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

Please complete all fields and return this form by e-mail to:

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1. Policy

Members of the ENIGMA Consortium include investigators from different centers around the world who are actively engaged in neuroimaging research and who have contributed results from primary analyses of imaging, genetic data, and/or algorithm development for the purpose of meta-analysis, replication, and/or algorithm testing in a collaborative manner.

Although the data contributed to the ENIGMA consortium consist of group-level summaries and post-estimation statistics rather than raw genotype and phenotype data, there is theoretically a minute risk of determining whether a given individual participated in a study. While the re-identification of samples requires access to the raw genotype data of the target individual and constitutes scientific misconduct, most groups have opted to appoint a gate-keeper approach rather than allowing full public access to the results of their analyses or meta-analyses. Within the ENIGMA-PD working group any consortium member wishing to access the results of specific analyses or meta-analytic results will be asked to complete a short proposal describing why they wish to access the results files from each group, and submit that for review.

All consortium members are encouraged to submit such proposals, to follow up on ideas which the group as a whole cannot pursue, which involve novel analyses, or subsets of the available sites. The ENIGMA-PD working group will screen PD -relevant proposals for scientific interest, and will help enlist members who might be interested in collaborating. Proposals will be discussed on ENIGMA-PD working group calls and emails to encourage the broadest participation.

The proposal will then be posted on an ENIGMA forum page and an email will be sent to all consortium members alerting them to the posting. ENIGMA members will have 14 days from the time of the posting to opt-out of the analysis, ask for clarification, voice concerns or objections and/or give feedback to the proposal. No site data will be shared without the consent of the PI of that site, who may opt to impose specific conditions or limitations on the use of the data; also ENIGMA PIs and members are not required to take part in any proposed project, they can opt out.

If the author of the proposal agrees to the authorship and publication policies of the consortium the access request will be granted to the results files for those groups who have not opted-out of the analysis and a member of the Enigma PD working group or Enigma support group will be assigned as a project liaison. The Enigma support group liaison will be responsible for providing the data and answering any queries relating to the project, and providing the contributing site PIs with updates. If there is no possibility of determining if a particular individual participated in a study (e.g. limited imaging or genetic markers are requested), results from these markers may be sent by the liaison to other sites if available. If genome-wide results are requested from individual groups, the person submitting the proposal may be granted an account on Imaging Genetics Center (IGC) servers or may visit IGC, if desired, to make it easier to complete the analysis. All approved proposals are welcome to use services at IGC. The data can be housed in IGC and will not to be transferred or mirrored to other sites.

We request that the 'ENIGMA Consortium' or the specific working group(s), and the liaison person will be listed as co-authors. The ENIGMA Consortium on the byline, or the ENIGMA Working Group on the byline, will reference the PIs of each study, in addition to contributors at their site. In this way the authors contributing data to the consortium will be appropriately acknowledged on any publication.

2. Requestor Information

Date of Submission:	13/02/2020
Name:	Sarah Al-Bachari

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Have you signed and return the ENIGMA Memorandum of Understanding? Yes
If no, please find the Memorandum of Understanding here.

2. Results request proposal

Proposal title: MR Vascular Measures in Parkinson's disease

Co-author names and e-mail addresses:

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Proposed Timeline for Completion of Study:

In terms of current data available allowing time for retrieval, analysis and write up of data a 3-year time-line would be proposed. However if there is an understanding that future studies due to be included in the ENIGMA-PD database can also be analysed then the next stage of collaboration would be ongoing for much longer.

Please confirm that you have reviewed the ENIGMA website for potential areas of overlap. If you see a project that may overlap, please list along with any plans for addressing this:

Vascular MR measures are heterogeneous and it is useful to take a multi-modal approach to measuring both structural and functional measures. One, of several measures, is DTI analysis of white matter integrity. I note the ENIGMA-DTI project is underway, this would simply be complementary to our work and perhaps our analysis of other measures would aid in understanding the DTI findings. Therefore, our work would potentially be complementary not overlapping.

Please list any conflicts of interest:

Nil

Please describe the proposed analyses. Include hypothesis, specific results requested, a brief analysis plan and methods, and references.

Neurodegenerative disorders such as PD are understood to be multi-factorial; until the complex factors are understood and potentially modifiable factors identified, there will remain to be no effective disease modifying or neuroprotective 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 [3-11]. 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 [12-16]. 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 [17-24]. Therefore understanding these changes and finding effective markers in the clinical setting is paramount [25].

MRI techniques have paved the way to investigating various vascular measures, in a non-invasive, highly reproducible manner [26-28]. Our work, looking at structural measures of small vessel disease (SVD), namely white matter lesion (WML) burden, using visual rating scales showed an increased burden in PD when compared to controls. Interestingly functional measures of perfusion using arterial spin labelling (ASL), revealed posterior cerebral hypoperfusion (in keeping with other studies [21, 23, 29]) and diffuse prolonged arterial arrival time (AAT) in PD compared to controls, a novel and intriguing finding – which may represent altered vasculature or compensatory mechanisms [30, 31]. In addition, measures of BBB permeability using MR DCE have revealed increased BBB permeability in PD (awaiting press). Thus highlighting the range of cerebral vascular pathology identified in PD. Work is currently underway to further refining and developing vascular measures so they can easily be applied in imaging studies. For the purposes of this proposal and as included in our hypothesis below, we define 'cerebral vascular pathology' as pathology of blood vessels (including endothelial dysfunction, altered vasculature etc.), blood flow changes, and/or parenchymal tissue injury reflecting ischaemia/altered BBB (such as WMLs).

Measuring these vascular changes in the clinical setting does remain a challenge. ASL and DCE data to date in the context of PD are minimal, yet potentially the most relevant and informative. This is due to the magnitude of differences in these measures between PD and controls (for example, we have observed AAT to be 10% higher in PD than in controls), whereas differences can be more subtle with other measures, as well as their greater sensitivity and specificity for purely vascular pathology. All-the-same, WML burden (as a surrogate marker of SVD [32]), have been the most applied in the PD setting, yet despite more than a decade of work, is still producing conflicting results [33-38], with only some studies reporting an increased WML burden in PD. This might be due to relatively small, heterogeneous study populations, so it is crucial to perform analyses across much larger study populations. However, whether WML burden *per se* or the anatomical distribution of WMLs is most relevant also remains unclear. It appears that WMLs distributed in clinically eloquent areas may be more relevant to the underlying PD pathology regardless of total WML burden [16, 39-44]. For example, periventricular and deep white matter lesions have been associated with bradykinesia and axial problems [45-47]. Additionally longitudinal studies have highlighted the importance of measuring WML burden over time, as baseline WML lesion burden has been shown to impact the Unified Parkinson's Disease Rating Scale score (UPDRS) for disease severity and has been associated with increased cortical loss , over time [37, 48, 49].

Our hypothesis is that vascular changes occur in the context of PD and multi-modal MR imaging techniques can help to identity, track (including over time) and understand such changes, in the clinical setting, and in particular, the impact cerebral vascular pathology has on disease progression. As vascular changes are potentially more readily modifiable than other factors leading to neuronal loss, it is important to understand these changes further. Our aim would be to overcome the inevitable problems presented by the relatively small sample sizes in MR studies by undertaking analysis of key vascular markers in a much larger study population. We envisage taking a stepwise approach; with the first line of analysis starting with WML volume measurements. The ENIGMA-PD presents an unparalleled opportunity for this given most centres having acquired appropriate imaging sequences for WML measurements. WML measurements tools have been widely tested and can be readily rolled out to most centres [50]. It is envisaged that future work would include ASL measures of perfusion and arterial arrival time as well as measures of BBB integrity (such as DCE).

The initial research questions based on WML data are:-

1) Is there an excess of cerebral vascular pathology (as measured by WML burden) in PD compared to controls?
2) Does WML burden and/or distribution correlate with certain clinical aspects (motor [such as phenotype as measured by UPDRS sub-scores] and non-motor [such as cognition as measured by MoCA])?
3) Does WML burden and/or distribution correlate with UPDRS (as a measure of disease severity) or cortical volume loss? NB Where longitudinal data are available; we aim to determine whether baseline WML volume predicts disease progression as defined by change in UPDRS score and cortical volume loss.

Brief Outline of Methods:

The Lesion Segmentation Tool (LST), provides an automated approach to WML volume estimation; a recent study compared various approaches, highlighting the LST-LGA tool (https://www.statistical-modelling.de/lst.html)) for accuracy and ease of use [50]. We are currently comparing optimal techniques for regional analyses including voxel-level and tract-specific approaches (awaiting press). WML volume and distribution will then be correlated with the various outcomes measures (UPDRS andsub-scores for phenotype, MoCA etc.), using the linear mixed effects model and ANOVA.

We feel the ENIGMA-PD consortium would provide an excellent platform to integrate and analyse already collated vascular measures to help overcome difficulties of small and heterogeneous sample sizes. If the DTI group would benefit from sharing of our analyses that would be an exciting avenue to explore also. It would be of great interest to discuss with the ENIGMA-PD team the potential of communicating with collaborators who wish to provide future work. The aim would be to discuss the possibility of facilitating the addition of noninvasive and time-efficient perfusion measures to their protocols; our collaboration with the PAMIR group allowed for such an addition to be made (https://www.neurodegenerationresearch.eu/survey/pamir-parkinson-mr-imaging-repository/) (analysis ongoing).

We thank the ENIGMA-PD consortium for their expertise and dedication towards research in imaging and Parkinson's and being such a pleasure to work with.

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