Enhancing Neuro Imaging Genetics through Meta-Analysis Consortium (ENIGMA)
Parkinson's Disease Secondary Analysis Proposal – ENIGMA-PD Vasc Project

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Overview:

Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by progressive and selective loss of neurons. The factors leading to and driving this loss are now considered to be multi-factorial; however, until the complex factors are understood and potentially modifiable factors identified, there will remain to be no effective disease modifying or neurodegenerative agents [1, 2].

The neurovascular (NV) model of neurodegeneration is a rapidly evolving concept. It advocates the contribution of blood-brain barrier (BBB) dysfunction and hypoperfusion to the other key players contributing to selective neuronal dysfunction and loss [3-13]. In addition, co-existing cerebrovascular disease has been associated with more significant PD-related disability, and with gait and cognitive phenotypes that tend to be less responsive to L-dopa treatment [14-19]. Indeed, with improved vascular measures of subtle small vessel disease and with the advent of large, multi-centre longitudinal studies in PD, an association of PD with vascular changes and risk factors (in particular hypercholesterolemia and BP abnormalities) is rapidly emerging [20-27]. Therefore, understanding these changes and finding effective markers in the clinical setting is paramount [28].

MRI techniques have paved the way to investigating various vascular measures, in a non-invasive, highly reproducible manner [29-32]. Our work, looking at structural measures of small vessel disease (SVD), namely white matter lesion (WML) burden, showed an increased burden in PD when compared to controls [33]. Interestingly, functional measures, including arterial spin labelling (ASL) measures of perfusion, revealed posterior cerebral hypoperfusion (in keeping with recent studies [24, 26, 34]) and diffuse prolonged arterial arrival time (AAT) in PD compared to controls, which may represent altered vasculature or compensatory mechanisms [33, 35]. In addition, measures of BBB permeability using dynamic contrast-enhanced MRI (DCE-MRI) have revealed increased BBB permeability in PD [36]. Thus, these findings highlight the range of cerebral vascular pathology identified in PD and how MR imaging can measure these changes and help inform mechanisms.

WML burden (as a surrogate marker of SVD [37, 38]), has been the most applied in the PD setting, yet despite more than a decade of work, is still producing conflicting results [39-46], with only some studies reporting an increased WML burden in PD. This might be due to relatively small, heterogeneous study populations, therefore it is crucial to perform analyses across much larger study populations [47]. However, whether total WML burden *per se* or the anatomical distribution of WML and corresponding clinical phenotypes is most relevant also remains unclear. It appears that WML distributed in clinically eloquent areas may be more relevant to the underlying PD pathology regardless of total WML burden [18, 48-56]. For example, periventricular and frontal and occipital deep white matter lesions have been associated with bradykinesia and axial problems [57-61]. Additionally longitudinal studies have shown greater baseline WML burden (or high vs low WML burden) correlated with greater disease severity, decline in certain clinical characteristics and increased cortical loss, over time [43, 62, 63]. All associations remained, despite correcting for vascular risk factors (VRF).

Our hypothesis is that vascular changes occur in the context of PD and location of vascular pathology has an impact on PD phenotype, severity and progression. We also hypothesize that vascular changes are not purely driven by or dependent on conventional vascular risk factors such as diabetes and hypertension. As vascular changes are potentially more readily modifiable than other factors leading to neuronal loss, it is important to understand these changes further. The initial analyses will focus on WML due to the availability of data, with future work expanding to other vascular modalities including DTI and ASL.

Aims and Analyses:

1) To evaluate the relationship between total and regional white matter lesion burden in PD compared to controls.
2) To evaluate the extent to which WML burden and distribution correlates with certain clinical aspects; motor (such as phenotype as measured by Unified Parkinson's Disease Rating Scale score [UPDRS] sub-scores), non-motor (such as cognition as measured by the Montreal Cognitive Assessment tool [MoCA]) and disease severity (as measured by UPDRS total and sub-scores and Hoehn and Yahr stage). Where available, other clinical sub-scores will also be associated with WML patterns.
3) Where longitudinal and prodromal data are available, we aim to determine whether baseline WML volume predicts disease progression as defined by change in UPDRS score, and clinical phenotype.

**In all analyses vascular risk score will be included as a confounder to ensure the changes are not simply driven by vascular risk factors.*

Outline of Methods:

We have developed a white matter lesion (WML) pipeline, https://github.com/UCL-ARC/Enigma-PD-WML.This pipeline allows WML to be segmented from a subject's T1-weighted and FLAIR MRI images from the same scanning session. The pipeline contains all the code and software required to produce accurate WML binary maps in both native and MNI standard space. All sites with T1-weighted and FLAIR data who wish to contribute will be asked to run the pipeline on their data and send the derived outputs to the ENIGMA-PD-WML group. In parallel, clinical data will also be requested. We then plan to do in-house statistical analyses using multiple regression modelling to predict clinical outcomes based on WML patterns. For the WML binary maps, we will use either a non-parametric permutation approach or a custom regression model

to calculate the association between lesions in key brain regions and white matter tracts with clinical features. Key features will include the UPDRS total and motor score III, Hoehn and Yahr stage, clinical phenotype (based on the UPDRS sub-scores), MoCA score and orthostatic hypotension, with sub-analysis of other clinical features dependent on availability of data. LEDD and vascular risk factors will be corrected for as confounders in the main analysis. We will also explore more complex statistical models with WML as a predictor.

Ethical Considerations:

This research will be conducted in accordance with the World Medical Association's Declaration of Helsinki. Approval from the respective institutional review boards and written consent from participants were obtained at each source institution

Rationale and Impact:

Evidence is accumulating that cerebrovascular changes are associated with more severe gait and cognitive problems in PD, that tend to be less responsive to levodopa treatment and associated with greater disability in PD. Through large-data analysis of cerebrovascular patterns in PD and their association with disease progression and key clinical features, this research allows for a move towards a precision medicine, targeted approach to PD management and clinical trials alike.

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