UNITE-PD

Unraveling the neural mechanisms underlying compensation strategies for gait impairments in Parkinson's Disease: a transnational, multimodal approach (UNITE-PD)

Gait impairments are common in Parkinson's disease (PD) and significantly impact mobility, independence and quality of life. The application of compensation strategies - such as external or internal cueing - is an essential and evidence-based element of gait rehabilitation in PD. Cueing can be highly effective in improving mobility, but not every patient benefits equally from the same cueing strategy. A one-size-fits-all approach to gait rehabilitation therefore does not suffice. At present, the underlying working mechanisms of cueing strategies are poorly understood, and it is unknown how the efficacy of different modes of cueing changes longitudinally. Improving the understanding of the key mechanisms underlying compensation at the neurological systems level will help to refine cueing strategies and their timely delivery for a hallmark impairment in PD.

In this transnational collaborative project, we bundle a unique set of complementary and synergistic methods to study the working mechanisms of gait compensation. First, we intend to have a shared approach to characterizing our patient cohorts behaviourally and clinically to converge our study efforts. Next, we will combine our world-leading expertise in ambulatory electroencephalography (EEG), functional and structural MRI, concurrently delivered transcranial magnetic stimulation and EEG, and neuromodulation in PD. For the first time, we will adopt a multi-modal approach to study the neural mechanisms of cueing to create an encompassing framework for explaining the brain responses to cueing in PD. As such, we have a dual ambition: (1) to reveal and compare the regulatory control mechanisms underlying effective cueing; and (2) to make a tangible step forward in understanding what drives neuronal compensation in a wider sense, as a basis for personalized rehabilitation strategies in current clinical care, while also pointing to new avenues for neuroscientific inquiry in this domain.

This project aims to achieve 4 goals: (1) we identify the brain network involved in mediating the effects of cueing as an important compensation strategy; (2) we will identify differences in brain connectivity patterns elicited by internal versus external cueing, so as to identify shared and dissimilar neural circuitries; (3) we will compare brain connectivity patterns between patients who benefit from cues versus those who do not, to identify the key effective components of the compensatory networks in the brain; and (4) we will identify the temporal network changes elicited by long-term use of cueing in order to ascertain how adaptation to cueing manifests in the brain. Based on our recent ambulatory EEG study on the cortical activity during external auditory and internal cueing in PD, and the available literature, we hypothesize that both modes of cueing will improve central motor activation by recruiting frontal-striatal, frontal-parietal and cortico-thalamo-cerebellar loops. We also expect that each strategy will have a distinct neural fingerprint, potentially explaining why one strategy may work in one patient but not in the next. With respect to the efficacy of cueing over time, we hypothesize that consistent long-term use of cueing induces neuroplasticity, strengthening the efficiency within-compensatory and locomotor pathways and possibly reducing between-compensatory and locomotor network connectivity. As the long-term efficacy of compensation strategies will be mediated by compliance, we will measure this crucial factor objectively using wearable technology to enable building robust models of compensation. In short, this project will reveal key fundamental knowledge on the role of compensatory brain function, which will facilitate the development of innovative rehabilitation interventions to improve walking in persons with PD.

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