CONTROL-PD Abstract

Parkinson's disease (PD) has a long prodromal phase, in which latent cerebral changes can manifest itself as prodromal symptoms, for example idiopathic REM-sleep behavioural disorder (RBD), hyposmia, and cognitiveaffective symptoms (e.g. anxiety and depression). Increasing evidence suggests that the propagation of brain dysfunction in PD may take different routes, i.e. bottom-up (brainstem-to-cortex) or top-down (cortex-to-brainstem), and that it may affect focal versus diffuse brain systems. Here we aim to link these different neurobiological routes of PD propagation to distinct neurocomputational mechanisms of cognitive-affective dysfunction. We hypothesize that brainstem-to-cortex versus cortex-to-brainstem propagation routes are associated with deficits in distinct cognitive computations, as well as distinct genetic and prodromal clinical phenotypes. By leveraging computational model-based analyses of cognition, we will localize specific cognitive deficits to cerebral systems (brainstem or cortex, focal or diffuse). These data will be linked to multi-modal neuroimaging markers of propagation, epidemic spreading models of brain dysfunction, and genetic risk factors (polygenic risk scores, and separate groups of nonmanifesting GBA and LRRK2 mutation carriers). We will take advantage of existing longitudinal cohorts (>220 idiopathic RBD patients, >100 non-manifesting GBA/LRRK2 mutation-carriers, >750 early PD patients), where multi-modal imaging and genotyping is available. These data will be enriched by deep, online cognitive/affective phenotyping. This study will, for the first time, link inter-individual differences in neurodegeneration propagation to prodromal cognitive-affective and clinical phenotypes. This may help to further improve the predictive value of already recognized prodromal factors, and it may offer a mechanism-based approach to treatment in prodromal PD.