Project Details	
Project Code	MRC23PHSCa Webber
Title	Personalising Parkinson's: identification Brain-first versus Body-first subtypes
Research Theme	Population Health Sciences
Summary	Medical imaging and biopsy studies suggest that Parkinson's disease starts at different places in the body: in some Parkinson's patients, the brain is damaged (brain-first subtype) before the peripheral nervous system and in others, the opposite is seen (body-first subtype). To determine Parkinson's body vs brain subtypes and their consequence, we will exploit big data in healthcare, genetics and imaging.
Description	Background: Parkinson's disease (PD) is a group of heterogeneous disorders, thus to develop/match the best treatment to an individual, it is necessary to go further than a diagnostic based on a subset of clinical symptoms. Medical imaging studies of PD patients and studies of biopsies and gut and brain tissue from biobanks suggest in some patients, the brain is affected before the peripheral nervous system - brain first and in others, the opposite pattern is seen -body first. The existence of both subtypes, has been proposed from a limited number of PD patients using advanced medical imaging technologies and from autopsy examination This PhD program aims to distinguish brain-body subtypes in the clinical cohort or the general population for which other data types are available. Hypothesis(H) / Question (Q) H1 – There are two genetic Parkinson's subtypes: No molecular mechanism differentiating these subtypes has been proposed. We hypothesise that the genetic variants associated with the body-first subtype must act outside of the central nervous system e.g. gut cell types. Q1: Does PD genetic risk support the existence of both aetiologies? In which cell types in which peripheral tissues does PD genetic risk highlight in the body-first subtype? H2: There are two clinical Parkinson's subtypes: The brain-first and body-first aetiologies may be distinguished in the symmetry of neuropathology that a body-first aetiology will affect when reaching the brain symmetrically, while a brain-first aetiology starting in the brain may arise asymmetrically. The DaTscan is a Positron emission tomography imaging visualisation in the earlier stages of the loss of dopaminergic neurons and thus can detect which side of the brain are affected. Q2: Do patients with a symmetric DaTscan have more peripheral symptoms than patients with an asymmetric DaTscan? Can we predict the most informative clinical features to predict two subtypes? Do these clinical subtypes coincide with genetic subtypes? H3: There are two prodromal subtypes Both subtypes are likely more distinguishable at the earlier stages of the disease than later: where the alpha-synuclein clumps in multiple organ systems and both subtypes converge clinically. UK Biobank offers an exceptional resource to study PD retrospectively. We demonstrated we can identify PD's years before the diagnosis using physical activity measured via a wrist-worn accelerometer [3] Here we suppose to distinct both subtypes by extracting the features associated with an asymmetric movement. Q3: Is it possible to distinguish these subtypes in the general population by combining electronic health records, accelerometer data and individual genetics data? Do these prodromal subtypes coincide with genetic and

	clinical subtypes? Objectives/Supervisor/Time: 1: Identification of body & brain subtypes by combining the human single-cell atlas and genetic data [Pf Webber single-cell atlas/ Dr Sandor Genetics] / 1 year 2: Identification of body & brain subtypes in the large deeply phenotyped clinical cohorts by combining hundreds of clinical measured, brain imaging data and genetic data [Dr Lancaster medical imaging/ Pf Ben-Shlomo Deeply phenotyped Parkinson's cohort, Computational modelling/Dr Sandor Genetics] / 1 year 3: Identification of the body & brain subtypes in the general population by combining electronic medical cohort, accelerometer and genetic data [Pf Ben-Shlomo Epidemiology-Population Heath /Dr Sandor UK Biobank Accelerometer data] / 1 year 4: – Training/Conferences/Writing Manuscripts/All / 1 year
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