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COMMENTARY

Neuropsychiatric sequelae of Parkinson's disease: what every clinician needs to know†

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SUMMARY

Jones et al's review of the assessment and management of the neuropsychiatric manifestations of Parkinson's disease serves as a practical guide to clinicians. This commentary outlines some of the underlying neuroscience and psychological sequelae of this range of conditions, offering a take-away message to the clinician with an interest in Parkinson's neuropsychiatry.

KEYWORDS

Parkinson's; neuropsychiatric disorders; clinical neurology; motor disorder; assessment.

There is an increasing trend to conceptualise Parkinson's disease as a neuropsychiatric disorder with associated motor characteristics, rather than predominantly a motor disorder. This is due to the high prevalence of psychiatric syndromes, which are comprehensively covered in this issue of *BJPsych Advances* by Jones and colleagues. Their article is a narrative review from a range of clinicians experienced in the assessment and management of the neuropsychiatric manifestations of Parkinson's disease (Jones 2020). It will be of use to any physicians, psychiatrists or allied healthcare professionals who wish to update their knowledge in this field. The neuroscience underlying these conditions is an area where the translational aspects of research are constantly evolving. An up-to-date review is therefore very welcome.

Contributory neuropathology of Parkinson's disease

It is always worthwhile remembering the underlying neuroscience that serves as a contributory factor to the development of these disorders. In that regard, Braak's staging of α-synuclein pathology (recognised as key to Parkinson's disease pathogenesis) provides a useful road map to the neuropsychiatric, motor and non-motor components of the condition (Braak 2003). On the basis of Parkinson's patients' post-mortem findings, Braak and colleagues hypothesised that neuronal loss tends to occur in a progressive neuroanatomical pattern. These were grouped into six stages. Stages 1 and 2: Pathology is initially most prevalent in the brain stem and olfactory bulb. The former resulting in sleep dysfunction (e.g. REM sleep behaviour disorder) and progressive autonomic dysfunction (e.g. constipation, erectile dysfunction), and the latter resulting in anosmia. Stage 3 and 4: Progression into the cortex anteriorly to the medial orbitofrontal cortex (personality change – disinhibition and apathy) and posteriorly to the occipital cortex (visual hallucinations). Stages 5 and 6: Further cortex progression, leading to temporal (amnestic disorders) and parietal (agnosias, visuo-spatial impairment) lobes. Those with an underlying vulnerability may progress to dementia. With this framework in mind, I would point readers to a recent paper highlighting the neuropsychiatric progression of the disease (Weintraub 2020).

Psychological sequelae

Jones and colleagues' inclusion of cognitive–behavioural therapy (CBT) trials is a strength of the paper. The presence of positive therapeutic outcomes further challenges the Cartesian dichotomy that may offer the view of psychiatric manifestations in Parkinson's disease as purely biological entities, or purely secondary to the sequela of the motor disability. It is, of course, clear that even with the greater propensity for a biological contribution in this disorder than in other long-term physical conditions, all such diseases manifest in a social context, with thoughts and beliefs about one's circumstance playing a contributory role to one's ability to function. CBT attempts to address some of the factors that may serve to maintain or prolong these disorders over time.

In relation to the range of psychiatric disorders covered, the review is well written and clear. There is a useful comparison of depression and apathy, allowing the reader to conceptualise each as the 'differential diagnosis' of the other. Antidepressant treatment in Parkinson's disease still requires

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higher-quality randomised controlled evidence, and it is thus worthwhile monitoring the progress of a large placebo-controlled trial of escitalopram versus nortriptyline (ADepT-PD), which may provide clarity on the tolerability and efficacy of the tricyclics compared with the selective serotonin reuptake inhibitors (SSRIs) in Parkinson's disease (ClinicalTrials.gov identifier: NCT03652870). The authors, however, appear to have overlooked one of the higher-quality randomised controlled trials of CBT for depression ($n = 80$), which indicated a large effect size on depressive symptoms and includes a useful secondary analysis on predictors of outcome (Dobkin 2011).

The review highlights the relative dearth of evidence in some areas, such as the relatively weak evidence base for treatments of anxiety disorders in Parkinson's disease, despite their commonality. Such also appears to be the case for evaluations of cost-effectiveness of treatments of all the neuropsychiatric conditions described, meaning that there is little to incentivise the 'purchase' of psychological medicine services in Parkinson's disease, or in the neurosciences in general (for expert opinion on recommended good practice in this area see Taylor et al, 2016). Such real-world implications of therapeutic interventions warrant further exploration, as it is clear from Jones and colleagues' review that neuropsychiatric symptoms are predictors of the highest rates of institutionalisation and are associated with a greater reduction in quality of life than severe motor deficits alone.

Regarding psychosis in Parkinson's disease, the review provides an overview but has little oppourtunity to elaborate on the phenomenology of hallucinations and delusions in Parkinson's disease. Visual hallucinations and illusions are often seen, as are 'delusions of presence' and 'morbid jealousy'. Despite a number of randomised controlled trials indicating little to no treatment benefit, clinically we often see an improvement on low-dose quetiapine, and I would recommend this as a first-line intervention (National Institute for Health and Care Excellence 2017). The disparity in findings is almost certainly due to underpowering of studies, and possibly to the inappropriate adoption of psychosis assessment tools designed for the general adult population (note that the clozapine studies used Clinical Global Impression of Change scale, rather than the more schizophrenia-based questionnaires seen in the quetiapine trials). Whilst many have concerns about clozapine as a second-line agent to manage such a condition, so it may be a reassurance to know that the evidence suggests reasonable tolerability, and oftentimes doses as low as 25–37.5 mg/day for a treatment effect (Friedman 2010).

Medication-related disorders

The section on medication-related disorders serves as a good introduction to those less familiar with this range of conditions such as impulse control behaviours (ICBs). Omitted from the review, these also include repetitive stereotyped activities that range from the simple (punding) to the more complex (hobbyism), alongside the compulsive overuse of Parkinson's medication seen in a subset of patients. These phenomena have at their core a disruption in the reward-based pathways in Parkinson's disease, although patients with high scores in ICB severity also seem to have high scores in both apathy and depression. This suggests that apathy and ICBs are not simply opposite ends of a spectrum consisting of reward and reward absence (Baig 2019). As is the case with many of the conditions discussed in this review (e.g. psychosis), management may involve the cessation or withdrawal of Parkinson's disease medications, and is often a fine balancing act between the presence of ICBs and the risk of worsening motor symptoms. Understandably, the review does not touch on the subjects of fatigue, insomnia or REM sleep disorder, all of which have a heavy neuropsychiatric association.

Takeaway messages

So, what are the practical takeaway messages from this review? Each of the conditions leads to distress – either for the patient or the carer. The clinician may be best advised to start by asking about distress in the patient–carer dyad and then 'working backwards' to the underlying neuropsychiatric syndrome(s) that may be contributing to such distress, rather than simply working their way through the listed range of disorders.

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Declaration of interest

None.

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Demystifying neuroscience laboratory techniques used to investigate single-gene disorders

ARTICLE

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SUMMARY

There is considerable work being carried out in neuroscientific laboratories to delineate the mechanisms underlying single-gene disorders, particularly those related to intellectual disability and autism spectrum disorder. Many clinicians will have little if any direct experience of this type of work and so find the procedures and terminology difficult to understand. This article describes some of the laboratory techniques used and their increasing relevance to clinical practice. It is pitched for clinicians with little or no laboratory science background.

LEARNING OBJECTIVES

After reading this article you will be able to:

- understand models used in single-gene disorder research
- recognise some of the common methods used in laboratory science to investigate single-gene disorders
- understand how each technique contributes to our understanding of the pathophysiology of intellectual disability and autism spectrum disorder.

KEYWORDS

Single-gene disorders; autism spectrum disorders; intellectual disability; neuroscience; SYNGAP1.

The importance of psychiatrists having an understanding of neuroscience has been increasingly recognised in recent years (Schildkrout 2016; Steele 2019). However, owing to lack of direct personal experience of laboratory work, the language and methods used are daunting for many clinicians. This potentially leaves relevant pathophysiological work impenetrable and clinicians may be less able to read and critically appraise neuroscientific research that could contribute to their understanding of their patients' presentations (Schildkrout 2016). The Royal College of Psychiatrists' Neuroscience Project, funded by the Gatsby Foundation and Wellcome Trust, aims to integrate modern neuroscience into the psychiatry curriculum (https://www.rcpsych.ac.uk/training/neuroscience-in-training/neuroscience). It is hoped that this will address some of these problems.

Within psychiatry, many psychiatric conditions are polygenic, including depression, schizophrenia and bipolar affective disorder. This means that they are mediated by a combination of many different genetic variants, each having a small individual effect. This makes the study of their underlying biology very complex. In the psychiatry of intellectual disability, single-gene disorders are much more common, therefore offering an advantage when it comes to understanding the pathophysiology of the conditions presenting in clinic. The Simons Foundation Autism Research Initiative (2019) now associates over 900 genes with autism spectrum disorder and by 2015 over 700 genes related to intellectual disability had been identified, with that figure predicted to rise (Vissers 2015). The Deciphering Developmental Disorders multicentre study recruited over 12 000 children who had marked developmental delay, but no identified cause. It was estimated that 42% carried a genetic variant that was felt to underlie their condition (McRae 2017). It is important to note that the

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