Journal of the Neurological Sciences 374 (2017) 9–16

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

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

Kaylena A. Ehgoetz Martens *, Simon J.G. Lewis

Parkinson Disease Research Clinic, Brain and Mind Centre, University of Sydney, 100 Mallet Street, Camperdown, 2050, NSW, Australia

ARTICLE INFO

Article history:
Received 22 December 2016
Accepted 28 December 2016
Available online 29 December 2016

Keywords:
Pathology
Parkinson's disease
Neuropsychiatric
Anxiety
Depression
Apathy
Fatigue
Impulse control disorders
Psychosis
Hallucinations
Sleep
Dementia

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

* Corresponding author.
E-mail address: Kaylena.ehgoetzmartens@sydney.edu.au (K.A. Ehgoetz Martens).

http://dx.doi.org/10.1016/j.jns.2016.12.062

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