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: December 6, 2023

Name: Boris Gutman & Emile d'Angremont

Institution/Affiliation: IIT & Amsterdam UMC

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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: Multi-symptom Progression Modeling

Co-author names and e-mail addresses:

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Proposed Timeline for Completion of Study:

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:

There is some overlap with the SuStaIn project, so here we shortly address the methodological differences:

- We will only apply EBM, as applied in the SuStaIn project, as an initial proof-of-concept step, with the addition of connectome priors (based on either individual DWI or an average connectome model).
- Clinical subtyping measures (e.g. PIGD vs. TD) will be given special treatment to constrain disease trajectory subtypes, making the subtyping a priori more clinically meaningful.
- The disease staging in this project is intended to be continuous, not consisting of discrete events, as is the case in EBM. This will require some longitudinal data.

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:
Quantitative models of disease progression, referred as Disease Progression Models (DPMs), aim at quantifying the dynamics of the changes affecting the brain during the whole disease span (1-3). DPMs estimate a long-term disease evolution from the joint analysis of multivariate data acquired cross-sectionally or on a short-term time-scale (4-6). Due to the temporal delay between the disease onset and the appearance of the first symptoms, DPMs rely on the identification of an appropriate temporal reference to describe the long-term disease evolution (7, 8). These approaches thus allow us to reconstruct biomarker trajectories along an ideal long-term disease progression by optimally "stitching" together short-term individual measurements. Each subject is characterized by specific time parameters quantifying their pathological stage with respect to the estimated long term group-wise evolution.
The complex symptomatology of Parkinson's disease (PD), its staged symptom appearance and staged underlying pathology (Braak's hypothesis), have made developing DPM for PD especially challenging. Improved models are needed – models that account for this complex constellation of neurodegeneration. With such models we may be better positioned to detect the multi-layered clinical changes at their earliest stages, and optimize clinical trial design through better stratification or target identification. Such models will also allow for the possibility of use as a surrogate biomarker in a point-of-care setting, informing treatment decision by the clinician.

Aim:
We propose to apply state-of-the-art DPM on the ENIGMA-PD dataset, with the specific aims of (1) developing an integrated multi-dimensional biomarker predictive of individual cardinal subtype specifics (PIGD vs. TD) and cognitive decline, and indicative of phenoconversion risk; (2) developing and freely disseminating a PD-specific computational pipeline with utility beyond MR markers to generate and test hypotheses regarding PD symptom+marker clusters and phenoconversion; (3) applying this pipeline to identify neurodegenerative "juncture" events, i.e. data patterns signaling an approaching onset of new symptoms or a concurrent hastening of cognitive decline. Design of the models will be based on the following hypotheses:
1.Neurodegenerative cascade hypothesis: This hypothesis holds that each quantitative phenotype of neurodegeneration has a specific period of the disease-related decline, the completion of which triggers decline elsewhere. The Amyloid Cascade Hypothesis in Alzheimer's Disease (9, 10) is one realization of this idea. Importantly, each phenotype has a unique "activation" period. DPMs are designed precisely around this hypothesis: the task to identify the ordering and progression rate of all phenotypes. The result is then an objective unified progression score of the disease, grouping complex phenotypes into progression stages (11, 12).
2. Network Diffusion Hypothesis: In this hypothesis, neurodegeneration spreads over brain regions based on the cortical white matter network in a highly stereotyped sequence. Rationale: This idea has been successfully exploited in Alzheimer's disease (AD) (13, 14) by the PI and others, and correlates strongly with Braaks' AD staging (15, 16). We posit that PD-related degeneration similarly diffuses over the WM structural network, which can be revealed with the help of diffusion MRI-based connectome models.
3. Branching Cascade Hypothesis: The branching cascade concept tackles the complexity of PD by treating each symptom cluster onset as a specific neurodegenerative cascade. The cascades are interdependent, with specific biomarker changes acting as juncture points in the disease progression, i.e. an event that is contained with a specific symptom cascade may be a departure for the cascade associated with another symptom cluster progression. Juncture events may be particularly important to identify as surrogate targets in clinical trials.

Analysis plan:
First, we will apply a disease staging model as previously applied in Alzheimer's disease ((17); kurmukovai/ebm-connectivity-prior: Reproducing results of the paper "Constraining Disease Progression Models UsingSubject Specific Connectivity Priors" (github.com)) using structural MRI measures (cortical and subcortical regional as well as vertex-wise measures), combined with connectivity matrices derived

from diffusion imaging to serve as connectome priors. If diffusion imaging is not available, we will use an average connectome model. MoCA and UPDRS-III subscores will be used to define subtypes, specifically tremor dominant vs. PIGD and MCI vs. normal cognition.
Second, we will fit a DPM based on ordinary differential equations (ODE-DPM), for causal modeling of phenotype dynamics associated with multiple symptoms (UPDRS-III subscores and MoCA). This method has also previously been applied in Alzheimer's disease (7, 18), and has extensive documentation available: Epione / GP_progression_model · GitLab (inria.fr). A schematic representation of ODE-DPM is provided in Figure 1. Fitting of this model will require at least some longitudinal data. ODE-DPM fitting will allow us to create personalized progression dynamics, predicting disease progression for individual subjects, based on current symptom scores (Figure 2). We will use this model to identify specific junction points, i.e. imaging data patterns signaling an approaching onset of new symptoms or a concurrent hastening of cognitive decline. Figure 3 summarizes the here proposed analysis.

Data request:

Minimal data

- UPDRS-III individual items or TD/PIGD sub scores
- MoCA
- Cortex + subcortex regional measures (output from Freesurfer)

Ideal data

- Longitudinal data
- Vertex-wise subcortical measures (available from shape project)
- Vertex-wise cortical measures (this will require sites to run a quick resampling pipeline)
- Diffusion imaging
    - Standard TBSS regional FA/MD values (available from TBSS project)
    - Connectivity matrix (or minimal information needed to create connectivity matrix) from additional DTI analysis pipeline

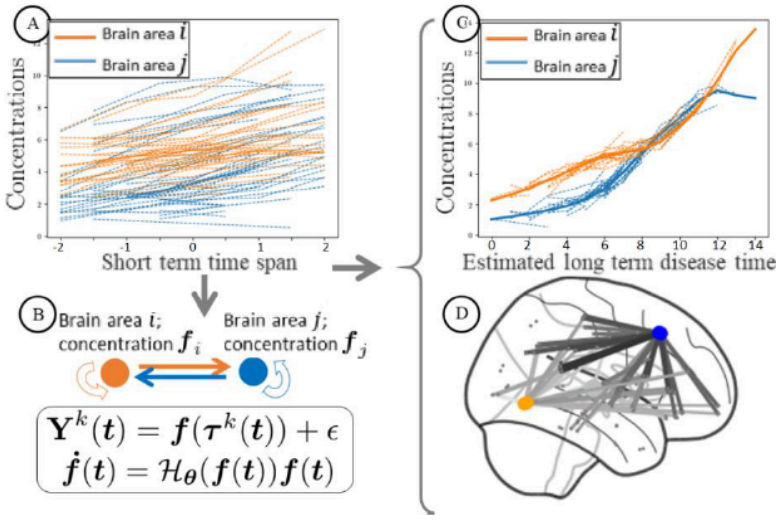

Figure 1. Schematic representation of the ODE-DPM. Regional biomarker measurements (e.g. amyloid PET) are collected for k subjects over a short term time span t, encoded in a measurement array $Y_k(t)$ (A). The dynamics of such biomarkers are described in terms of a functional H, with unknown parameters, encoded in a dynamical system (B). The proposed framework estimates such parameters, encoding the strength of propagation (D) as well as the long-term biomarker evolution (C). Figure reproduced from Garbarino and Lorenzi, 2021.

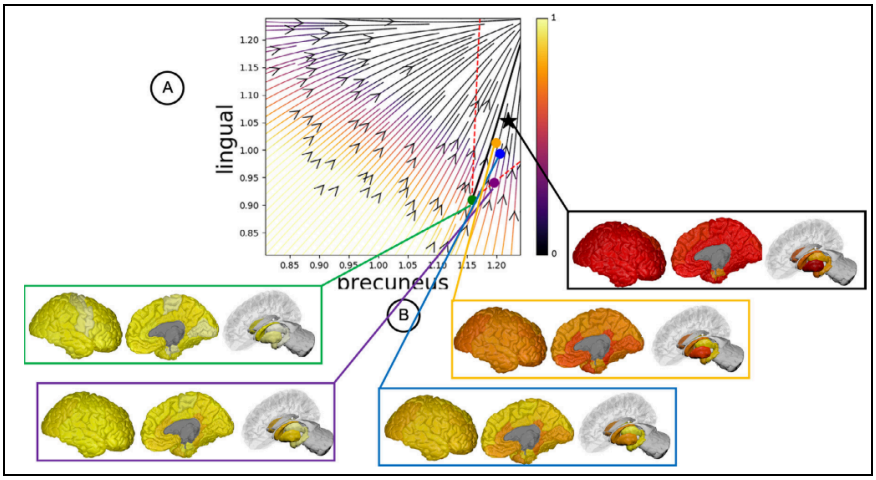

Figure 2. Example of personalized disease progression modeling, here applied in Alzheimer's disease. X and Y axes represent amyloid deposition in the precuneus and lingual gyrus, respectively. The colored dots and corresponding brain images represent predicted cumulative amyloid deposition for an individual subject, based on an initial condition. Figure copied from Garbarino et al. (18).

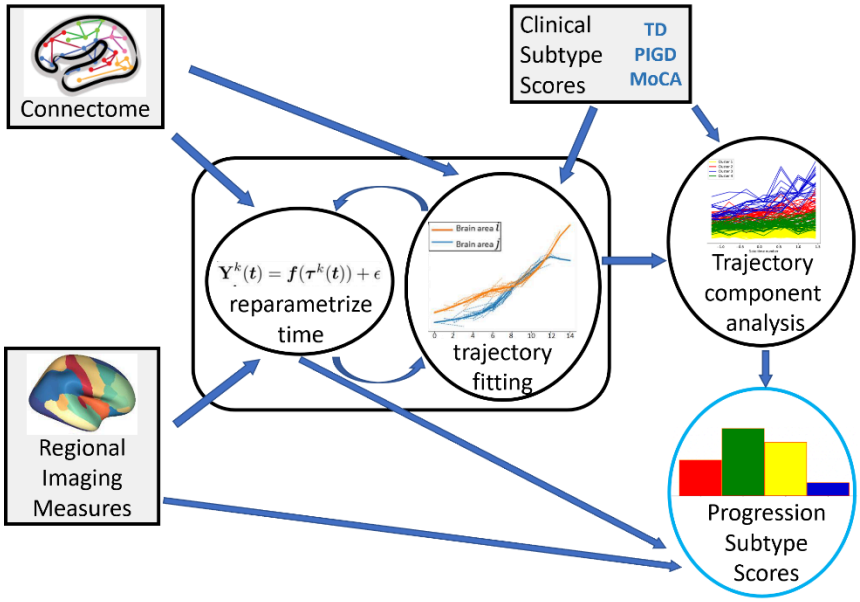

Figure 3. Schematic representation of the proposed analysis.

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