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

Please complete all fields and return this form by email 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: 28.8.2023

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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:
Neurocognitive responses to Parkinson’s disease pathology

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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:

I am not aware of any overlap

Please list any conflicts of interest:

No conflict of interest

Please describe the proposed analyses. Include hypothesis, specific results requested, a brief analysis plan and methods, and references.
The search for pathological markers over the past decades emphasized early network disruption and the buildup and spread of pathological proteins. Nevertheless, previous years brought a new shift in perspective which includes active brain responses to a physiological disruption manifesting as topological changes in the large-scale functional connectome of the brain. While the primary principle of a healthy network organization adheres to optimization of metabolic and informational efficiency achieved by a small-world topology - relatively high clustering, short average path length, and a modular community organization with relatively few highly connected nodes (i.e., brain hubs), this changes in case of physical disruption.[1,2] Network topology flexibly adjusts to an insult in order to preserve cognitive functioning and prevent information loss, for example, by creating redundant connections which can over time lead to hyperconnectivity.[3] In the case of Parkinson's disease (PD), we may hypothesize that a goal of alterations in the global network topology is to sustain communication despite numerous dysfunctions in the dorsal attention network, salience network, frontoparietal network, etc.[4] In contrast to this view, others argue, that hyperconnectivity can be toxic and predicts conversion to dementia.[5,6] For instance, in emerging Alzheimer's disease, the most highly connected hubs of networks contain disproportionately higher depositions of ß-amyloid[7,8] over time leading to hypoconnectivity in developed AD.[9] In light of these empirical observations, one principal question arises: *Are alterations in functional network topology in Parkinson's disease associated with cognitive decline or resilience?*

A: In case only cross-sectional data are available, we propose to investigate functional connectome metrics (operationalized as graph theory metrics) corresponding to cognitive performance and motor symptoms in PD relative to HC. Hypotheses:

1. PD patients with normal cognition (NC) and mild cognitive impairment (MCI) display higher global network modularity than HC controls.
    - Global modularity is one of the expressions of hyperconnectivity of more separate networks.
2. Higher global modularity in PD patients correlates with deranged local functional connectome, e.g., with longer path length, lower node strength, etc. in FPN, SN, or other injured networks relevant to PD.
3. Higher global modularity in PD patients corresponds to preservation of lower, bottom-up cognitive functions, but impaired complex top-down cognitive functions for which such network topology is no longer effective.
    - Instances of bottom-up vs. top-down are made in the analyses section.
4. Topological network changes in HC, PD NC, and PD MCI do not correlate with volumetric changes. Topological changes (e.g., hypoconnectivity and lower modularity) in PDD correlate with atrophy.

B: In case of availability of cognitive data from which crystallized or premorbid intelligence can be estimated (e.g., using tests and scales that are age or disease-invariant), we propose to evaluate the relation between the global graph theory metrics and the estimated past performance. More specifically, association with the decline of cognitive functions from a premorbid cognitive state would invalidate alternative explanations (e.g., baseline difference in brain connectome due to other reasons, sampling). Hypothesis:

5. A model with premorbid and fluid intelligence predicts a graph theory metric (e.g., modularity) more strongly than fluid intelligence alone.

C: In the case of the availability of longitudinal data, there is a potential to uncover the timing of the peak of a topological change (e.g., the metabolic output of high modularity) and decline when the network succumbs to late-stage cortical atrophy. The question remains whether the magnitude of a topological change, e.g., the hypothesized modularity steepens the slope of later decline. Hypotheses:

6. PD NC and PD MCI have increased topological changes (e.g., modularity) in comparison to HC; PDD have the lowest magnitude of a topological change.
7. The cognition of patients with particularly elevated graph metrics (e.g., modularity) declines more steeply than the cognition of patients with lower magnitude.

Analyses:

To examine the multivariate relationships between graph theory metrics on one side and cognitive tests on the other side (hypothesis 1) we propose to conduct **canonical correlations (CCA)**. It allows the depiction of complex brain-cognition relationships in a multivariate fashion by creating latent variables (variates) out of two sets of observed variables which help infer the highest possible correlations by reducing the measurement error and the need for multiple comparisons.[10] The graph theory variate would include global metrics, such as modularity, average clustering coefficient, characteristic path length, gamma, normalized characteristic path length λ, small-worldness σ, average node strength, and global efficiency; and the second variate representing cognition would contain available neuropsychological tests, preferably covering all cognitive domains. The neuropsychological tests would be represented by age-normalized Z-scores.

The primary interest in the CCA is the Rc values which indicate the shared correlation structure between the variates, and their respective loadings from the component variables (rs) which provide insight into their importance to the final solution.[10,11] The variables with the loading of > |.3| are considered significant and will be replicated in the subsequent regression models (e.g. the linear mixed model).

Calculation of **latent scores** for the subsequent predictions offers a multivariate approach in which neuropsychological tests (i.e., manifest variables in the latent modeling terminology) can be used to infer unobserved (latent) scores which account for measurement error in observed scores and thereby increase statistical power. For hypothesis 3, we propose to calculate one latent score for the bottom-up functions, which could include scores of simple perceptual or attentional processing (e.g. *R-O Figure*

Copy, *Judgement of Line Orientation*, *Boston Naming Task*, *Trail Making Task A*,…) and one latent score for the top-down functions including tests requiring synchronization of multiple cognitive domains (e.g., *Digit span*, *Digit-Number Sequencing*, *Verbal Fluency Test*, *Brief Visuospatial Memory Test*…). For hypothesis 5, we propose to calculate latent scores of the fluid (performance scores combined) and the premorbid (e.g., using *Vocabulary test*, *National Adult Reading Test*, educational attainments, etc.) intelligence.

The subsequent **LMM** enables testing of specific dose-dependent effects of the significant graph theory metrics (as predictors) on different aspects of performance as dependent variables for hypothesis 3 (2 separate LMMs for each dependent variable). LMM including random factors allows for evaluation of the influence of subjects´ individuality using likelihood estimation on Chi-square distribution. For hypothesis 5, the graph theory metrics that explained a significant portion of the variance in cognitive functions (from the previous CCA, we hypothesize it being global modularity) will be set as the dependent variable, predicted by latent scores of fluid and premorbid intelligence. The rationale is to explain specifically how much variance in the graph metrics is explained by fluid and premorbid intelligence when one of them is held constant – in other words, in case premorbid and fluid intelligence are significant, we may interpret the graph theory as related to decline (as hypothesized) from premorbid levels. In case only the fluid intelligence is significant, the connectome topology is associated with current levels of cognitive performance.

For hypotheses 2 and 4 Pearson's **correlation** will be conducted between the significant global graph theory metrics and local graph theory metrics in the hypothesized networks (e.g., FPCN, SN, DAN); and between the significant global graph theory metrics and regional brain volumes.

For hypotheses 6 and 7, we propose to conduct **Cox proportional hazard models** to investigate the association between our graph theory metrics and diagnosis, and risk of dementia (dichotomous variable: dementia at follow-up: yes/no). Since there is no cut-off for modularity abnormality, we propose to use the Z-transformed global modularity magnitude stratified into groups of low (-), moderate (*), and high (+). Combining modularity and diagnosis variables we would create a multi-level variable, e.g., HC +/*/-, PD NC +/*/-, PD MCI +/*/-. The time variable will be set for time to progression in case of clinical progression to PDD, or time to last visit for those that remain non-demented upon follow-up.

Additionally, we propose LMM to investigate the association between stratified modularity and neuropsychological test performance over time. We will include time, modularity, and time*modularity interaction terms as fixed factors, age, sex, and education as covariates, and neuropsychological test scores as dependent variables (separate models for each neuropsychological test).

Additionally, another LMM will test whether adding a formal diagnostic group improves the model fit and predicts change in neuropsychological scores better than just modularity over time.

We expect there will be several samples with different neuropsychological assessments. If the evaluation across datasets is complementary (i.e., covering similar neuropsychological domains), we propose to run sensitivity analyses to replicate our results on models with different settings.

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