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REVIEW ARTICLE

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The Enhancing NeuroImaging Genetics through Meta-Analysis Consortium: 10 Years of Global Collaborations in Human Brain Mapping

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Abstract

This *Special Issue* of *Human Brain Mapping* is dedicated to a 10-year anniversary of the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium. It reports updates from a broad range of international neuroimaging projects that pool data from around the world to answer fundamental questions in neuroscience. Since ENIGMA was formed in December 2009, the initiative grew into a worldwide effort with over 2,000 participating scientists from 45 countries, and over 50 working groups leading large-scale studies of human brain disorders. Over the last decade, many lessons were learned on how best to pool brain data from diverse sources. Working groups were created to develop methods to analyze worldwide data from anatomical and diffusion magnetic resonance imaging (MRI), resting state and task-based functional MRI, electroencephalography (EEG), magnetoencephalography (MEG), and magnetic resonance spectroscopy (MRS). The quest to understand genetic effects on human brain development and disease also led to analyses of brain scans on an unprecedented scale. Genetic roadmaps of the human cortex were created by researchers worldwide who collaborated to perform statistically well-powered analyses of common and rare genetic variants on brain measures and rates of brain development and aging. Here, we summarize the 31 papers in this *Special Issue*, covering: (a) technical approaches to harmonize analysis of different types of brain imaging data, (b) reviews of the last decade of work by several of ENIGMA's clinical and technical working groups, and (c) new empirical papers reporting large-scale international brain mapping analyses in patients with substance use disorders, schizophrenia, bipolar disorders, major depression, posttraumatic stress disorder, obsessive compulsive disorder, epilepsy, and stroke.

KEYWORDS
big data, DTI, ENIGMA, genetics, GWAS, international research, MRI, neuroimaging, neuroscience, reproducibility

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1 | INTRODUCTION

In December 2009, the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium was formed by researchers aiming to understand how common variants in the human genome relate to brain measures derived from neuroimaging. The vast data sets needed to perform well-powered genetic analyses could only be assembled through a consortium that united researchers worldwide, and by providing a consistent way to analyze data and yield reproducible findings in ethnically diverse cohorts. ENIGMA's early genetic studies, which identified common genetic variants that contributed to normal variations in brain structure (Hibar et al., 2015; Stein et al., 2012), led to the formation of over 50 working groups to study neurological and psychiatric disorders, neurodevelopmental conditions, brain aging and neurodegeneration, and brain trauma—across the lifespan and across the world.

As ENIGMA completed its first decade of research in 2019, the Editors of *Human Brain Mapping* invited us to assemble a *Special Issue* of the journal to include a range of technical, clinical, and empirical papers that describe the challenges and successes of our last decade. Six guest editors solicited contributions to highlight key findings to date, pointing to general guidelines and lessons learned in pooling brain data from diverse sources. In this Introduction to the *Special Issue*, we summarize the papers contributed, the main themes, as well as emerging challenges and future directions in the international analysis of brain data. In addition to this Introduction, the *Special Issue* is organized in four sections, dedicated to (1) reviews, (2) methods for data integration, (3) genetic studies, and (4) clinical studies.

2 | OVERALL ORGANIZATION OF ENIGMA—REVIEWS OF WORKING GROUP FINDINGS

Figure 1 shows an up-to-date chart of ENIGMA's working groups; Figure 2 shows the distribution of actively participating members across the world. ENIGMA includes clinical groups that study specific disorders and conditions - such as schizophrenia, bipolar disorder, major depressive disorder (MDD), addiction, and posttraumatic stress disorder (PTSD). Technical working groups support the harmonized analysis of different kinds of brain-related data being collected worldwide—such as anatomical and diffusion magnetic resonance imaging (MRI), resting state and task-based functional MRI, electroencephalography (EEG), magnetoencephalography (MEG), and magnetic resonance spectroscopy (MRS), as well as genetic and epigenetic variation, and factors in the environment that affect disease risk and outcomes.

Of these working groups, 14 groups summarize their last decade of findings in a total of 12 papers in this *Special Issue*.

In-depth, review articles cover a broad range of efforts by ENIGMA's clinical working groups on bipolar disorder (Ching et al., 2020), obsessive compulsive disorder (OCD; van den Heuvel

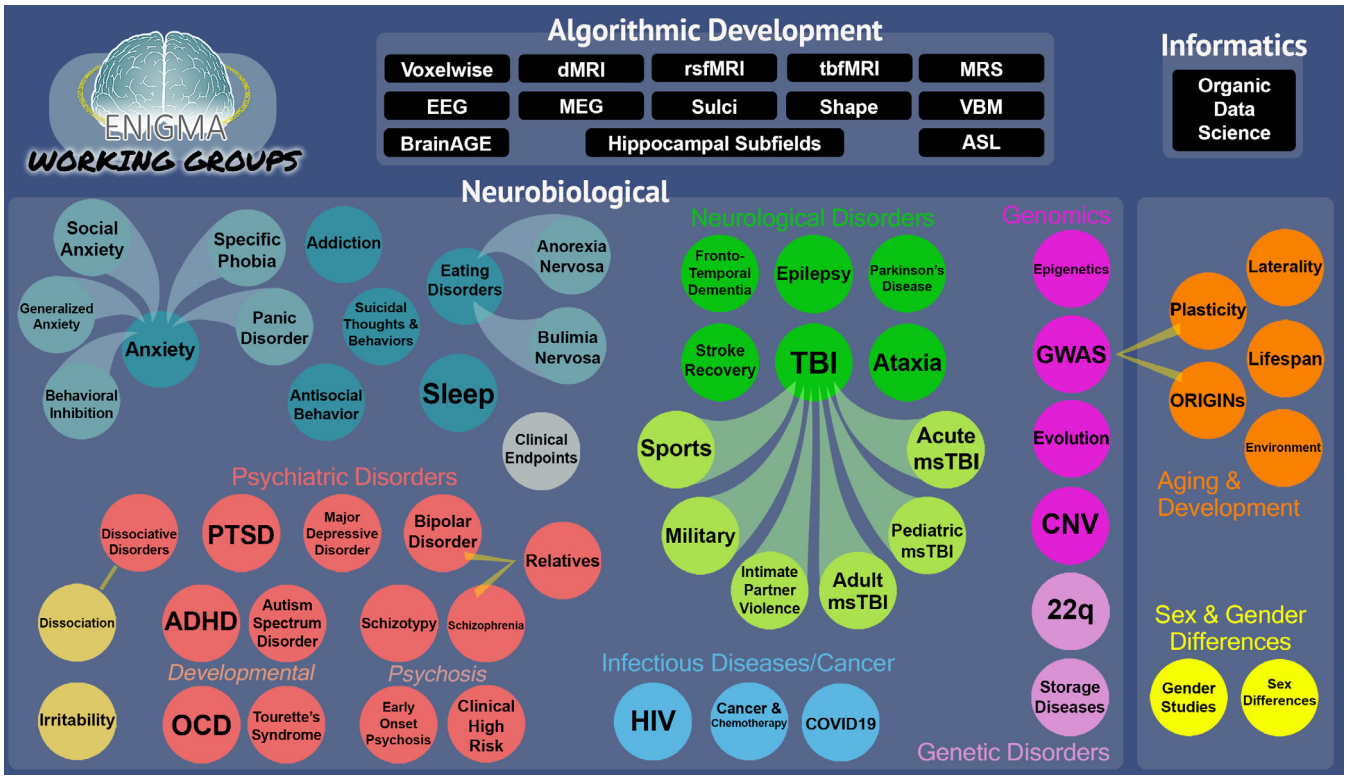

FIGURE 1 Current chart of the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium's clinical and technical working groups

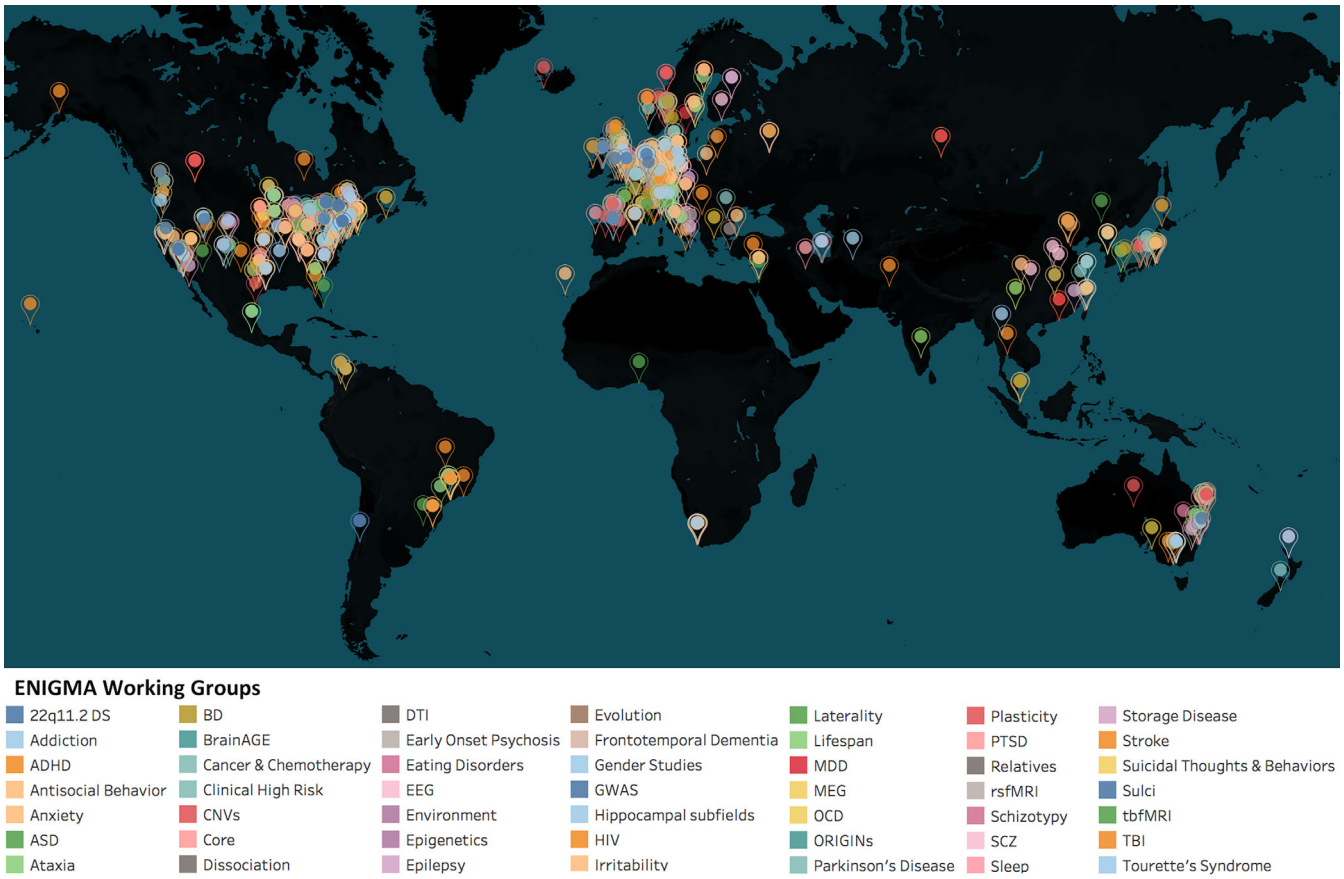

FIGURE 2 Distribution of actively participating members across the world in the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium's working groups

et al., 2020), epilepsy (Sisodiya et al., 2020), attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD; Hoogman et al., 2020), anxiety (Bas-Hoogendam et al., 2020), and traumatic brain injury[1] (TBI; Dennis et al., 2020).

3 | METHODS FOR DATA INTEGRATION AND TECHNICAL ISSUES IN HARMONIZING BRAIN DATA

Several papers in this *Special Issue* focus on technical challenges in harmonizing brain data from different sources worldwide. These challenges were addressed by developing harmonized protocols to analyze specific brain measures, such as hippocampal subfields (Sämann et al., 2020). As many disorders studied by ENIGMA have found abnormalities in the hippocampus, Sämann et al. (2020) offer a comprehensive review of approaches and methods used to study hippocampal subfields in clinical populations, offering a finer-grained analysis of hippocampal structure. Based on experience applying subfield analysis to diverse data worldwide, they present in-depth guidelines for segmentation and quality control of subfield measures as part of an illustrated and validated protocol for the quality control and analysis of subfield data—one that is widely used across ENIGMA. Complementary approaches that use deep learning for anatomical segmentation of the hippocampus are compared and reviewed in an empirical study by Zavaliangos-Petropulu et al. (2020). With the renewed interest in deep-learning methods and their application to large-scale biobanks, we may soon be able to automate the quality control of data from many more imaging modalities (Petrov et al., 2018). Even now, when large-scale brain morphometry studies examine over 50,000 scans, quality control is still a bottleneck and a rate-limiting step.

3.1 | Statistical design considerations for multisite analyses

Zugman et al. (2020) write on behalf of ENIGMA's Anxiety working group, and discuss three main models of analysis that have emerged across ENIGMA's working groups—(1) *meta-analysis*, where sites analyze their own data with an agreed protocol, and then share statistical summaries with a central site, (2) *mega-analysis*, in which derived individual data is shared with a central site, and (3) *raw image sharing*, which lends itself to voxel-based and deep learning analyses not possible otherwise. The sociological, legal, and practical aspects of each type of data sharing are discussed in depth, along with

recommendations for setting up analyses that comply with international data governance policies, such as the General Data Protection Regulation (GDPR) rule in the European Union.

Since its inception, ENIGMA has decentralized analyses to the greatest possible extent, offering opportunities to train researchers around the world in data analysis. Researchers from many countries worldwide have also led their own international collaborative studies. This has had an effect on bringing the neuroscience community together to work on common problems, including scientists from low-middle income countries such as India, Pakistan, and Nigeria (Palk, Illes, Thompson, & Stein, 2020), and researchers from countries that have not traditionally worked in international consortia (Namazova-Baranova et al., 2020). Picking up on this theme, White, Blok, and Calhoun (2020) note the challenges of data sharing and safeguarding privacy in neuroimaging research; they note the benefits of distributed computation for safeguarding privacy while allowing iterative computations on remote data. COINSTAC (Plis et al., 2016) offers one such method to perform distributed computations on remote data. As analyses move from case–control studies to machine-learning and deep-learning studies, it can help to distribute computations as analyses progress beyond 100,000 brain scans and into ever-more complex data modalities, including whole genome sequences and dynamic data. Machine learning is far from straightforward in a multisite setting—the methods need to deal with site specific effects and confounds, and need to handle imbalanced data across sites; this mandates careful design. Hahn et al. (2020) present a careful approach that uses machine learning to predict alcohol dependence based on brain data from multiple sites and sources. They note a number of design criteria that are needed to avoid pitfalls and mistakes when training and testing machine learning methods on multi-site data, and they present a toolkit to implement such analyses.

3.2 | Normal brain variation and statistical charts for brain aging across the lifespan

A trio of papers examines the trajectories of cortical and subcortical morphometry across the lifespan (Dima et al., 2021; Frangou et al., 2021). The authors also show how these patterns of variation differ by sex (Wierenga et al., 2020). The availability of brain MRI data from 88 cohorts and 18,605 individuals (aged 3–90 years) allowed the ENIGMA-Lifespan group to detect subtle sex differences in brain aging. They note that men appear to lose brain tissue faster than women, on average, until age 60 or so, and then women lose brain tissue faster thereafter. Their new normative charts offer a guide to factors that modulate brain development and aging, and a means to test whether these factors generalize to different cultures across the world. In related work—that includes a remarkable 99 cohorts worldwide—Kong et al. (2020) review a series of papers by ENIGMA's Laterality group. This group has examined left/right hemisphere asymmetries in brain structure, finding consistent patterns of brain asymmetry worldwide, that depend to some extent on a person's age and sex—but not on handedness. Brain asymmetry was subtly altered in autism (Postema et al., 2019) but not in major depressive disorder (de Kovel et al., 2019). These findings show how large-scale consortia can rigorously address long-standing questions in the history of neuroscience, including hypotheses of disrupted brain asymmetry in disorders such as schizophrenia (hypothesized by Crow, 1990, with mixed evidence over the years).

Koshiyama, Miura, et al. (2020) describe the parallel development of the COCORO consortium in Japan. They have analyzed brain MRI and diffusion tensor imaging (DTI) data from a range of psychiatric disorders using the same protocols as used in ENIGMA (Koshiyama, Fukunaga, et al., 2020). The agreement in findings between this work in Japan and the rest of ENIGMA—even in the rank order of brain metrics that show differences in each psychiatric disorder—underscores the robustness of findings when tested across cultures and diverse environments. This also motivates future work on risk factors for disease in the genome and environment that differ across cultures around the world (such as the India ENIGMA Initiative for Global Mental Health; John, Thompson, & Venkatasubramanian, 2020).

3.3 | Diffusion-weighted MRI and personalized prognosis

The review of the 10 years of activity of ENIGMA's DTI working group (founded in 2010) summarizes the findings from ENIGMA's clinical working groups that used the DTI workflow to report illness related findings in large-scale studies of neurological and psychiatric brain disorders (Kochunov, Fan, et al., 2020). This includes schizophrenia spectrum disorder, bipolar disorder, MDD, OCD, PTSD, TBI, and 22q11 deletion syndrome. Kochunov, Fan, et al. reviewed these findings, showed their robustness and reproducibility in independent cohorts, and demonstrated that deficit patterns are shared, to some extent, across illnesses, motivating cross-diagnostic research. The high reproducibility of regional deficits in independent cohorts provided an opportunity to build individual-level "vulnerability" indices based on the similarity of the individual brain to the group findings in specific disorders. Kochunov, Hong, et al. (2020) and Kochunov, Fan, et al. (2020) describe a "regional vulnerability index" (RVI), which measures an individual's resemblance to the pattern of group deficits found by ENIGMA for a number of specific brain disorders. The application of RVI to schizophrenia demonstrated that the similarity to the expected deficit patterns in schizophrenia may be useful for early diagnosis, providing quantitative targets for more effective treatment strategies and for cross-disorder analyses.

4 | GENETIC STUDIES

Medland et al. (2020) write on behalf of the ENIGMA Genetics working group—the first working group to be formed. They explain the motivation for creating ENIGMA, in response to the replication crisis that was felt in the emerging field of imaging genetics. Their review article covers several concepts in the genetic analysis of brain images,

and how the large scale pooling of brain data using harmonized protocols led to a series of highly rigorous papers on the genetic architecture of the cerebral cortex (Grasby et al., 2020), the hippocampus, and subcortical structures (Satizabal et al., 2019), with ever-increasing power. These efforts were recently extended to genome-wide screens of single nucleotide polymorphisms that are associated with functional synchrony of the brain, assessed using EEG (Smit et al., 2018), and the discovery of markers in the genome associated with the rate of brain development and aging, in over 10,000 people scanned longitudinally with MRI (Brouwer et al., 2020). Complementary to this work on GWAS, Sønderby et al. (2021) review ENIGMA's work on genetic disorders—including the 22q11.2 deletion syndrome, and other rarer genetic deletions and duplications. The scale of the datasets available worldwide now permits well powered analysis of the effects on the brain of rare genetic variants that confer heightened risk for autism, schizophrenia, epilepsy, and many other conditions. ENIGMA-CNV, whose work is reviewed by Sønderby et al., is beginning to create the first catalog of the effects of rare copy number variants (CNVs) on the brain, in order of prevalence, with replicated effects across large-scale international populations and biobanks.

A paper by Matoba, Love, and Stein (2020) offers a salutary note regarding sample sizes needed to discover the common variants in the genome associated with brain measures. Building on work by Holland et al. (2020), Matoba et al. note that as the datasets grow beyond 100,000 scans, we are still far from detecting the majority of the common variants that affect brain structure. In the future, multivariate methods (e.g., van der Meer et al., 2020)—and even deep learning methods—may more efficiently discover markers in the genome that affect brain trajectories and disease risk throughout life. In the next decade, by pooling data, expertise, and resources worldwide, we are likely to discover as yet unknown subtypes and mechanisms for the brain disorders we have observed so far, offering a new range of treatment targets in the genome and environment.

5 | CLINICAL STUDIES: LARGE-SCALE EMPIRICAL STUDIES OF BRAIN DISORDERS AND CONDITIONS

The use of the same analytic methods to analyze brain data across multiple disorders allows the opportunity to directly compare the effects. Building on the 151-cohort analysis of OCD, ASD, and ADHD reported by Boedhoe et al. (2020), Navarri et al. (2020) show how substance use disorders compare to other common psychiatric conditions in terms of the scope and extent of brain abnormalities on MRI. This work is part of a broad-based cross-disorder initiative in ENIGMA to compile common data elements across cohorts, enabling transdiagnostic studies of shared and distinct risk factors across common conditions. Using a similarly harmonized across ENIGMA approach as detailed in Sämann et al. (2020) to facilitate future cross-diagnostic studies, Haukvik et al. (2020) report the largest study to date of hippocampal subfields in bipolar disorder. Such fine scale brain maps for the major neuropsychiatric conditions are offering insight into the topography of their effects on the hippocampus—the subcortical structure most consistently affected across all disorders studied by ENIGMA.

Large-scale data pooling in ENIGMA has also made it possible to detect brain differences in unaffected relatives of patients with psychiatric disorders. Building on earlier work that suggested a "compensatory" effect in unaffected first-degree relatives of patients with bipolar disorder, de Zwarte et al. (2020) note the modulating effects of cognitive performance and educational attainment on brain abnormalities in those at familial high risk for bipolar disorder and schizophrenia. A related paper by Gurholt et al. (2020) examines intracranial and subcortical volumes in adolescents with early-onset psychosis—a severe and often progressive form of the disorder. Recently, ENIGMA working groups have been created to study various conditions on the schizophrenia spectrum—including the first large-scale international studies of schizotypy (Kirschner et al., 2021). These analyses will lend insight into the schizophrenia prodrome and factors that confer resilience to psychosis in unaffected relatives and in the general population.

5.1 | Sex differences in the prevalence and effects of brain disorders

The meta-analytic aggregation of brain data across the world is an important first step toward detecting factors that modulate disease effects, such as age, sex, and variations in the genome and environment. Two papers in the *Special Issue* examine sex differences in the profiles of brain abnormalities in various psychiatric and neurological conditions. Salminen et al. (2021) discuss the marked sex differences in prevalence for many of the brain disorders studied by ENIGMA—substance use, ADHD, ASD, and externalizing disorders, for example, are more prevalent in men than women, yet major depression, anxiety, and other internalizing disorders are more prevalent in women than men. Rabin et al. (2020) note sex differences in the anatomical effects of cocaine use disorder on the human brain, in a new empirical study—the largest of its kind. In their analysis of sex differences in disease effects, Salminen et al. (2021) point to numerous drivers of these sex differences—in the genome, the endocrine system, and the major neurotransmitter systems. Sex differences in disease onset, expression, and prognosis are the focus of intense and ongoing research, including a dedicated ENIGMA Sex Differences Initiative.

5.2 | From region of interest analysis to brain maps

Three papers in the *Special Issue* report novel empirical studies where surface-based computational anatomy methods were applied across multiple sites, and the resulting statistical effects were meta-analyzed, to map brain abnormalities in schizophrenia (Gutman, et al., 2021) and MDD (Ho et al., 2020). Fine-scale mapping of disease effects can help us understand the systems affected based on data from multiple imaging modalities. Ongoing work is also beginning to reveal how brain abnormalities overlap with finer scale gene expression data from the

Allen Brain Atlas, offering clues to which cell types are affected in specific psychiatric disorders (Patel et al., 2020).

As ENIGMA now moves into its second decade, there are many new and emerging themes and goals. With the rapidly growing success of deep learning, artificial intelligence (AI), and machine-learning methods across all of science, we will no doubt see greater use of AI methods to better understand diseases by building predictive models of prognosis and treatment response. Machine learning will also help for better subtyping and clustering of disorders based on biomarkers such as those derived from neuroimaging. ENIGMA's datasets offer the large N, the ethnic and cultural diversity, and international coverage to optimize training and testing of machine learning models, and to ensure these methods work well when tested on new samples. Recent ENIGMA papers have been dealing with machine-learning challenges, such as imbalances or incompleteness of data across sites, and a range of statistical harmonization methods to co-calibrate data from multiple scanners, while moving into vertex-wise and whole-brain deep-learning approaches that survey a broader range of features. Distributed computations are being tested, as well (the ENIGMA-COINSTAC project). A second emerging theme for ENIGMA is the move from primarily structural analyses of brain MRI and DTI to deeper forms of brain mapping; the newly formed groups on MEG, MR spectroscopy, and arterial spin labeling (ASL) will complement the already productive groups on fMRI and EEG, and we may see the first genome-wide genetic and epigenetic studies of MEG and other modalities in the near future. In genetics, deeper sequencing of cohorts (including the growing availability of whole exomes and genomes for tens of thousands of individuals with neuroimaging) presents exciting challenges for discovery with large samples required as the depth of phenotyping increases (to 3 billion base pairs). Newer approaches for genome representation (such as tiling) are being tested for cross-cohort data reduction and harmonization, and studies of rare genetic variants are yielding unexpected insights into the brain circuits involved in polygenic, complex psychiatric illnesses. Ongoing epigenetics work is sufficiently well powered in ENIGMA (with the first epigenome-wide associations with brain morphometry recently detected in an 11-cohort sample of just over 3,000 people). Soon, there may be rapid advances in the arc of discovery for epigenetics, similar to how the Genetics and CNV groups found consistent and replicable effects of common and rare genetic variants on the brain. Most importantly, the international spirit and highly dynamic network of collaborators across ENIGMA is likely to take the consortium into new and challenging clinical and technical fields, including a new Environment working group, using geocoding to link information on climate, environmental hazards, and epidemics to brain imaging biobanks. One key to future innovations is the varied perspectives and cultures of the scientists participating in ENIGMA, which offers a means to achieve a better worldwide understanding of the human brain in health and disease.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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ENDNOTE

[1] ENIGMA's Brain Injury working group coordinates a diverse set of separate, autonomous working groups that focus on brain trauma in children and in adults, military related brain injury, sports concussion, and intimate partner violence, among others. Within this overall Brain Injury "umbrella," specialized working groups have emerged to harmonize data on cognitive endpoints and MR spectroscopy; these working groups present updates in a separate Special Issue of the journal *Brain Imaging and Behavior* on ENIGMA Brain Injury (Wilde et al., 2021).

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