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

Please complete all fields and return this form by e-mail to:
Lianne Schmaal and Dick Veltman
Email: l.schmaal@ggzingeest.nl, dj.veltman@vumc.nl

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-MDD 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-MDD working group will screen depression-relevant proposals for scientific interest, and will help enlist members who might be interested in collaborating. Proposals will be discussed on ENIGMA-MDD 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 MDD working group or one of the Enigma MDD working group PIs will be assigned as a project liaison. The liaison will be responsible for providing the data and answering any queries relating to the project, and providing the contributing site PIs with updates. The results files from each group will be housed at the VU medical center, Amsterdam, The Netherlands. 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.

We request that the ‘ENIGMA MDD Working Group’, and the liaison person will be listed as co-authors. The ENIGMA MDD 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: 21st July 2015
Name: Philipp G. Sämann
Institution/Affiliation: Max Planck Institute of Psychiatry, Munich, Germany
Email: saemann@mpipsykl.mpg.de

Have you signed and return the ENIGMA Memorandum of Understanding? Yes
If no, please find the Memorandum of Understanding here. (login at enigma mdd members page: http://enigma.ini.usc.edu/ongoing/enigma-mdd-working-group/mdd-members-only/ with password enigma@mdd first)

3. Results request proposal

Proposal Title: Hippocampal subfield changes in first episode and recurrent MDD

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

From the MPI of Psychiatry, Munich: Philipp G. Sämann (saemann@psych.mpg.de)
David Höhn (hoehn@psych.mpg.de)
Immanuel Elbau (immanuel_elbau@psych.mpg.de)
Michael Czisch (czisch@psych.mpg.de)

From other institutions: Lianne Schmaal (l.schmaal@ggzingeest.nl)
Dick Veltman (dj.veltman@vumc.nl)
Juan Eugenio Iglesias (e.iglesias@bcbl.eu)
Christopher Whelan (cwhelan@usc.edu)
Neda Jahanshad (neda.jahanshad@gmail.com)
Theo van Erp (tvanerp@uci.edu)

In addition, all members of the ENIGMA-MDD working group who contribute data for this project and edit the manuscript, will be coauthors.

Proposed Timeline for Completion of Study:

Invitation to sites: 30th July 2015
Confirm participation deadline: 16th August 2015
Sending out first protocols/scripts: 31st August 2015
Deadline to contribute data: 1st October 2015
Meta-Analysis results/feedback: 31st October 2015
Drafting Manuscript/ Feedback: 1st December 2015

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 other project plans to address this.

Please list any conflicts of interest:

None.
**Hypothesis:** Data from multiple independent studies on MDD and the ENIGMA-MDD guided analysis on subcortical volumes strongly suggest that MDD and in particular recurrent MDD is associated with reduced hippocampal volume (HV). Several studies with mostly moderate sample sizes have investigated the question of subregional specificity of this finding and on genetic, endocrinological or environmental causes as well as influences by clinical moderators. Due to known co-associations of HV reduction with poor treatment outcome, it is particularly important to understand this vulnerability in more detail. Here we want to use recent hippocampus segmentation techniques to fully exploit the ENIGMA-MDD sMRI sample to investigate if (1) there is a subregional emphasis of this effect, (2) if a specific spreading pattern from first episode to recurrent episode can be detected and (3) if effects of moderator variables on these MR phenotypes exist.


**Specific results requested:**

We are interested in performing meta-analyses of hippocampal subfields in close analogy to the subcortical volume project of ENIGMA-MDD. All ENIGMA-MDD centers are invited to extend the segmentation to the FreeSurfer based subfield segmentation v6.0, run analysis scripts that correlate the subfield volumes with the clinical phenotypes, and return their results for a meta-analysis.

**Analysis plan (overview):**

Each site needs to run the hippocampus subfield segmentation and perform a QC. Then each site will perform a set of analyses as for the hippocampus for its subfields separated by left and right hemisphere, again according to distributed protocols. Results will then be meta-analysed.

**Analysis steps:**

We will follow a similar approach to that of the subcortical analyses of the ENIGMA-MDD working group:

- Run hippocampus subfield segmentation v6.0 on the basis of already performed recon-all step using v5.3.
  
  NB: new groups have to run recon-all in v5.3, and then append the v6.0 subfield segmentation.

- Generate result lists from this segmentation step according to a distributed script and perform a QC.

- Use this list to produce a new `LandRVolumes_subfields.csv` file (i.e. file with SubjID, volumes per hippocampal subfield, ICV) that includes the (already available) total hippocampal volumes and subfield volumes.

- Use this file in combination with the `covariates.csv` file and run R scripts provided by the analysis team.

- Email summary stats to: saemann@psych.mpg.de
**Resources:** Please describe what resources you can commit to the project - junior researcher time, troubleshooting, computational server time, helping writing and testing scripts, etc.

In the first phase, the QC protocols and other methodological issues will be worked on by the MPIP and external colleagues from the ENIGMA-MDD consortium (Christopher Whelan, T. van Erp, L. Schmaal, D. Velten, J. E. Iglesia, N. Jahanshad). The resulting scripts may also be used by later other hippocampal subfield projects. The MPIP will dedicate time to beta-test the volume extraction and QC scripts before they are spread to the working group.

In the second phase the MPIP will recruit and contact interested centers and also serve as main contact partner in the case of technical problems, questions on the QC or the clinical phenotypes. The computational time is about 1 hour per case if the general segmentation step has already run. The subfield segmentation is suitable for multithreading.

In the third phase, the meta-analysis will be performed by P. G. Sämann and L. Schmaal whereby the analysis approach is strongly parallel to the ENIGMA-MDD subcortical volumes project. Results will be presented and discussed at an early stage in telephone conferences to decide if further analyses are needed.

In the manuscript phase, the MPIP is dedicated to generate and supervise the joint production of the first draft, will coordinate correcting input from all participating sites, handle coauthorship issues and subsequent revisions.