Title: Cerebral Mechanisms underlying tremor variability

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Background: Tremor is one of the most common symptoms of Parkinson's disease and could impact approximately 85% of the patient population. However, despite its prevalence our understanding of tremor in Parkinson's disease is limited, influencing treatment of this common symptom. To date, pharmaceutical therapies available for the treatment of Parkinson's disease had limited effect on tremor; with some studies reporting approximately 60% of patients' tremor not responding to dopaminergic medication. These observations have motivated our research into alternative stimulation based treatment strategies for tremor such as peripheral median nerve stimulation, non-invasive transcranial alternating current stimulation and invasive deep brain stimulation[1]. This work has exposed an important consideration to take into account while developing novel treatment strategies: *the natural variability of tremor*. Natural variability of tremor which has consequences over undulations in tremor severity and how patient's trembling limb moves in space over seconds, hours and days has a significant impact on how we evaluate efficacy of new treatment strategies. Beyond its impact on treatment development, we also hypothesize that natural variabilities in tremor, as assessed from wearable technologies, provide a window into their origin in the central brain network.

Project Description: We will explore the cerebral mechanisms underlying spontaneous transitions between different tremor modes, by testing for brain activity time-locked to these events using combined tri-axial accelerometery and fMRI[2] based on the **Personalised Parkinson's Project dataset**[3]. Finally, by grouping data across patients depending on how often their tremor switches between different modes, we will evaluate potential links between tremor-related brain activity and inter-regional connectivity, using combined accelerometery-fMRI, and measures of their *natural tremor variability* as evaluated from the wearable sensors.

Training: The project will take place in the Medical Research Council Brain Network Dynamics Unit at the University of Oxford and students will benefit from the both the extensive generic and transdisciplinary skills training available within the Unit. The student will spend part of their PhD at the Donders Institute where Personalised Parkinson's dataset has been acquired. This particular project will also offer the following specific training on signal processing of data obtained from wearable sensors and fMRI analysis.

Key Publications:

1. Cagnan, H. *et al.* Stimulating at the right time: phase-specific deep brain stimulation. *Brain* **140**, 132–145 (2017).
2. Helmich, R. C., Janssen, M. J. R., Oyen, W. J. G., Bloem, B. R. & Toni, I. Pallidal dysfunction drives a cerebellothalamic circuit into Parkinson tremor. *Annals of Neurology* **69**, 269–281 (2011).
3. Bloem, B. R. *et al.* The Personalized Parkinson Project: examining disease progression through broad biomarkers in early Parkinson's disease. *BMC Neurology* **19**, 160 (2019).

Funding: The successful applicant will be considered for a Clarendon fund or other University scholarship. Students with their own independent funding will also be considered.

Contact: Prof Hayriye Cagnan will be happy to discuss the project and PhD further. Please contact them by email on hayriye.cagnan@ndcn.ox.ac.uk