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The ENIGMA-Neuromodulation working group – A mission statement

Dear Editor, Founded in 2009, the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) [1] consortium brings together 2000+ researchers from over 47 countries with the shared mission of pooling brain imaging and other relevant data to advance scientific understanding of major brain diseases, disorders, and conditions, covering influential genetic, environmental and interventional factors. The ENIGMA Neuromodulation (ENIGMA-NeMo: https://enigma.ini.usc.edu/ongoing/enigma-neuromodulation/) working group was formed in 2020 to connect scientists utilizing numerous neuromodulation modalities. Currently, the working group is comprised of neuroscientists, neurologists, neurosurgeons, psychiatrists, neuropsychologists, psychologists, experts at national-level regulatory and funding agencies (e.g. US National Institute of Health), and other allied research and clinical professionals, and all with relevant backgrounds and interests are welcome to join. At present, ENIGMA-NeMo includes deep brain stimulation (DBS), transcranial magnetic stimulation (TMS), transcranial electric stimulation (tES), transcranial focused ultrasound (tFUS), photobiomodulation (PBM), and peripheral stimulation techniques (e.g., peripheral nerve stimulation [PNS]/vagus nerve stimulation [VNS]) (Table 1). ENIGMA-NeMo actively collaborates with other ENIGMA working groups. A machine learning and artificial intelligence core was added to address the scale, complexity, and high dimensionality of the parameter spaces of neuromodulation data. Dedicated chairs with expertise in each neuromodulation modality were recruited to lead subgroups.

The initial impetus for ENIGMA-NeMo arose from the neuromodulation research community's desire to overcome limitations inherent to the need for internationally coordinated research efforts. Patient samples gathered by a single lab may have limited geographic or ancestral diversity, thereby yielding conclusions that do not generalize. Moreover, studies focused on a single diagnosis have limited capacity to identify transdiagnostic symptom-level (as opposed to syndrome-level) psychological or neurobiological mechanisms of disease and recovery (Insel et al., 2010), while promising symptom-level treatment targets are currently in development (Siddiqi et al., 2020). Additionally, small sample sizes limit statistical power to detect subtle effects and are at risk of overestimating effects and non-replicable findings, particularly in the presence of publication bias [2]. Neuromodulation is vulnerable to diverging findings and slow protocol development due to: a) the massive parameter space, both within [3] and across modalities and populations leading to diverging findings and slow protocol development; b) the lack of significant, reproducible biomarkers of brain target efficacy and engagement [4]; and c) limited biobehavioral assessment, cross-modality studies, and integration efforts. By bringing together researchers from around the globe to integrate large-scale, cross-modality neuroimaging, targeting, safety, and outcome data, ENIGMA-NeMo seeks to address these issues empirically. With a primary focus on leveraging multi-modal brain imaging data, ENIGMA-NeMo's initial goals include: 1) understand mechanisms of action of neuromodulation on a brain circuit level; 2) aggregate safety data and accelerate development of therapeutic parameters for clinical neuromodulation efficacy across disease populations; 3) develop neurophysiological and neuroimaging-based read-outs of brain circuit engagement/modulation and identify treatment biomarkers for precision medicine; 4) improve reproducibility of neuromodulation-related neuroimaging findings; 5) propose and evaluate standards for neuroimaging research in neuromodulation.

To provide standardization across neuromodulation studies, ENIGMA-NeMo supports the current extension of the Brain Imaging Data Structure format [5] into Non-invasive Brain Stimulation (NIBS--BIDS https://bids.neuroimaging.io/bep037) to enable standardized documentation of NIBS procedures within the BIDS framework. The standardized structure provided by NIBS-BIDS also streamlines data analysis by making data and metadata readable by processing applications. By adhering to BIDS, researchers ensure their data align with the principles of FAIR - Findable, Accessible, Interoperable, and Reusable [6], which helps foster extensive collaborations and fair, open science practices.

ENIGMA-NeMo will encourage the adoption of best practice guidelines within data analysis projects and support joint consensus for best practices in transparent design and reporting for neuromodulation interventions. For clinical research, the CONSORT (consolidated standard of reporting trials) checklist was a major milestone introduced in the mid-1990s to introduce more transparency and comparability in the reporting of clinical trials [7]. To support consensus, standardization, and quality control in neuromodulation research, *checklists for specific use cases of TMS* [8] and neurofeedback training [9] have been introduced. Building upon this prior work, ENIGMA-NeMo is working towards a comprehensive checklist, the Consensus on the Reporting and Experimental Design of clinical and cognitive-behavioral neuromodulation studies (CRED-NeMo) checklist. CRED-NeMo will cover reporting and design aspects for the neuromodulation research techniques represented in the working group and will aim to foster transparency (e.g., study preregistration and reporting of null findings), replicability (e.g., parameter specifications, documentation of stimulation locations, sample size planning), reproducibility (e.g., model specification, code and data sharing) and comparability/generalizability (e.g., demographic and clinical characteristics) as the pillars of robust research [10].

Data shared with ENIGMA-NeMo will require institutional review board (IRB) approval and signing of written, informed consent by all study participants. Investigator approval, IRB approval for sharing de-identified data, inter-institutional material use and data use agreements, and compliance with local/regional privacy regulations, study protocols, and informed consent documents will be required prior to aggregation of data within ENIGMA-NeMo. Participating sites may contribute extracted values for mega-analysis or de-identified imaging

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Table 1
Neuromodulation modality comparison.

Modality	Invasive?	Regulatory Approval?	Target Focality	Included in the consortium?
Transcranial magnetic stimulation (TMS) *Rapidly Changing Magnetic fields are applied to change brain activity.*	No	Yes	Medium	Current
Deep brain stimulation (DBS) *Electrical stimulation by a surgically-implanted device.*	Yes	Yes	High	Current
Transcranial focused ultrasound (TFUS) *Focused ultrasound waves are delivered to a specific brain target. Low-intensity waves are used for neuromodulation. High-intensity waves are used for non-invasive ablation.*	No	Low Intensity: No; High Intensity: Yes	High	Current
Transcranial electric stimulation (tES) *Low-strength electric currents are used to change brain activity.*	No	Yes	Conventional: Low; HD: Medium	Current
Photobiomodulation (PBM) *Neuromodulation by red and near-infrared light.*	No	No	High	Current
Peripheral nerve stimulation (PNS) *Electrical or ultrasound stimulation to peripheral nerves such as the vagus nerve.*	Yes or No (depends on type)	Yes	Indirect	Current
Magnetic seizure therapy (MST) *High Intensity and Frequency rTMS to induce seizure.*	No	No	Low	Future
Electroconvulsive therapy (ECT) *Controlled application of electrical stimulation to induce seizure.*	No*	Yes	Low	Future

Table 1: An overview of the invasiveness, regulatory status, and target focality of individual brain stimulation techniques included in ENIGMA-NeMo, as well as the techniques that the consortium plans to expand to in the future. Regulatory approval status of "no" means no regulatory approval; "yes" means technique is approved in at least one jurisdiction for at least one clinical indication. Invasive in this context means requiring surgery.
*Convulsive therapies can be considered invasive because they generally require anesthesia and carry serious, though rare, medical risks. However, they do not require surgery, which is the definition of "invasive" used here.

files to the ENIGMA-NeMo data repository, currently housed within the Center for Cognitive Neuroscience at the University of California, Los Angeles. With regulatory approval, raw, de-identified DICOM or NIFTI, along with neuromodulation parameter details and neuropsychological data, can also be shared directly with the leader of a specific research proposal. Research proposal leaders can also provide harmonized data processing pipelines to data contributors so that the pipeline can be run in-house, and then the resultant derivative data can be shared.

In sum, ENIGMA-NeMo, a new ENIGMA working group, seeks to integrate researchers across neuromodulation modalities with neuroimaging datasets from around the globe. The combined expertise will allow ENIGMA-NeMo to assess, compare, and suggest standards for data collection, analysis, and best practices in imaging-based neuromodulation research. Additionally, ENIGMA-NeMo will bring together the large datasets (e.g., 300+ participants) necessary to develop models of brain circuit engagement and clinical outcomes across parameters, modalities, and disease populations. The goal is to accelerate the discovery and advancement of neuromodulation methods toward individual-based precision medicine with maximal treatment efficacy and safety. To join ENIGMA-NeMo, please reach out to Taylor Kuhn at tkuhn@mednet.ucla.edu and visit our website (https://enigma.ini.usc.edu/ongoing/enigma-neuromodulation/).

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Declaration of competing interest

Taylor Kuhn is a consultant and stockholder in Sanmai Technologies, PBC. Gregory Fonza received consulting fees from Synapse Bio AI and Alto Neuroscience and owns equity in Alto Neuroscience. Desmond Oathes received an equipment loan from Rogue Research. Elisa Kallioniemi received consulting fees from Nexstim Inc. Mohamed Sendi received consulting fees from NIJI Corp. Sarah Holly Lisanby is inventor on patents and patent applications on electrical and magnetic brain stimulation therapy systems held by the NIH and Columbia University, with no remuneration. Sarah Holly Lisanby and Lindsay M Oberman are supported by the NIMH Intramural Research Program (ZIAMH002955). The opinions expressed in this article are the author's own and do not reflect the views of the National Institutes of Health, the Department of Health and Human Services, or the United States government. All other authors report no conflicts.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.12.1477.

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