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 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: 03/16/2023

Name: Prof Marcondes C. França Jr and Dr Thiago Junqueira R. de Rezende

Institution/Affiliation: Department of Neurology, University of Campinas (UNICAMP), Brazil

Email: mcfjr@unicamp.br and Thiago.jrezende@gmail.com

Have you signed and returned the ENIGMA Memorandum of Understanding? If not, please find the Memorandum of Understanding here.

3. Study proposal

Proposal title: Spinal Cord morphometry in Parkinson`s Disease

Co-author names and e-mail addresses:

Thiago JR Rezende, thiago.jrezende@gmail.com
Marcondes C. França Jr, mcfjr@unicamp.br

Proposed Timeline for Completion of Study:

1. Gathering data: 3 months; 2. Imaging Processing: 6 months; 3. Data analysis: 6 months; 4. Write Manuscript: 2 months.

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:

We have reviewed the ENIGMA website and found no overlapping study.

Please list any conflicts of interest:

None

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

Parkinson's disease (PD) has been considered primarily a brain disorder. However, recent post-mortem data point out that neurodegeneration extends to the spinal cord (SC) in the disease, with pathological evidence of local accumulation of alpha-synuclein (Del Tredici and Braak, 2012; Buchman et al, 2018). In parallel, a very recent functional MRI study in a cohort of PD patients found abnormal SC resting state connectivity in the disease (Landelle et al, 2023). Additional evidence of SC involvement in PD comes from studies reporting the beneficial effects of SC neuromodulation – both invasive and non-invasive – in some PD-related manifestations, such as the freezing of gait (Reis Menezes et al, 2020). Some authors indeed suggest that PD-related SC damage may underlie some motor and nonmotor (urinary, sexual, and gastrointestinal,) symptoms (Raudino and Leva, 2011).

Despite these data, no study attempted so far to characterize SC damage in PD *in vivo*. Moreover, the clinical correlates of such damage remain elusive. Hence, the main goal of this project is to perform a comprehensive evaluation of cervical SC damage in PD using a large dataset collected within the ENIGMA-Parkinson group. We sought to characterize the pattern of damage and how it evolves across disease subgroups, stratified according to the time from onset and disease severity.

To accomplish these objectives, we will use brain T1 datasets to explore upper cervical SC morphometry. Data processing will be done using a harmonized, published and public protocol developed by the ENIGMA-Ataxia consortium (Rezende et al, 2023; http://enigma.ini.usc.edu/ongoing/enigma-ataxia/), based on the Spinal Cord Toolbox (De Leener et al, 2017).

To measure the cross-sectional area (CSA) and eccentricity, we will employ the Spinal Cord Toolbox (SCT) version 5.8. Briefly, we will automatically segment the cervical SC using a deep-learning algorithm and visually inspect all segmentations for manual correction if necessary. Before registering the images of the subjects into the PAM50 template, we will manually mark the C2 and C3 vertebral levels at the posterior tip of the vertebral discs. The CSA is defined by the number of pixels underlying each slice of the segmented spinal cord. On the other hand, the eccentricity is computed by fitting an ellipse to each axial spinal slice and estimating the smallest and largest diameters to determine the deviation of the ellipse relative to a perfect circle. Since we will use brain MRIs displaying limited spinal cord coverage, we are capable of assessing only the upper cervical spinal cord. In this sense, the spinal cord coverage might be slightly different across the subjects due to field-of-view placement and head size variability, leading to different sample sizes for each vertebral level assessed.

Buchman AS, Nag S, Leurgans SE, Miller J, VanderHorst VGJM, Bennett DA, et al. Spinal Lewy body pathology in older adults without an antemortem diagnosis of Parkinson's disease: spinal lewy bodies in older adults. *Brain Pathol* 2018;**28**:560–568.

De Leener B, Lévy S, Dupont SM, et al. SCT: Spinal Cord Toolbox, an open-source software for processing spinal cord MRI data. Neuroimage. 2017;145:24-43.

Del Tredici K, Braak H. Spinal cord lesions in sporadic Parkinson's disease. Acta Neuropathol. 2012 Nov;124(5):643-64. doi: 10.1007/s00401-012-1028-y. Epub 2012 Aug 29. PMID: 22926675.

Landelle C, Dahlberg LS, Lungu O, Misic B, De Leener B, Doyon J. Altered Spinal Cord Functional Connectivity Associated with Parkinson's Disease Progression. Mov Disord. 2023 Feb 21. doi: 10.1002/mds.29354. Epub ahead of print. PMID: 36802374.

Raudino F, Leva S. Involvement of the spinal cord in Parkinson's disease. Int J Neurosci. 2012 Jan;122(1):1-8. doi: 10.3109/00207454.2011.613551. Epub 2011 Sep 12. PMID: 21834616.

Reis Menezes J, Bernhart Carra R, Aline Nunes G, da Silva Simões J, Jacobsen Teixeira M, Paiva Duarte K, Ciampi de Andrade D, Barbosa ER, Antônio Marcolin M, Cury RG. Transcutaneous magnetic