fatigue [66]. There is also a small amount of evidence which suggests that serotonergic lesions in the ventral striatum, cingulate cortex and amygdala are correlated with fatigue [68]. However, to date fatigue remains one of the most understudied non-motor symptoms of PD

with regards to its pathophysiology and treatment. Much more research is needed to explore the neural underpinnings and pathology underlying fatigue and how dissociable it is from apathy and depression.

2.1.3. Impulse control disorders

Treatment related abnormalities within the non-motor frontostriatal loops have been suggested to be primarily responsible for impulse control disorders (ICD) due to 'excessive dopaminergic drive' [10]. This proposed pathogenesis is in keeping with studies which report greater release of dopamine within the ventral striatum after levodopa intake as well as increased dopamine D2/D3 receptor availability in the anterior cingulate cortex in PD patients with pathological gambling [69–71]. Likewise, reductions in gray matter volume have also been found in the frontal lobe in PD patients with ICDs [72] and functional neuroimaging data highlighted that PD patients with ICDs (i.e. problem gambling or compulsive shopping) showed reduced activation in the ventral striatum, anterior cingulate cortex and orbitofrontal cortex along with more risky behaviors [73]. Taken together, regions that play an important role in risk evaluation, impulse control and response inhibition, as well as dysfunction within the reward circuit [73] all seem to be related to ICDs in PD.

2.1.4. Psychosis

High densities of Lewy bodies, as well as plaques and tangles, have been found in a variety of areas throughout the brain in PD patients with hallucinations including frontal, parietal, and temporal areas, notably the amygdala and parahippocampus [10,74–77]. Likewise, cortical alpha-synuclein pathology can also be a major determinant for the onset of psychosis in PD [10,18]. Furthermore, several neurotransmitter systems (i.e. dopamine, serotonin, and acetylcholine) have also been implicated in PD psychosis [18]. The dopaminergic system is considered to play a pivotal role, especially in the later stages of the disease, whereby an overflow of dopamine and overstimulation of mesocorticolimbic dopamine D2 receptors in the limbic and cortical areas have been suggested to produce psychosis in a similar way that motor dyskinesias are brought about [78–80]. Interestingly, amantadine whilst reducing dyskinesia in many patients can also trigger hallucinations in some but not all. These observations suggest that this NMDA antagonist may be influencing the neurobiology through a combination of dopaminergic and glutaminergic processes, which may be subject to other influences (e.g. genetic, medication combination/doses, other monoaminergic pathways) at the individual level. There has also been evidence that PD patients with hallucinations have increased serotonin A2 binding and receptor density in ventral visual pathways, as well within the dorsolateral prefrontal cortex, orbitofrontal cortex and insula [81]. Similar to the hypothesis put forward for mood disorders, increased serotonergic receptor function might reflect serotonergic neurons acting as false transmitters or compensatory postsynaptic serotonergic up-regulated from reduced dopamine or serotonin [18]. A reduction in glutamate levels has also been noted in PD patients with psychosis, which might contribute to dopaminergic over activity [82]. This might explain amantadine's psychosis enhancing effect, however further research is needed to elucidate this point.

Several neuroimaging studies have attempted to identify the underlying substrates of hallucinations in PD, however to date results remain inconsistent (for review – see [18]). Greater atrophy has been reported in hallucinators across the visual processing and cognitive pathways compared to non-hallucinators [83]. Likewise, white matter reduction in the parahippocampus, posterior cingulate cortex and occipital areas were found in PD patients with hallucinations compared to non-hallucinators. Decreased metabolism in visual cortical areas has been reported frequently but is partly confounded by the coexistence of cognitive impairment [84,85]. Increased functional connectivity in the default mode network [86,87], as well as reduced activation in prefrontal and cingulate cortex [83] has also been linked to hallucinations in PD. More recent work has highlighted the role of dysfunctional attentional networks that mediate visual and perceptual processing, which likely underpin hallucinations and psychosis in PD [88–92].

2.2. Sleep disorders

Cellular loss in PD has been documented in nearly all circadian control areas, especially neuronal networks governing the sleep-wake cycle [93–95]. Thus, PD patients can often experience several sleep disorders including Rapid Eye Movement (REM) sleep behavior disorder (RBD); excessive daytime sleepiness (EDS); insomnia and Restless Legs Syndrome (RLS). Disturbed sleep in PD has been associated with alpha-synuclein pathology within locus coeruleus and raphe nuclei, as well as hypothalamic areas and subcortical/limbic areas such as the amygdala, thalamus, and enterorhinal cortex [94,96]. Widespread tau pathology has also been reported in PD cases with "more sleep problems" [96]. However, it is important to note that the pathological mechanisms underlying these sleep disorders remains for the most part unclear.

Early degenerative processes in PD, as noted in the Braak staging model, disrupt the medullary and pontine circuits, which are important for controlling REM sleep atonia [97,98] offering a possible explanation as to why RBD symptoms can present years before PD motor symptom onset [99,100]. In keeping with this hypothesis, alpha-synuclein deposition and Lewy bodies have been reported in the subcoeruleus region in idiopathic RBD without PD [101–104]. Reduced striatal dopamine levels have also been noted in RBD patients, similar to that of PD [105,106] and continuous loss of presynaptic dopaminergic function has also been reported over a 3-year longitudinal study of RBD patients [107,108].

Other data have implicated GABAergic, glutaminergic, serotonergic, noradrenergic, cholinergic and hypocretinergic systems in RBD [99,109–112], due the impairment of brainstem structures in the pontine-tegmentum, which are also known to play an important role in modulating REM sleep. Whilst changes in gray and white matter of the thalamus and brainstem have been reported in RBD [102,103,113–115], many neuroimaging results remain inconsistent and yet to be confirmed (see recent review [116]). A recent resting state study demonstrated reduced functional connectivity within the basal ganglia network in RBD patients (who did not manifest PD), which was remarkably similar to PD patients (although the presence of RBD was not assessed in the PD patients) [117]. Furthermore, a highly specific metabolic brain network, marked by metabolic increases in pallidothalamic, pontine and cerebellar regions and decreased activity in premotor and parietal regions, has been identified in PD and is associated with motor symptoms [118]. Interestingly, this 'motor related' PD pattern has also been found to be elevated in RBD patients [119,120]. Whilst this field is still in its infancy nonetheless, it is becoming clear that RBD and PD overlap substantially in their pathology and may be an important target for future disease-modifying therapies delivered at the earliest possible time, since the majority of these patients develop one of the three alpha-synucleinopathies.

EDS have been hypothesized to have a number of causes including exogenous medications, loss of dopamine, loss of norepinephrine and serotonin (alerting monoamines), loss of hypocretin pathways, loss of autonomic function, and loss of circadian control [94]. However, no specific pathological study has attempted to correlate dopamine cell loss, serotonergic or noradrenergic specifically with EDS whereas, a few studies have found marked reduction of CSF hypocretin, as occurs in narcolepsy [121]. Similarly, there is also relatively little data exploring insomnia and circadian disturbance in PD. Whilst a small number of studies have investigated alterations in the pattern of melatonin secretion in PD [122–124] along with the impact of disease progression [125] and dopaminergic medication [126] more detailed studies are required to inform our understanding.

Explorations of the pathophysiology of RLS in PD has mainly focused on homeostatic iron dysregulation in the brain. Specifically, previous studies have shown a reduction in iron stores in the striatum and substantia nigra of patients with idiopathic RLS [127,128]. However,

PD is generally associated with increased iron levels in the basal ganglia structures and work comparing PD patients with and without RLS has not identified significant differences in iron deposition [129,130]. Although dopaminergic medications typically improve RLS, there has been little evidence of dopamine deficiency associated with RLS in PD. Furthermore, non-dopaminergic medications used to treat PD, such as anticholinergic, SSRI and anti-psychotics have been suggested to exacerbate RLS [94]. In sum, there are no clear pathologic similarities between PD and RLS to date.

2.3. Dementia

Parkinson's disease dementia (PDD), like many other behavioral symptoms described here, also has a complex and multifactorial pathogenesis, especially since it typically affects PD patients in the later disease stages. Although cortical Lewy body pathology (in the frontal, cingulate and hippocampal areas) has been argued to be the primary pathological substrate, amyloid beta plaques and neurofibrillary tangles have also been found to be associated with cognitive decline in PDD [131–134]. The dopaminergic and cholinergic systems both play a key role in functional and structural remodeling of cortical circuits, and thus an imbalance within the dopamine-acetylcholine synergistic function of these pathways might lead to impaired cognitive processing [135]. Faster rates of decline in striatal dopaminergic binding, as well as more severe striatal presynaptic dopaminergic deficiencies, particularly in the caudate has been noted in PDD [136–138]. However, substantial evidence also emphasizes that dysfunction within the ascending cholinergic systems underlies dementia, particularly in PD and Dementia with Lewy Bodies (DLB) more so than Alzheimer's disease (AD) [139,140]. Extensive cholinergic neuronal loss has been noted in the nucleus basalis of Meynert in AD and to a similar or even greater extent in PD [141]. Thalamic cholinergic denervation has been found across PDD, DLB and to a lesser extent in PD [142]. Whilst individuals with AD seem to have preserved thalamic pathways [142], similar white matter hyperintensities in cholinergic pathways were found between AD, DLB and PDD [143]. Furthermore, in vivo PET studies have shown decreased acetylcholinesterase activity and nicotinic acetylcholine receptor density in both cortical and subcortical brain tissues in PDD [144–147]. Additionally, PDD have shown a greater and more widespread loss of vesicular acetylcholine transporter levels when compared to PD patients without dementia who show reduced levels only in the parietal and occipital areas rather than the entire cortex [148].

These pathological and neurochemical abnormalities are associated with structural and functional brain changes, including atrophy and altered network connectivity (for full review please see [149]). A linear progression of atrophy has been suggested to occur across the cognitive stages in PD (i.e. PD-MCI to PDD), mainly affecting temporal, frontal and parietal areas [150–156]. Additional subcortical areas that become atrophic as mild cognitive impairment (MCI) transitions into dementia include the thalamus [150], caudate [150–159], putamen [150], amygdala [151,159] and hippocampus [151,158,159]. Major white matter tracts have also been suggested to be altered in PD-MCI and PDD compared to controls, and have been associated with a decline in global cognition as well as executive impairments [160–164].

Associations between regional activations and more specific cognitive domain deficits have also been made. For example, abnormal frontostriatal responses have been associated with deficits in executive functioning [149,165]. Although few studies have investigated brain metabolism in PDD, recent longitudinal research suggests that reduced glucose metabolism in occipital and posterior cingulate regions heralds those PD patients who will convert to PDD [166]. The default mode network has emerged as a key functional substrate for cognitive deficits within PD. The dorsal attention network has been found to be affected in PD-MCI and to correlate with attentional and executive deficits [167]. PDD patients show further reductions in functional connectivity within the DMN beyond non-demented PD patients and controls [168], and others have shown that impaired deactivation of the default mode network can occur specifically during executive tasks in PD [169,170].

3. Discussion: What remains unknown?

As highlighted above, many questions regarding the pathophysiology of behavioral disturbance in PD remain unresolved. For example, questions like how does neuronal toxicity occur and why/how does it spread? More broadly, does abnormal activity within a network contribute to the transmission of pathology, exhaustion and/or plastic changes to other networks? Furthermore, disease heterogeneity exists across multiple levels and magnifies the difficulty in not only replicating findings, but also limits the generalizability for future therapies and drug trials. Many studies described above have failed to consider age of onset, disease stage, medication profile, genetic polymorphisms or clinical phenotype. A combination of these factors is likely to interact and play a significant role in the rate of progression and underlying pathology. For example, age of onset is well known to influence alpha-synuclein deposition, and yet remains a major confounder in many studies to date [171]. Furthermore, cell loss is impossible to assess if the loss doesn't leave a marker or if the loss isn't large enough to create an imaging deficit, thus suggesting that we don't yet know what we don't know. Greater precision is also needed in the classification of subgroups under study and the coexistence of the symptoms being evaluated (e.g. hallucinators, PD-MCI, PD patients with depression, anxiety, apathy, RBD, etc.). In our opinion, future research should focus on histopathological validation, longitudinal studies (in support of cross-sectional work) and multi-modal imaging techniques to promote replication of findings.

In conclusion, many interfacing systems are affected in PD leading to a vast array of behavioral symptoms. Although the presence of alpha-synuclein, Lewy bodies and in some cases amyloid plaques and tau provide logical possibilities for producing behavioral problems in PD, the pathophysiology remains complex, and these complexities are still not adequately understood given the highly interconnected nature of the brain and the cascade of dysfunction at many levels, where localized pathology can extend to abnormalities in global network activity [2]. To this end, a more in depth understanding of the pathological mechanisms of PD behavior is needed in order to provide insight for future treatment strategies.

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