Supplementary Appendix

ENIGMA and Global Neuroscience: A Decade of Large-Scale Studies of the Brain in Health and Disease across more than 40 Countries

Correspondence: Paul M. Thompson, pthomp@usc.edu

A. Technical Contributions of ENIGMA

Technical Contributions of ENIGMA. ENIGMA’s ongoing technical contributions include large-scale testing and refinements of protocols to standardize the pre-processing, harmonization, and analysis of multiple types of imaging and genetic data, as well as new data modalities such as magnetic resonance spectroscopy (MRS; Bartnik-Olson 2019) and EEG (Smit 2018). These contributions have simplified the process for merging and comparing multi-source brain data in large-scale analyses across fields of psychiatry, neurology, and developmental neuroscience.

I. Genetics. ENIGMA’s genetics protocols (http://enigma.ini.usc.edu/protocols/genetics-protocols/) enabled over 50 sites to participate, on an unprecedented scale, in large-scale GWAS studies of brain-derived MRI measures including subcortical and cortical volumes, ICV (Stein 2012; Hibar 2015; Satizabal 2019; Grasby 2019; Hofer 2019), as well as EEG (Smit 2018). The genetic analysis protocols include methods to impute data from multiple genotyping chips, to conduct statistical association tests across the genome (in both unrelated samples and family designs), and meta-analysis protocols for combining genome-wide association data from many sites. Extensive quality control procedures are included. A recent extension of this work includes protocols for genome-wide epigenetic analysis (EWAS) of brain traits, which were applied to discover loci where methylation levels relate to hippocampal volumes by pooling evidence across multiple datasets worldwide (Jia 2019). To widely disseminate the results of these genome-wide analyses, the ENIGMA-Vis portal (Shatokhina 2018) provides access to the summary statistics from ENIGMA’s GWAS. Hundreds of users have downloaded these data, including researchers in psychiatric and behavioral genetics who study interactions between genes, brain, and behavior. Many researchers have used the summary data to test methods for computing genetic correlations, genomic structural equation modeling (SEM), to relate GWAS findings to maps of gene expression, or to optimize predictive models based on polygenic risk scores. As an example of the impact of ENIGMA on work in related fields, others have used the data to study the overlap between genes affected in in vitro models of cell aging with those regulating hippocampal volume.

II. Structural MRI. The ENIGMA structural image processing protocols include a wealth of methods for analyzing T1-weighted brain MRI including cortical and subcortical volumes and surface areas, sulcal analysis, longitudinal analysis and vertex-wise subcortical shape analysis.
FreeSurfer, a brain imaging software package developed for analyzing brain MRI scans, is primarily used to preprocess and label neuroanatomical structures in the data (Fischl 2002). Detailed instructions for analysis and quality control for each method may be found on the ENIGMA website (http://enigma.ini.usc.edu/protocols/imaging-protocols/). ENIGMA’s Ataxia group has also developed and tested Docker-based pipelines for analyzing cerebellar structure, by meta-analyzing statistical maps across multiple sites and cohorts (Harding 2019a, 2019b).

III. Diffusion MRI. ENIGMA’s DTI protocols (http://enigma.ini.usc.edu/protocols/dti-protocols/), now used in the largest diffusion MRI studies of 8 different brain disorders (Kelly 2018, van Velzen 2019, Favre 2019, Villalon 2019; Dennis 2018, 2019; Piras 2020, Hatton 2019; Jahanshad 2017, 2013; Acheson 2017, Kochunov 2016, 2015, 2014), allow the pre-processing, quality control, and meta-analysis of data collected with diverse diffusion imaging protocols. The ENIGMA-DTI protocol is based on tract-based spatial statistics and includes steps for motion and eddy currents correction, echo-planar imaging distortion correction and tensor fitting. The ENIGMA-DTI protocol may be found on the ENIGMA website (http://enigma.ini.usc.edu/protocols/dti-protocols/) and is detailed in Jahanshad (2013). This protocol has excellent reproducibility for the analysis of white matter microstructure (Acheson 2017). Recent diffusion MRI studies by ENIGMA also show the benefits of using additional data harmonization methods, such as the batch-effect correction tool ComBat (Fortin 2017; Hatton 2019 compare global analyses of epilepsy data with and without using ComBat, showing its advantages; see also Zhu 2018; Nir 2018 on DTI data harmonization).

IV. Anatomical Shape. ENIGMA’s Subcortical Shape Analysis toolbox (http://enigma.ini.usc.edu/ongoing/enigma-shape-analysis/; Gutman 2015) has been used to meta-analyze local effects of genetic variation (Roshchupkin 2016), psychiatric and neurological disorders, and modulators of disease, on 3D surface models of subcortical structures. The toolbox has been used to support multi-site analyses of subcortical shape in MDD (Ho 2019), OCD (Fouche 2019), schizophrenia (Gutman 2019), addiction (Chye 2019), 22q11.2 deletion syndrome (Lin 2017; Ching 2019), and Parkinson’s disease (Laansma 2020). It has also been used to create surface based maps of SNP effects for genetic loci discovered in ENIGMA’s GWAS (Hibar 2015). In recent innovations, deep learning has been adapted to vertex-based data created by the ENIGMA Shape Analysis toolbox to enhance diagnostic classification. For quality control, we have adapted standard deep learning approaches to handle subcortical and cortical meshes (Petrov 2017; Zeng 2020).

V. EEG. ENIGMA’s EEG working group is currently developing methods for analyzing resting state EEG (Smit 2018). Historically, EEG has used highly calibrated recording systems and strict electrode localization protocols (Jasper 1958), extended to denser systems (Oostenveld and Praamstra 2001). The analysis protocols for the first ENIGMA-EEG article aimed to converge EEG preprocessing and analysis steps as much as possible across the wide variety in electrodes available across the older cohorts. In the future, novel analyses will use higher electrode density recordings to run GWAS for functional connectivity (Smit 2010; Stam 2014), oscillatory dynamics (Linkenkaer-Hansen 2007), and theta-beta ratio (Arns 2013; Smit 2005) and take advantage of higher density recordings by increased cleaning quality and increased local activity detection. To harmonize these analyses, the group is following strict analysis protocols using automated data cleaning steps tested against the still gold standard of visual cleaning in a subset of the data. Subsequent EEG parameter extraction algorithms are then easily applied. Finally, QC
is performed by comparing each value against a value imputed using the high-density electrode scheme. Further in the future, ENIGMA-EEG will perform source localization to increase the specificity of connectivity and reduce spurious effects in scalp recorded signals.

VI. Resting-State Functional MRI. Resting-state functional MRI (rs-fMRI) is an approach to understand patterns of synchronized brain activity at rest, which can be further decomposed into networks with known functions (e.g., default mode, salience, attention networks). Measures derived from these networks can be associated with multivariate patterns in other types of images, or with clinical symptoms using methods such as latent factor analyses or canonical covariates analysis (CCA; Adhikari 2019). Harmonized processing of rs-fMRI in ENIGMA has used one of two pipelines thus far: (1) a single modality AFNI-based pipeline that does not require the use of anatomical MRI datasets (Adhikari 2018a,b, 2019); and (2) a pipeline known as fMRIprep+ (Veer 2019), based on the fMRIprep approach (Esteban 2019) that can be used for analysis of multi-site task-based fMRI.

VII. Multi-site statistics: Meta- and Mega-Analyses, and Machine Learning. Early work by ENIGMA focused on developing technical approaches to meta-analyze effects of disease or genetic variation on the brain, after performing computations at many remote sites. The results of published meta-analyses were imported into a publicly available online 3D viewer - the ENIGMA Viewer - to help users interactively visualize the effects of disease on various brain measures, overlaid on a 3D brain model (http://enigma-viewer.org/About_the_projects.html; Zhang 2017). ENIGMA’s early meta-analyses were extended to ‘mega-analyses’ (see Boedhoe (2019) for a comparison of the two approaches), in which individual-level data are pooled across sites for more sophisticated multivariate analyses; over 300 such analyses are now underway across ENIGMA working groups. ENIGMA also developed protocols to meta-analyze voxel-based data, including multi-site tensor-based morphometry (TBM; Jahanshad 2019). This technique allows each site to compute statistical models on their own brain template, and then to pool or compare findings after nonlinear registration of group data to a common neuroanatomical template. More recently, projects have begun to perform machine learning on both raw image data and derived data, to build predictive models that can be trained and thoroughly tested on diverse datasets worldwide (Nunes 2018; Bruin 2019).

VIII. Informatics for Large-Scale Multi-Site Projects. The organization, management, and tracking of projects and meta data on such a vast scale has benefited from informatics approaches that represent large-scale collaborative studies. One tool being developed is the ENIGMA Organic Data Science framework (Jahanshad 2015), a semantic media wiki based site that integrates information and relationships among co-authors, cohorts, projects, working groups, and the data types and properties relevant to each category. ENIGMA-ODS (Jahanshad 2015) is currently designed only to store meta-data for cohorts, to include, for example, the imaging and genetic data types collected, the number and type of participants, and the scanning locations, allowing for automatic generation of cohort description tables and supplementary information (Jang 2017). Situations encountered throughout ENIGMA analyses fuel continuously updated features in the wiki, necessary before widespread deployment. For example, the continued data collection in some cohorts, as opposed to others, results in a previous version of one cohort’s data being used for older projects compared to newer ones; therefore, a “project cohort” page allows for unique subsets of cohorts that were contributed to certain projects to be described and fixed, while allowing the meta-data for the cohort at large to be updated. ENIGMA-ODS provides an
environment for ENIGMA researchers initiating a project to search meta-data for other cohorts with relevant data collection types and recruit researchers to participate in new endeavours. The project proposals also provide an option for registering hypotheses and analysis plans to the research network to ensure proper scientific research guidelines are met. Neuro-DISK (Garijo 2019), an extension of the Automated DIscovery of Scientific Knowledge (DISK) framework (Gil 2016) to support multi-site studies of neuroimaging genetics, is currently underway. This framework provides and implements a detailed description of statistical analyses so that they can be re-run, supplemented, and updated as new data become available. This level of continuous data monitoring and updating supports the growing call for reproducible data science (Gundersen 2018).

IX. Distributed Computation. An upcoming innovation in ENIGMA’s data analyses includes the use of COINSTAC (Plis 2016, Ming 2017) - a framework that allows computation on distributed brain imaging data. Distributed computation allows a user to compute on remotely stored data, using workflows that can iterate over multiple datasets and servers. This kind of approach helps to coordinate analyses without requiring the data to be centralized in one place; initial tests of COINSTAC in ENIGMA are underway in the schizophrenia, bipolar disorder, and MDD working groups.

The technical scope of ENIGMA is constantly evolving. The last year has seen the creation of working groups to harmonize data from MRS (Bartnik-Olson 2019), and to compare approaches to compute BrainAGE (Han 2019; Lam 2020).

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