CONTROL-PD

Cognitive Propragation in Prodromal Parkinson's disease

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 cognitive affective 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 non-manifesting 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.

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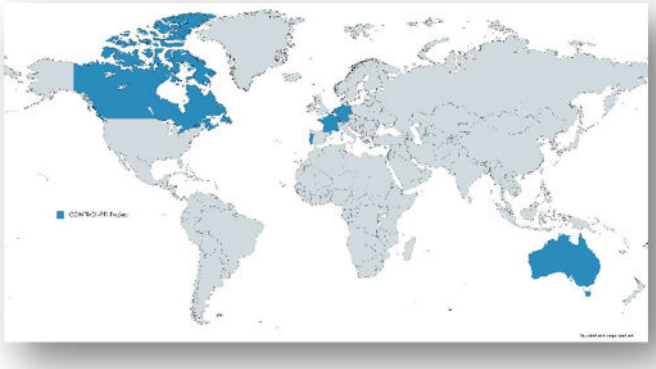

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