Parkinsonism and Related Disorders

Reply to 'Impulse control disorders are associated with lower ventral striatum dopamine D3 receptor availability in Parkinson's disease: A [11C]-PHNO PET study.'

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Corresponding Author:	Pedro Barbosa, M.D. Reta Lila Weston Institute of Neurological Studies, University College London London, UNITED KINGDOM
First Author:	Pedro Barbosa, M.D.
Order of Authors:	Pedro Barbosa, M.D.
	Bimali Hapuarachchi
	Atbin Djamshidian
	Kate Strand
	Andrew J Lees
	Rohan de Silva
	Janice L Holton
	Thomas T Warner
Abstract:	Pagano and collaborators have recently reported lower ventral striatum D3 receptor availability in Parkinson's disease using PET scan. Our group conducted the first postmortem study of individuals with PD who had ICD and related behaviours in life and reported lower alpha-synuclein pathology and D3R levels in the nucleus accumbens of such individuals. The findings by Pagano and co-authors of low D3R binding in PD patients at baseline, when taken together with our findings of lower Lewy pathology and D3R in the nucleus accumbens, favour the hypothesis that D3R levels are downregulated because of excessive synaptic dopamine.
Suggested Reviewers:	Daniel Weintraub daniel.weintraub@uphs.upenn Expertise in the field
	Mark Edwards medwards@sgul.ac.uk Expertise in the field

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6. All sources of financial support for the work have been declared in the Acknowledgements section of the manuscript. Any additional conflicts of interest must also be declared. Please include declarations of any consultancy or research funding received from relevant companies from three years prior to performance of the research until the time of manuscript submission. If the research is supported by internal funds, that should be stated as well.

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Pedro Melo Barbosa

To the Editors of Parkinsonism and Related Disorders **10/10/2021**

Subject: Correspondence in reply to **'Impulse control disorders are associated with lower ventral striatum dopamine D3 receptor availability in Parkinson's disease: A [11C]-PHNO PET study.'**

Dear Editors,

Please find enclosed a correspondence in reply to a recent publication by Pagano and collaborators, reporting lower ventral striatum D3 receptor availability in Parkinson's disease using PET scan. In the correspondence we attempt to explain the findings of the study in light of our findings from the first *post mortem* study of D3 receptors in PD published in 2018.

We hope that you will find our correspondence interesting and worth publishing.

Looking forward to hearing from you.

Kind regards,

Dr Pedro Barbosa
Reta Lila Weston Institute of Neurological Studies, Department of Clinical Movement Disorder and Neuroscience, Institute of Neurology, University College London,
London, UK
1 Wakefield Street, WC1N 1PJ, London, UK.
Tel: +55 11 966123476.
E-mail: pmbarbosa@me.com

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Authors:

Pedro Barbosa[1,2], Bimali Hapuarachchi[1], Atbin Djamshidian[1,3], Kate Strand[2], Andrew J Lees[1,2], Rohan de Silva[1], Janice L Holton[2], Thomas T Warner[1,2]

1. **Reta Lila Weston Institute of Neurological Studies, Department of Clinical Movement Disorder and Neuroscience, UCL Queen Square Institute of Neurology, London, UK**
2. **Queen Square Brain Bank for Neurological Disorders, UCL Queen Square Institute of Neurology, London, UK.**
3. **Department of Neurology, Innsbruck Medical University, Innsbruck, Austria**

Reply to 'Impulse control disorders are associated with lower ventral striatum dopamine D3 receptor availability in Parkinson's disease: A [11C]-PHNO PET study.'

Authors:
Pedro Barbosa[1,2], Bimali Hapuarachchi[1], Atbin Djamshidian[1,3], Kate Strand[2], Andrew J Lees[1,2], Rohan de Silva[1], Janice L Holton[2], Thomas T Warner[1,2]

1. **Reta Lila Weston Institute of Neurological Studies, Department of Clinical Movement Disorder and Neuroscience, UCL Queen Square Institute of Neurology, London, UK**
2. **Queen Square Brain Bank for Neurological Disorders, UCL Queen Square Institute of Neurology, London, UK.**
3. **Department of Neurology, Innsbruck Medical University, Innsbruck, Austria**

We read with great interest the recently published article by Pagano and collaborators.[1] In view of the scarcity of *in vivo* imaging data on dopaminergic D3 receptors (D3R) this study is a welcome addition to the literature. By using a highly selective D3R tracer the authors hope to avoid the problems of interpretation present in some earlier studies where the radio ligand used also binds to D2 receptors.

Reduced D3R binding has already been reported in pathological gambling in Parkinson's disease (PD),[2] but this is the first study to report similar findings in other impulse controls disorders (ICDs) in PD and to correlate lower D3R binding levels in the ventral striatum with their severity, as measured by the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS).

ICDs and related behaviours, such as dopamine dysregulation syndrome (DDS) and punding, are linked with dopaminergic treatment.[3] Our group conducted the first *postmortem* study of individuals with PD who had ICD and related behaviours in life and reported lower alpha-synuclein pathology and D3R levels in the nucleus accumbens of such individuals.[4] Considering that so far, no additional *postmortem* studies have been conducted to confirm or contradict our findings, it is reassuring to see our results replicated by a neuroimaging study.

The majority of patients in our pathological study had dopamine dysregulation syndrome whereas in the study by Pagano et al, compulsive buying was the most common behavioural abnormality. However, a comparison of the data is justified as previous studies have suggested the existence of a central hedonic representation in the brain, leading different ICD and related behaviours to activate similar brain circuits.[5]

Neuroimaging studies need to be interpreted according to the status of the individual studied. If the imaging is taken after stimulus presentation, reduction of tracer binding may result from excessive synaptic dopamine.[5,6] On the other hand, in studies that assess

patients at baseline, off medication and without stimulus presentation, a reduction in tracer binding does not necessarily imply increased dopaminergic tone, and may also be the consequence of reduced expression of dopaminergic receptors.[7]

The findings by Pagano and co-authors of low D3R binding in PD patients at baseline, when taken together with our findings of lower Lewy pathology and D3R in the nucleus accumbens, favour the hypothesis that D3R levels are downregulated because of excessive synaptic dopamine. However, if excessive dopaminergic stimulation is the sole culprit, downregulation should occur when other dopaminergic receptors are studied. In our study there was a trend for lower D2R in the accumbens that did not reach statistical significance, perhaps as a consequence of the small sample size.

Lower alpha-synuclein burden implies a more preserved ventral striatum in individuals with PD and ICDs and related behaviours making it more susceptible to overstimulation by dopaminergic drugs and more capable of triggering physiologic adaptions to increased synaptic dopamine. This is the central argument of the 'dopamine overdose' hypothesis.[8]

There is still much to be learnt about the pathophysiology of impulse control disorders in Parkinson's disease. Future neuroimaging studies should ideally compare tracer binding in the resting state, after dopaminergic therapy and stimulus presentation in the same individual. Additional *postmortem* studies will be important to confirm our findings and extend them looking at other potential markers, such as delta-FosB, opioid and serotoninergic receptors.

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