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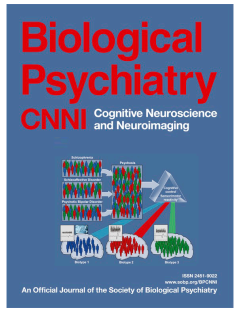


ENIGMA-Meditation: Worldwide consortium for neuroscientific investigations of meditation practices

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# ENIGMA-Meditation: Worldwide consortium for neuroscientific investigations of meditation practices

**Short Title:** ENIGMA-Meditation: worldwide meditation consortium

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## Abstract

Meditation is a family of ancient and contemporary contemplative mind-body practices that can modulate psychological processes, awareness, and mental states. Over the last 40 years, clinical science has manualised meditation practices and designed various meditation interventions (MIs), that have shown therapeutic efficacy for disorders including depression, pain, addiction, and anxiety. Over the past decade, neuroimaging has examined the neuroscientific basis of meditation practices, effects, states, and outcomes for clinical and non-clinical populations. However, the generalizability and replicability of current neuroscientific models of meditation are yet to be established, as they are largely based on small datasets entrenched with heterogeneity along several domains of meditation (e.g., practice types, meditation experience, clinical disorder targeted), experimental design, and neuroimaging methods (e.g., preprocessing, analysis, task-based, resting-state, structural MRI). These limitations have precluded a nuanced and rigorous neuroscientific phenotyping of meditation practices and their potential benefits. Here, we present ENIGMA-Meditation, the first worldwide collaborative consortium for neuroscientific investigations of meditation practices. ENIGMA-Meditation will enable systematic meta- and mega-analyses of globally distributed neuroimaging datasets of meditation using shared, standardized neuroimaging methods and tools to improve statistical power and generalizability. Through this powerful collaborative framework, existing neuroscientific accounts of meditation practices can be extended to generate novel and rigorous neuroscientific insights, accounting for multi-domain heterogeneity. ENIGMA-Meditation will inform neuroscientific mechanisms underlying therapeutic action of meditation practices on psychological and cognitive attributes, advancing the field of meditation and contemplative neuroscience.

Meditation encompasses contemplative mind-body practices characterized by diverse techniques, philosophies, and religious traditions (1–5). Broadly, meditation involves purposeful attention, voluntary regulation of psychological and embodied processing, and modulation of conscious awareness (6–9). Meditation practice can enable salutary psychological, psychosomatic and/or spiritual states of consciousness with acute and enduring positive impacts on mood, cognition, and general well-being (10–12). Scientific investigations of meditation have predominantly involved techniques including mindfulness (e.g., present-centered focus with non-judgemental observation of experience), focused attention (e.g., sustaining breath-focused attention), open-monitoring (e.g., continuous, effortless monitoring of experiential content), loving-kindness (e.g., sustained repetition of benevolent thoughts), compassion (e.g., sustained generation of compassionate feeling), mantra (e.g., focus on repetition of a mantra), non-dual awareness (e.g., awareness of awareness, transcending subject-object duality), and their variations (refer to (2,9,13,14). Some of these meditation forms have been incorporated directly into Western medical contexts in psychotherapies such as Mindfulness-based Stress Reduction (MBSR) (15), Mindfulness-based Cognitive Therapy (MBCT) (16), Mindfulness-Oriented Recovery Enhancement (MORE) (17), compassion meditation training (18), transcendental meditation training (19), etc. (20), and have indirectly influenced interventions, such as Acceptance and Commitment Therapy (ACT) (21) and Dialectical Behavior Therapy (DBT) (22) among others (20). Such psychotherapeutic meditation interventions (MIs) have transdiagnostic value (23), and can impart neuroprotective effects (24), improve stress management in medical conditions like cancer, chronic pain, and fibromyalgia, and combat psychiatric conditions including anxiety, depression, posttraumatic stress disorder (PTSD), and alcohol and substance-use disorders (25–28). However, similar to other clinical interventions (29), MIs can also sometimes produce adverse events (30).

The past several decades have witnessed burgeoning neuroscientific examinations of meditation practices using magnetic resonance imaging (MRI) and electroencephalography

(EEG). Meta-analyses of MRI and EEG literature suggest that meditative practices are associated with acute and enduring changes in brain structure (31,32) and function (13,33–39), including alterations in functional networks, morphology, and neural oscillations (40,41) associated with relevant cognitive and psychological processes (such as self-related processing, awareness, attentional and emotional regulation). However, the replicability and generalizability of neuroscientific findings from the meditation literature are challenged by modest sample sizes and substantial heterogeneity in experimental design, data processing techniques, and meditation practices, impeding deep neuroscientific phenotyping of meditation. Developing a more nuanced and rigorous understanding of the neural basis of meditation can potentially improve estimates of moderators and mediators of the effects of different meditation practices, and identify predictors of individual differences in brain mechanisms underlying clinical action of MIs, which may enable effective patient stratification for MI-based clinical trials, improve prognostic assessments of clinical outcomes of MIs, and inform augmentation approaches such as neuromodulation, biofeedback, and personalization.

Here we introduce Enhancing Neuroimaging Genetics through Meta Analysis (ENIGMA)-Meditation - a newly established innovative global consortium for collaborative neuroimaging of meditation that will aim to address existing challenges and deepen the neuroscientific understanding of meditation. ENIGMA-Meditation brings together neuroimaging data from meditation researchers worldwide to facilitate large-scale meta- and mega-analysis projects using shared, strategically-planned, standardized processing and statistical analyses. The goal of ENIGMA-Meditation is to systematically and reliably characterize the neuroscience of different meditation practices, evaluate commonalities and distinctions between diverse practice forms and stages, and investigate how their neuroscientific substrates relate to psychological, physiological, clinical, and cognitive outcomes. Traditionally, meditation practices were deeply rooted in cultural, religious, and philosophical contexts, primarily focusing on spiritual growth rather than treating mental or physical conditions or enhancing mental capacities. While ENIGMA-Meditation also seeks to explore the neuroscience of meditation within such traditional contexts, the focus of the current paper is primarily on the neuroscience of contemporary, secular adaptations of meditation practices and their benefits on health and well-being (see Supplementary Note).

## Neuroimaging literature of meditation in healthy individuals

Meta-analyses of the functional MRI (fMRI) literature on cross-sectional investigations of meditation in healthy populations indicate widespread involvement and interplay between distributed brain regions spanning the default-mode network (DMN), salience network (SN), and central executive network (CEN) (13,33,35,36). These brain networks are typically thought to underpin putative neurocognitive mechanisms of meditation practice, such as self-referential processing and stimulus-independent thought (DMN), arousal and interoceptive awareness (SN), and executive function and attentional regulation (CEN) (6,8,42). Emerging evidence also highlights inter-individual variations in self-report measures of dispositional mindfulness (33,39,43–45) and differences in meditation experience between adept practitioners and novices (34,39,46–50) influencing functional connectivity (FC) and activation changes within and between some of these brain networks. The insula, associated with emotional processing, awareness, and interoception (51,52)) and the anterior cingulate cortex (ACC) implicated in attentional regulation and conflict monitoring (53,54) are two key SN regions commonly engaged in diverse meditation techniques (13). Similarly, while structural MRI differences between adept meditators and novices may be widespread throughout the brain (55), meta-analytic evidence from cross-sectional literature suggests these differences may be more pronounced in the insula and ACC (SN) (31,32).

Neural correlates of MI-related improvements among healthy individuals in memory (56) and executive functioning (57), emotion regulation and reactivity (58,59), and pain perception (60) are widely associated with dissociable activation and FC changes within the DMN, SN, and/or CEN, as well as the amygdala (61), thalamus, and orbitofrontal cortex (OFC) (60). Recent meta-analysis (62), review (38) and trials (63–68) examining longitudinal resting-state FC changes associated with mindfulness-focused MIs have identified modifications in these networks, implicating dorsolateral prefrontal cortex (DLPFC) (CEN), PCC (DMN) and insula (SN). Evidence on longitudinal brain structure alterations associated with MIs however remains mixed. Some studies have found distributed training-related morphometric effects within DMN and SN (69–73) but others have not replicated earlier findings (74,75).

Taken together, in healthy individuals, meditation is associated with functional and structural changes in intrinsic brain networks linked to self-referential processing, interoception, awareness, and executive functioning (i.e., DMN, SN, CEN), among other networks. While some studies and reviews implicate DMN, SN and CEN, or a subset of these networks, others, particularly those using structural MRI, report no effects, revealing inconsistency in the literature. Changes in the insula related to meditation are most frequently reported but show considerable variability.

## Neuroimaging literature of meditation in individuals with clinical conditions

The neural substrates that appear to underlie impacts of MIs in transdiagnostic clinical samples also show overlap with DMN, SN and/or CEN among other brain networks and regions, as evidenced by reviews and seminal randomized control trials (RCTs).

A review of FC effects of MIs found that in individuals with chronic stress and disorders including MDD and PTSD, MIs commonly modulate resting-state FC between PCC (DMN) and DLPFC (CEN) (39) which may relate to attentional control over mind wandering. Recent meta-analytic evidence of structural alterations associated with MIs in both healthy and clinical samples implicate the insula (SN) and precentral gyrus (76). A review of MIs for pain suggested that the analgesic effect of MIs involves functional changes in ACC and insula (SN), thalamus and reward/evaluation-related OFC (77). A systematic review of MIs for substance-use disorders observed therapeutic action consistently accompanied by changes in ACC (SN) and striatum (78). A recent RCT reported that emotion regulation strategies adopted by social anxiety patients after MBSR training involve differential engagement of ACC (SN), medial PFC (DMN) and DLPFC (CEN) (79). Several RCTs involving MIs for major depressive disorder (MDD) have reported that FC, activation, and structural (80) changes in DLPFC (CEN) (80–82) and amygdala (80,82) accompany clinical outcomes. An RCT involving MI for attention deficit and hyperactivity disorder (ADHD) observed dominant activation changes in the insula (SN), precuneus (DMN) and inferior parietal lobe (CEN) following the intervention, with hyperactivity symptoms linked to medial PFC and PCC (DMN) activity changes (83). Improvements associated with a 3-month MI targeting age-related mild cognitive impairment (MCI) were tracked by changes in FC dynamics primarily involving ACC (SN), PCC and superior temporal gyrus (DMN), and insula (SN) (84). Another RCT investigating white matter changes observed effects in the ACC (SN) following an MI for panic disorder (85).

Taken together, MIs targeting diverse clinical conditions often modulate the function and structure of hubs within DMN, SN and/or CEN, while also sometimes engaging additional cortical and subcortical circuits, including the amygdala, OFC, and striatum, related to social-emotional, threat, and reward processes. Variability in implicated neural circuits across the literature may arise from factors such as the type of disorder, underlying brain network dysregulation, and specific features of the interventions and comparison groups.

## Limitations in the current state of meditation neuroscience

The existing cross-sectional and longitudinal neuroimaging studies of meditation have mapped functional and structural brain changes underlying various meditation practices in clinical and non-clinical populations that include novices and experienced practitioners. The current state of meditation neuroscience, while providing valuable insights, confronts significant variability and methodological challenges.

Although existing meta-analyses in the field find convergent activation / FC / structural changes in DMN, SN and/or CEN, the concordance between meta-analytic findings at the level of specific brain regions remains low, with changes in insula being the most consistent finding (13,31–36,38,76). Such low generalizability, specificity and discordance likely stem from inadequate statistical power driven by small study samples (< 20 studies) of meta-analyses (86) and considerable variability in sample characteristics, control conditions, task, inclusion criteria, and statistical processes. Similar challenges also hinder the generalizability of findings from reviews, many of which collapse inferences from studies involving varying meditation techniques, levels of meditation experience, and manualized MIs (32,39,78,87,88), with limited consideration of this heterogeneity across studies. Another concern is lack of adequate control for confounds (physiological responses, head motion, multiple comparisons) that can substantially contaminate fMRI signals and inferences (89). For example, less than 20% of the reviewed cross-sectional fMRI literature on focused attention meditation accounted for these confounds in their analyses (33).

Several cortical (e.g., somatomotor and attention network regions, occipital regions, OFC), subcortical (e.g., amygdala, hippocampus, thalamus, striatum) and cerebellar areas have also been implicated in the clinical and non-clinical literature, albeit variably across studies and clinical conditions. For instance, MIs can impact MDD symptoms by modulating the amygdala which is involved in affective processing (80,82), pain by modulating OFC and thalamus which are implicated in sensory evaluation and processing (60), and addiction by modulating striatal regions involved in reward-processing (78). Gaps still remain in characterizing the key brain mechanisms unique to and common across different clinical conditions and their mechanisms of action. Brain networks widely associated with meditation like the DMN, CEN and SN have also been otherwise implicated in general cognitive task demands (90,91), dysfunction across diverse psychiatric disorders (triple network model of psychopathology (92)), and other psychological processes like hypnosis (93). Greater clarity is required on the functional specificity of such brain networks pertaining to meditation practices. Meditation may also involve whole-brain distributed or multivariate effects on brain function (94–97) and structure (55,97), beyond their impact on localized regions, circuits, or networks. Robust decoding of such neural effects requires greater statistical power.

To address gaps in the literature and reliably decode the roles of diverse brain areas and complex whole-brain states unique to meditation and MIs, unified analytical methods that can increase statistical power and sensitivity, and account for confounds, are warranted. To that end, we have adopted the ENIGMA framework.



## The ENIGMA framework

The ENIGMA consortium was founded in 2009 to improve the replication and generalizability of neuroimaging and genetics analyses. Early ENIGMA projects focused on genome-wide associations to detect genetic markers influencing brain morphometry, by leveraging existing worldwide brain MRI and genetic datasets and applying standardized processing, quality control, and analysis techniques (98). The ENIGMA approach differs from the classic literature-based meta-analysis (combining effects from published studies that used variable processing and analysis techniques) as it uses standardized processing, quality control and analyses shared across all the participating datasets to boost statistical power. The ENIGMA consortium now includes over fifty Working Groups (WGs) developing scalable, open-source methods to study neurological conditions such as Parkinson's disease, epilepsy, psychiatric disorders, from schizophrenia and MDD to anxiety and Tourette syndrome, as well as normative brain variation (99). Today, in addition to meta-analysis, many ENIGMA Working Groups perform both federated analyses as well as pooled mega-analysis where participant-level raw or derived brain measures are centralized to facilitate more complex analyses (e.g., machine / deep learning, etc.) (100–103). Through numerous large-scale collaborative projects, ENIGMA WGs have mapped the structural and functional brain correlates of various disorders in large demographically and ancestrally diverse samples. The scale of these studies allows for the modeling of complex clinical and comorbid features (e.g., symptom severity, duration of illness, and medication) both within and across brain conditions (104).

By using pre-existing, independently collected data, the ENIGMA approach boosts sample sizes and statistical power in a cost-effective manner. The standardized application of open-source neuroimaging pipelines and analytical models used within ENIGMA improves the reliability and transparency of study findings. Notably, the pipelines are rigorously validated by the ENIGMA consortium across scanner protocols and datasets for robustness and sensitivity. Once validated, these versions are kept consistent within and across project lifecycles to minimize biases from frequent pipeline and software updates. By pooling diverse samples from around the world, ENIGMA studies improve replication power and generalizability of results. For instance, an all-Japan cohort investigating schizophrenia independently replicated the regional gray matter volume effect sizes observed by ENIGMA-Schizophrenia (105).

An ENIGMA meta-analysis typically involves two stages: 1) estimation of site-level summary statistics (such as effect sizes, standard errors / confidence intervals) from participant-level data using standard quality checks and statistical protocols performed at participating sites, and 2) centrally performed meta-analysis of the derived summary statistics for inference across sites. Additionally, the ENIGMA framework also confers a unique capacity for world-wide "mega-analysis" involving samples much larger than individual study samples. Mega-analysis is a single-stage analysis that uses shared standard methods and computing environments to directly analyze participant-level raw data and/or derived data (e.g., brain structure volumes, or FC values) furnished by the participating sites to the central facility (106).

## ENIGMA-Meditation

ENIGMA-Meditation is a recently launched WG that aims to conduct large-scale meta- and mega-analyses of globally distributed datasets using unified analytical processes to elucidate and clarify the neuroscience of meditation. The primary goal of ENIGMA-Meditation is to advance the field of meditation neuroimaging by addressing limitations described earlier. The current literature primarily comprises small datasets with heterogeneity along several domains, including (i) meditation techniques (e.g., focused attention, open monitoring), (ii) MIs (e.g., MBSR, MBCT), (iii) characteristics and meditation experience of samples (e.g., novice vs. experienced, tradition of practice, demographics) (iii) experimental design (e.g., longitudinal, RCT), (iv) control conditions and comparison groups (e.g., rest or active task, exercise or relaxation for comparison intervention), (v) neuroimaging parameters (e.g., imaging protocols, sampling rates), (vi) analysis methods (e.g., FC, activation, multivariate), and (vii) preprocessing steps (e.g., denoising, smoothing, filtering). Consequently, the generalizability and specificity of inferences drawn from existing neuroimaging reviews and meta-analyses in the field are limited.

Meta- and mega-analyses using participant-level data from diverse sites enabled by ENIGMA-Meditation will boost statistical power and account for some of the heterogeneity within a tightly controlled analytical framework **(Figure 1)**. Pooled datasets can be harmonized using shared, standardized analysis and preprocessing protocols, and the effect of different covariates (e.g., meditation experience, meditation technique, physiological confounds, key sample characteristics, cultural identity, religious affiliation, clinical disorders) can be controlled for /

modeled at the site-level (meta-analysis) or even participant-level (mega-analysis) as mediators or moderators. As data accumulates with ENIGMA-Meditation, subsets of the aggregated data with comparable study designs and protocols (cross-sectional or longitudinal paradigms of functional or structural MRI), and / or homogenous samples can also be pooled and harmonized separately to enable targeted participant-level meta- or mega-analyses. For example, aggregating fMRI data exclusively from MBSR studies will reveal robust resting-state FC changes and clinical effects specific to MBSR while maintaining sample homogeneity. Similarly, another project can exclusively analyze fMRI activation data during focused attention meditation in healthy novices, excluding other techniques. Additionally, the statistical power of such ENIGMA-Meditation projects will generate insights into replicable alterations of brain function and structure that are generalizable across meditation techniques and interventions, and levels of meditation experience among healthy and clinical populations. ENIGMA-Meditation will also evaluate transdiagnostic as well as disorder-specific neural mechanisms of action underlying various documented clinical effects of MIs. Recent cross-diagnostic analyses across ENIGMA WGs have successfully compared brain structural aberrations across diverse psychiatric disorders including schizophrenia, bipolar disorder, MDD, ADHD, PTSD and others (107,108). Similar analyses within ENIGMA-Meditation will enable systematic comparisons of effect sizes and brain maps across distinct meditation techniques and interventions, varying levels of meditation experience, and clinical disorders targeted by MIs.

Participant-level mega-analyses within ENIGMA-Meditation may also help disentangle physiological responses (e.g., changes in breathing, heart rate) and other nonspecific artifacts (e.g., head motion) from fMRI signals and inferences that are typically attributed to meditative states and effects (e.g., fMRI signals of DMN (89)). Similarly, Neurobehavioural associations underlying meditation states, self-report measures and clinical scales can potentially be examined by harmonizing distinct but related assessment scores across sites and datasets (109,110). Overall, the large-scale, well-powered collaborative efforts enabled by ENIGMA-Meditation may facilitate detection of consistent trends that may not attain statistical significance in individual underpowered studies (111), and illuminate the role of complex whole-brain states and diverse cortical, subcortical and cerebellar regions in meditation practices and related states and traits.

## Future directions

Some of the key future directions and scope possible with ENIGMA-Meditation include:

- Different frameworks describe states and practices of meditation using varied terms and concepts (2,5,9,112). Reliable neural maps enabled by ENIGMA-Meditation may help to identify and harmonize common constructs across varied meditation practices and states by exploring their subjective, cultural, semantic and conceptual pluralities (9,113,114). For example, compassion, empathy, meta-awareness, equanimity, bliss, non-duality, and decentering among others are often considered essential outcomes, phenomenological dimensions and states across different meditation practices (9,14,112,115–119). Statistically empowered participant-level mega-analyses from ENIGMA-Meditation can potentially illuminate some of the relationships between these phenomenological and neuroscientific dimensions.
- In meditation research, outcomes, quality, expertise, and experience associated with meditation practices and states are often based on self-report measures (rather than the detailed interviews utilized in micro-phenomenological approaches), which are prone to interpretational, retrospective and demand biases (120–122) especially among novices and developing practitioners (121,123). Linking such self-report assessments to robust

neuroscientific ("third-person") accounts derived from ENIGMA-Meditation findings can alleviate some of these biases (114,124,125), and also leverage a dimensional and multi-level approach to meditation research.

- Several ENIGMA WGs use data-driven methods, such as non-linear, multivariate, machine and deep learning approaches to identify brain-aging related abnormalities in MDD (100), predict alcohol dependence (101), or classify anxiety disorder cases vs. controls (102) from MRI data. Similarly, ENIGMA-Meditation can develop powerful computational models that use neuroscientific data to distinguish levels of meditation experience (46,126) or predict individual-level/patient-level responses to specific meditation practices and MIs (127), complementing efforts that predict meditation outcomes using self-report data (128). Other approaches implementing voxel-wise machine learning can enable classification of neural states and quantification of their temporal dynamics during meditation at the single-subject level using task-fMRI data (95,96,129–131). Such computational efforts may help demystify the neuroscientific mechanisms and predispositions underlying various documented contraindications to meditation practice (30,132), and inform neural decoding algorithms in emerging non-invasive neuromodulation (133) and neurofeedback (134) technologies aimed at augmenting meditation practice. With larger samples, cultural and demographic variability can also be incorporated as additional features in these models to assess their impact on prediction performance.
- Neuroimaging studies of meditation have typically involved young-to-middle aged adults. However, the emergence of individual studies exploring meditation-related effects on children (135), adolescents (136) and older individuals (57) will enable large-scale aggregate analyses with ENIGMA-Meditation that dissect age-related differences and potential developmental effects of meditation on brain function and structure.

- Verifying first person subjective experiences within a 'third person' neuroimaging paradigm remains a substantial challenge, even in widely-used paradigms like resting-state fMRI (137). ENIGMA-Meditation can begin to tackle this for meditation neuroimaging by analyzing aggregated neuroimaging data of expert meditators who can reliably enter and identify prespecified meditative states, and report associated phenomenological characteristics (e.g., clarity, depth). By aggregating precision functional mapping (138,139) – intensively sampled neuroimaging datasets from small samples – with detailed phenomenological measurements (140–142), we aim to enhance the accuracy of meditative state verification. Additionally, linking real-world behavioral and clinical effects with neural and experience sampling during meditation tasks can further help validate the attainment of meditative states.
- ENIGMA-Meditation's collaborative framework may promote the collection of neuroimaging data for currently underrepresented meditation forms like non-dual awareness. Aggregating these datasets over time could enhance the statistical power of neuroscientific investigations into these practice forms.



## Current state

As of April 2024, several research groups have expressed interest to contribute data to ENIGMA-Meditation from published studies as well as prospective trials, which span over 65 investigators across North America, Oceania, Asia and Europe. **Figure 2** shows a map illustrating the current geographic diversity of ENIGMA-Meditation.

Supplementary Table 1 lists details of the neuroimaging datasets currently available to ENIGMA-Meditation. The datasets include multimodal MRI neuroimaging data already or imminently acquired pre-to-post interventions and during meditation-related tasks, across various samples (healthy, clinical, novices , experts), contemplative practices and MIs . A number of resting-state and task-based EEG datasets have also been identified for future inclusion. Most of the datasets also include standardized self-report measurements such as Five Facet Mindfulness Questionnaire (FFMQ), State Mindfulness Scale (SMS), etc. Overall, ENIGMA-Meditation currently has access to MRI data from >200 expert meditators, >1300 healthy beginner-level individuals, and >600 patients with different psychiatric disorders, including MDD, PTSD, dissociation, social anxiety and early-life adversity.There is an ongoing call for additional groups / investigators to join ENIGMA-Meditation. Information on how to participate is available on the ENIGMA-Meditation website (https://enigma.ini.usc.edu/ongoing/enigma-meditation/).

## Challenges with ENIGMA-Meditation

ENIGMA-Meditation and the broader ENIGMA framework present significant opportunities for advancement but also face challenges. Data quality limitations arise from legacy datasets with outdated technology and methods, while newer datasets using advanced neuroimaging techniques or other modalities (e.g., multi-band, 7T, fNIRS, MEG) are still limited. It can hence be challenging to fully account for heterogeneity in data quality, neuroimaging site, and depth of phenotyping (99). However, the global ENIGMA framework has been consistently developing methods and tools to address some of these limitations (143–145), such as harmonization of distinct symptom / neuropsychological scales, self-report measures, and site and protocol effects (109). This aspect is vital for ENIGMA-Meditation, since assessments of subjective experience and compliance with meditation instructions are often lacking, biased, or inconsistent across meditation neuroimaging studies (146). Technical expertise from both the broader ENIGMA consortium and the specialized focus groups within ENIGMA-Meditation will aim to facilitate the effective transformation and integration of key contextual and subjective variables into neuroimaging analyses. Data aggregated by ENIGMA-Meditation will not be sufficiently large or powered for reliable population-level inferences that are possible with prospectively-sampled large-scale neuroimaging databases like UK biobank (N>500,000) (147). However, findings from ENIGMA-Meditation can motivate large-scale prospective data collection efforts specific to meditation in the future.

Meditation and contemplative practices are culturally and geographically sensitive. ENIGMA-Meditation, like other ENIGMA WGs, aims to map neuroscientific correlates across and within culturally diverse samples, acknowledging that cultural variability may affect outcomes but can enhance generalizability and clinical utility (148). The focus is on addressing methodological limitations in meditation neuroimaging using existing datasets rather than resolving general theoretical challenges in meditation research. Furthermore, due to the expense of MRI scanning, representation from low- and middle-income countries will be limited (149). Although ENIGMA-Meditation might not fully capture the wide spectrum of meditation practices globally, it can stimulate contributions from underrepresented regions by encouraging future studies, regardless of sample size. To further enhance global representation, the WG plans to integrate cost-effective modalities like EEG, which is more accessible in economically disadvantaged areas (current EEG datasets in Supplementary Table 1), enabling multi-modal integration and cross-validation for meditation phenotyping. Future plans also include forming ENIGMA-Meditation sub-groups incorporating culturally diverse practice forms like Yoga and Tai Chi, and exploring emerging technologies such as wearable MEGs, fNIRS, and portable MRI to diversify data and perspectives.

## Conclusions

We present a global collaborative consortium - ENIGMA-Meditation - which currently comprises >65 neuroimaging research groups across four continents. This consortium aims to perform rigorous neuroscientific examinations of meditation and other contemplative practices while accounting for key issues of multi-domain heterogeneity and modest sample sizes prevalent in the current literature. By enabling large-scale integration of meditation neuroimaging datasets across continents and cultures, this initiative will set out to test and elaborate on the prevailing neuroscientific models of meditation practices with high analytical power. ENIGMA-Meditation will rigorously examine nuanced and novel neurocognitive and neuroplastic mechanisms that subserve the assortment of meditation practices, states, and their documented effects on psychopathology, health, and wellness. The standardized processing and statistical protocols along with advancements in big data analytics developed and tested over a decade by the ENIGMA framework and neuroimaging community will empower ENIGMA-Meditation to systematically elucidate and demystify the links between neuroscientific processes and meditation practices, experience, expertise, states, and therapeutic outcomes. By ensuring transparency, cultural sensitivity, humility, and inclusivity in its research practices, ENIGMA-Meditation is well-positioned to advance the field of meditation and contemplative neuroscience in a respectful, culturally informed, and scientifically rigorous manner.

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Supplementary Text and Table S1

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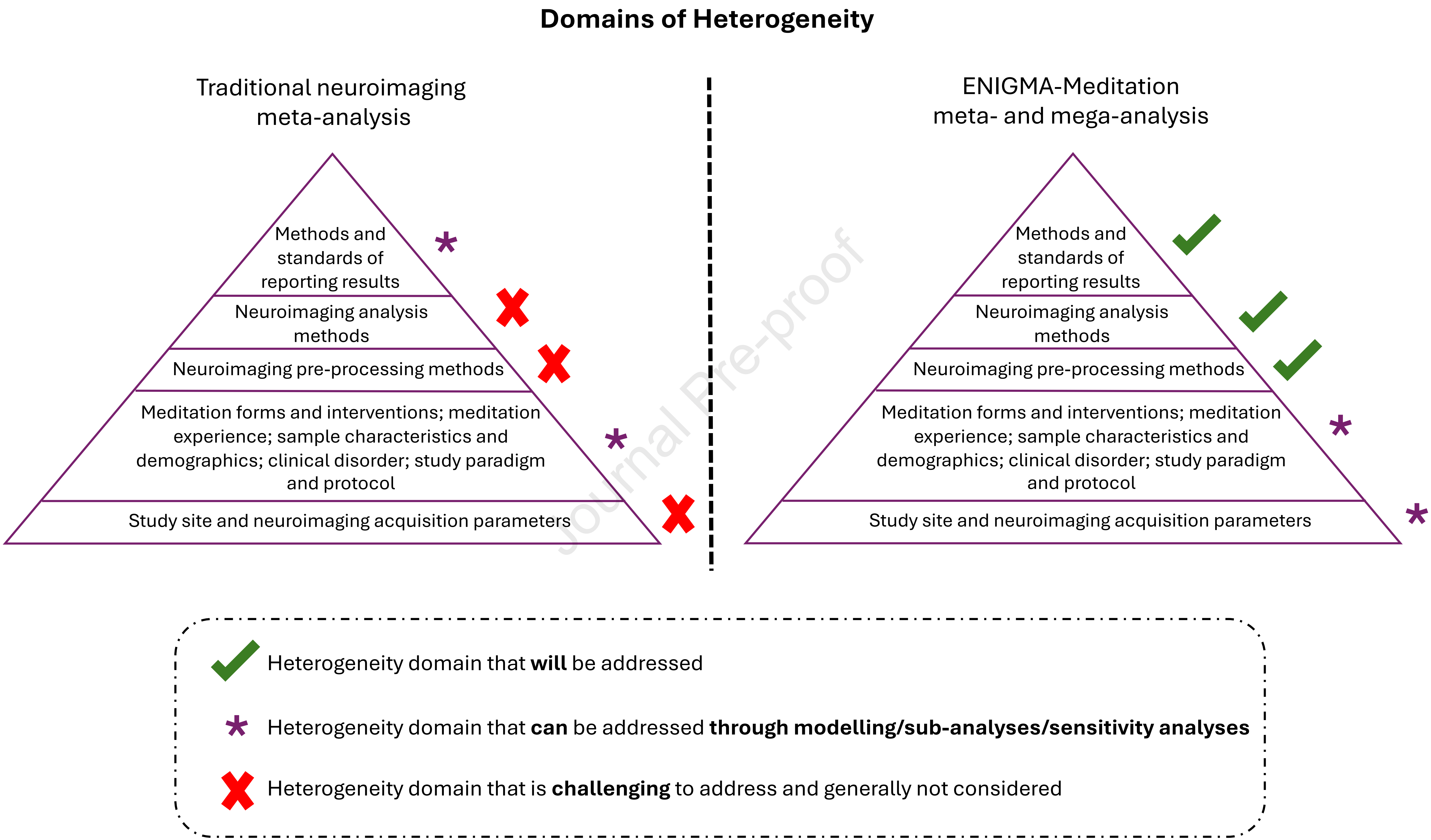
## Figure Legends

**Figure 1:** Comparison of the traditional meta-analytic approaches with ENIGMA-driven approaches, which can offer greater power to control for, or model, heterogeneity across multiple domains.

**Figure 2:** Geographical distribution of the current ENIGMA-Meditation membership (as of April 2024).


Domains of Heterogeneity
Traditional neuroimaging meta-analysis
ENIGMA-Meditation meta- and mega-analysis
Methods and standards of reporting results
Neuroimaging analysis methods
Neuroimaging pre-processing methods
Meditation forms and interventions; meditation experience; sample characteristics and demographics; clinical disorder; study paradigm and protocol
Study site and neuroimaging acquisition parameters
Methods and standards of reporting results
Neuroimaging analysis methods
Neuroimaging pre-processing methods
Meditation forms and interventions; meditation experience; sample characteristics and demographics; clinical disorder; study paradigm and protocol
Study site and neuroimaging acquisition parameters
Heterogeneity domain that will be addressed
Heterogeneity domain that can be addressed through modelling/sub-analyses/sensitivity analyses
Heterogeneity domain that is challenging to address and generally not considered