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: June 4th 2024
Name: Eva van Heese
Institution/Affiliation: Amsterdam UMC
Email: e.vanheese@amsterdamumc.nl

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

3. Study proposal
Proposal title: Brain morphology correlates of neuropsychiatric symptoms in Parkinson's Disease

Co-author names and e-mail addresses:
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Proposed Timeline for Completion of Study:
Start project: September-October 2024
Data Inventorisation and organisation: September-December 2024
Data Analysis: January-April 2025
First Draft paper: May 2025

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:
Confirmed

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.
Background: Parkinson's Disease, primarily known for its motor symptoms, has increasingly been recognized as a neurodegenerative disorder involving non-motor features, such as neuropsychiatric symptoms. This study aims to overcome limitations of previous, small investigations and explore the brain morphology correlates of these neuropsychiatric symptoms in a well-powered dataset from the ENIGMA-PD working group.

Objective: To investigate brain morphology correlates of neuropsychiatric symptoms in Parkinson's Disease

Sub-objectives: To investigate brain morphology correlates of …

- depression
- apathy
- anxiety
- hallucinations / psychosis
- impulse control disorders
- sleep disturbances

… in Parkinson's Disease.

Data request:

- FreeSurfer 7 processed metrics (as part of the "update to FS7 project" that is running in parallel)
- Neuropsychiatric outcomes (according to availability), measures for
    - depression (MADRS, HRDS, BDI, GDI, IDS, SHAPS, HAMD, other)
    - apathy (AS, AES, other)
    - anxiety (HAMA, BAI, PAS, STAI, WOQ, other)
    - hallucinations or psychosis (PANNS, PPRS, SAPS-PD, QPE, UM-PDHQ, other)
    - impulse control disorders (QUIP-rs, other)
    - sleep disturbances (insomnia; restless legs; REM sleep behaviour disorder as measured with RBD1Q, RBDSQ; SASDQ; PDSS; ESS; KSS; ISI; PSQI; other)

For the neuropsychiatric outcomes, we will inventorise for each site which constructs and which scales are available. In the analysis phase, data from commonly used scales that are available for multiple sites will be pooled and, if possible, different scales will be converted according to validated conversion approaches to allow pooling of data.

Data processing and harmonisation:

Data will be processed in a harmonised manner using the Micapipe pipeline, including FreeSurfer functionalities. Quality control will consist of statistical outlier detection and visual inspection of the images based on output from the FreeSurfer Quality Control (FS-QC) pipeline. To address site-specific effects (systematic MRI scanner and protocol differences), we will apply Combat batch adjustment. Combat is a method built on an empirical Bayes framework to estimate site effect distributions. In our pilot study, findings driven by site effects were better eliminated compared to random intercept models, and hereby increased statistical significance of true effects.

MRI outcome measures:

Cortical thickness and surface area for cortical and volumetric measures for subcortical brain areas as calculated by FreeSurfer. We will include 68 cortical regions of interest (ROI), 19 subcortical ROIs, and an additional 22 subdivision ROIs derived from the subsegmentations divided over 5 subcortical regions (thalamus, amygdala, hippocampus, brainstem, hypothalamus).

Statistical models:

We will apply multiple regression models to investigate the effect of the presence of neuropsychiatric symptoms (i.e. depression) on brain morphology (i.e. cortical thickness of an ROI), controlling for age and sex (and ICV for subcortical volumes). We will run several sensitivity analyses with age- and sex-matched controls, or with focus on HY stages instead of Parkinson's Disease versus controls.