

Magnetoencephalography for brain electrophysiology and imaging

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We review the aspects that uniquely characterize magnetoencephalography (MEG) among the techniques available to explore and resolve brain function and dysfunction. While emphasizing its specific strengths in terms of millisecond source imaging, we also identify and discuss current practical challenges, in particular in signal extraction and interpretation. We also take issue with some perceived disadvantages of MEG, including the misconception that the technique is redundant with electroencephalography. Overall, MEG contributes uniquely to our deeper comprehension of both regional and large-scale brain dynamics: from the functions of neural oscillations and the nature of event-related brain activation, to the mechanisms of functional connectivity between regions and the emergence of modes of network communication in brain systems. We expect MEG to play an increasing and pivotal role in the elucidation of these grand mechanistic principles of cognitive, systems and clinical neuroscience.

After 45 years of its development and use^{1–3}, we reflect here on the position of MEG among the techniques available to explore and resolve brain function and dysfunction. This review focuses on the aspects that uniquely characterize MEG. We emphasize the specific strengths of the modality, such as its source imaging capabilities. We also identify and discuss practical challenges, in particular in signal extraction and interpretation.

Because MEG and electroencephalography (EEG) appear to be sister electrophysiological techniques that are both sensitive to the electrochemical current flows within and between brain cells, MEG is sometimes thought to be equivalent to EEG, with limited scientific added value. We refute this misconception and explain how distinct physical principles make these two modalities complementary in many respects, rather than purely redundant. In particular, we argue that MEG is the modality with the best combination of direct and noninvasive access to the electrophysiological activity of the entire brain, with sub-millisecond temporal resolution and ability to resolve activity between cerebral regions with often surprising spatial and spectral differentiation and minimum bias. Indeed, unlike EEG, the accuracy of MEG source mapping is immune to the signal distortions caused by the complex layering of head tissues, with highly heterogeneous conductivity profiles that cannot be measured with precision *in vivo*.

We explore these ideas herein in details and conclude that MEG, used independently or in combination with other brain imaging techniques, contributes uniquely to our deeper comprehension of both the regional and large-scale neural dynamics of the brain: from the clarification of the nature of spontaneous and event-related brain activation to the elucidation of the mechanisms that yield functional connectivity between regions and the emergence of modes of network

communication in brain systems. As the function and dynamical principles of the signal components present in the volumes of dense and intricate MEG data become better understood, we explain how MEG plays an increasing and pivotal role toward the elucidation of the grand mechanistic principles of cognitive, systems and clinical neuroscience. To this end, we emphasize that MEG is particularly equipped to bridge human data with animal and computational models of electrophysiology in health and disease.

We also review the principles of MEG signaling and the state of the art of the technology, with a perspective on innovations on the horizon. We then highlight key MEG contributions to neuroscience and discuss translations to clinical practice. Along the way, while we discuss limitations, current difficulties and uncertainties associated with the technique, we also wish to correct some mistaken perceptions of MEG.

Measurement principles and instrumentation

The basic principles of MEG are simple; the sophistication lies in the sensing technology involved and the methodology required to extract relevant signal information in the widest variety of experimental contexts. Fundamentally, any electrical current produces magnetic induction (often popularly confounded with a magnetic field⁴), whose strength can be measured remote from the current source—for example, with a pick-up coil. The magnetic flux across the coil surface induces an electrical current in the coil wiring material, whose amplitude is instantaneously proportional to that of the magnetic induction and is readily measurable.

Basic signal origins. In MEG, the electrochemical currents circulating within and between neurons generate the magnetic induction. Postsynaptic potentials (PSPs) are considered the main generators of these ionic currents^{3,5}. There is also convincing though limited evidence that fast ripples present in MEG signals in the range of 500–1,000 Hz could be related to cell discharges^{6,7}. Yet they may also be explained by large spike components of PSP activity due to voltage-dependent channel conductance⁸ (Fig. 1). The useful frequency band

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of MEG signals is about 0.5–1,000 Hz, with 1–80 Hz being the most typical⁹. We discuss below the possible functions and interdependence across this wide spectral range of brain signals¹⁰.

Instrumentation: innovations on the horizon. In practical terms, the magnetic signal produced by neural currents in the nanoampere (10^{-9} A) range is formidably weak. Extracranial magnetic inductions are typically measured on a scale of femtoteslas (10^{-15} T), about 10 to 100 million times smaller than the Earth's static magnetic field. This reality imposes a need for sensitive sensor technology. The present industry standards rely on pick-up coils coupled with superconducting interference devices (SQUIDS)^{2,3}. SQUIDS exploit the principles of quantum physics for the detection of small electrical currents, like those induced by weak magnetic signals, with high sensitivity and large dynamic ranges.

State-of-the-art commercial systems feature coil magnetometers arranged in whole-head arrays of about 300 independent channels, sampled at up to 30 kHz simultaneously. Magnetic induction travels through the air: MEG sensors are not attached to the scalp, as the entire sensing apparatus is embedded in a thermally insulated tank, called a dewar, filled with 70–100 L of liquid helium. Superconducting temperatures minimize thermal noise and therefore optimize data quality. Consequently, subject preparation times are much shorter than in EEG, as the contactless and gel-free sensors do not need to be positioned and carefully verified manually.

Another distinctive property of MEG is that magnetic induction is a vector signature of electrodynamics. In concrete terms, MEG signals depend on the location and orientation of the pick-up coils with respect to neural sources, which vary between system manufacturers and are relative to the subject's head position in the helmet. This represents a clear practical difference from EEG, which measures differences of scalar electrical potentials between electrodes attached to the scalp. Although the head's shape and size obviously vary between individuals, the standardization of electrode montages scaled to the individual anatomy and with a common nomenclature¹¹ has greatly contributed to streamlining the dissemination and comparison of EEG results between instruments, studies and individual subjects, including patients. In MEG, both the monitoring of head movements during data acquisition and the registration of head positions between participants are therefore important factors for data quality and comparison, respectively. Besides online video monitoring of subjects, all MEG systems feature real-time measurements of head position. Limited offline software solutions for head movement compensation are available and can be necessary with special populations, such as infants¹². Creative hardware solutions have been recently proposed, using adjustable head casts to consistently reposition the subject within and between sessions with millimeter accuracy¹³.

Also unlike EEG data, MEG measures are reference-free: magnetic induction values are not relative to a common measure. The measurement of absolute physical quantities is an asset of MEG. In principle, though, EEG datasets can always be re-referenced with respect to their instantaneous arithmetic mean as a form of standardization¹⁴. Furthermore, the dependence of MEG signal strength on head position mitigates the advantage of collecting reference-free quantities. We shall see below that source imaging obviates the limitations attached to sensor data analysis and affords one specific strength of MEG with respect to EEG.

Overall, the MEG sensing technology is mature but its sophistication and maintenance impose substantial capital and operating costs. Fortunately, emerging opportunities for more cost-effective solutions bode well of the long-term sustainability and greater affordability of MEG as a research tool.

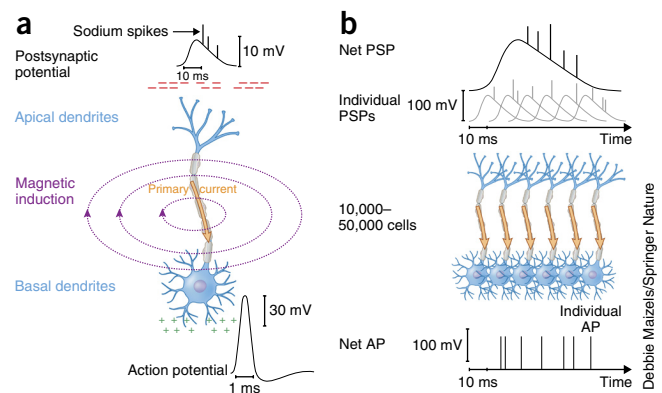


Figure 1 Cellular origins of MEG signals. **(a)** For simplicity, we take the cortical pyramidal neuron to epitomize the elementary cellular generator of MEG signals. All physiological currents from all cell types generate a magnetic induction; the elongated morphology of the pyramidal neuron constrains the net primary current circulation along the cell, which is a factor in creating greater signal strength in comparison to those from more stellate cellular morphologies. The primary current results from an imbalance in electrical potentials between the apical dendritic arborescence of the cell and its soma and more basal dendrites. The magnetic induction isolines in purple are perpendicular to the primary current flow and can be picked up outside the head. The sources are twofold: the postsynaptic potentials (PSPs), including fast, large-amplitude sodium spikes, and axonal discharges (action potentials, AP). The slower components of the PSPs are substantially smaller in amplitude than the APs. **(b)** At the scale of cell assemblies, the mass effect of slower PSPs is stronger than that of APs owing to their greater overlap in time without requiring rigorous synchronization. Computational models and empirical evidence show that a minimum of 10,000 to 50,000 cells are required to produce a signal detectable with MEG⁸. It is possible, in principle, that fast PSP spiking activity, and possibly shadows of APs, are detectable in MEG.

Helium-based cryogenics are constantly threatened by a looming shortage in natural resources. Hence the development of alternative sensing and instrument technology is vital to MEG, as well as other high-end instruments such as MRI scanners. Practical onsite helium recycling solutions have emerged and approach 90% efficacy. They reduce weekly refills to one or two per year. Still, thermal insulation negatively affects the sensitivity of the instrument: sensors are separated from the head surface by a distance of at least 2 cm. Recent integration of SQUID sensors in a partially adjustable helmet is a true breakthrough, improving signal strength and encouraging developmental neuroscience MEG research¹⁵.

New sensing technology is maturing. Non-cryogenic HyQUID detectors with noise performance equivalent to that of traditional SQUIDS is already found in a commercially available system. Similarly, optically pumped magnetometers¹⁶ (OPM) based on radically different sensing physics principles also represent an alternative to SQUID-based technology. Although less sensitive, OPMs can be positioned directly on the scalp surface and therefore pick up stronger field strengths as they are brought closer to the brain¹⁷. OPMs are very cost-effective, which also bodes well for easier access and therefore greater adoption of MEG by more neuroscientists.

The extreme sensitivity of present and future MEG sensing technology is challenged by many electromagnetic nuisance sources. Any moving metal object (for example, car traffic, elevators, carts or hospital beds) or electrically powered instrument generates magnetic induction that is orders of magnitude stronger than the brain's. Their influence can be reduced by combining magnetometers to emphasize brain signals with respect to environmental noise. Such gradiometers,

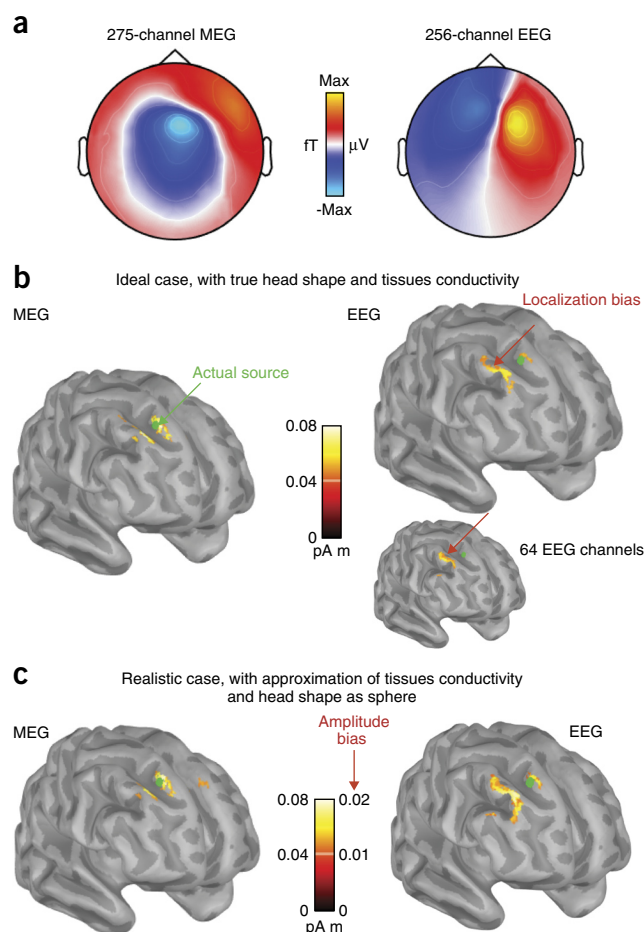


Figure 2 An example comparing MEG and EEG. Synthetic data were generated by impressing a simulated uniform current density on a 1-cm² patch of cortical surface (green in **b,c**). The cortical surface and the other tissue compartments (scalp, skull bone, cerebrospinal fluid) were that of the ICBM152 template, available in the Brainstorm open-source application¹³⁸. The corresponding, ground-truth MEG data were simulated on the sensor configuration of a 275-channel CTF (axial gradiometers) system. The 256-channel EEG sensor configuration was that of Electrical Geodesics. The reference head model was derived using the OpenMEEG boundary element method¹³⁹ with default parameters, also available in Brainstorm. **(a)** Resulting MEG and EEG sensor topographies for the simulated cortical source. **(b)** Estimated cortically distributed currents using the weighted-minimum norm estimator available in Brainstorm, with default parameters (amplitude thresholded above 50% of maximum): the EEG source map has a localization bias pointing at the gyral crown lateral to the actual source location. This bias is emphasized when using a more typical electrode density of 64 channels (inset). **(c)** Source estimates obtained using approximations of the head model: three-shell concentric spheres adjusted to the scalp surface, and altered conductivity values (+25% for scalp, -25% for skull bone). As predicted from physics of magnetic induction, the MEG source map is immune to geometric and conductivity approximations, whereas the EEG is not. This latter has considerably lower amplitude than the actual current strength (note distinct color scales for MEG and EEG).

arranged either in a radial or tangential (planar) fashion with respect to the head surface, greatly improve signal quality but still require magnetic shielding from the environment. The best solution remains the installation of a heavy (20-ton), multilayered shielding room to host the MEG instrument. However, this represents about a quarter of the investment cost and can be difficult to site. Lighter and slightly

more compact shielding solutions based on the active shielding technology are possible alternatives.

Finally and remarkably, MEG sensing technology can be used to detect magnetic resonance phenomena at ultralow fields (in the 10–100 mT range). In addition to special magnetic resonance-related advantages, there are potential benefits in such all-in-one hybrid imaging technology: combined MRI and MEG can be obtained simultaneously, thereby limiting registration errors¹⁸. Yet the lower magnetization induces weaker signal strength and imposes longer magnetic resonance acquisition times. It remains unclear whether this technology will truly penetrate neuroscience applications.

Distinct capabilities for electrophysiology and imaging

MEG as a method of electrophysiology. In featuring channels arrays around the head and sensor signals originating from brain physiological currents, MEG and EEG are sister techniques for noninvasive electrophysiology. This apparent similarity has fueled a certain amount controversy about the actual scientific and clinical added value of MEG. Some EEG scientists consider the technology to be simply redundant and not worth the extra cost^{19,20}. This misconception has been exacerbated by the fact that to obtain measurable markers of brain activity, early MEG studies and even many recent ones have resorted to the signal extraction techniques of EEG, averaging multiple trials of sensor signals time-locked to specific stimulus or behavioral events¹¹. The fact that both the timing and spatial properties of the resulting event-related fields (ERFs) are only partially consistent with the extensively studied nomenclature of event-related potentials (ERPs) cannot be interpreted in favor of or against MEG or EEG. If we imagine that ERFs were entirely concordant with ERPs, shall we conclude that MEG is simply redundant with EEG? If ERF counterparts of ERPs are absent, does this mean ERPs are actually artifactual? This apparent discordance is also true for the power and spatial distribution of sensor signals in the typical frequency bands of electrophysiology (delta, theta, alpha, etc.; see below).

To understand why MEG and EEG are actually different and complementary techniques for observing the electrical activity of the brain, we need to go back to Maxwell electrodynamics^{4,5}. These rules show that the spatial topography of magnetic induction and electrical potentials created by the same current source depend very differently on key factors. First and foremost, EEG signals are primarily and strongly affected by the substantial difference in electrical conductivity between the scalp, skull and other biological tissues. Magnetic permittivity, the magnetic equivalent of conductivity, is homogenous and identical across all compartments, including the air between the scalp and sensors. Consequently, the spatial topography of MEG sensor data is visually and quantitatively less smeared and distorted than that of EEG electrical potentials produced by the same physiological brain sources. This contributes to a clearer interpretation of MEG sensor topography in terms of the putative anatomical locations of its underlying brain sources. It also helps separate the contributions of brain signals from ambiguous physiological contaminants, such as ocular microsaccades²¹ and muscular artifacts^{22,23}, which can be confounded with high-frequency brain signals in EEG but are more clearly distinguished on the basis of their distinctive sensor topography with MEG. Artifact components can be eliminated or corrected when good-practice guidelines are respected²⁴.

The laws of physics however, impose a different set of challenges on MEG. MEG's signal-to-noise ratio (SNR) decreases faster with source depth—that is, the distance between neural generators and external sensors. Hence there is a belief that MEG cannot see deep into the brain. This should rather be interpreted as decreased sensitivity

Box 1 Toward increased clinical adoption

The actual value of clinical MEG for epilepsy is now well documented and argued, with large-volume retrospective studies reporting on the level of agreement between the noninvasive test and standard-of-care approaches (for example, invasive EEG) in severe cases^{113,132,133}. Yet retrospective studies are also limited by design: if MEG is concordant with invasive tests, then it is deemed as good as the latter; if it is discordant and points at other possibly epileptogenic brain regions, results need to be carefully assessed depending on whether interventions based on the standard-of-care data actually led to long-term freedom from seizures. Ideally, multicenter prospective trials of MEG predictions would need to be conducted, with intracranial explorations guided in part by MEG source imaging, followed by surgical resections, to fully assess the insight provided by MEG.

Other practical limitations include the very duration of present MEG tests. These are typically limited to hour-long recordings to minimize cost and maximize patient comfort. This is often very short for capturing canonical epileptiform events such as interictal spikes and, even more rarely, seizures, which are still considered of the highest value for clinical diagnosis. Tests are also often performed as outpatient procedures, with patients on medication, which further reduces the yield in terms of epileptiform events.

Considering a patient brain as constantly under siege by a neurological or neuropsychiatric disorder, clinical MEG research needs to point at other possible markers of aberrant ongoing or stimulus-response brain activity as alternative expressions of disease. A considerable body of work in autism spectrum disorder indicates that simple MEG measures of delayed early auditory responses, easily implementable in the clinic, are indicative of the syndrome's severity^{28,115} and are concordant with magnetic resonance tractography and with predisposing gene dosage¹³⁴.

Altered expression of background brain rhythms represents another source of electrophysiological MEG markers that remains relatively uncharted. This is an opportunity for MEG clinical research to verify the promises of animal research and diseases models in the great variety of insults and disorders that affect the human brain^{135–137}. Such research can only benefit from the consolidation and growing availability of large databanks of control MEG volumes, to help identify how these new disease markers deviate from normative variants⁸⁴ (Fig. 4).

MEG is clinically prescribed and reimbursed in a few countries for specific indications, such as pharmacologically intractable epilepsy and presurgical functional mapping of brain tumors. We note in passing that clinical recognition, including reimbursement, for fMRI tests is still largely lacking as well. In principle, clinical demand will boost the number of installations and improve access for researchers, eventually closing the virtuous loop back to more clinical indications for MEG tests. This wishful scenario has not entirely happened yet: MEG clinical programs typically see anywhere between a dozen and a maximum of a couple of hundred epilepsy cases annually. This situation can pose challenges in terms of financial sustainability if not complemented by a critical mass of funded research studies or intramural institutional commitment. Brain tumor cases are rarely seen because MEG analysis pipelines remain time-consuming. This is a factor typically incompatible with the time pressures of clinical decision-making and surgical interventions in neuro-oncology.

It is the present reality that, so far, MEG vendors have delivered beautifully crafted instruments without investing enough resources in developing truly efficient software analysis pipelines to serve the special needs of clinical practitioners. Productive MEG clinics are those who have invested in the brain power to compensate for these commercial lacunae.

with depth, not as an absolute inability to detect activity from medial cortical or subcortical brain regions, as we discuss further below. MEG is also less sensitive to neural current flows with a radial orientation—that is, those aligned along a virtual radius of the head, from its center to the scalp envelope. Here too, the conception that MEG is entirely blind to radial sources would actually be valid only if the shape of the head were a perfect sphere⁵.

For all these reasons, and if we assume that brain activity, including the sources of event-related components, involves regions presenting a variety of depths and current flow orientations, there can be at best limited correspondence between MEG and EEG sensor data. We also need to bear in mind that these modalities actually measure different, nonredundant physical quantities. Consequently, direct comparison studies between the femtoteslas of MEG and the microvolts of EEG sensor data can prove more challenging than initially thought. The appreciation of converging or complementary evidence between the techniques can be best conducted by assessing their respective abilities to resolve the physiological currents at their source, as discussed below.

Yet we also need to acknowledge that many neuroscience questions may not require brain mapping: there is established and continued scientific interest in and clinical significance for MEG sensor data analyses, in their ability to discriminate between experimental conditions, including with spatial-filtering²⁵ and decoding techniques²⁶, and to correlate with or predict behavior²⁷. They also suggest simple and practical new disease markers²⁸. We re-emphasize, however, that the anatomical interpretation of scalp signals remains ambiguous, even in MEG. The cross-talk between sensors due to signal smearing represents a source of severe confounds, especially to functional connectivity measures²⁹ applied to scalp data. Source imaging can alleviate these issues.

MEG as an imaging modality. Relatively to EEG, the advanced sensing technology involved in MEG has attracted the continued interest and expertise of the physics and electrical engineering community. This influence manifests in approaching source localization and imaging as inverse modeling, a category of problems common to many subfields of applied physics and biomedical imaging⁵. Indeed, one truly distinctive advantage of MEG is arguably in producing time-resolved maps of neural currents that are considerably less prone to distortion by modeling approximations than EEG. There is strong evidence that EEG source models suffer from uncontrolled biases caused by inevitable approximations in defining the head shape³⁰, especially the bone of the skull³¹. The presence of blood vessels also affects EEG source modeling³². More generally, the conductivity of head tissues remains in practice unmeasurable *in vivo*^{33,34}, and the approximated values used also impose a localization and amplitude bias on estimated EEG sources^{35,36} (Fig. 2). Further approximations in modeling the electrode size and drifts in skin-contact impedances also contribute negatively³⁷.

Ground-truth direct-comparison studies of MEG and EEG source localization, using electrical sources implanted in realistic skull phantoms^{38,39}, confirms the greater sensitivity of EEG to model approximations. Localization errors of up to 25 mm were produced by EEG source modeling, while the maximum MEG localization bias was limited to about 1 cm under the same experimental circumstances. Multimodal comparison studies taking fMRI as reference tend to show lesser differences⁴⁰, especially when simultaneously recorded MEG and EEG data is processed jointly to yield, in principle, a superior, superadditive joint source model of cortical generators^{41,42}. Therefore, whenever possible, a good-practice guideline is to record from at least a few EEG electrodes simultaneously with MEG. This augments the chances of obtaining converging evidence about the underlying brain processes.

The sources of bias that are specific to MEG are well identified and controlled. The sensitivity and therefore the spatial resolution of MEG source imaging are indeed uneven across the brain: for instance, superficial cortical sources produce MEG signals up to 100 times stronger than deeper, subcortical structures at equivalent current strengths^{43,44}. However, there is both modeling⁴⁵ and increasing experimental evidence that with optimized paradigm designs and signal extraction techniques, brain regions as deep as the insula⁴⁶, thalamus⁴⁷, hippocampus⁴⁸, amygdala^{49–51} and brainstem^{52,53} can be resolved with MEG.

Concerning the influence of current flow direction, brain regions in sulcal walls (tangential current flow) produce MEG signals that are stronger than sources along gyral crowns (radial current flow). We also emphasize that, SNR differential effects notwithstanding, the orientation of primary currents affects positively the spatial resolution of MEG source imaging: recent empirical results in the visual cortex indicate that the activity of cortical locations separated by about 0.5 mm can be resolved if the angle between their respective current flow is at least 45°, a range compatible with typical cortical gyrification⁵⁴. These results confirm simulation studies that demonstrate the sensitivity of MEG signals to minute changes between cortical layers⁵⁵ and at the sub-millimeter scale of cortical columns⁵⁶.

All these factors influencing the sensitivity of MEG source imaging are fully characterized quantitatively from the physical forward model of an individual's anatomy. SNR can also be estimated routinely using empty-room recordings, with no participant under the sensor array. This is another advantage of MEG with respect to EEG, for which actual skin contact of the electrodes is required.

Nevertheless, with substantial operating costs and a capital investment that compares to that of an MRI scanner, a research organization needs further reasons to support the initiation and development of an MEG program. The comparison with MRI is relatively unfair: in the early years, a crucial factor that facilitated the development of MRI neuroimaging research was the fast-growing installation of clinical scanners that were also made partially available to researchers. Hence scientists were not required to primarily cover the platform's operating costs. The clinical recommendation and recognition for MEG, although growing⁵⁷ (**Box 1**), have not been sufficient yet to increase the number of clinical MEG units to a level that would facilitate access to the broadest research community. Hence, the decision to initiate and maintain an MEG program is a matter of institutional research strategy. The initiative needs to be supported by a sufficiently large and diverse critical mass of investigators intrigued by the assets of the technique. Financially, a clear plan needs to be laid out so that operating costs can be assumed by a combination of fees for access and institutional funds.

Strategically, MEG imaging represents a strong scientific asset in the neuroscience portfolio of a research intensive institution: it is directly sensitive to neural electrophysiology and therefore independent of a signal transduction model. The millisecond temporal resolution of neural signal dynamics across the entire brain is obviously another hallmark of MEG compared to functional MRI (fMRI), positron emission tomography (PET) or optical techniques⁵⁸. We have seen that multiple factors expose EEG imaging to uncontrolled sources of localization bias. Other electrophysiological methods, such as intracranial stereotactic EEG and electrocorticographic implants, have obvious limitations in terms of invasiveness, and coverage of the cerebrum is confined to a limited number of disease-prone regions.

Other practical advantages over in-bore scanning with PET and fMRI include a safe, quiet and open environment inducing minimal claustrophobic stress, especially in special populations, with posture

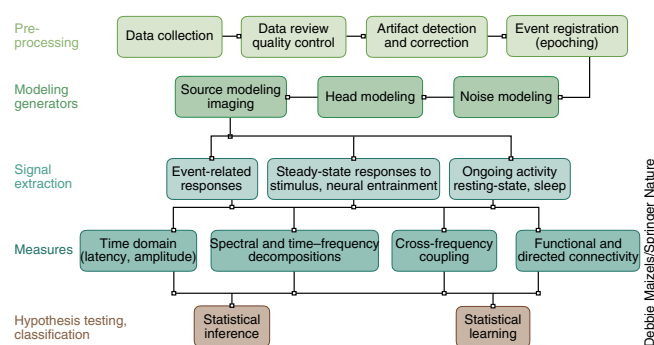


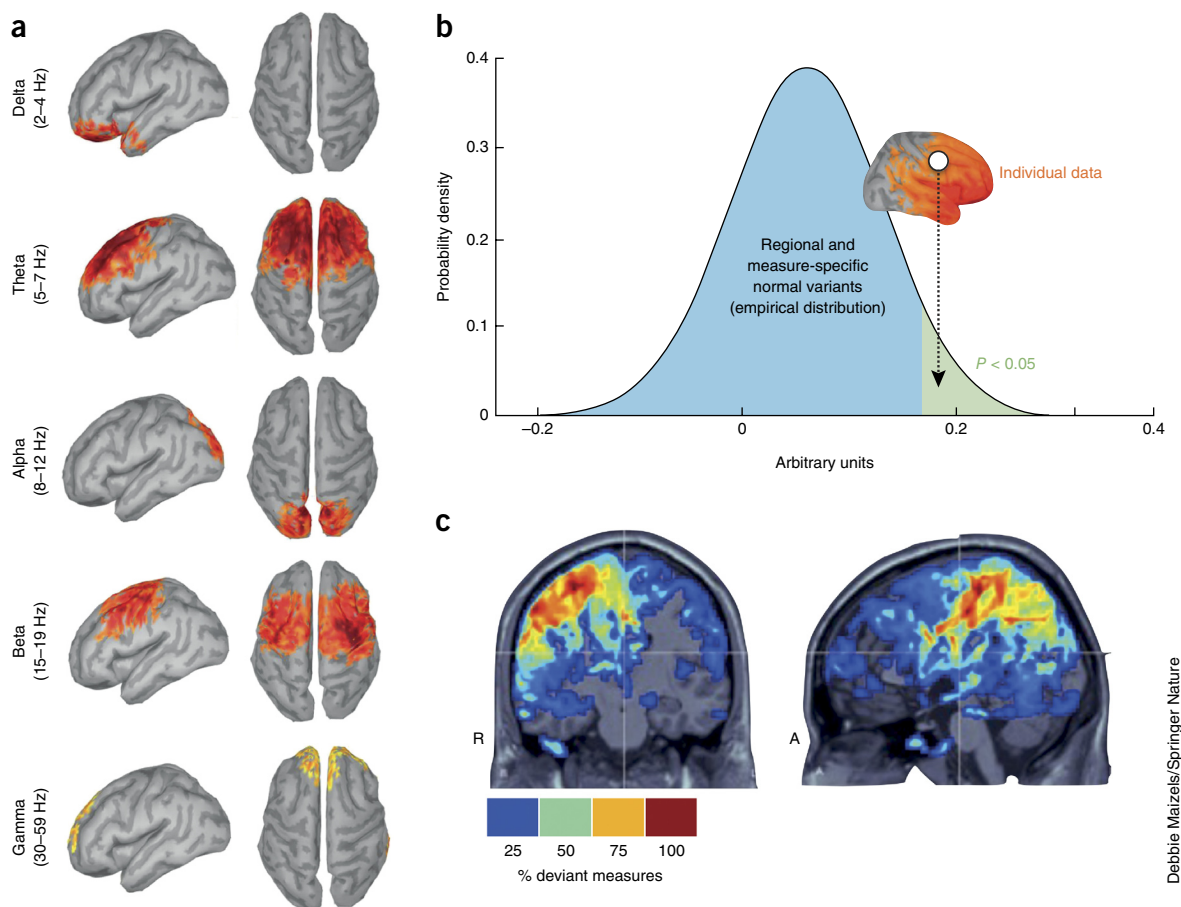
Figure 3 Major steps required and possibilities offered by MEG analytics. Like other brain imaging modalities, MEG requires that several important procedures be followed in data analytics. (1) The preprocessing steps are crucial to assure that data quality is optimal at the time of collection and before engaging sophisticated signal extraction procedures. Data segments contaminated by artifacts need to be identified and rejected or attenuated. (2) The modeling stage for MEG imaging requires that a few important options for parameters selection be considered carefully (for example, template versus individual head shape, noise definition, image reconstruction parameters). (3) Signal extraction usually depends on the design of the experiment and is very versatile in MEG. The set of possible measures is immense because of the multidimensional components of the data (space, time, frequency). (4) The final statistical steps can either include inference and hypothesis testing, or statistical learning techniques for signal classification, and other derivatives.

adjustable anywhere between upright and supine. Ferromagnetic elements used in dental works and implants can cause complex artifacts⁵⁹ but, unlike in MRI, do not pose safety concerns.

MEG also offers remarkably versatile concurrent signal acquisition and analytic combination opportunities for the realization of genuine multimodal studies, with high-density scalp EEG^{60,61}, intracranial local field potentials^{62–64}, deep-brain^{65,66} and scalp^{67,68} current stimulation devices; all kinds of peripheral measures to study their coupling with brain activity (eye tracking and pupil diameter, heart rate, skin conductance, muscle electrophysiology, motion capture, behavioral equipment, etc.); and real-time neurofeedback^{69,70}.

Reduced analytic complexity for greater adoption. One recurrent bottleneck to the broader adoption of MEG has been the perceived intricacies of its data workflow. The reasons are multifaceted (**Fig. 3**). First, MEG signals are rich and complex: we will review in the next section how this is a matter of active research. Still, it also remains a source of uncertainty to MEG users. They therefore need to be offered the best possible guidance to define the signals of interest in their data and navigate the plethora of signal extraction measures available. A constructive stance is to encourage investigators to formulate their research hypotheses in terms of electrophysiological markers (for example, event-related responses, oscillatory components, cross-frequency interactions, inter-regional coherence, etc.) of mechanisms related to a theoretical framework. Exploratory MEG studies are essentially bound to fail, considering the volume of data and the analysis dimensions enabled by MEG's mass electrophysiology.

Another element that has somewhat inhibited MEG's development is that, as in EEG, the physics principles underlying source imaging are fundamentally ill-posed. This means that an infinite number of source models can fit the sensor data equivalently well. Such manifestation of mathematical ill-posedness is very common in many fields of physics, signal detection and estimation theory, and can be addressed with sound methodological principles⁵. Nevertheless, this originally gave



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Figure 4 Toward big-data MEG. (a) Example of the outcome of an MEG imaging database (data from OMEGA⁸⁴). Ninety-six healthy participants were scanned in the resting state for 15 min with their eyes open. MEG imaging of their cortical activity was performed using the same method as for **Figure 2**. The average distribution of the magnitude of ongoing brain rhythms (from delta to gamma) found in the cohort are registered to and represented on the Colin27 brain template cortical surface. Data were thresholded at 50% of maximum amplitude across the cortex. (b) Large data repositories such as OMEGA can be used to establish normative and patient variants of any analytic measure taken from MEG source signals. This is illustrated here, where for each measure and each brain location, the values obtained in a tested individual or group dataset can be assessed with respect to their empirical distribution in the databank. (c) Practical summarizing and visualization solutions can reveal the anatomical locations where, for example, a single or cumulated measures from the individual data from one patient deviate from those observed in the reference normative repository. Here, for instance, the colored brain locations indicate where abnormal strengths of oscillatory brain activity have been detected in the resting state and in multiple frequency bands in a patient with epilepsy.

room for too many methods to present unverifiable evidence of claims to excellence, aggravated by a lack of sharing with the community following journal publication. This did not contribute to building confidence among potentially new users of MEG. Fortunately, this phase has receded: the methods have grown mature and pragmatic, with now high-quality commercial and academic software packages that have greatly augmented users' access to training, their productivity and their deeper understanding of methods and their limitations⁷¹.

Opportunities for machine learning and big-data neuroscience. New approaches to MEG signal analysis have recently spun off from the tremendous developments and growing availability of data classification and feature extraction techniques, based on the principles of machine learning⁷². These methods emerged only recently in the MEG arena, although they are already demonstrating very significant potential in augmenting the scientist's toolkit.

Relatively simple implementation of machine-learning decoding techniques for multidimensional signal classification showed impressive applications in identifying early components of visual object categorization⁷³ and in tracking the temporal organization of spatial

patterns of brain activity⁷⁴ or that of a mnemonic template in the context of perceptual decisions⁷⁵. The fact that these methods are, for now, fairly independent of signal models make them an attractive complement to MEG researchers for rapid evaluation of their data—for example, to assess the presence and spatiotemporal topography of effects between experimental conditions or cohorts. Such approaches were recently and beautifully extended to joint multimodal processing of MEG and fMRI data⁷⁶: a form of machine learning-based conjunction analysis of similar representations of features in both datasets resulted in fMRI voxel clusters being animated with MEG's millisecond temporal resolution. Representations similarity analyses of a similar kind were also extended to the joint processing of MEG data with the outputs of a deep neural network, respectively obtained from and trained on the same visual categorization task⁷⁷. This highly innovative, multimodal approach promises to take best advantage of neuromimetic models to refine, and maybe discover, new mechanistic principles of brain function, potentially generalizable to other functional systems and patient populations.

The present renaissance of artificial intelligence methods is also boosted by access to readily available computing and large data storage

resources. More generally, resorting to big-data tools and methods is becoming increasingly strategic in neuroscience research involving brain imaging: analysis pipelines have grown in sophistication, and data volumes have inflated concurrently with the augmented spatial and temporal resolution of instruments. There is also a growing scientific motivation to combine multiple data types (genotypes, imaging and behavioral phenotypes, clinical data, tissue samples, etc.), which transforms every research participant's record in a big-data volume. In parallel, community awareness is now growing toward expanding the curated value and lifetime of data collections in public research: the increasing number of open data-sharing initiatives emphasize and incarnate stronger educational, economical, ethical and societal values in science⁷⁸. For the neuroimaging community, this represents a vital opportunity to validate methods more thoroughly and to overcome the limitations of small-sample, low-powered and consequently poorly reproducible studies that are eventually detrimental to the credibility of the field⁷⁹.

Until recently, MEG was lagging behind MRI in that respect^{80–82}. Reasons include the lack of a standard file format for MEG raw data and the large volume occupied by high-density recordings (typically >100 MB per minute). Fortunately, these bottlenecks are gradually, and at least partially, being overcome by the increasing availability and versatility of software readers for most native data formats. Storage capacity, especially in the cloud, has now become ubiquitous and more affordable. The Human Connectome Project was first to distribute MEG data on a large scale, from a subsample of its cohort, along with extensive multimodal MRI, behavioral and genetic data⁸³. With about 150 data volumes available, the Open MEG Archives (OMEGA) is the second-largest repository of resting-state MEG data, and it contains T1-weighted MRI volumes of participants⁸⁴ (Fig. 4a). The recent CAM-CAN initiative features data from about 650 healthy participants ages 18–88, combined with multimodal MRI and extensive cognitive testing⁸⁵.

We rejoice that more of these initiatives are on the horizon, as they will with no doubt increasingly contribute to improving data integrity and consistency across sites, reproducibility of research results, and the development and benchmarking of new analysis methods that were statistically too low powered with smaller data cohorts (Fig. 4b). Finally, flexible statistical inference methods based on non-parametric approaches have been designed to adequately handle the multiple dimensions of MEG data (space, frequency and time, typically) and efficiently control for multiple comparisons in hypothesis testing^{86,87}.

To conclude, MEG occupies a unique, strong position in the landscape of human neuroscience techniques. Conceptually and effectively, it plays a privileged and scientifically significant role in bridging human electrophysiology with other imaging signals and modalities. The access the technique provides to large-scale neurodynamics is a tremendous opportunity to bridge the study of human brain activity with the mechanisms identified and readily testable with animal and disease model electrophysiology, as we shall see in the next section.

A window on large-scale neurodynamics

Many researchers who are new to MEG find themselves puzzled, if not frustrated, by the sheer volume and complexity of experimental data produced. What is signal? Is this noise? How to implement a test to detect signal changes between experimental conditions? How to measure functional connectivity? These interrogations are active research topics in MEG. They contribute to the broader objective of comprehending and exploiting how brain activation, in terms of regional and large-scale neural dynamics, is expressed in electrophysiology⁸⁸.

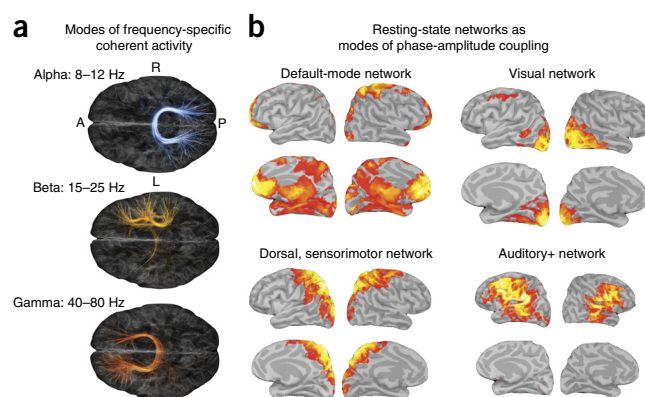


Figure 5 Frequency-dependent expressions of inter-regional connectivity. (a) Illustration of frequency-dependent functional connectivity measures. MEG source imaging of 5-min resting-state (eyes open) data in typical alpha, beta and gamma frequency bands was obtained using the same methodology as in Figure 4 (the strengths of cortical currents are not shown here; data sample from OMEGA⁸⁴). Coherence in all frequency bands of interest between every pair of cortical source locations was extracted and thresholded above the 90th percentile. Virtual white-matter tracing yields convenient and anatomically compatible representations (shown here for visualization purposes) of such complex, multidimensional connectivity data (S. Dery and S.B., unpublished data). (b) Resting-state networks obtained with MEG imaging. Regions that demonstrate similar dynamics of phase amplitude coupling fluctuations over minutes of resting-state MEG recordings segregate in networks that are similar to those found in fMRI. The first four principal spatial modes of connectivity found across 12 subjects are shown. See ref. 101 for details on the approach.

Yet many potential users of MEG are under the impression that the field is not mature enough or that the technique is too complicated altogether. All things considered, these are questions that actually concern all electrophysiology and imaging methods: the apparent simplicity of fMRI data and of some widely used analysis pipelines, for instance, should not mask their intrinsic limitations^{89,90} and the share of fragility in their methodological assumptions and sophistication⁹¹.

MEG signals: rich and complex. Event-related components such as ERFs represent only a small fraction of the wealth of information present in MEG signals. One key scientific objective is indeed to understand how transient or tonic responses emerge from and reshape the busy resting-state activity of the brain^{92,93}. This represents a conceptual, and somewhat iconoclastic, shift from the classical tradition of considering spontaneous, ongoing brain activity as ‘neural noise’. It is necessary, though, to comprehend the rich expressions of distributed and interdependent neural dynamics available in MEG signals and to make the most of the modality's imaging capacity. Electrophysiology is not the only domain of biology undergoing a similar change of paradigm, exploiting the higher order statistics of experimental measures beyond the traditional trial or group average.

Bridging with other imaging modalities and animal electrophysiology contributes to a deeper comprehension of the nature of brain signals observed with MEG imaging⁹⁴. For instance, the explosion of interest in fMRI resting-state and task-based connectomics prompts the identification of equivalent signaling mechanisms in neural electrophysiology^{95,96}. Counterintuitively, there is little correspondence between MEG and fMRI resting-state networks when MEG source signals are extracted in the frequency bands that show the strongest correlation between electrophysiology and fMRI, namely gamma^{97,98},

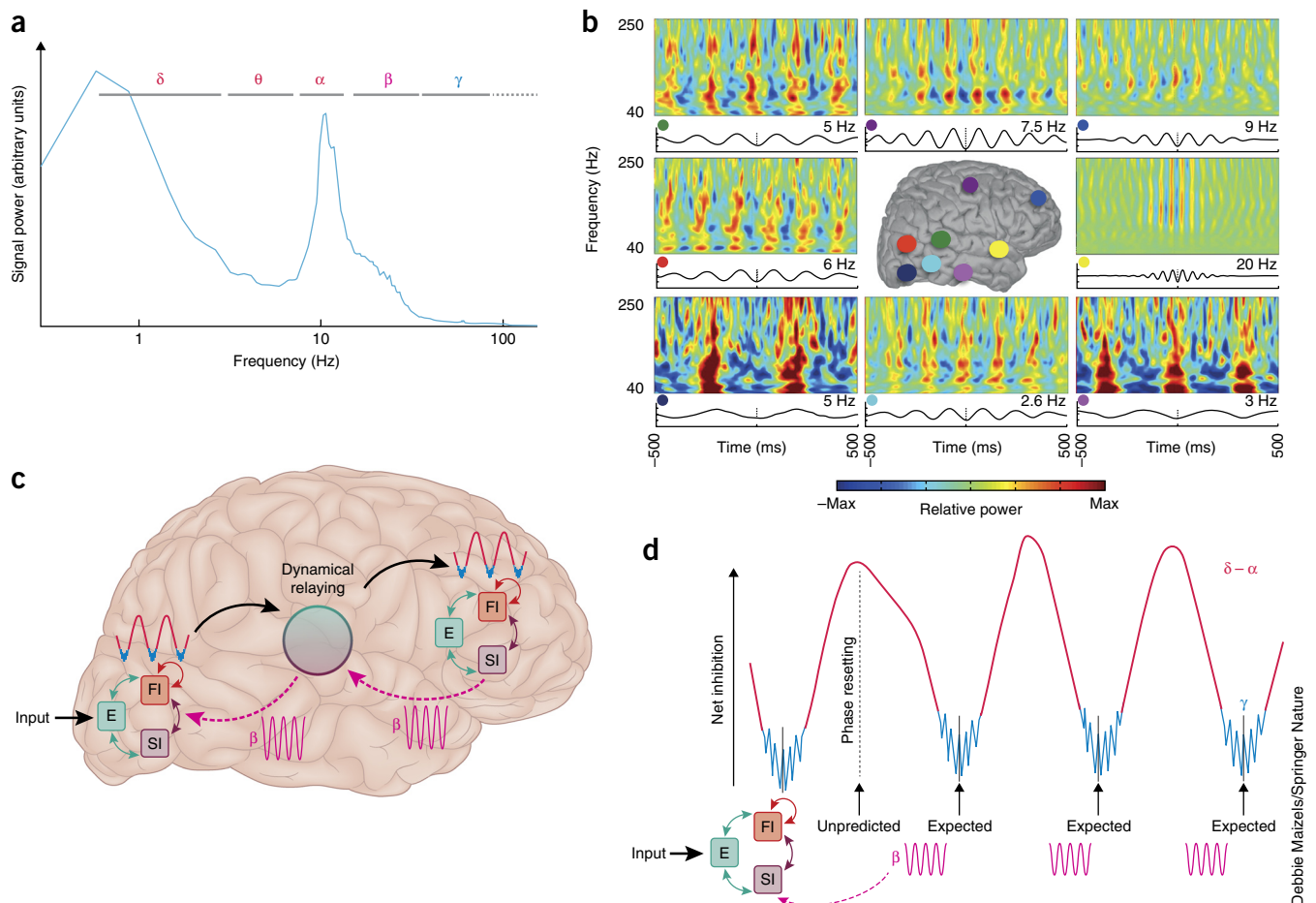


Figure 6 A possible mechanistic framework of polyrhythmic brain activity. **(a)** A typical power density spectrum (80-s resting-state data from a 55-year-old healthy adult with eyes open; Welch's method, 2-s windowing) shows the distribution of power averaged across all 275 channels of a CTF MEG system. Typical brain rhythms are marked; note the prominent peak in power in the 8- to 12-Hz alpha range. **(b)** These rhythms are coupled and interdependent, which can be revealed by measures of cross-frequency interaction, such as phase–amplitude coupling (PAC). Here, PAC analysis of MEG traces obtained in the resting-state (10 min) of a healthy 40-year-old adult (eyes open) shows that the amplitude of gamma activity is modulated by the phase of slower oscillations. Each panel indicates (i) the average of ongoing MEG source time series epoched on a [−0.5, 0.5] s time window about the trough of the local slow oscillation the most highly coupled with fast gamma activity in the 80- to 150-Hz range and (ii) the average time–frequency decomposition of the power of the MEG source signal, indicating how it is modulated with the phase of the underlying oscillation (see ref. 101 for details). The colored dots indicate the locations on the cortex where the sample signals were extracted. **(c)** The slower delta to alpha rhythms mark the net excitability of cell assemblies consisting of slow and fast inhibitory (SI and FI, respectively) and excitatory (E) cells. Possible theoretical frameworks for the organization of brain rhythms, such as the model of synchronized gating¹⁰¹ and others^{140,141}, consider brain network formation and communication to be enabled by the phase alignment of these cycles between regions. This can be facilitated by the mechanism of dynamical relaying¹⁴² via the thalamus or cortical hub regions. While gamma bursts could contribute to bottom-up signaling (black arrows), beta bursts could manifest top-down modulations of upstream regions (magenta arrows) and thereby contribute to the implementation of contextual predictive inference of input signals. **(d)** Such a dynamical scaffold, among others possible, helps formulate testable hypotheses from MEG signals. For instance, the occurrence of a stimulus (input) interferes with the ongoing E/I dynamics in a primary sensory region. This may provoke the resetting of the phase of local E/I cycles and trigger the temporal prediction of the next stimulus occurrence via an afferent volley of beta oscillations. This process repeats and paces the net inhibition of the local cell assembly according to the next anticipated stimulus occurrences. Such a model predicts that input signals to a brain network would fall optimally at the phase of maximum net excitability of the input node. One consequence would be to maximize the perceptual processing of the stimulus by facilitating the relaying of its neural representation downstream¹⁰⁶.

but also slower oscillatory ranges such as delta and theta⁹⁹. In fact, MEG time series in the beta range (15–35 Hz), when processed with fMRI-like data-driven resting-state pipelines, were first to reveal resting-state networks compatible with fMRI's topography¹⁰⁰. Studies had shown indeed that local field potentials in the beta band were weakly negatively correlated with blood oxygen level-dependent (BOLD) traces⁹⁹. Gamma and the slower BOLD-correlated frequency bands (delta through alpha) were later shown to also form an electrophysiological scaffold for resting-state networks¹⁰¹, when combined using

cross-frequency coupling measures translated from animal and intracranial human electrophysiology¹⁰² (Figs. 5 and 6b).

Bringing everything together: polyrhythmic mechanisms of brain functions. Taken together, and although seemingly complicated, these observations are actually mutually compatible when considering a mechanistic construction. Here we propose one possible model of polyrhythmic integration to reconcile published reports that are seemingly disparate across the frequency spectrum of

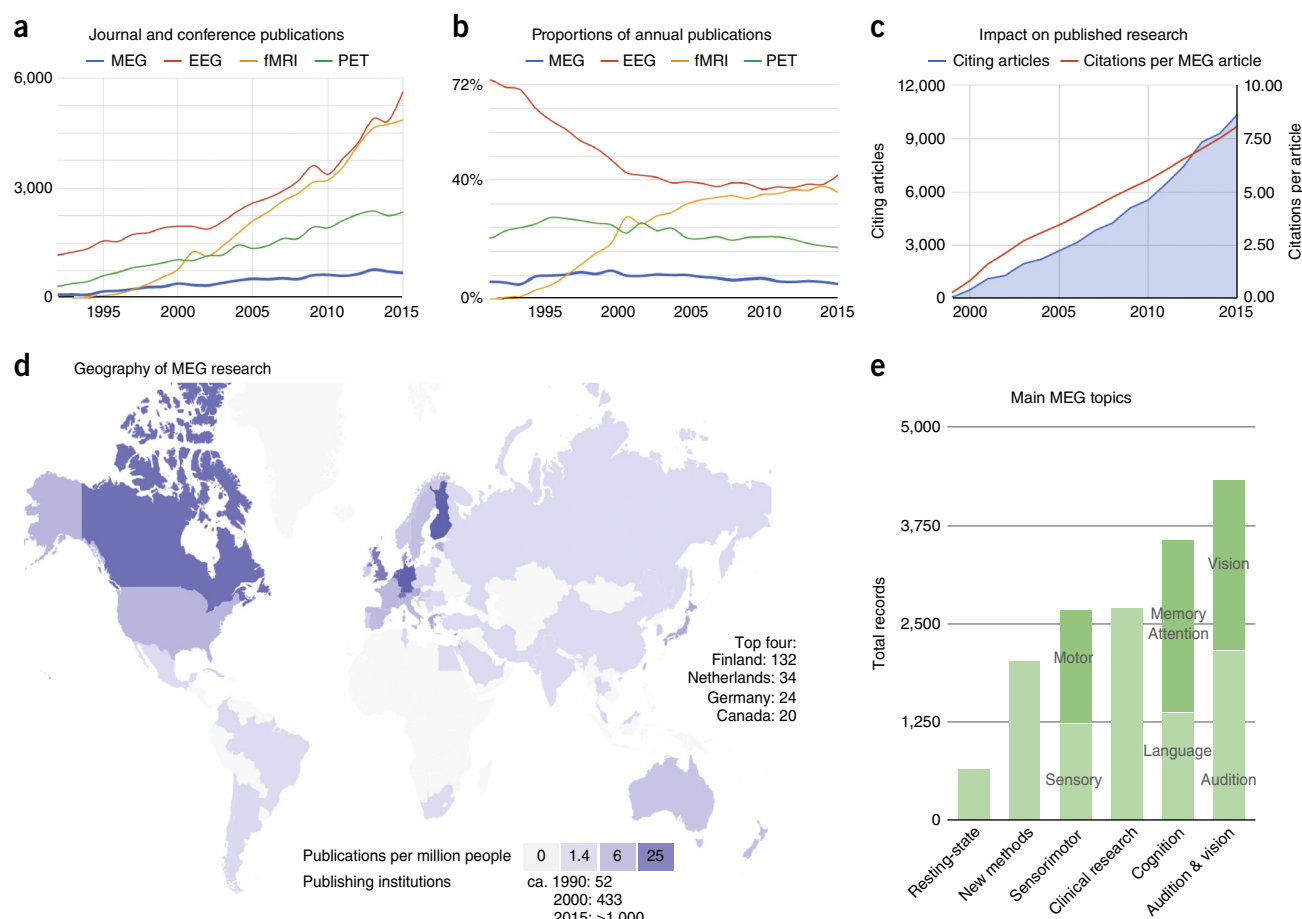


Figure 7 Snapshots of MEG science. **(a)** Annual volume and **(b)** proportion of published articles and conference proceedings concerning the major techniques for measuring brain activity noninvasively. **(c)** Impact of MEG on published research, measured in terms of citing articles and citations per MEG article, on an annual basis. **(d)** Geographic distribution of published MEG articles per million people. Insets indicate the top four countries with highest rate of publication per capita and the number of institutions whose scientists have coauthored a MEG-related publication over the indicated 5-year periods (encompassing 1988–1992, 1998–2002 and 2011–2015). **(e)** Main topics covered by MEG research so far. Data are from the over 10,000 MEG-related indexed publications (source of bibliographic data: Web of Knowledge).

electrophysiological signals. The purpose is essentially to propose a roadmap to guide future research, including the formation of testable hypotheses for scientists interested in MEG. At the mesoscopic regional scale, slower rhythms (delta through alpha) mark the phase of relative excitability of cell assemblies^{10,103}. Gamma bursts tend to occur in volleys nested at certain phases of these slower rhythms, a well-studied phenomenon of coupling across frequencies captured by, for example, phase-amplitude coupling^{104,105} measures (Fig. 6a,b). There is increasing evidence¹⁰⁶ that gamma cycles could represent timed opportunities for neural representations of, for example, incoming stimuli to be registered by cell assemblies and propagated further downstream in a bottom-up fashion.

Beta oscillations so far have not been found to pace gamma bursts and do not seem to be driven directly by colocalized slower rhythms in the human resting state¹⁰¹. According to computational models and nascent experimental data¹⁰⁷, they are rather thought to signal top-down modulations from higher order, executive regions in brain networks (Fig. 6c,d).

A global roadmap for MEG to build on these recent and still relatively sparse advances would ideally consist in (i) further clarifying the physiological principles structuring the local-to-global dynamics of neural oscillations, (ii) defining measures of regional activation

and inter-areal communication in brain systems that are driven by these biological principles (iii) using these measures to survey the dynamical repertoire of the resting brain, which remains largely uncharted, and (iv) understanding how sensory inputs interact with this repertoire, enabling functional integration and eventually behavior. Approaching future MEG research with this plan would open considerable perspectives—for instance, by verifying that aberrant repertoire phenotypes are expressed in diseases. This would enable a new generation of electrophysiological markers of pathology and eventually new forms of intervention.

Contributions to neuroscience

Research productivity. Our bibliographic survey (source: Web of Knowledge) indicates that, in volume, the yearly production of scientific publications concerning MEG has been increasing over the past 25 years. About 750 indexed journal articles and conference proceeding entries are published on an annual basis (Fig. 7a). However, although fMRI and PET were developed more recently, fMRI some 20 years after MEG, their respective volume of research production approaches three (for PET) to eight (for fMRI) times that of MEG's. The historically oldest technique of all, EEG, remains the leading integrative neuroscience tool, with fMRI as a close runner-up. In addition

to continued scientific pertinence, EEG's longevity and preeminence are supported by its relative affordability, which facilitates access in most research organizations, and the emergence of low-cost, consumer-grade EEG products for a new range of applications such as brain-computer interfaces and biofeedback explorations¹⁰⁸. One particular distinction of MEG with respect to EEG's considerable volume of research is source imaging and modeling as a particular topic of interest. This concerns only about 6% of all EEG research, compared to at least one-third in MEG. We also note that since the turn of the twenty-first century, the research output of all techniques has been slowly declining relatively to fMRI's (Fig. 7b).

MEG at present contributes 5% of the neuroscience research that uses the techniques surveyed, although with increasing impact (Fig. 7c). As of 2015, about 10,400 articles cited published MEG research, with an average of eight citations per MEG article. Further, the geographic distribution of the community shows healthy diversity (Fig. 7d) and growing stamina: in a 5-year period around 1990, 52 organizations had researchers publishing with MEG. This number grew to 433 around the year 2000 and is now above 1,000 research organizations involved in or collaborating on MEG research over the past 5 years.

Highlights. We have already reviewed the unique contributions and potential of MEG for studying the large-scale dynamics of brain activity. This represents the strongest scientific asset of the technique. More thematically, MEG users have been investigating the principal topics of systems and behavioral neuroscience, with greater representation from systems, cognitive and clinical research studies, the strong presence of methodological developments, and emerging themes such as resting-state brain research (Fig. 7e). Excellent topical reviews are available to dive into each subfield in detail: methods¹⁰⁹; the integrative neuroscience of language¹¹⁰; consciousness^{111,112}; and translational aspects of clinical neuroscience, including epilepsy^{113,114}, autism spectrum disorders¹¹⁵ and movement disorders¹¹⁶.

We wish to highlight an experimental approach that is not specific to the modality, but which has gained significant momentum in MEG. It consists in entraining neural systems with steady-state sensory stimulation or detecting brain activity that is temporally coherent with behavioral or peripheral measures, such as movement parameters. Such experimental models take great advantage of the temporal resolution of the technique and enhance SNR by 'tagging' neural responses with stimulus-imposed or stimulus-induced frequencies of interest. A body of compelling work has grown in audition¹¹⁷, including prosodic features of natural speech^{118,119} and music¹²⁰ perception; vision^{121,122}; attention^{123,124} and motor system¹²⁵ research using such methodology. The reader may refer to our annotated bibliography and other recent reviews^{9,126} for more detailed highlights of MEG contributions to neuroscience.

Conclusions

We have reviewed MEG as a neuroimaging modality in its own right, for the widest range of integrative neuroscience research topics. Although its scientific presence is strong, MEG could attract a larger and broader community of scientists. Advances in research methods and practical tools are now available to make MEG more accessible. Although the signals are complex, their extraction and interpretation can be facilitated by the emergence of testable mechanistic frameworks of interdependent neural dynamics.

Like those for MRI and PET, initiatives to share large MEG data openly in repositories are now well underway. This is beneficial to establishing normative and disease-specific variants of

electrophysiological activity and to the reproducibility and generalization of research methods and results.

Commercial entities could at present better manage the expectations of practitioners to avoid misconceptions about MEG as a routine clinical modality. Looking forward, they could make stronger efforts toward the integration of research tools into certified analytic pipelines. This would with no doubt increase the yield of MEG in the epilepsy clinic and see the modality penetrate more subspecialties of neurology and neuropsychiatry.

We also emphasize that MEG is a technique that readily bridges with other measures and methods such as electrophysiology (intracranial local field potential recordings and scalp EEG), blood flow and oxygen metabolism (near infrared spectroscopy), brain stimulation (transcranial direct current stimulation and transcranial alternating current stimulation), all of which can be performed concurrently with MEG. This offers researchers tremendous opportunities to cross-validate findings between techniques and between human and animal bodies of work, and to build on the superaddition of jointly processed multimodal data volumes.

To conclude, the sensitivity of MEG to a large spectrum of fast, oscillatory brain signals, combined with its superior ability to map their anatomical origins, makes it a powerful tool for verifying predictions from theoretical frameworks concerning brain functions, the mechanisms of directed connectivity in brain networks^{127,128} and, more generally, perception and behavior as biological expressions of predictive inference^{129–131}.

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COMPETING FINANCIAL INTERESTS

The author declares no competing financial interests.

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