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Gut-initiated neuroprotection in Parkinson's disease: When microbes turn the tables in the battle against neuroinflammation

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Parkinson's disease, the second-most common neurodegenerative disorder, is characterised by motor impairments including tremor, rigidity, and slowness of movement (Poewe et al., 2017) as well as non-motor symptoms (Felice et al., 2016). The cardinal motor features arise as a consequence of dopamine depletion tracking neuronal loss in the substantia nigra in the brains of Parkinson's disease patients (O'Neill, 2019). Complementary avenues of investigation across clinical and preclinical research have converged to indicate a role for the gut microbiome in the neurobiology underpinning symptom expression in Parkinson's disease (Romano et al., 2021; Sampson et al., 2016; Travagli et al., 2020) (see Fig. 1). This includes the BBI Impact award winner for 2022, an award given solely based on citations, which provided an important microbial perspective on the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of Parkinson's disease (Sun et al., 2018).

Using this model, Sun and colleagues further highlighted the importance of focusing on gut-brain axis communication as an important mechanism in Parkinson's disease pathology (Sun et al., 2018). This and other neurotoxin-based models have been valuable resources to study the mechanisms underpinning neurodegeneration in Parkinson's disease and to aid in the development of useful neuroprotective strategies to control the motor symptoms and associated neuropathology that occur in this disease (Bove and Perier, 2012). There has been broad agreement that systemic administration of MPTP leads to accumulation of this blood–brain-barrier penetrant toxin in the CNS, where astrocytes convert MPTP to a toxic metabolite (the 1-methyl-4-phenylpyridinium (MPP+) ion) that subsequently initiates nigral cell and striatal dopamine loss and behavioral deficits (Meredith and Rademacher, 2011). Sun and colleagues demonstrated that the motor impairment and striatal neurotransmitter decrease in this model is also associated with a remodelled gut microbiota (Sun et al., 2018).

Investigating the causal role of disease-associated microbiota configurations often relies on fecal microbiota transplantation (FMT) in rodents (Gheorghe et al., 2021; Secombe et al., 2021). Sun and colleagues used this approach to elegantly demonstrate both that the remodelled gut microbiota from the MPTP model of Parkinson's disease mice induced motor impairment and striatal neurotransmitter decrease in normal mice, and that transplantation of the gut microbiota from normal mice into the mice administered MPTP was neuroprotective. The benefits for the recipient animals included a rescue of the neurotransmitter alterations, motor function and the aberrant gut microbiota profile. Importantly, the authors also investigated the mechanisms underpinning these observations to implicate suppression of neuroinflammation following the FMT (Sun et al., 2018). This is consistent with the important role of neuroinflammation in MPTP-induced neurotoxicity (Meredith and Rademacher, 2011) and microbial regulation of microglial maturation, activity and function (Erny et al., 2015; Erny et al., 2021; Lynch et al., 2021).

Clearly, these findings could have important implications for future approaches to the development of neuroprotective strategies in Parkinson's disease. In addition to the accumulating evidence implicating the gut microbiota as a potential trigger for the gastrointestinal and CNS

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pathology in this disorder (Challis et al., 2020; O'Donovan et al., 2020; Stockdale et al., 2021), the authors confirm that neuroprotection with a microbiota-targeting intervention is also a possibility in a CNS-initiated model (Sun et al., 2018). Nevertheless, there are some important caveats to consider when interpreting these results, many of which relate to limitations of the MPTP model itself. It is well known that the motor deficits produced in the MPTP model do not fully replicate those seen in Parkinson's disease nor are the neurobiological alterations equivalent (Meredith and Rademacher, 2011). For example, the misfolded α-synuclein aggregates that form Lewy bodies, a histological hallmark of Parkinson's disease, is not recapitulated in the MPTP model (Bove and Perier, 2012; Travagli et al., 2020). This is a particular concern in the acute single dose MPTP approach deployed in the report from Sun and colleagues where the phenotype produced is not progressive in nature (Meredith and Rademacher, 2011; Sun et al., 2018) and may have broader implications for the validation of the FMT-based model as a routine screening tool for neuroprotective strategies, as has been noted for the MPTP model in general (Bove and Perier, 2012). It has been reported that chronic low doses of MPTP are also capable of inducing the clinical intestinal pathology of Parkinson's disease, with the

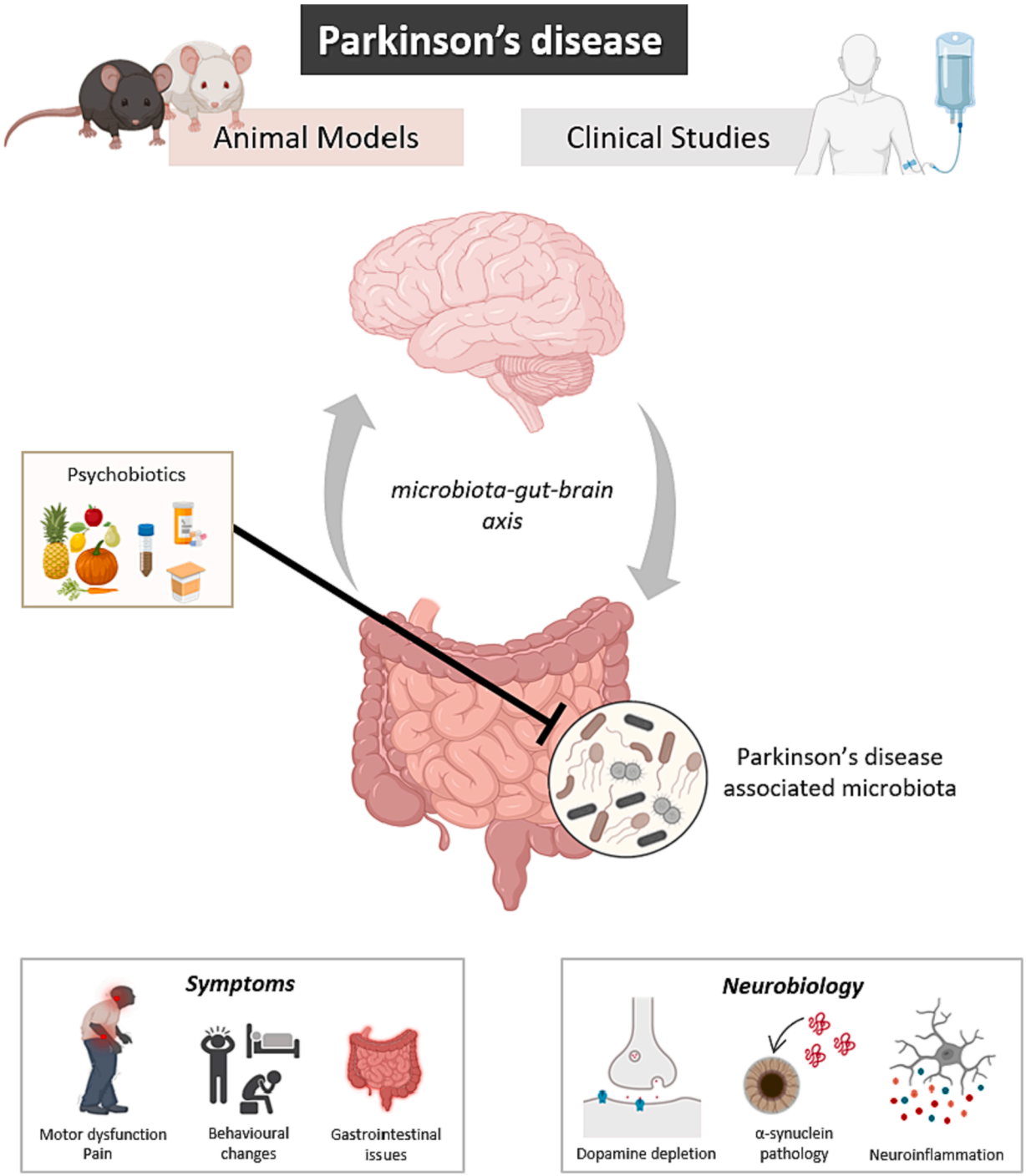

Fig. 1. The gut microbiota and neuroprotection in Parkinson's disease Clinical and preclinical observations indicate a role for the gut microbiota in the symptom profile and neuropathology associated with Parkinson's disease, including the dopamine depletion and the α-synuclein pathology. The work of Sun and colleagues demonstrates that the Parkinson's disease associated gut microbiota produced in the MPTP animal model may have a causal role in driving these prominent features of the disorder, opening up the possibility of gut-initiated neuroprotection strategies.

gastrointestinal dysfunction and intestinal pathology occurring prior to the motor dysfunction features (Lai et al., 2018). The use of more progressive models, based on repeated injections and/or escalating doses of MPTP may offer advantages over acute dose approaches from a translational perspective (Meredith and Rademacher, 2011).

It is important to note that the microbiota has also been associated with the motor deficits and neuroinflammation in a rodent model of Parkinson's disease based on the α-synuclein pathology (Sampson et al., 2016). A prebiotic high-fiber diet also attenuated motor deficits and reduced α-synuclein aggregation in the substantia nigra of α-synuclein overexpressing mice (Abdel-Haq et al., 2022). Interestingly, a recent report in this journal indicated that the microbial metabolite p-Cresol, which is increased in Parkinson's disease patients, is associated with dopaminergic dysfunction, an important new lead that warrants evaluation in Parkinson's disease models (Cirstea et al., 2020, Laudani et al., 2023).

The compositional gut microbiota alterations reported by Sun and colleagues in the MPTP model overlaps with those reported in recent *meta*-analysis that looked at common alterations in the gut microbiota of Parkinson's disease patients across multiple clinical cohorts (Romano et al., 2021). An intriguing question that remains open following the work of Sun and colleagues (Sun et al., 2018) pertains to the origin of the remodelled gut microbiota reported, given the presumably CNS-initiated basis of deficits induced in the MPTP model. The mechanisms implicated in the CNS actions of MPTP, including oxidative stress, apoptosis, mitochondrial dysfunction and inflammation could also be relevant locally in the gastrointestinal tract in reshaping the gut microbiota although it would be expected that monoamine oxidase A is less effective in the bioactivation of MPTP in the gut (Billett, 2004). While we should not discount the bidirectional nature of brain-gut axis communication in the reported compositional microbiota alterations, the reciprocal interactions between xenobiotics and gut microbes are increasingly coming into focus in this regard (Clarke et al., 2019). This is an important consideration in light of findings around the impact of gut bacterial tyrosine decarboxylases in restricting the availability of levodopa, the key current treatment option for Parkinson's disease (Maini Rekdal et al., 2019; O'Neill, 2019; van Kessel et al., 2019).

The work reported by Sun and colleagues adds substantially to our knowledge about the role of the gut microbiome in Parkinson's disease, including establishing a potential causal role and bringing key mechanistic insights that likely have implications for both the motor and non-motor symptoms (Sun et al., 2018) (See Fig. 1). The authors have provided the impetus for new avenues of investigation and their observations have been supported by numerous additional reports in the 4–5 years since publication. By showing us that gut microbes can be used to turn the tables in the battle against neuroinflammation in neurodegenerative disorders, they are worthy recipients of the BBI Impact award for 2022.

Declaration of Competing Interest

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Data availability

No data was used for the research described in the article.

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