Serotonergic loss underlying apathy in Parkinson's disease

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Commentary on Maillet et al "The Prominent Role of Serotonergic Degeneration in Apathy, Anxiety and Depression in de novo Parkinson's disease"

Disentangling the contribution of dysfunction in various neurotransmitter systems to specific clinical manifestations in Parkinson's disease (PD) is an important prerequisite for understanding their pathogenesis and for the development of effective treatments. The clinical phenomenology of PD encompasses a range of motor and non-motor disorders, of which neuropsychiatric presentations such as depression, anxiety, dementia, impulse control disorders and apathy are some of the most deleterious for both patients' and carers' quality of life. Apathy, characterized by diminished goal-oriented behaviour, cognition, interests, and emotional expression[Starkstein 2012], is common in PD, affecting approximately 40% of patients in cross-sectional studies. It is under-recognised [Gallagher *et al.* 2010] and often confused with dementia or depression, of which it can also be an integral part[Pagonabarraga *et al.* 2015]. Understanding its distinct nature can help improve families' understanding and appropriate management. The underlying pathology of apathy is currently poorly understood, although clinical and imaging findings support the role of dopaminergic dysfunction in the pathophysiology of apathy in PD [Wen *et al.* 2016;Magnard *et al.* 2016] and in patients without PD [Pagonabarraga, Kulisevsky, Strafella, and Krack2015;Starkstein2012]. In this issue Maillet et al, for the first time, report on the differential contribution of serotonergic and dopaminergic mechanisms to apathy in PD using positron emission tomography (PET) molecular imaging.

Evidence from animal, biochemical, post-mortem and human *in vivo* studies have demonstrated loss of striatal and extra-striatal serotonin markers in the course of PD indicating that the serotonergic system plays a key role in PD pathology [Politis and Niccolini 2015]. The data from the study by Maillet et al (2016) support the involvement of serotonergic system also to the development of apathy in PD. They used [^{11}C]DASB and [^{11}C]PE2I PET to index presynaptic serotonergic and dopaminergic function, respectively, in 15 apathetic and 15 non-apathetic untreated patients with PD and in controls. Their findings demonstrate greater serotonergic loss in the basal ganglia in the apathetic PD compared to PD patients without apathy, with both PD groups showing reduced dopaminergic uptake compared to controls. Moreover, greater serotonergic loss in caudate and orbitofrontal cortex correlated with the severity of apathy in patients with PD, whereas apathy was not associated with dopaminergic deficits.

PET is a molecular imaging technique for the quantitative and non-invasive imaging of biological functions. The distribution and kinetic profiles of compounds targeting specific biological molecules in tissue reflect specific biological functions in the living body. PET used together with specific serotonin radioligands has played a major role in elucidating the pathophysiology of serotonergic system in PD. Over the past several years, we have seen the development of several PET radioligands tagging serotonin targets in the human brain. [^{18}F]MPPF for 5-HT$_{1A}$ receptors, [^{18}F]setoperone for 5-HT$_{2A}$ receptors and [^{11}C]AZ10419369 for 5-HT$_{1B}$ receptors, and [^{11}C]DASB to image the 5-HT

transporter (SERT) are few examples of PET techniques for studying the serotonin system in the human brain.

Studies using [^{11}C]DASB PET have demonstrated that PD pathology is characterised by a progressive and non-linear loss of serotonergic terminals, which is slower compared to the dopaminergic degeneration. PET molecular imaging has shown that the clinical implications of the serotonergic pathology in PD have been associated with the development of non-motor symptom burden and specifically with symptoms of depression, fatigue , weight loss, and visual hallucinations. [^{11}C]DASB PET studies suggest that the serotonergic system is also implicated in the development of tremor in PD, which has a variable response to dopaminergic treatment, whereas this is not the case for bradykinesia and rigidity that are underlined by dopaminergic deficits [Loane *et al.* 2013]. Disturbance of serotonergic relative to dopaminergic innervation in the striatum has also been shown to be responsible for the development of levodopa-induced and graft-induced dyskinesias in patients with PD[Politis and Niccolini2015], illustrating the interrelation of serotonergic and dopaminergic mechanisms in PD. The striatal serotonergic terminals under significant overexpression or when there is dopaminergic denervation, such as in PD, become a major source of endogenous or levodopa-derived dopamine release[Carta *et al.* 2007] Serotonergic neurons lack an effective mechanism for the regulation of synaptic dopamine levels, which leads to fluctuations in synaptic dopamine levels and to pulsatile stimulation of striatal postsynaptic dopamine receptors and, subsequently, dyskinesias.

Maillet et al (2016) findings on apathy add to the list of PD motor and non-motor symptoms and complications, which are underlined by serotonergic pathology. Even in this early cohort, there was more pronounced reduction in serotonin transporter (SERT) binding than dopamine transporter (DAT) binging in those with apathy, thus challenging the concept of predominantly dopaminergic involvement in the early disease stages.

These imaging findings may change approaches to treatment of apathy in PD. Treatment options for apathy are currently limited. The profound loss of motivation, initiative and low mood, which can been seen in patients following withdrawal of dopamine agonists (Dopamine Agonist Withdrawal Syndrome, DAWS,[Solla *et al.* 2015] and following dose reductions after Deep Brain Stimulation for PD[Hindle, I *et al.* 2016], and the improvement after increasing the dosage of dopamine agonist, suggest an important role of the dopaminergic system which mediates reward and motivation. However, currently there is little evidence from treatment trials for the optimal treatment of apathy in PD unrelated to these specific situations. Small controlled studies and case series report improvement with dopaminergic medications and noradrenergic and serotonergic antidepressants and stimulants. In addition, recently, a small trial with the butyryl cholinesterase inhibitor rivastigmine in 30 patients with PD without cognitive impairment reported improvement of apathy scores, suggesting a role for cholinesterase inhibitors in the treatment of apathy in PD and for cholinergic dysfunction in apathy in PD [Devos *et al.* 2014].

The underlying biochemical substrates of apathy are therefore likely to be complex. Coexisting syndromes and medications also make interpretation of many clinical and imaging studies difficult. Maillet et al (2016) studied *de novo* PD patients. This avoided difficulties in interpretation of results in patients already treated with dopaminergic or serotonergic medications. However, patients also had increased depression and anxiety scores, and PET data correlated with apathy severity but also with depression and anxiety levels. Previous PET studies have shown that serotonergic mechanisms play a role also in these neuropsychiatric disorders and therefore, disentangling these disorders, and identifying the pathophysiology of each individual disorder, remains a challenge. Nevertheless, the results of this study suggest that medications acting on serotonergic targets may be efficacious in

the treatment of apathy and other neuropsychiatric disorders in PD. Whilst a plethora of symptoms in PD have now been associated with serotonergic dysfunction, no treatments that specifically target these deficits exist. Such agents may provide a future avenue for the treatment of these disorders even in early PD. Future studies should additionally explore the involvement of other neurotransmitter systems in the development of motor and non-motor symptoms and complications in patients with PD. Such examples are the noradrenergic, cannabinoid and cholinergic systems, which could be studied with PET molecular imaging together with clinical observation.

Reference List

Carta M, Carlsson T, Kirik D, Bjorklund A. Dopamine released from 5-HT terminals is the cause of L-DOPA-induced dyskinesia in parkinsonian rats. Brain 2007; 130: 1819-1833.

Devos D, Moreau C, Maltete D *et al*. Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomised clinical trial. J Neurol Neurosurg Psychiatry 2014; 85: 668-674.

Gallagher DA, Lees AJ, Schrag A. What are the most important nonmotor symptoms in patients with Parkinson's disease and are we missing them? Mov Disord 2010; 25: 2493-2500.

Hindle F, I, Pall HS, Mitchell RD, Kausar J, Cavanna AE. Apathy in patients with Parkinson's disease following deep brain stimulation of the subthalamic nucleus. CNS Spectr 2016; 1-7.

Loane C, Wu K, Bain P, Brooks DJ, Piccini P, Politis M. Serotonergic loss in motor circuitries correlates with severity of action-postural tremor in PD. Neurology 2013; 80: 1850-1855.

Magnard R, Vachez Y, Carcenac C *et al*. What can rodent models tell us about apathy and associated neuropsychiatric symptoms in Parkinson's disease? Transl Psychiatry 2016; 6: e753.

Pagonabarraga J, Kulisevsky J, Strafella AP, Krack P. Apathy in Parkinson's disease: clinical features, neural substrates, diagnosis, and treatment. Lancet Neurol 2015; 14: 518-531.

Politis M, Niccolini F. Serotonin in Parkinson's disease. Behav Brain Res 2015; 277: 136-145.

Solla P, Fasano A, Cannas A *et al*. Dopamine agonist withdrawal syndrome (DAWS) symptoms in Parkinson's disease patients treated with levodopa-carbidopa intestinal gel infusion. Parkinsonism Relat Disord 2015; 21: 968-971.

Starkstein SE. Apathy in Parkinson's disease: diagnostic and etiological dilemmas. Mov Disord 2012; 27: 174-178.

Wen MC, Chan LL, Tan LC, Tan EK. Depression, anxiety, and apathy in Parkinson's disease: insights from neuroimaging studies. Eur J Neurol 2016; 23: 1001-1019.