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: 04-08-2025

Name: Tim D. van Balkom

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

3. Study proposal

Proposal title: Neuroanatomical heterogeneity underlying cognitive impairment in Parkinson's disease—a normative modelling study

Co-author names and e-mail addresses:

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Proposed Timeline for Completion of Study:

2026 Q2/3: completion of data collection ENIGMA-PD
2026: development of brain charts based on healthy samples (UKB, HCP, ENIGMA-PD)
2027 Q1-2: application of brain charts to ENIGMA-PD clinical sample and data analysis

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:

The project shows overlap with the overall aims of the CentileBrain project, which is part of the ENIGMA Lifespan working group. This project has, however, to date mainly focused on brain age or equivalent models of normative brain structure, while in this study we will aim to develop charts of brain function and apply these to get a better understanding of cognitive heterogeneity in Parkinson's disease.

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.

Rationale

Cognitive impairment is a devastating symptom of Parkinson's disease (PD). Commonly present at disease diagnosis,[1] it develops into dementia in the majority of individuals.[2] Cognitive impairment is associated with a lower quality of life,[3,4] and increased caregiver burden[3] and societal costs.[5] Research has shown that cognitive impairment in PD exhibits a heterogeneous profile.[6] Group comparisons have illustrated similar heterogeneity of brain circuits that can be affected in PD-related cognitive impairment,[11-14] but rarely translate to the individual. This (behavioral and neuroanatomical) heterogeneity may underlie difficulties in development of effective treatment options to reduce cognitive impairment to date.

Aim

The aim of this study is to dissect this heterogeneity using normative modelling.[11] The method enables individualized evaluation of deviating development and plays a pivotal role in advancing personalized medicine. Normative modelling is best known in its use for paediatric growth charts of length and weight, but is increasingly used to assess heterogeneity in brain structure and function. Based on normative models in neuroimaging—hereafter referred to as brain charts—we can identify individual fingerprints of brain regions that show deviations in structure or function. Their importance for dissecting neuroanatomical heterogeneity has already been shown in psychiatric disorders and neurodegenerative diseases.[12-17] Given the involvement of various functional brain circuits in PD-related cognitive impairment that shows high interindividual variety, we aim to dissect this heterogeneity by applying normative modelling to functional MRI. In the future, these models may inform treatment protocols that can modulate brain circuit function, such as repetitive transcranial magnetic stimulation, to treat cognitive impairment in PD.

Hypotheses

1. Individuals with PD show deviations from brain charts that represent impaired functional connectivity
2. Individuals with cognitive impairment in PD show additional/increased deviations from brain charts in brain circuits relevant for cognitive impairment, including the default mode network, cortico-striato-thalamo-cortical circuits, frontoparietal network and dorsal/ventral attention networks.
3. Deviation from brain charts in brain regions in the aforementioned brain circuits show associations with severity of cognitive impairment.
4. Deviation from functional brain charts in individuals with PD cluster into different deviation profiles that correspond to specific profiles of cognitive impairment.

Analysis plan

An overview of the proposed study is shown in Figure 1.

1. Sample/data request: this secondary proposal will make use of functional connectomes (constructed on functional MRI data) collected in the "Neurocognitive responses to Parkinson's disease pathology" ENIGMA-PD project by Mitterová et al. We aim to use to following data:
    a. Minimal data: presence of functional connectome using Schaefer 400P7N atlas, Montreal Cognitive Assessment, (MDS-)UPDRS-III score and demographic variables including sex, age and education level
    b. Ideal data: preprocessed (HALFpipe, see below) resting-state fMRI image/T1w image (to apply different atlas to), additional presence of other neuropsychological assessments, such as (but not limited to) the Rey Auditory Verbal Learning Test, Benton Judgment of Line Orientation, Trail Making Test, Tower of London test, Rey-Osterrieth Complex Figure test and WAIS Digit Span

    For development of the functional brain charts we will—in addition to ENIGMA-PD healthy control subjects—include the Human Connectome Project-Aging dataset (N≈750)[18] and UK Biobank fMRI dataset (N≈40.000).[19]
2. Preprocessing: preprocessing will be based on the HALFpipe ENIGMA functional imaging preprocessing protocol.[20]
3. Parcellation: we will use the Schaefer 7 Networks/400Parcels parcellation, due to its specificity to functional MRI data.[21]

4. Outcomes: for the development of the functional brain charts, we will use node strength and betweenness centrality as nodal outcomes, as these graph metrics show fair to excellent reliability (see Figure 1.1).
5. Normative modelling approach: we will use Hierarchical Bayesian Regression to fit a growth curve of node strength or betweenness centrality for every brain region in the healthy control samples, using age, sex and education level (if available in a sufficient sample) as covariates, cohort as random factor and with a random intercept (Figure 1.2). To ensure generalizability of the model, we will use a 70% train-30% test split, randomly distributed across cohorts and sites. For each healthy individual and individuals with PD, deviation scores—i.e., a Z-score signifying deviation from the brain charts—will be extracted for every brain region (Figure 1.3).
   Test-retest reliability of deviation scores will be assessed in a subsample that underwent multiple fMRI instances, which are available in the UK Biobank and HCP-A datasets, using the intraclass correlation coefficient.
6. Statistical analysis: We will assess PD versus HC group differences in deviation from the brain charts for every brain region using t-tests (H1). We will additionally assess differences in deviation scores between individuals with and without cognitive impairment in PD (H2). In these frequentist analyses, we will use the false discovery rate to control for false positives given the amount of comparisons. To assess the association of deviation scores with cognitive impairment (H3), we will apply Bayesian Multilevel Modelling[22] using the Montreal Cognitive Assessment or other relevant neuropsychological assessment data as predictors and deviation scores of every brain region as multivariate outcome. Clusters of deviation scores (H4) will be assessed by applying latent class analysis to deviation scores of every brain region. We will compare demographic, clinical and neuropsychological characteristics of the resulting latent classes (Figure 1.4).

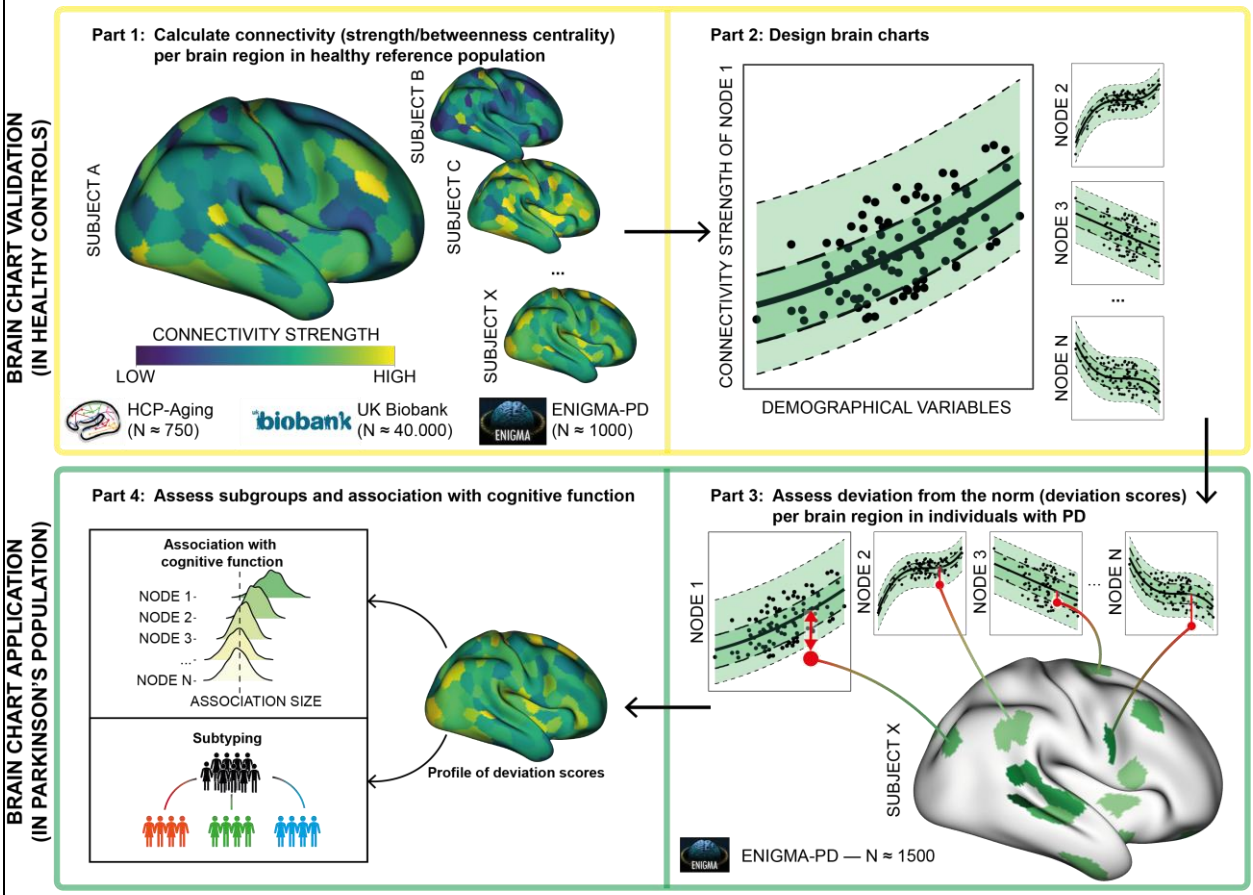

Figure 1 Overview of the proposed study.

References:
1 Muslimovic, D., Post, B., Speelman, J. D. & Schmand, B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology* **65**, 1239-1245 (2005). https://doi.org/10.1212/01.wnl.0000180516.69442.95
2 Aarsland, D. *et al.* Parkinson disease-associated cognitive impairment. *Nat Rev Dis Primers* **7**, 47 (2021). https://doi.org/10.1038/s41572-021-00280-3
3 Aamodt, W. W. *et al.* Caregiver Burden in Parkinson Disease: A Scoping Review of the Literature from 2017-2022. *J Geriatr Psychiatry Neurol* **37**, 96-113 (2024). https://doi.org/10.1177/08919887231195219
4 Leroi, I., McDonald, K., Pantula, H. & Harbishettar, V. Cognitive impairment in Parkinson disease: impact on quality of life, disability, and caregiver burden. *J Geriatr Psychiatry Neurol* **25**, 208-214 (2012). https://doi.org/10.1177/0891988712464823
5 Chaudhuri, K. R. *et al.* Economic Burden of Parkinson's Disease: A Multinational, Real-World, Cost-of-Illness Study. *Drugs Real World Outcomes* **11**, 1-11 (2024). https://doi.org/10.1007/s40801-023-00410-1
6 Carceles-Cordon, M., Weintraub, D. & Chen-Plotkin, A. S. Cognitive heterogeneity in Parkinson's disease: A mechanistic view. *Neuron* **111**, 1531-1546 (2023). https://doi.org/10.1016/j.neuron.2023.03.021
7 Owen, A. M. Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. *The Neuroscientist* **10**, 525-537 (2004). https://doi.org/10.1177/1073858404266776
8 Trujillo, J. P. *et al.* Impaired planning in Parkinson's disease is reflected by reduced brain activation and connectivity. *Hum Brain Mapp* **36**, 3703-3715 (2015). https://doi.org/10.1002/hbm.22873
9 Wolters, A. F. *et al.* Resting-state fMRI in Parkinson's disease patients with cognitive impairment: A meta-analysis. *Parkinsonism Relat Disord* **62**, 16-27 (2019). https://doi.org/10.1016/j.parkreldis.2018.12.016
10 Reich, M. M. *et al.* A brain network for deep brain stimulation induced cognitive decline in Parkinson's disease. *Brain* **145**, 1410-1421 (2022). https://doi.org/10.1093/brain/awac012
11 Rutherford, S. *et al.* The normative modeling framework for computational psychiatry. *Nat Protoc* **17**, 1711-1734 (2022). https://doi.org/10.1038/s41596-022-00696-5
12 Han, L. K. M. *et al.* Brain aging in major depressive disorder: results from the ENIGMA major depressive disorder working group. *Mol Psychiatr* **26**, 5124-5139 (2021). https://doi.org/10.1038/s41380-020-0754-0
13 Verdi, S. *et al.* Revealing Individual Neuroanatomical Heterogeneity in Alzheimer Disease Using Neuroanatomical Normative Modeling. *Neurology* **100**, E2442-E2453 (2023). https://doi.org/10.1212/Wnl.0000000000207298
14 Rutherford, S. *et al.* Evidence for embracing normative modeling. *Elife* **12** (2023). https://doi.org/ARTN e85082
15 Marquand, A. F. *et al.* Conceptualizing mental disorders as deviations from normative functioning (vol 24, pg 1415, 2019). *Mol Psychiatr* **24**, 1565-1565 (2019). https://doi.org/10.1038/s41380-019-0451-z
16 Kasper, J. *et al.* Resting-State Changes in Aging and Parkinson's Disease Are Shaped by Underlying Neurotransmission: A Normative Modeling Study. *Biol Psychiatry Cogn Neurosci Neuroimaging* **9**, 986-997 (2024). https://doi.org/10.1016/j.bpsc.2024.04.010
17 Mansour L, S. *et al.* Spectral normative modeling of brain structure. *medRxiv*, 2025.2001.2016.25320639 (2025). https://doi.org/10.1101/2025.01.16.25320639
18 Bookheimer, S. Y. *et al.* The Lifespan Human Connectome Project in Aging: An overview. *Neuroimage* **185**, 335-348 (2019). https://doi.org/10.1016/j.neuroimage.2018.10.009
19 Mansour, S. *et al.* Connectomes for 40,000 UK Biobank participants: A multi-modal, multi-scale brain network resource. *Neuroimage*, **283**(1), 120407 (2023). https://doi.org/10.1016/j.neuroimage.2023.120407
20 Waller, L. *et al.* ENIGMA HALFpipe: Interactive, reproducible, and efficient analysis for resting-state and task-based fMRI data. *Hum Brain Mapp* **43**, 2727-2742 (2022). https://doi.org/10.1002/hbm.25829
21 Schaefer, A. *et al.* Local-Global Parcellation of the Human Cerebral Cortex from Intrinsic Functional Connectivity MRI. *Cereb Cortex* **28**, 3095-3114 (2018). https://doi.org/10.1093/cercor/bhx179
22 Chen, G. *et al.* Handling Multiplicity in Neuroimaging Through Bayesian Lenses with Multilevel Modeling. *Neuroinformatics* **17**, 515-545 (2019). https://doi.org/10.1007/s12021-018-9409-6