

Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA)

Epilepsy Working Group



June 2021

Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Memorandum of Understanding

Updated April 2021

ENIGMA-Epilepsy Working Group Specifics

This memorandum of understanding (MOU) pertains to the ENIGMA-Epilepsy, hereinafter referred to as Working Group or WG.

This Working Group is chaired by Dr. Sanjay Sisodiya and Dr. Carrie McDonald, hereinafter referred to as Working Group Chairs or chairs.

The e-mail addresses of the Working Group Chairs are:

s.sisodiya@ucl.ac.uk

camcdonald@health.ucsd.edu

The members of Working Group's support group and the participating sites and their PIs are listed on the ENIGMA Working Group website:

<http://enigma.ini.usc.edu/ongoing/enigma-epilepsy/>, hereinafter referred to as *ENIGMA Working Group website*.

In all publications that use the ENIGMA Working Group data, the text "for the ENIGMA-Epilepsy Working Group", hereinafter referred as "for the ENIGMA Working Group", will appear at the end of the author list.

The Overall ENIGMA PI is Dr. Paul M. Thompson.

Introduction

This document outlines the policy for sharing data from the ENIGMA Working Group as well as policies for publication and publication credits for those who use ENIGMA Working Group data. The intent of these policies is to facilitate the sharing of data, to encourage academic productivity, and to provide a mechanism for tracking and archiving data requests, intended analyses, and publications related to and resulting from ENIGMA WG data.

Members of the Working Group 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, and/or genetic data, and/or algorithm development for the purpose of meta-analysis and/or mega-analysis, replication, and/or algorithm testing in a collaborative manner. The Working Group's initial effort is to demonstrate the success of collaborative, systematic neuroimaging analyses across multiple centers to clarify the effect of epilepsy phenotypes on brain structure.

This ENIGMA Working Group is expected to work collaboratively on a growing dataset of contributed results from brain phenotypes in several large samples, potentially being extended later to include genetic data. This database will likely be useful to investigators both within and outside of this ENIGMA Working Group who may request to use parts of the dataset for secondary analyses. In addition, this Working Group will conduct future primary analyses of different brain phenotypes, agreed in each case by contributors. This wealth of data requires (1) organization, (2) protection of authorship rights, and (3) direction for future analyses.

To accomplish these three aims, the ENIGMA Working Group's scientific initiatives and policies will be guided and overseen by group chairs. ENIGMA chairs are composed of a selection of principal investigators participating in the Working Group. ENIGMA chairs are responsible for ensuring that work is carried out in a timely manner, and within the appropriate ethical guidelines for research on human subjects. Part of this responsibility is to ensure that all sites have obtained approval from their local Ethics Committees, and that such assurances are updated regularly in accordance with Office for Human Research Protections (OHRP) and GDPR regulations. In addition, ENIGMA chairs will be responsible for oversight of authorship, whether a paper constitutes a Working Group Publication, and whether the scientific contributions of the sites have been correctly and fairly acknowledged in the publication.

The Working Group chairs are listed in the section Working Group Specifics at the top of this document. The members of ENIGMA support group and the participating sites and their PIs are listed on the ENIGMA Working Group Website.

Projects and Publications

What Constitutes a Working Group Publication?

ENIGMA Working Group publications are papers or abstracts based on investigations that: (1) rely on intellectual resources of the Working Group or (2) use data collected through the efforts of the Working Group, or (3) rely, in whole or in part, on information obtained through Working Group membership.

Publication, Embargoes & Conferences

In agreeing to contribute data to an ENIGMA Working Group analysis for a given phenotype, the members at that site also agree that they will not publish or publicize (to the media or on the Internet) the results of the analyses for that phenotype prior to the publication of the Working Group analysis. Prior to publication, findings may be presented at conferences after consulting in advance with the ENIGMA Working Group chairs. This consultation is designed to ensure that they comply with embargo policies of top-tier journals, protecting the interests of other Working Group members. In addition, secondary analyses based on the findings of the Working Group (for example functional imaging correlates of a related brain structure found through an analysis by

the ENIGMA Working Group), may not be submitted to journals for publication until after the original Working Group paper is accepted for publication. This is intended to avoid the risk of duplicate submissions that may jeopardize a Working Group publication.

Any participating site may choose to publish and present the results of brain imaging analysis for a given phenotype conducted at their own site, which does not contain analyses conducted as part of the ENIGMA Working Group. These publications *do not* constitute Working Group publications. If an ENIGMA Working Group analysis for a given phenotype is proposed and a group is already engaged in an analysis for that same phenotype, the site agrees to disclose their participation in the ongoing project(s) for that phenotype if they wish to participate in the ENIGMA analysis. This is also intended to avoid the risk of duplicate submissions that may jeopardize a Working Group publication.

Guidelines for Primary Publications of the ENIGMA Working Group

ENIGMA Working Group publications may be classified as primary or secondary publications. Primary publications of the ENIGMA WG are those for which an analysis is conducted for the first time by the Working Group on a phenotype of interest (for example analysis of subcortical brain volumes).

The ENIGMA Working Group will be listed as an author (consortium author) on all Working Group publications, including manuscripts on which all contributing Working Group members are listed by name. The text “*for the ENIGMA Working Group*” (see Working Group Specifics section) will appear at the end of the author list.

Based upon the level of contribution, authorship at each site may vary from one publication to another. For each discrete publication, each site PI is responsible for preparing authorship and acknowledgment lists for their site.

Authorship for all ENIGMA Working Group papers will be weighted by current effort and contribution rather than on past contribution to ENIGMA Working Group research. Working Group members will be reasonable and self-critical in their claims for authorship. If a question arises regarding the appropriateness of authorship of (a) member(s), other Working Group members will be asked to advocate for these members in order to avoid putting members in the awkward position of having to advocate for themselves.

Guidelines for secondary ENIGMA Working Group projects

Secondary publications are those that rely upon data collected in primary publications (for example re-analyzing ENIGMA Working Group data using a novel technique or using a different clinical phenotype).

Each proposal for a publication with ENIGMA Working Group data will be submitted to the ENIGMA Working Group chairs using the analysis plan form that can be requested from the

ENIGMA WG chairs. All ENIGMA WG consortium members are encouraged to submit such proposals, which typically involve novel analyses, answering new questions, and may involve subsets of the available sites. Non-Working Group members can, after consultation with the ENIGMA WG chairs and members, also submit a proposal for data-analysis and publication and will be asked to sign the Memorandum of Understanding regarding authorship and publishing. The ENIGMA WG chairs will screen the proposals for scientific interest, quality, overlap with other plans, appropriateness and feasibility of the proposed timeline, and whether the proposed resources committed to the project are sufficient.

Analysis plans should include a proposal for publication of a specific scientific paper, not for multiple papers on a more general topic or for a "line of work". This implies that the analysis plan should include specific research questions and hypotheses and a detailed plan for data analysis to answer those specific research questions. To attempt to avoid overlap between papers resulting from different analysis plans, the data analyses and results reported in the manuscript are limited to those described in the analysis plan. For additional analyses not described in the analysis plan, a new analysis plan needs to be submitted, even if this concerns a similar topic but different data or different analyses on the same data.

When the analysis plan is approved by the ENIGMA WG chairs, the proposal will be circulated amongst ENIGMA WG members. ENIGMA WG members will have 14 days from the time of the posting to ask for clarification, voice concerns or objections and/or give feedback to the proposal. Each analysis plan will be discussed during a conference call before the project can be initiated and the project leader can invite sites to participate. 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, participation in projects will be on an opt-in basis. The ENIGMA WG chairs will help enlist members who might be interested in collaborating and will assist in general coordinating tasks. Proposals will be discussed on ENIGMA WG calls and emails to encourage the broadest participation.

Submission of a proposal implies actual plans for a publication, which will be worked on within a reasonable time frame specified in the proposal. When within 6 months after submitting a proposal there are no provable activities in that direction, the subject can be released for other interested parties.

Data sharing

Individual subject level Working Group data will be stored at *UC San Diego*. Together these sites are hereinafter referred to as *Main Working Group Data Storage Sites*. Individual subject level data may also be stored at the University of Southern California, the ENIGMA lead PI (Dr. Paul Thompson) site. Sites with approved secondary proposals may also receive ROI-level datasets from cohorts for which the PIs have approved data transfer, and have completed any and all

necessary data use agreements and/or material transfer agreements. Together these sites are hereinafter referred to as *Project Specific Data Storage Sites*.

Cohort level results and meta-data

Such data include all statistical summaries and results from all analyses that were run for inclusion in any project; the aggregate group level data may be made public upon manuscript publication. This includes information gathered across all cohorts participating in the given project, for example: mean and standard deviations for each covariate assessed, case/control effect sizes and standard errors, sample size for each regression in the analysis. This data includes no individual level subject information. Site PIs understand that all such data are being shared for inclusion in an eventual manuscript and will be publicly available through the manuscript text and supplementary material. This information may be presented in the form of Forest plots, and supplementary tables describing cohort attributes in any manuscript that arises. The exception to this is genome-wide association study (GWAS) or other genetic results, for which cohort-level results that include allele frequency information will not be made available without explicit approval from site PIs to ensure re-identification of participants is not feasible. In the case of GWAS, the site PIs do consent to having their data included in the overall meta-analysis, as well as any reasonable request for a leave one or more sites-out meta-analysis. This is typically requested when a site PI would like to use the meta-analysis results for prediction on their own cohort data, and thus asks for a version of the meta-analysis with their dataset removed.

Cohort level inclusion and exclusion criteria will also be made publicly available as part of the manuscript. Meta-data unique to the cohort and not used in the publication will not be shared. Upon completion, the manuscript and supplementary tables and figures will be shared with site PIs who will approve cohort level meta-data to be shared. Ideally, any questions or concerns must be brought up to the working group chair and project leads *before* cohort-level data and results are sent to the working group/project leads, but PIs will also have a chance to go over the material before publication.

As summary results at the cohort level, along with cohort-specific meta-data level information, will largely be made publicly available, the site PI(s) acknowledge/s future work with these statistical summary measures may be feasible; this may be with the consent of the PIs and the ENIGMA leads (for example if a leave-one-out meta-analysis is requested).

Individual level data

Sharing participant-level data (such as raw images, imaging measures, covariates, etc.) is not required to join a working group. However, this level of data sharing allows for a wider variety of projects and applications, and is encouraged. The security of the data is of utmost importance.

For groups that can share de-identified subject-level data for the purposes of mega-analyses within or across working groups.

Any Working Group member wishing to access individual subject level data will need to complete an analysis plan. The analysis plan will clearly state which variables will be included in the analysis, and thus what data is requested from each of the participating sites. The level of data-sharing will also be mentioned in the analysis plan, so that it is clear whether raw imaging and/or genetic, cognitive, individual structural or functional imaging measures derived from software packages including, but not limited to, FreeSurfer or TBSS (hereinafter referred to as 'individual data'), or group-level summaries and post-estimation statistics will need to be shared for the project.

The site PIs are responsible for ensuring appropriate anonymization of their site's MR and phenotypic or genetic data. Both the site PIs who contribute data to the project as well as the project leader are responsible to comply with all relevant rules and regulations imposed by their institutions. This may mean that the project needs to be approved or declared exempt by a committee that oversees research on human subjects, e.g. a local IRB or Ethics Committee. Depending on the existing ethical approval and the level of data sharing required by the project, sites may need to obtain additional approval for sharing anonymized data with the project leader. The project leader of an approved analysis plan is required to keep track of ethical approval of each participating cohort when raw data or individual data needs to be shared for the project and will be able to provide this list when asked for, and include relevant information in the subsequent publication.

The project leader of an approved analysis plan is not allowed to share the data of participating cohorts to third parties inside or outside the ENIGMA consortium. Individuals who will have access to the data during the project shall all be named in the Analysis Plan. In case of sharing raw or individual data, the project leader keeps a document stating who has access to these data. In case of a project using a mega-analytical approach, the location of data storage, the people who will have access to the data, and a timeline for finishing the project shall be stated in the analysis plan. At the end of the proposed timeline the project leader individual level data can continue to be stored on their local data storage for archival purposes, but *cannot conduct any additional statistical analyses on the data from participating ENIGMA WG members beyond the scope of the approved analysis (i.e., analyses that have not been explicitly described in the approved analysis plan)*. If a site PI decides to withdraw from a project they had previously enrolled in and committed data towards, the project leader will comply and remove the dataset in question from all future analyses. Prior to this, all efforts would be made by ENIGMA WG chairs to address any concerns the withdrawing PI may have and to determine if the project has deviated from proposed plans.

Email addresses

Members agree that their email addresses may be included on ENIGMA consortium mailing lists, can be shared with other members of the consortium if deemed necessary for the scope of work, and can be used in filling out authorship forms for publications and when submitting to conferences or journals.

Authorships

Specific authorship policies for:

Manuscript

1. We request that manuscripts resulting from approved analysis plans will be submitted to the ENIGMA WG chairs (see Working Group Specifics section) prior to circulating it to all co-authors and prior to submitting to a journal. This review is intended to ensure that provisions described in the analysis plan are correctly implemented and to avoid overlap with other ENIGMA WG proposals/manuscripts. The ENIGMA WG chairs maintain confidentiality of the manuscript and will complete its review within 2 weeks.
2. Authorship credit should be based on substantial contribution to: (1) the measurement of structural, diffusion, or functional brain scanning and imaging phenotypes or genotypic or other substantive data for a ENIGMA WG analysis; (2) contributions or generation of data used in the analysis; (3) contributions to the conception, design, analysis and/or interpretation of the data; (4) drafting the manuscript or revising it critically for important intellectual content, and (5) final approval of the manuscript version to be published.
3. People involved in the primary design, analysis and writing parts of the project will be listed as first (or joint first - denoted with an asterisk) and senior (last or joint last) authors. In addition, the ENIGMA WG chairs and all members of the ENIGMA Working Group who contribute data for this project and edit the manuscript will be listed as co-authors. Membership of the WG alone does not constitute grounds for authorship.
4. The phrase "for the ENIGMA-Epilepsy Working Group" (see Working Group Specifics Section) can be included on the author line of the manuscript, particularly if there is a restriction on the total number of co-authors. The ENIGMA Working Group website (see Working Group Specifics Section) can be used as the affiliation, which may include a list of all people involved in the particular ENIGMA project or working group.
5. Funding by all supporting programs will be acknowledged in the support acknowledgement section of the manuscript using language similar to the following:

The *ENIGMA Working Group* acknowledges the NIH Big Data to Knowledge (BD2K) award for foundational support and consortium development (U54 EB020403 to Paul M. Thompson).

For a complete list of ENIGMA-related grant support please see here:

<http://enigma.ini.usc.edu/about-2/funding/>.

6. All authors have at least two weeks to inspect the article before it is initially submitted to a preprint server and/or journal.
7. Active approval of all authors on the article's content and their co-authorship is required before it is submitted to a journal.
8. It is the responsibility of the first and last authors that the sample and the research-methodology are described correctly and that references to former relevant ENIGMA Working Group publications where appropriate are made.

The Chairs may provide a more thorough authorship guidelines document as an addendum to the MOU. It is the responsibility of the first and last authors leading the project to follow those guidelines for all manuscripts, conference abstracts, and symposium presentations. Disclosures are often required for submission to a journal, and these will be collated from all authors by the submitting author.

Conference poster and talk abstracts

1. If the conference allows listing all contributing authors, please include all contributing authors on the author line. For most conferences, additional names may need to be submitted to the conference separately.
2. If the conference has a hard limit on contributing authors (many do), include the project leaders / major contributors and, as co-authors, the ENIGMA Working Group chairs, overall ENIGMA PI, and the statement "for the ENIGMA Working Group" (see Working Group Specifics Section). For this ENIGMA Working Group, include at least FIRST AUTHOR (Presenter), the Working Group Chairs, the overall ENIGMA PI, LAST AUTHOR, and "for the ENIGMA Working Group" (see Working Group Specifics Section). Of course other important contributors can be included, as well.
3. If not all authors can be listed, consider putting in the abstract "Contributing Authors are listed at ENIGMA Working Group Website".
4. Regardless of the names listed on the abstract, it is best to list all contributors on the conference poster and/or the conference acknowledgement slide. PDF copies of the conference abstracts can be used by all ENIGMA WG members to list abstracts on CVs.

Symposium submissions

1. List the presenting author, and if possible, on behalf of the ENIGMA-Epilepsy Working Group. Again, if possible consider putting in the abstract "Contributing Authors are listed at ENIGMA Working Group Website".
2. Regardless of the abstract, all contributors should be listed on the symposium talk acknowledgement slide.

Participation in the ENIGMA Working Group

Admitting New Sites as Members

Success of the first publications is anticipated to lead to a larger, long standing Working Group. New Working Group members will sign the Memorandum of Understanding (MOU) indicating that they agree with the policies listed here and that they have obtained the required ethical clearances to participate or send data.

Expulsion from the ENIGMA Working Group

Expulsion from the ENIGMA Working Group will be considered when a site fails to uphold this MOU or does not contribute significantly to the work of ENIGMA WG either in data collection, data analyses, or its goals. It is the responsibility of ENIGMA WG chairs to assemble evidence and present the reasons for possible expulsion to the PIs of sites participating in ENIGMA WG. Expulsion from ENIGMA WG will require a simple majority vote of the PIs.

A site may request to withdraw from ENIGMA WG. Requests for withdrawal will be reviewed by the ENIGMA WG chairs. The withdrawing site will need to agree in writing to a moratorium on publication of any data that were obtained in the context of ENIGMA WG work, or where the interpretation of the data relies in any part on unpublished ENIGMA WG work.

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ENIGMA Working Group Membership is contingent upon signing the following statement:

I agree that I will be an active contributing member, in the following ways (tick or add text as appropriate):

- Provision of data: (tick)
Leading secondary projects (at least data collation, analysis, drafting of ms) (tick)
Other (specify): (text)

I confirm that all data provided will have been gathered under a protocol approved by the institutional ethics review board/committee, and that written informed consent/assent has been provided by each subject (tick)

I AGREE:

1. To consider participation in primary and secondary analyses proposed by this ENIGMA Working Group, subject to constraints or limitations that I can impose in each case.
2. To abide by the guidelines for data sharing, authorship and publication, and other guidelines described in this document.
3. Not to distribute or communicate any privileged information to individuals who are not members without consent of the entire ENIGMA Working Group. This includes any other existing collaborators who are not members of this ENIGMA WG. Privileged information includes results of any unpublished analyses completed by members of this ENIGMA WG.
4. Not to distribute or copy any data collected by this ENIGMA WG without prior written consent of all Working Group members.
5. That the ENIGMA WG chairs will review and evaluate future scientific opportunities, and will make recommendations regarding the needed expertise and research program to maximize those opportunities in the best possible way.
6. That failure to uphold this agreement may result in my expulsion from this ENIGMA Working Group (but I will still be bound by publication moratorium on this ENIGMA WG's work, as described above).

Signature

Date

Please print name

Carrie R. McDonald

Carrie R. McDonald
ENIGMA-Epilepsy Co-Chair



Sanjay Sisodiya
ENIGMA-Epilepsy Co-Chair