MEG for Brain Electrophysiology & Imaging

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Sylvain Baillet

McConnell Brain Imaging Centre

Montreal Neurological Institute, McGill University

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Abstract

We review the aspects that uniquely characterize magnetoencephalography (MEG) amongst the techniques available to explore and resolve brain (dys)functions. While its specific strengths in terms of millisecond source imaging are emphasized, we also identify and discuss current practical challenges, in particular in signal extraction and interpretation. We also clarify some disadvantageous perceptions of MEG, including the misconception that the technique is redundant with electroencephalography (EEG). Overall, MEG uniquely contributes to our deeper comprehension of both the regional and large-scale brain dynamics: from the functions of ongoing 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 explain how MEG is bound to play an increasing and pivotal role in the elucidation of these grand mechanistic principles of cognitive, systems and clinical neuroscience.

After 45 years[1–3] of developments and utilization, we shall reflect on the position of MEG amongst the techniques available to explore and resolve brain (dys)functions. This review focuses on the aspects that, in our opinion, uniquely characterize MEG. We emphasize the specific strengths of the modality, such as its source imaging capabilities. We also identify and discuss current practical challenges, in particular in signal extraction and interpretation.

Because MEG and electroencephalography (EEG) are apparent sister electrophysiological techniques that are both sensitive to the electrochemical current flows within and between brain cells, MEG is sometimes assimilated to be equivalent to EEG, with limited scientific added value. We clarify these misconceptions 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, spectral differentiation and minimum bias. Indeed and relatively to EEG, the accuracy of MEG source mapping is immune to the signal distortions caused by the complex layering of head tissues, with highly heterogenous conductivity profiles that cannot be measured with precision in vivo.

We explain these notions herein in details and conclude that MEG, used independently or

in combination with other brain imaging techniques, uniquely contributes 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 functional role and dynamical principles of the signal components present in the dense and intricate MEG data volumes are getting clarified and better understood, we explain how MEG plays an increasing and pivotal role towards the elucidation of the grand mechanistic principles of cognitive, systems and clinical neuroscience. To this end, we shall 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 the clinical practice. Along the way, while we put forward actual limitations, current difficulties and uncertainties associated with the technique, we also wish to clarify some disadvantageous 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 a magnetic induction (often popularly assimilated to a magnetic *field*[4]), whose strength can be measured remotely from the current source e.g., 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 the magnetic induction's and readily measurable.

Basic signal origins

In MEG, the electrochemical currents circulating within and between neurons generate the magnetic induction. Post-synaptic potentials (PSPs) are considered the main generators of these ionic currents[3,5]. There is also convincing evidence, though limited in volume, that fast, 500–1000-Hz range ripples present in MEG signals 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 conductance[8] (Fig. 1). The useful frequency band of MEG signals is within [0.5-1000] Hz, with [1-80] Hz being the most typical[9]. We discuss below the possible functional roles and interdependence across this wide spectral range of brain signals[10].

Instrumentation: innovations on the horizon

In practical terms, the magnetic signal produced by neural currents in the nano-Ampere (10^{-9}A) range is formidably weak. The extracranial magnetic inductions are indeed typically measured on a scale of femto-Teslas (10^{-15}T), about ten to hundred million times smaller than the Earth's static magnetic field. This reality imposes to resort to superiorly sensitive sensor technology. The present industry standards rely on pick-up coils coupled with super-conducting interference devices (SQUIDs)[2,3]. SQUIDs implement 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 equipment is embedded in a 70-100 L thermally insulated tank, called a *dewar*, filled with liquid helium. Superconducting temperatures minimize thermal noise and therefore optimize data quality. Consequently, subject preparation times are greatly reduced with respect to EEG as the contact-less 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. What this means concretely is that 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 participant's head position in the helmet. This represents a clear practical difference with EEG, who measures differences of scalar electrical potentials between electrodes attached to the scalp. Although the head's shape and size obvisouly vary between individuals, the standardization of electrode montages scaled to the individual anatomy and with a common nomenclature[11] has greatly contributed to streamline the dissemination and comparison of EEG results between instruments, studies and individual participants, 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 of 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 infants[12]. Creative hardware solutions have been recently proposed, using adjustable head casts to warrant consistent repositioning of the subject within and between sessions with millimeter accuracy[13].

Also contrarily to EEG, MEG measures are reference-free: magnetic induction values are not relative to a common measure. To measure absolute physical quantities is sometimes

appreciated as a strong asset for MEG. In principle though, EEG datasets can always be re-referenced with respect to their instantaneous arithmetic mean as a form of standardization[14]. Further, the dependence of MEG signal strength on head position tampers with the advantage of collecting reference-free quantities. We shall see below that source imaging obliterates the limitations attached to sensor data analysis, and asserts one specific strength of MEG with respect to EEG.

Overall, the MEG sensing technology is very 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.

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, and other high-end instruments such as MRI scanners. Practical onsite helium recycling solutions have emerged and approach 90% efficacy. They reduce weekly refill interventions and costs to that of one or two cycles per year. Still, thermal insulation affects negatively 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 to improve signal strength, and to encourage

developmental neuroscience MEG research[15].

New disruptive sensing technology is becoming mature and is about to be ready for prime time. Cryo-free HyQUID detectors with equivalent noise performance than traditional SQUIDs are now proposed in a commercially available system. Similarly, optically-pumped magnetometers[16] (OPM) based on radically different sensing physics principles also represent an alternative to SQUID-based technology. Although less sensitive, OPMs can be positioned directly onto the scalp surface and therefore pick up stronger field strengths as they are brought closer to the brain neural sources[17]. OPMs are very cost-effective, which also bodes well for easier access and therefore, greater adoption of MEG methods by more neuroscientists.

The extreme sensitivity of present and future MEG sensing technology is challenged by multiple sources of electromagnetic nuisances. Any moving metal object (e.g., car traffic, elevators, carts and hospital beds) or electrically-powered instruments generate magnetic inductions that are 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*, arranged either in a radial or tangential (planar) fashion with respect to the head surface, improve greatly signal quality but still require magnetic shielding from the environment. The best solution remains the installation of a heavy (20 tons) and 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 also used in MRI installations are possible alternatives.

Finally and remarkably, the MEG sensing technology can be used to detect magnetic resonance phenomena at ultra-low fields (in the 10 to 100 mT range). In addition to specific MR-related special advantages, there are potential benefits in resorting to such all-in-one hybrid imaging technology: combined MRI and MEG can be obtained simultaneously, thereby limiting registration errors[18]. Yet, the lower magnetization induces weaker signal strength and imposes longer MR acquisition times. It remains unclear whether this research will truly penetrate neuroscience applications eventually.

Distinct capabilities for electrophysiology and imaging

MEG as a method for electrophysiology

By featuring channels arrays around the head and sensor signals originating from brain physiological currents, MEG and EEG are sister techniques of 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 that the technology is simply redundant and not worth the extra cost[19,20]. This misconception has

been entertained by the fact that to obtain measurable markers of brain activity, early and still many current MEG studies have resorted to the signal extraction techniques of EEG, by averaging multiple trials of sensor signals, time-locked to specific stimulus or behavioral events[11]. The fact that both the timing and spatial properties of the resulting event-related fields (ERF) are only partially consistent with the extensively studied nomenclature of event-related potentials (ERP) 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 (δ, θ, α, etc.; Fig. 6a).

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 the physics of 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. 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 ho-

mogenous 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, to a certain extent, contributes to a clearer interpretation of MEG sensor topography in terms of the putative anatomical locations of its underlying brain sources. This also helps separate the contributions of brain signals from ambiguous physiological contaminants, such as ocular micro-saccades[21] and muscular artifacts[22,23], which can be confounded with high-frequency brain signals in EEG, but are more clearly identified from their distinctive sensor topography with MEG. Artifact components can be eliminated or corrected when good-practice guidelines are respected[24].

The laws of physics however, impose a different set of challenges to MEG. MEG's signal-to-noise ratio (SNR) decreases faster with source depth, i.e. the distance between neural generators and external sensors. Hence the belief that MEG cannot see deep in the brain.This shall rather be interpreted as decreased sensitivity with depth, not as a plain inability to detect activity from medial cortical or subcortical brain regions, as we review further below. MEG is also relatively less sensitive to neural current flows with a radial orientation, i.e. 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 sphere[5].

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 only and at best, limited correspondence between MEG and EEG sensor data. We also simply need to bare in mind that these modalities actually measure different, non-redundant physical quantities. Consequently, direct comparison studies between the femto Teslas of MEG and the micro Volts of EEG sensor data can prove more challenging than initially thought. The appreciation of converging or complementary evidence between the techniques can actually be best conducted by assessing their respective ability 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 and clinical significance for MEG sensor data analyses, in their ability to discriminate between experimental conditions, including with spatial-filtering[25] and decoding techniques[26], and to correlate with or predict behavior[27]. They also suggest simple and practical new disease markers[28]. We shall however re-emphasize 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 measures[29]

applied on 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 imaging[5].

Indeed, one truly distinctive advantage of MEG is arguably in producing time-resolved maps of neural currents that are considerably less prone to modeling approximations than EEG. There is strong evidence that EEG source models suffer from uncontrolled biases caused by inevitable approximations in defining the head shape[30], especially the skull bone[31]. The presence of blood vessels also affects EEG source imaging[32]. More generally, the conductivity of head tissues remains non-measurable practically 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 play a similar negative role[37].

Ground-truth direct-comparison studies of MEG and EEG source localization, using electrical sources implanted in realistic skull phantoms[38,39] confirmed 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 a centimeter, under the same experimental circumstances. Multimodal comparison studies taking fMRI as reference tend to show lesser differences[40], 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 proper 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 modeling[45] and increasing experimental evidence that with optimized paradigm designs and signal extraction techniques, brain regions as deep as the insula[46], thalamus[47], hippocampus[48], 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 (*ra-*

dial current flow). We shall 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 ½ mm can be resolved, if the angle between their respective current flow is at least 45°, a range compatible with typical cortical gyrification[54]. These results confirm simulation studies that demonstrate the sensitivity of MEG signals to minute changes between cortical layers[55] and at the sub-millimeter scale of cortical columns[56].

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, i.e. when no participant is present under the sensor array. This is another distinctive 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 sound reasons to back up the initiation and development of an MEG program. The comparison with MRI is relatively unfair though: 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

primarily required to cover the platform's operating costs. The clinical recommendation and recognition for MEG, although growing[57], have not been sufficient yet to increase dramatically the number of clinical MEG units to a level that would facilitate access to the broadest research community (see Box). 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 unique assets of the technique. Financially, a clear plan needs to be laid out upfront so that operating costs can be assumed by a combination of fees for access and institutional funds.

Strategically, MEG imaging represents a strong and unique scientific asset in the neuroscience portfolio of a resarch 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 landmark of MEG compared to functional MRI (fMRI), positron emission tomography (PET), or optical techniques[58]. We have seen that multiple factors expose EEG imaging to uncontrolled sources of localization bias. Other electrophysiological methods, such as intracranial stereotactic EEG (SEEG) and electrocorticographic implantations (ECoG) have obvious limitations in terms of invasiveness and coverage of the cerebrum 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 adjustable anywhere between upright to supine. Ferromagnetic elements used in dental works and implants can cause complex artifacts[59] but, contrarily to 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 and 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 presently a matter of active research. Still, this 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 (e.g., 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 negatively affected MEG's development is that, akin to 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 principles[5]. Nevertheless, this has originally given room to too many methods presenting non-verifiable evidence of claims to excellence, aggravated by a lack of sharing with the community following journal publication. This did not contribute to building confidence amongst potentially new users of MEG.

Fortunately, this phase has recessed: the methods have grown mature and pragmatic, with now high-quality commercial and academic software packages that have tremendously augmented users access to training, productivity and their deeper understanding

of methods and their limitations[71].

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 learning (ML)[72]. These methods emerged only recently in the MEG arena, although already demonstrating very significant potential in augmenting the scientist's toolkit. Relatively simple implementation of ML decoding techniques for multidimensional signal classification showed impressive applications in identifying early components of visual object categorization[73], in tracking the temporal organization of spatial patterns of brain activity[74], or that of a mnemonic template in the context of perceptual decisions[75]. The fact that these methods are, for now, relatively independent of signal models make them an attractive complement to MEG researchers for rapid evaluation of their data e.g., to assess the presence and spatio-temporal topography of effects between experimental conditions or cohorts. Such approaches were recently and beautifully extended to joint multimodal processing of MEG and fMRI data[76]: a form of ML-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 analyzes 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 task[77]. This highly innovative, multimodal approach promises to take the best advantage of neuromimetic models to refine, and maybe discover, new mechanistic principles of brain functions, potentially generalizable to other functional systems and patient populations.

The present renaissance of artificial intelligence methods is also boosted by access to high-availability computing and large data storage resources. More generally, resorting to big-data tools and methods is becoming increasingly strategical in neuroscience research involving brain imaging: analysis pipelines have grown in sophistication tremendously, 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 towards expanding the curated value and lifetime of data collections in public research: the increasing number of open data-sharing initiatives emphasizes and incarnates stronger educational, economical, ethical and societal values in science[78]. 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 field[79].

Until recently, MEG was lagging behind the MRI community 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 >100MB per minute). Fortunately, these bottlenecks are gradually, and at least partially, being overcome by the increasing availability and versatility of software readers of 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 at a large scale, from a subsample of its cohort, along with extensive multimodal MRI, behavioral and genetic data[83]. With about 150 data volumes available, the Open MEG Archives (OMEGA) is the second largest repository of resting-state MEG data, and contains the T1-weighted MRI volumes of participants[84] (Fig. 4a). The recent CAM-CAN initiative features data from about 650 healthy participants within the 18-88 age range, combined with multimodal MRI and extensive cognitive testing[85].

We shall rejoice that more of these initiatives are presently 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. Importantly, 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 that 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 actual, very active research topics in MEG. They participate to the broader objective of comprehending and exploiting how brain *activation*, in terms of regional and large-scale neural

dynamics, is expressed in electrophysiology[88]. Yet, many potential users of MEG entertain the perception 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 screen their intrinsic limitations[89,90] and the share of fragility in their methodological sophistication[91].

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 presently, 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 disruptive 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 use the most of the modality's imaging capacity. Electrophysiology is not the only domain of biology presently going through 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 imaging[94]. For instance, the explosion of interest in fMRI resting-state and task-based connectomics prompts for the identification of equivalent signaling mechanisms in neural electrophysiology[95,96]. Counterintuitively, there is little correspondence between MEG and fMRI resting-state networks (RSNs), when MEG source signals are extracted in the frequency bands that showed the strongest correlation between electrophysiology and fMRI, namely γ[97,98], but also slower oscillatory ranges such as δ and θ[99].

In fact, MEG time series in the [15-35]-Hz β range, when processed with fMRI-like data-driven resting-state pipelines, were first to reveal RSNs compatible with fMRI's topography[100]. Studies had shown indeed that β-band LFP signals were weakly negatively correlated, with blood-oxygen dependent (BOLD) traces[99]. γ and the slower BOLD-correlated frequency bands (δ through α) were later shown to also form an electrophysiological scaffold for RSNs[101], when combined using cross-frequency coupling measures translated from animal and intracranial human electrophysiology[102] (Fig. 5 and Fig. 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 electrophysiological signals. Our 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 (δ through α) mark the phase of relative excitability of cell assemblies[10,103]. γ bursts tend to occur in volleys nested at certain phases of these slower rhythms, a well-studied phenomenon of coupling across frequencies captured by e.g., phase-amplitude coupling (PAC)[104,105] measures (Fig. 6b). There is increasing evidence[106] that γ cycles could represent timed opportunities for neural representations of e.g., incoming stimuli to be registered by cell assemblies and propagated further downstream in a bottom-up fashion. β oscillations so far have not been found to pace γ bursts, and do not seem to be driven directly by co-localized slower rhythms in the human resting-state[101]. According to computational models and nascent experimental data[107], they are rather thought to signal top-down modulations from higher-order, executive regions in brain networks (Fig. 6c & 6d).

A global roadmap for MEG to build on these recent and still relatively sparse advances would ideally consist in:

1. further clarifying the physiological principles structuring the local-to-global dynamics of neural oscillations,

2. defining measures of regional activation and inter-areal communication in brain systems that are driven by these biological principles,
3. using these measures to survey the dynamical repertoire of the resting brain, which remains largely uncharted,
4. understanding how sensory inputs interact with this repertoire, enabling functional integration, and eventually behaviour.

Approaching future MEG research with this plan would open further 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 interventions.

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 devel-

oped more recently – fMRI some 20 years after MEG – their respective volume of research production approaches 3 (for PET) to 8 (for fMRI) times that of MEG's. The historically oldest technique of all, EEG, remains the leading integrative neuroscience tool, with fMRI as 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 an updated range of applications such as brain-computer interfaces and biofeedback explorations[108]. 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 a third in MEG. We also note that since the turn of the 2000's, the research output of all techniques has been slowly declining relatively to fMRI's (Fig. 7b).

MEG presently contributes 5% of the neuroscience research resorting to the techniques surveyed, although with increasing impact (Fig. 7c). As of 2015, about 10,400 articles cited published MEG research, with an average of 8 citations per MEG article. Further, the geographic distribution of the community shows healthy diversity (Fig. 7d) and growing stamina: at the turn of the 1990's 52 organizations had researchers publishing with MEG. This number grew tremendously around the year 2000 with 433 contributing institutions, and is now reaching 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 to study the large-scale dynamics of brain activity. This truly represents he strongest scientific asset of the technique.

More thematically, MEG users have been investigating the principal topics of systems and behavioural 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 details: methods[109], the integrative neuroscience of language[110], consciousness[111,112], and translational aspects to clinical neuroscience, including epilepsy[113,114], autistic spectrum disorders[115], movement disorders[116], etc.

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 to detect brain activity that is temporally coherent with behavioral or peripheral measures, such as movement parameters. Such experimental paradigms take great advantage of the temporal resolution of the technique and enhance SNR by "tagging" neural responses with stimulus-imposed or

-induced frequencies of interest. A body of compelling work has grown in audition[117], including prosodic features of natural speech[118,119] and music[120] perception, vision[121,122], attention[123,124] and motor system[125] research using such methodology.

The reader may refer to our commented 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 quite strong, MEG could attract a larger and broader community of scientists. Mature 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. Akin to MRI and PET, initiatives to share large MEG data repositories openly 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 presently better manage the expectations of practitioners to avoid misconceptions about MEG as a routine clinical modality. Further and looking

forward, they could deliver stronger efforts towards the integration of research tools in certified analytic pipelines. This would with no doubt increase the yield of MEG in the epilepsy clinic, and see the modality penetrate more subspecialities of neurology and neuropsychiatry.

We shall also emphasize that MEG is a technique that readily bridges with other measures and methods such as electrophysiology (intracranial LFP and scalp EEG), blood flow and oxygen metabolism (NIRS), brain stimulation (tDCS, tACS), which can all be performed concurrently with MEG. This offers researchers tremendous opportunities to cross-validate findings between techniques, between human and animal bodies of work, and to build on the super addition 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 to verify 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].

Box: Towards 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 (e.g., 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 equivalently 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 the standard procedure actually led to long-term seizure-freedom. Ideally, multi-centre 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 unique insight provided by MEG.

Other practical limitations include the very duration of present MEG tests, typically hour-long recordings, essentially to minimize cost and maximize patient comfort. This is often very short to capture canonical epileptiform events such as interictal spikes and even more rarely so, seizures, which are still considered of 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 paroxystic epileptiform events.

Considering the premise that a patient brain is *constantly* the siege of 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 autistic spectrum disorder indicates that simple MEG measures, easily implementable in the clinic, of delayed early auditory responses are indicative of the syndrome's severity[28,115], are concordant with MR tractography, and predisposing gene dosage[134].

Altered expressions of background brain rhythms represent 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 greatest variety of insults and disorders that affect the human brain[135–137]. As we discuss and illustrate elsewhere in this review, 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 variants[84] (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 the clinical recognition, including reimbursement procedures of fMRI tests is still vastly lacking as well. In principle, clinical demand shall boost the number of installations, and improve access to re-

searchers, eventually and virtuously closing the 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 to 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 of MEG analysis pipelines that 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 to develop 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 make up for commercial lacunas.

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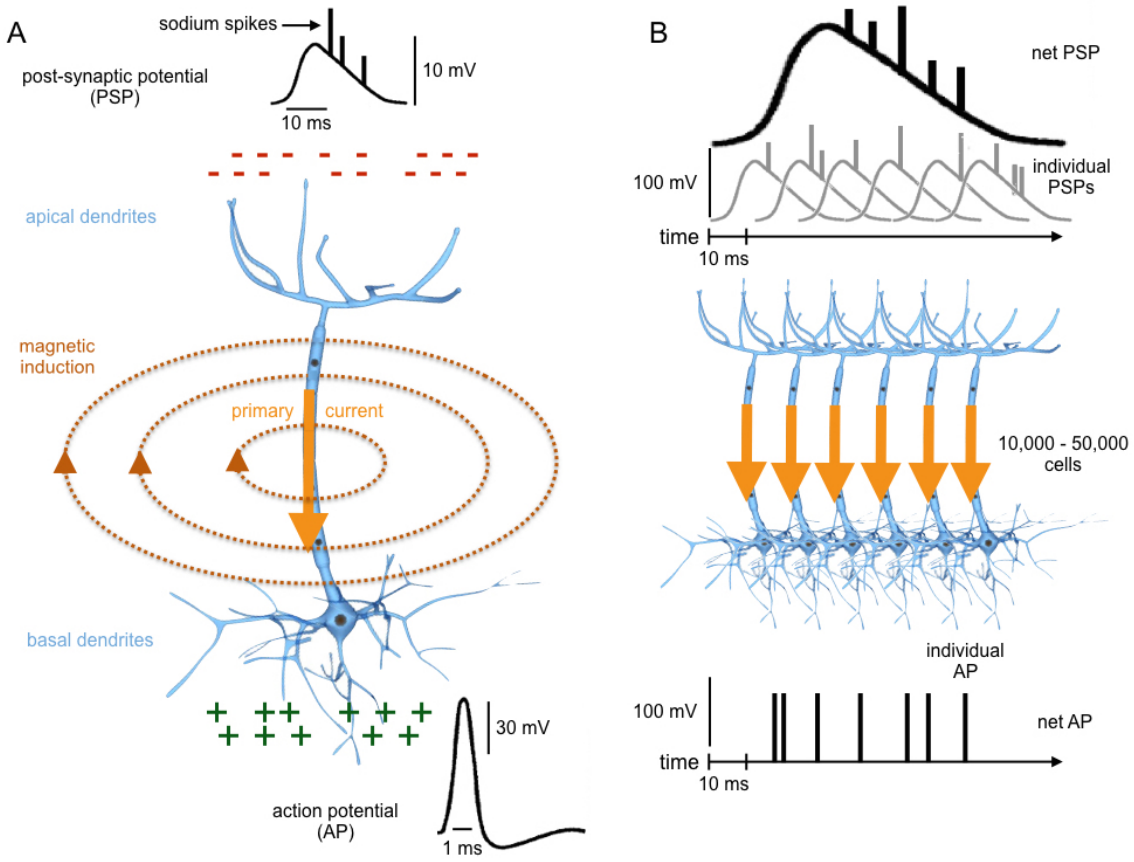

Figure 1: Cellular origins of MEG signals – (a) For the sake of simplicity, let us consider the cortical pyramidal neuron as the epitome of elementary cellular generator of MEG signals. All physiological currents from all cell types generate a magnetic induction; the elongated morphology of the pyramidal neuron makes the net primary current circulation relatively constrained along the cell, which is a factor of signal strength in comparison to 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 orange are perpendicular to the primary current flow and can be picked up outside the head. The source origins are twofold: 1) the post-synaptic potentials (PSP), including fast, large-amplitude sodium spikes (see text) and 2) 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, due 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 MEG[8]. It is possible, in principle, that fast PSP spiking activity, and possible shadows of APs, be detectable in MEG.

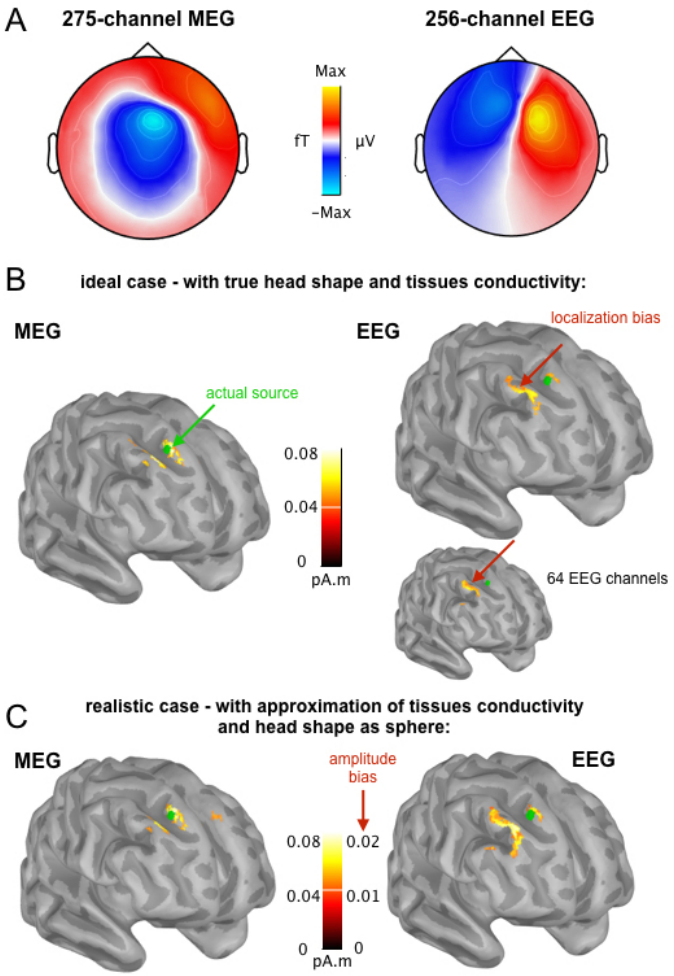

Figure 2: An example comparing MEG and EEG – Synthetic data was generated by impressing a simulated uniform current density within a 1-cm^2 patch of cortical surface (shown in green panels b and c). The cortical surface and the other tissue compartments (scalp, skull bone, cerebrospinal fluid) were that of the ICBM152 template, available in the Brainstorm open-source application[138]. The corresponding, ground-truth MEG data was 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 method[139] (BEM) 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 (Brain-Product montage). (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, relatively to the EEG's. This latter has considerably lower-amplitude than the actual current strength (note distinct color scales for MEG and EEG).

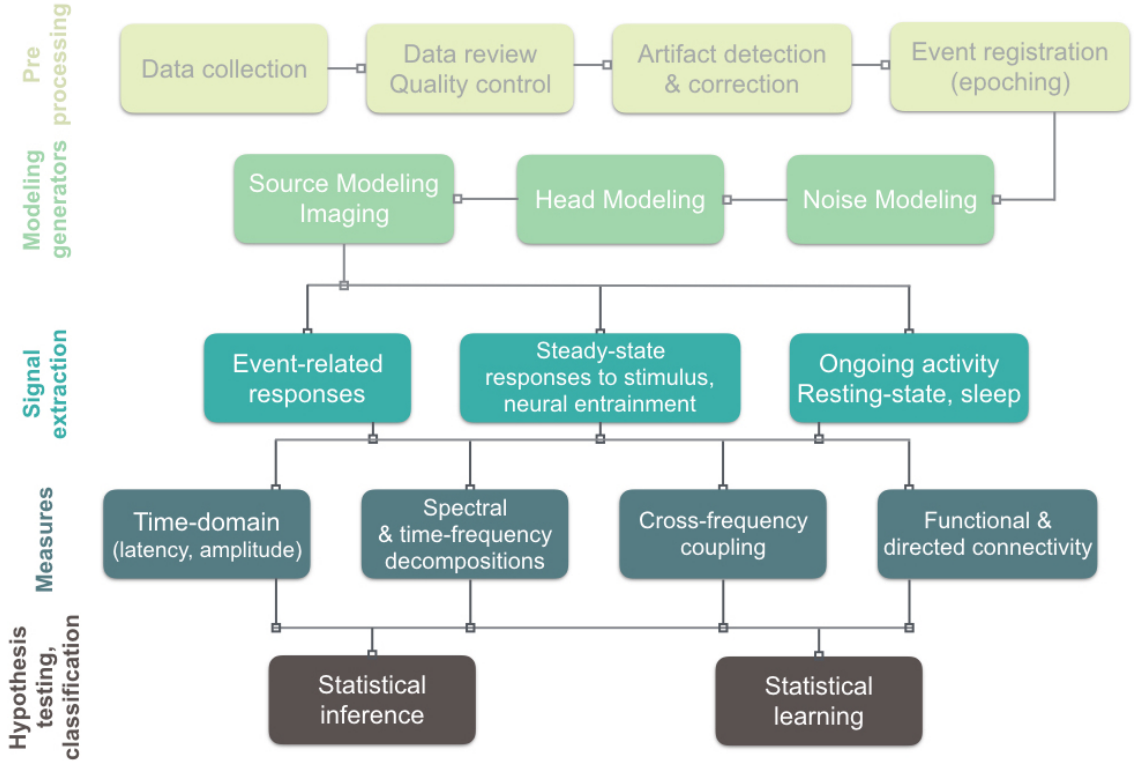

Figure 3: Major steps imposed and possibilities offered by MEG analytics – Akin to other brain imaging modalities, MEG requires that several important procedures are followed in data analytics. 1) The preprocessing steps are crucial to assure that data quality is optimal at the time of collection, and 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 (e.g., template vs. individual head shape, noise definition, image reconstruction parameters). 3) Signal extraction usually depends on the design of the experimental paradigm and is very versatile in MEG. 4) The set of possible measures is immense, because of the multidimensional components of the data (space, time, frequency). 5) The final statistical steps can either include inference and hypothesis testing, or statistical learning techniques for signal classification, and other derivatives.

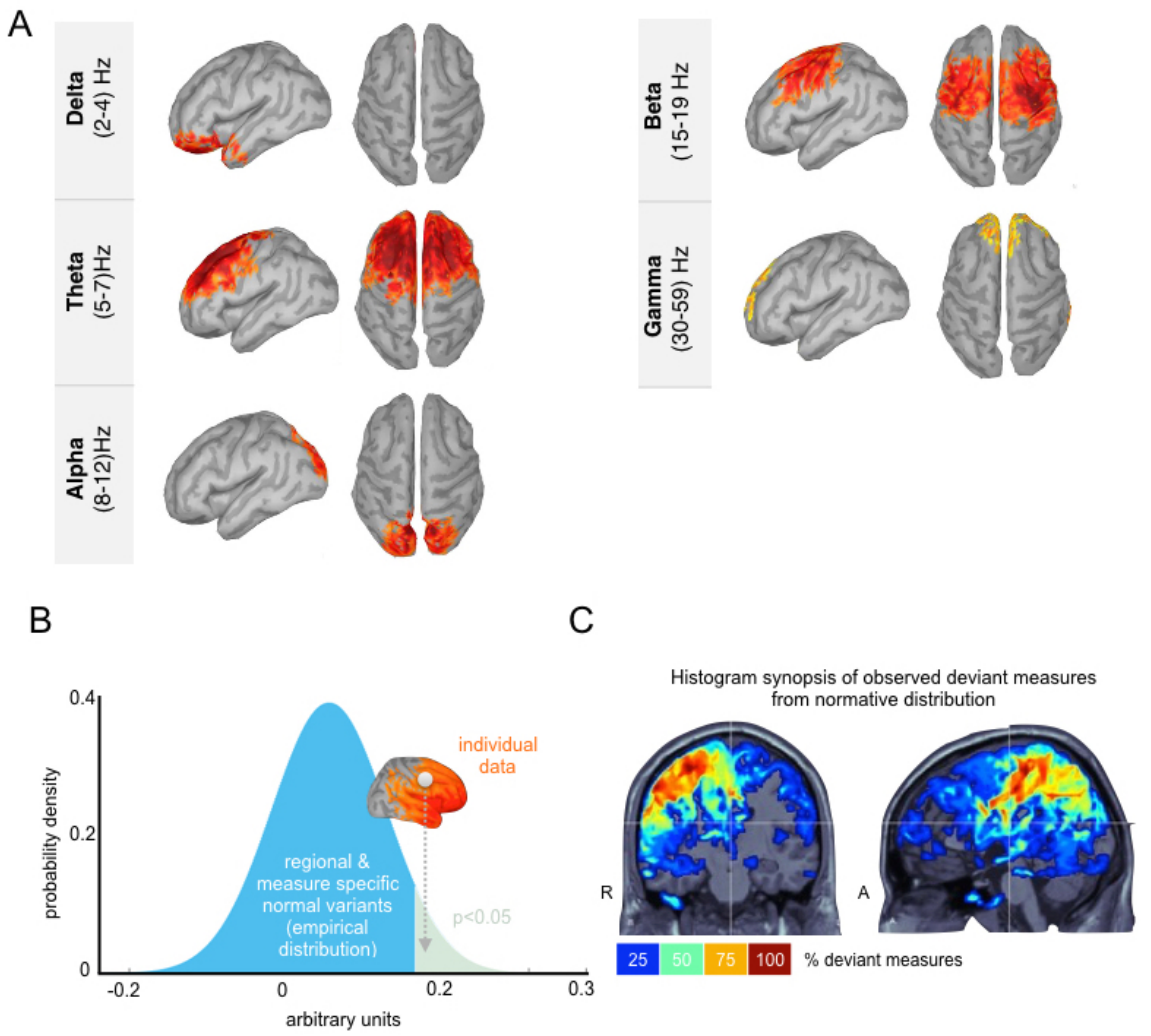

Figure 4: Towards big-data MEG? – (a) Illustrative example of the outcome of an MEG-imaging database (data from OMEGA[84]): 96 healthy participants were scanned in the resting-state during 15 minutes with their eyes open. MEG imaging of their cortical activity was performed using the same method as for Fig. 2. The average distribution of the magnitude of ongoing brain rhythms (from δ to γ) found in the cohort are registered to and represented on the Colin27 brain template cortical surface. (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 e.g., 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 an epileptic patient.

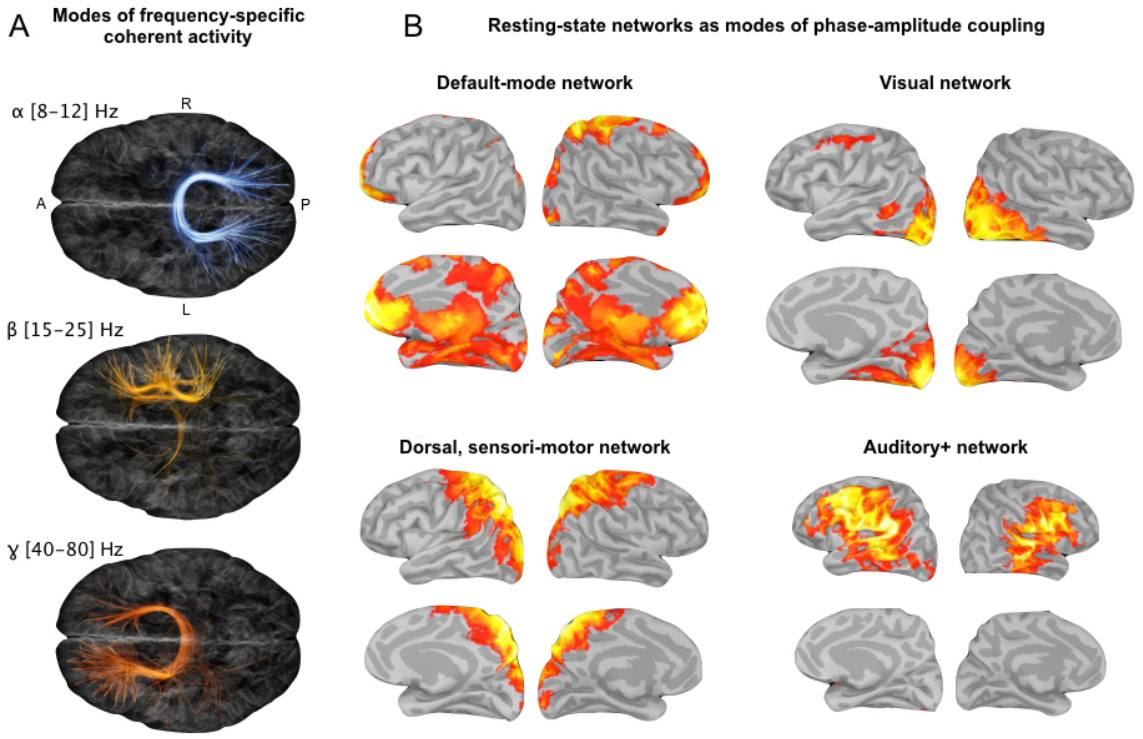

Figure 5: Frequency-dependent expressions of inter-regional connectivity – a) Illustration of frequency-dependent functional connectivity measures. MEG source imaging of 5-min resting-state (eyes open) data in typical α, β and γ frequency bands was obtained using the same methodology as in Fig. 4 (not shown here; data sample from OMEGA[84]). Coherence in all frequency bands of interest between every pair of cortical source locations was extracted and thresholded above the 90^{th} percentile. Virtual white-matter tracing yields convenient and anatomically compatible representations – here only for illustration purposes – of such complex, multidimensional connectivity data (Sebastien Dery: Baillet Lab). b) RSNs 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 (Florin & Baillet, 2015)[101] for details on the approach.

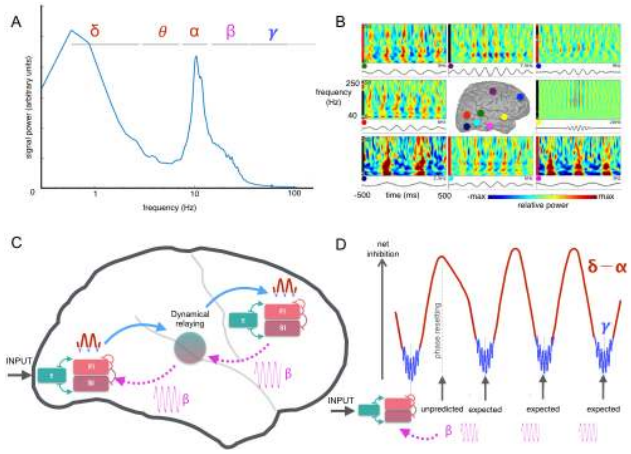

Figure 6: A possible mechanistic framework of polyrhythmic brain activity – (a) A typical power density spectrum (80-s resting-state data from a 55-year-old healthy adult [eyes open]; Welch's method, 2-s windowing) shows the distribution of power averaged across all 275 channels of a CTF MEG system. The nomenclature of typical brain rhythms is reported – note the prominent peak in α power in the [8–12]-Hz range. (b) These rhythms are coupled and interdependent, which can be revealed by measures of cross-frequency interactions, such as phase-amplitude coupling (PAC). Here, PAC analysis of MEG traces obtained in the resting-state (10 minutes) 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 insert 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 coupled (PAC) with fast γ activity in the [80-150]-Hz range. ii) the average time-frequency decomposition of the power of the MEG source signal indicates how it is modulated with the phase of the underlying oscillation [see (Florin & Baillet, 2015) for details]. The colored dots on the cortex indicate the locations where the sample signals were extracted. (c) The slower δ to α rhythms mark the net excitability of cell assemblies consisting of slow and fast inhibitory (SI and FI) and excitatory (E) cells. Possible theoretical frameworks on the organization of brain rhythms, such as the model of *synchronized gating*[101] and others[140,141] consider that brain network formation and communication is enabled by the phase alignment of these cycles between regions. This can be facilitated by the mechanism of *dynamical relaying*[142] via the thalamus or cortical hub regions. While γ bursts could contribute to bottom-up signalling (blue arrows), β bursts could manifest top-down modulations of upstream regions (magenta arrows), and thereby contribute to the implementation of contextual predictive inference of input signals (INPUT). (d) Such dynamical scaffold, among others possible, helps formalize 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 β oscillations. This process repeats and paces the net inhibition of the local cell assembly according to the next anticipated stimulus occurrences. Such 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 further downstream[106].

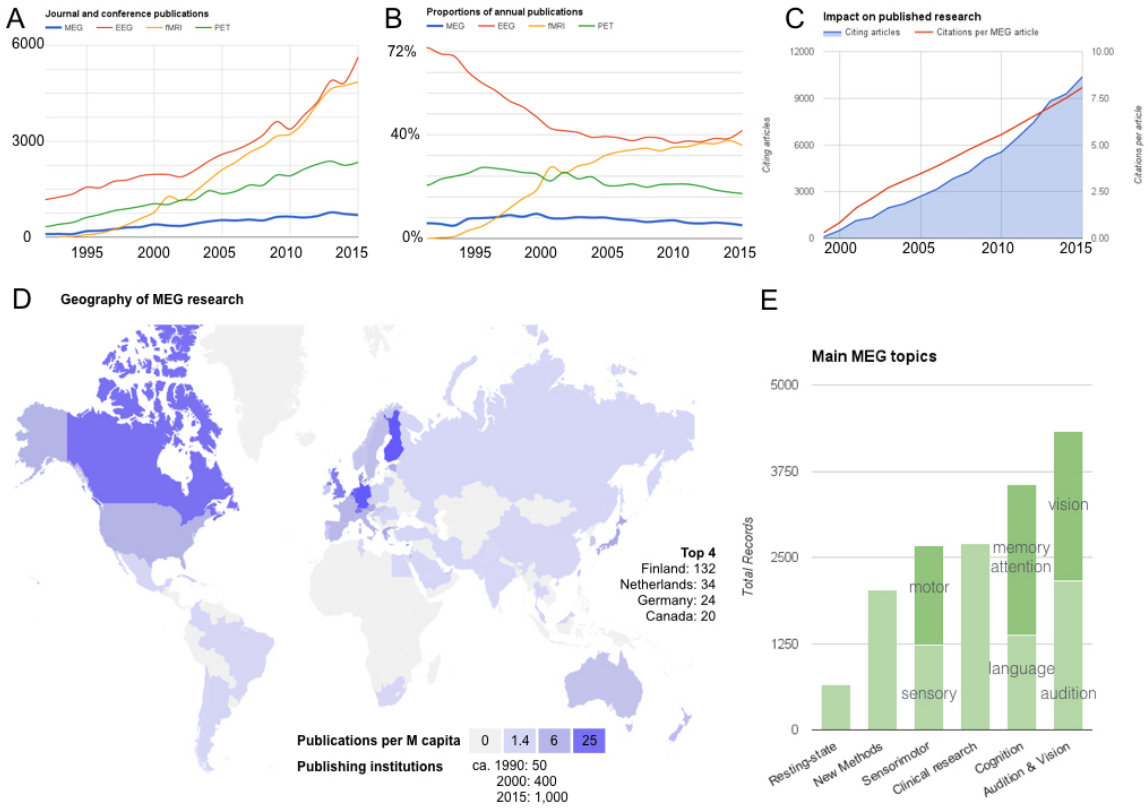

Figure 7: Snapshots of MEG science – (a) Annual volume and (b) proportion of published articles and conference proceedings concerning the major techniques for measuring brain actively non-invasively. (c) Impact of MEG on published research, measured in terms of citing articles and citations per MEG article, on an annual basis. (d) Geographic distribution of published MEG articles per million people. Inserts indicate the Top-4 countries with highest rate of publication per capita, and the number of institutions whose scientists have co-authored a MEG-related publication over a period of 5 years, circa the years indicated. (e) Main topics covered by MEG research so far: data is from the over 10,000 MEG-related indexed publications (Source of bibliographic data: Web of Knowledge).