Enhancing Neuro Imaging Genetics through Meta-Analysis Consortium (ENIGMA) – Schizophrenia Working Group Secondary Proposal Form

Please complete all fields and return this form by e-mail to: Jessica Turner & Theo van Erp
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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-SZ 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-SZ working group will screen schizophrenia-relevant proposals for scientific interest, and will help enlist members who might be interested in collaborating. Proposals will be discussed on ENIGMA-SZ 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 SZ 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 Laboratory of Neuro Imaging (LONI) servers or may visit LONI, if desired, to make it easier to complete the analysis. All approved proposals are welcome to LONI. The data will be housed in LONI and will not to 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: May 15, 2019

Name: Tomas Hajek

Institution/Affiliation: Dalhousie University, Halifax, Nova Scotia, Canada

Email: tomas.hajek@dal.ca

Have you signed and return the ENIGMA Memorandum of Understanding? I would be happy to sign, but the link does not seem to work.

If no, please find the Memorandum of Understanding here.

2. Results request proposal

Proposal Title: : Obesity as a risk factor for brain alterations in schizophrenia

Co-author names and e-mail addresses (initial list):

Anyone who is interested to join and has measures of obesity in their data.

Proposed Timeline for Completion of Study:

We hope to have the project reviewed and finalized by the time of the next Sch group teleconference in July, 2019. Initial data collection to start after that and continue for 9 months. As in our previous project, we will set a data freeze date, beyond which no new data would be accepted. This is necessary to prevent delays and re-analyses. We will proceed with analyses after the data freeze day and plan to submit the results to SOBP or Human Brain Mapping conferences in conjunction with the preparation of manuscript. We hope to submit the manuscript for peer review in 2021.

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:

No overlap.

Please list any conflicts of interest:

No conflicts of interest.

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

Background

Neurostructural alterations are a well-recognized feature of schizophrenia. Yet, the brain changes in schizophrenia are not distributed evenly. Meta-analyses, including the work by ENIGMA consortium, showed statistical heterogeneity of findings, i.e. patients with schizophrenia differed from healthy controls only in some sites/studies (1,2). A recent meta-analysis quantitatively demonstrated that the variability of brain imaging findings is consistently larger in participants with schizophrenia than in non-psychiatric controls (3). One potential source of this neuroimaging heterogeneity in schizophrenia is the comorbidity with medical conditions known to affect the brain. Perhaps, certain neuroimaging alterations in schizophrenia are associated with the presence of certain medical comorbidities.

Obesity is a pervasive problem, which may affect 40-60% of patients with psychotic spectrum disorders (4–6). The risk of obesity in schizophrenia is significantly greater than in non-psychiatric controls (6). Furthermore, obesity is associated with similar brain imaging alterations in frontal and mesotemporal regions, as schizophrenia (7). We and others have demonstrated that obesity is an additional factor, which contributes to brain alterations in psychiatric disorders, including BD and first episode of schizophrenia (8–11). Thus, the presence or absence of obesity could explain, why neurostructural alterations are more pronounced in some participants with schizophrenia. Focusing on obesity might help us reduce the neurostructural heterogeneity of schizophrenia.

In addition, the ENIGMA-Schizophrenia working group provides an ideal opportunity to investigate whether obesity interacts with the negative effects of schizophrenia on brain structure. Testing for interactions requires larger sample sizes than testing for main effects and thus would greatly benefit from the large sample sizes available through the ENIGMA consortium.

Specific Results Requested

Individual subject FSL/FreeSurfer ROI results, both subcortical and cortical, demographic and clinical variables (Covariates.csv) as previously prepared for the ENIGMA-SCH cortical/subcortical manuscripts.

Beyond adding mewasures of obesity, i.e. BMI, waist to hip circumference, this does not require additional work by the participating groups.

Mega-analyses have greater statistical power than meta-analyses, especially for regression problems, such as looking at association between BMI and brain structure. Thus, to make the most of the ENIGMA dataset, mega-analysis would be better suited to our particular questions than meta-analyses. Obviously, the data is anonymized, the ROI measures cannot be used to uniquely identify individual participants and the individual subject data would be used only for the purposes outlined here. Thus, sharing these highly pre-processed data should not be an issue and was done previously.

Brief Analysis Plan and Methods:

We will investigate the association between BMI and brain structure (ROI volumes, cortical thickness and surface area) in participants with schizophrenia and controls, as well as test for BMI x diagnosis interaction.

We hypothesize that BMI will be negatively associated with brain structure, positively associated with greater discrepancy between chronological and brain age. There will be an interaction between BMI and schizophrenia such

that the slope of the association between BMI and brain structure will be steeper in schizophrenia relative to control participants.

Using mixed effects regression models, we will investigate the association between individual neurostructural measures (cortical thickness, surface area, subcortical volumes) as dependent variables and diagnosis (Sch yes vs. no), BMI and their interaction as fixed effects, accounting for site as a random effect. All cortical thickness models will be adjusted for age and sex; all cortical surface area models will be corrected for intracranial volume, age, sex, age-by-sex, age-squared and age-squared-by-sex to account for any higher-order effects on cortical surface area of age and sex as well as head size, which do not appear to be detectable for cortical thickness measures.

Furthermore, we will use available clinical variables as random effects varying between sites about a group mean, to control for their effects and to investigate their contribution to the brain alterations in addition to BMI.

For numerical stability, continuous variables will be demeaned. Fixed-effects associations and random-effects distributions will be inspected graphically to ascertain satisfaction of model assumptions.

Resources: Please describe what resources you can commit to the project - junior researcher time, troubleshooting, computational server time, helping writing and testing scripts, etc.

We have experience with investigating the effects of metabolic alterations on the brain structure (8,12,13). Dr. Hajek will dedicate time to the management of the project, will supervise the analyses and contribute to writing of the manuscript. He will also provide funding for a student and research assistant who would be working on this project. We will also contribute data to this project from the ESO study.

REFERENCES

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