BRAIN
SCIENTIFIC COMMENTARY

A cholinergic contribution to postural control and freezing of gait in Parkinson's disease

This scientific commentary refers to 'Cholinergic system correlates of postural control changes in Parkinson's disease freezers' by Roytman *et al*. (https://doi.org/10.1093/brain/awad134).

Gait disorders and their consequences—most notably falls—are common manifestations of ageing and age-associated conditions such as Parkinson's disease, and adversely affect quality of life. Progressive and specific degeneration of the cholinergic system is widely implicated in Parkinson's disease, and may underpin the discrete gait impairments that are present even at disease diagnosis. One of the most debilitating gait difficulties in Parkinson's disease is freezing of gait (FoG), which is characterized by the failure of step initiation or turning on walking, and which becomes increasingly problematic as the disease progresses. FoG increases the risk of falls and is associated with neuropsychiatric symptoms such as apathy as well as with reduced quality of life.[1]

Molecular imaging methods using the PET radiotracer ^{18}F-fluroethoxybenzovesamicol (FEOBV), which has a high binding affinity and selectivity for the vesicular acetylcholine transporter (VAChT), have shown reduced VAChT expression in striatal cholinergic interneurons, in addition to limbic archicortical structures, in patients with Parkinson's disease and FoG, highlighting higher level cortical dysfunction.[2] These findings were distinct from the thalamic cholinergic deficits seen in individuals with frequent falls, and have potential implications for treatment targets.[2] To date, there is disagreement as to how postural instability and FoG are related: there is some evidence that postural instability may be reinforced and intensified by FoG, or vice versa; conversely it has been argued that the two may share similar neurobiological mechanisms without being fundamentally related.[3] In this issue of *Brain*, Roytman and colleagues[4] address some of these uncertainties by comparing novel postural control features, as measured using computerized posturography, between freezers and non-freezers, and by determining any association with cholinergic integrity as assessed by acetylcholinesterase PET. They postulate a shared cholinergic pathology underpinning both FoG and impaired postural control in people with Parkinson's disease, mediated by disruption to multisensory-motor and cognitive processing.

The authors assessed performance on a posture test platform called the Equitest Sensory Organization Test (SOT) (NeuroCom© International, Inc.) in both freezers and non-freezers in the OFF state. The SOT can determine reliance on visual, proprioceptive and vestibular cues in maintaining postural stability under conditions of varying visual input (eyes open/eyes closed), plate movement (fixed or sway), surrounding environment (fixed or sway-referenced) and sensory input (proprioceptive, visual, and vestibular). The authors then used acetylcholinesterase PET to examine whether any differences between freezers and non-freezers in postural control metrics were associated with cholinergic dysfunction.

The principal findings from the study were firstly that those with FoG were more reliant on proprioceptive cues, with differences between the freezer and non-freezer groups most evident when proprioceptive cues were rendered unreliable, highlighting the importance of visual-vestibular cues for maintaining postural control in freezers. Secondly, the most consistent predictor of freezer status in terms of exact postural control features was critical mean square displacement in the anterior-posterior axis, increases of which can be regarded as an overall reduction in the effectiveness of postural adjustments for maintenance of stability. As this feature plus the critical time interval (time taken for sensory information to travel, integrate with other modalities and be used via top-down postural control mechanisms) increased in freezers in the absence of reliable proprioceptive cues, the authors postulated that greater impairments in vestibular processing might lead to difficulties reconciling conflict between visual and vestibular sensory cues in those with FoG. This complements recent imaging work from the same group, where reduced cholinergic integrity of vestibular sensory conflict deficits in Parkinson's disease localized to structures involved in multi-sensory—particularly vestibular sensory—processing.[5] Vestibular sensory conflict deficit-associated cholinergic terminal loss had the strongest association with FoG status, followed by a history of postural instability and falls. Finally in their current study, the authors showed that right cortical cholinergic network changes underpinned balance during visual-vestibular conflict; changes which were destabilized by a greater anticholinergic burden.

Limitations of the study include the inability of acetylcholinesterase PET tracer to assess critical structures involved in visual-vestibular integration of postural control, including the cerebellum. Recent work using functional MRI with motor and visual imagery highlighted the importance of several cerebellar regions in freezers compared to non-freezers, with increased activation in the cerebellum in Parkinson's disease without FoG compared to controls.[6] This increased activation in non-freezers may be analogous to the compensatory upregulation of hippocampal cholinergic innervation in Parkinson's disease with normal cognition compared to Parkinson's disease with mild cognitive impairment,[7] and has implications for blanket pro-cholinergic treatment in this heterogeneous disease.

Notwithstanding the PET tracer limitation, the study by Roytman *et al*.[4] highlights the importance of the right cortical

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cholinergic system in postural control in Parkinson's disease, particularly with respect to maintaining stability under challenging conditions. A key clinical—and potentially actionable—take home message is that an anticholinergic burden score of ≥3 (for example, the prescription of amitriptyline at any dose) was associated with suppression of this right cortical cholinergic system and increased postural instability independent of motor disease and freezer status. Drugs with anticholinergic burden are commonly prescribed for non-motor symptoms such as overactive bladder, pain and hypersalivation in Parkinson's disease; the potential risks should be carefully discussed with patients at prescription, particularly with multiple drugs.

Finally, this work adds to the notion that personalized procholinergic interventions may be helpful in the management of gait and balance disorders in Parkinson's disease. A large interventional study of cholinesterase inhibitors in falls in Parkinson's disease has just reached its recruitment target,[8] with FoG as a secondary outcome measure; the results of this study will be informative in future management of advanced Parkinson's disease. Studies of novel non-pharmacological interventions such as non-invasive vagus nerve stimulation, which targets potentially cholinergically mediated gait impairments, are also underway.[9] Additional promising therapeutic non-invasive and neuromodulatory interventions that are relevant to the current study include caloric vestibular stimulation and targeting the acetylcholine-dependent microbiome through the gut-brain axis.[10] A better understanding of the nuances of cholinergic dysfunction and a personalized approach to treatment strategies is key to improving the management of debilitating symptoms in Parkinson's disease.

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Competing interests

The authors report no competing interests.

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