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**Magnetoencephalography: From SQUIDs to neuroscience: Neuroimage 20th Anniversary Special Edition**

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Review

Magnetoencephalography: From SQUIDs to neuroscience
Neuroimage 20th Anniversary Special Edition

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Abstract

Magnetoencephalography (MEG), with its direct view to the cortex through the magnetically transparent skull, has developed from its conception in physics laboratories to a powerful tool of basic and clinical neuroscience. MEG provides millisecond time resolution and allows real-time tracking of brain activation sequences during sensory processing, motor planning and action, cognition, language perception and production, social interaction, and various brain disorders. Current-day neuromagnetometers house hundreds of SQUIDs, superconducting quantum interference devices, to pick up signals generated by concerted action of cortical neurons. Complementary MEG measures of neuronal involvement include evoked responses, modulation of cortical rhythms, properties of the on-going neural activity, and interareal connectivity. Future MEG breakthroughs in understanding brain dynamics are expected through advanced signal analysis and combined use of MEG with hemodynamic imaging (fMRI). Methodological development progresses most efficiently when linked with insightful neuroscientific questions.

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Introduction

History of magnetoencephalography (MEG), and of electrophysiology in general, is tightly coupled to the progress of new instrumentation and signal analysis techniques. For example, sensitive mirror galvanometers were originally developed for detection and amplification of signals from the transatlantic telecommunication cable but allowed Richard Caton, already in 1875, to perform recordings of spontaneous brain activity and evoked responses in rabbits and monkeys (Caton, 1875).

At the time of the first human electroencephalogram, EEG (Berger, 1929), many important features of the brain’s electrical signals—such as different frequency bands, effects of sleep, anesthesia and death, arousal, epileptic discharges, and evoked responses to visual, tactile and auditory stimuli—had already been described (Brazier, 1961).

For decades, the clinical EEG work (Schomer and Lopes da Silva, 1962) and the subsequent fabrication of SQUIDs, Superconducting quantum interference devices (SQUIDs), allowed detection of the brain’s magnetic fields without an electric reference (Cohen, 1968). Over the years, the measurement devices evolved from single-channel instruments to sensor arrays housing hundreds of SQUID sensors; the first helmet-type whole-scalp MEG system with 122 sensors became functional in our laboratory in 1992 (Ahonen et al., 1993); in 1998, a system with 306 channels was introduced. With a single-channel device, coverage of the full field pattern—needed to identify, e.g., the cortical generators of responses to auditory or tactile stimuli—could take days, whereas with a modern-day whole-scalp system the recording lasts only a few minutes.

Compared with functional magnetic resonance imaging (fMRI), MEG has progressed slowly during its first four decades, as measured by the number of laboratories (in 2011, about 160 worldwide) that utilize whole-scalp MEG for exploration of normal and abnormal brain functions. The rapid spread of fMRI to thousands of laboratories over the course of two decades benefited from the existing clinical MRI scanners that were easily modified for fMRI use. Compared with the more readily automated analysis methods of fMRI, MEG requires more user intervention for reliable data analysis.

Space limitations prevent us from citing all relevant literature and, thus, the reader is encouraged to consult recent review articles and textbooks (e.g. Aine, 2010; Baillet et al., 2001; Del Gratta et al., 1999; Hämäläinen and Hari, 2002; Hansen et al., 2010; Hari, 2011; Hari et al., 2010; Salmelin, 2007).

MEG in brief

Neuronal generation of MEG signals

Electric currents are accompanied by an electromagnetic field. The main generators of the MEG signals—and of EEG as well—are synaptic and postsynaptic (intracellular) currents in the pyramidal neurons of the cerebral cortex (Hari, 1990). In the (nearly) spherical volume conductor formed by the head, the orientation of the magnetic field pattern reflects the direction of the intracellular current.

In cortical pyramidal neurons, the net neural current flows normally to the local cortical surface. MEG is most sensitive to cortical currents tangential to the skull, in the walls of cortical fissures, whereas EEG more readily picks up signals also from the depth of the brain and from the convoluted cortex (Hämäläinen et al., 1993; Hari, 1990).

Notably, as the relevant aspect in MEG is its sensitivity to the tangential component of the current, tilted currents are also detected, especially when they are located close to the surface (Hillebrand and Barnes, 2002). Because of their different sensitivities to source orientations and locations, MEG and EEG complement each other.

MEG instrumentation

Modern neuromagnetometers contain helmet-shaped arrays of more than 300 SQUID sensors that, for operation, have to be immersed in liquid helium at the temperature of 4 K (−269 °C). High-Tc SQUIDs have been tested for MEG but they suffer from high thermal noise that still limits their usability in brain research. New magnetoresisitive sensors can pick up magnetocardiographic signals (Pannetier-Lecoeur et al., 2011) but do not, with their present-day sensitivity, allow MEG recordings. Atomic magnetometers (Kominis et al., 2003) have been used to detect auditory-evoked brain responses (Xia et al., 2006). The recent introduction of SQUID-based low-field (microtesla) MRI has created a new means of integrating MEG and MRI information within the same recording, thus raising expectations for improved spatiotemporal accuracy of the measured signals (Zotev et al., 2008).

Even visual inspection of the MEG sensor-level data may provide plausible estimates of the source configuration. It is important to note, however, that different flux transformers have different sensitivity profiles. A simple loop, a magnetometer, is most sensitive to source currents a few centimeters outside of the loop. An axial gradiometer, with two oppositely wound loops along the same vertical axis, has a sensitivity pattern similar to that of a magnetometer but is less sensitive to ambient magnetic interference. A highly useful flux transformer is a “near-sighted” planar gradiometer with two oppositely-wound in-plane loops. It yields the maximum signal directly above the source current, thus markedly facilitating sensor-based estimation of source configuration as the first step of source analysis.

As a single local source can produce correlated signals on several sensors, even 10 cm apart—depending on the flux transformer geometry—caution must be exercised in making inferences about the source locations on the basis of the sensor-level local maxima and, in particular, in lending functional interpretations to correlations between sensor-level signals.

Analysis and interpretation of MEG signals

MEG signals are most efficiently interpreted by means of source models that can yield accurate information on the timing and direction of current flow; the direction reflects the underlying sulcal structure and can help to differentiate between spatially and temporally close but functionally separable source areas.
The simplest and most transparent, yet powerful, approach is to model a local population of active neurons with an equivalent current dipole (ECD). Theoretically, the current dipole is an infinitesimal concentration of directed current flow. The strength of an ECD (dipole moment = current multiplied by the effective distance of the current flow) typically varies from 2 to 100 nAm. The dipole parameters (location, direction, strength as a function of time) can be solved from the MEG pattern and related to individual anatomy obtained from structural magnetic resonance images (MRIs). Multiple ECDs can be identified separately and brought together in a multidipole model where the activation time courses may be estimated by allowing each ECD to vary in strength to best account for the signals detected by all MEG sensors (for a recent review, see Salmelin, 2010).

An alternative approach is to limit the solution space. One may place a large number of elementary sources (tiny current dipoles) throughout the cortex and estimate their strengths as a function of time. Such a distributed estimate has a unique solution if it, in addition to explaining the recorded MEG signals, involves minimization of the total current in the sense of, e.g., L2 or L1 norm (Hämäläinen and Ilmoniemi, 1994; Uutela et al., 1999), resulting in minimum-norm or minimum-current estimates (MNE/MCE), respectively. Because the minimization favors superficial currents closest to the sensors, depth weighting is often needed. The MNE/MCE spatial resolution may be increased by constraining the currents to the individual cortical anatomy, obtained from MRIs (Dale et al., 2000; Lin et al., 2006).

Yet another popular approach is beamforming where the brain volume is scanned by a sequential application of spatial filters that are optimized to pass activity from a specific brain area with maximum gain, while suppressing activity from other areas. Beamformers can be implemented in either time or frequency domain (Gross et al., 2001; Robinson and Vrba, 1997). However, none of these source analyses can circumvent the inherent ambiguity between neuronal currents and MEG patterns: the ‘inverse problem’ takes a different form in different analysis methods. Even a pointlike current appears spatially distributed when analyzed with a distributed model (e.g., MCE), whereas ECD analysis of a spatially distributed source current necessarily yields a focal current dipole (Hämäläinen and Hari, 2002). The ECD analysis makes the minimum number of assumptions (only that the source itself can be represented by a current dipole) but especially the multi-dipole analysis requires some expertise, e.g., in selecting sensors for source identification and rejecting implausible solutions. The more automatic minimum-norm and beamforming approaches can provide descriptive source-level values for any cortical point. However, the patterns can be spatially blurred or display ‘ghost’ sources that are difficult to discern from the real sources.

Sometimes the goal may be to extract the time course of an active area identified, e.g., by fMRI. However, since even a focal current produces a spatially widely spread magnetic field, the MEG time course estimated for a pre-specified volume may, in fact, reflect activity of a totally different source area. A full MEG-based analysis is necessary to verify the involvement of the target region.

Source analysis may help to identify subject-related magnetic disturbances (e.g., cardiac artifacts, magnetic material moving with body movements, eye movements and blinks, muscular activity, tongue and jaw movements) even when they are not obvious in the sensor-level signals. For example, source locations outside of the brain (e.g., close to the eye balls or the tongue) strongly speak for an artifactual origin. Note that when distributed source analysis constrains the solutions to the brain, artifacts may appear as false activations, especially in brain areas where the sensor array coverage (and, thus, the signal-to-noise ratio) is poor, such as the temporal poles and the ventromedial frontal cortex.

### Progress of MEG across its first four decades

The MEG method has now been around for four decades, with a marked speed-up of the progress during the last two decades. We will briefly discuss the advancement of MEG from the 1970s to 2010s, seeking to highlight the specific nature of MEG, complementary to that of EEG or fMRI, in understanding human brain function.

Over the years, the focus has moved from technical issues and examination of isolated sensory areas to a more integrative description of human brain function, including activation sequences, more sophisticated data analysis, and complementary use of other imaging modalities, especially fMRI.

**MEG in the 1970s—first recordings**

The 1970s were an era of MEG engineering, with the main interest to demonstrate the feasibility of the new method (Cohen, 1972). Recordings of evoked responses to visual (Brenner et al., 1975), tactile (Teyler et al., 1975) and auditory (Hari et al., 1979; Reite et al., 1978) stimuli demonstrated a likely origin of the signals in the sensory-specific cortices. However, with the single-channel devices available at that time the recordings were extremely laborious.

**MEG in the 1980s—focus on sensory processing**

In the 1980s, MEG was extensively used to pinpoint the cortical generators of various evoked and event-related potentials. The MEG source analyses often preceded those with EEG by several years; however, reflecting the imbalance in the number of EEG vs. MEG

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**Fig. 1.** Left: Averaged magnetic fields (N = 330) from parietal and frontal locations to 1-kHz 800-ms tones repeated once every 4 s and measured with a first-order axial gradiometer. Middle: Amplitude distribution of the measured transient (N100m) response in one subject; the sizes of the circles are proportional to the signal strength. Right: A source model of the signal pattern, with the ECD in the auditory cortex within the Sylvian fissure.

Modified from Hari et al. (1980) and Altoniemi et al. (1981).
MEG in the 1990s—brain rhythms and cognitive processing

The decade started with a heated debate about the merits of MEG vs. EEG (Crease, 1991) that was concluded with a consensus statement written by 15 clinicians and scientists (Anogianakis et al., 1992) to emphasize the complementary nature of the two methods.

In the 1990s, the introduction of whole-scalp systems finally transformed MEG into a genuine brain-mapping tool, with focus on activation sequences, supported by increasingly accurate visualization on spatially aligned anatomical MR images. The measurement times were markedly shortened and the quality of mapping was drastically improved as data were acquired simultaneously from the whole cortex. As a major step forward, whole-scalp MEG systems finally opened the path for studies on high-level cognition, such as language processing (Salmelin et al., 1994) (to be discussed in more detail in the section on the 2000s), and characterization of rhythmic activity throughout the cortex (Hari and Salmelin, 1997).

Sensory and motor systems and brain plasticity

Whole-scalp MEG systems made it possible to address, e.g., the relationship of ipsi- and contralateral auditory-cortex responses in both hemispheres (Mäkelä et al., 1993; Pantev et al., 1998b), and the influence of gender and native language on the interhemispheric balance (Salmelin et al., 1999). Auditory responses were applied to demonstrate, e.g., that auditory hallucinations involve the auditory cortex (Tiihonen et al., 1992), to study cortical correlates of directional hearing (McEvoy et al., 1993), and to show that visual input has access to the auditory cortex during McGurk illusion (Sams et al., 1991).

The spatiotemporal specificity of MEG was also successfully applied to demonstration of cortical plasticity, such as increased auditory cortical representations in musicians (Pantev et al., 1998a), modification of auditory pathways after cochlear implantation (Pelizzone et al., 1991) and unilateral congenital hearing loss (Vasama et al., 1994), reaction of the auditory cortex to vibration applied to palms of a deaf person (Levânen et al., 1998), and increased somatosensory finger representation in string players (Elbert et al., 1995). Cortical reorganization of somatosensory representations was linked with phantom-limb pain (Flor et al., 1995).

Brain rhythms

Study of oscillatory brain activity experienced a true renaissance in the 1990s with MEG whole-scalp spatiotemporal mapping, focusing on frequencies from 5 to 40 Hz (for a review, see Hari and Salmelin, 1997). The rolandic 20–Hz rhythm (Tiihonen et al., 1989), similar to intracranial motor-cortex signals (Jasper and Penfield, 1949), was modulated according to the moving body part in a somatotopical manner (Salmelin et al., 1995). This 20–Hz component of the rolandic mu rhythm provided a tool to demonstrate, e.g., motor-cortex involvement in motor imagery (Schnitzler et al., 1997) and action observation (Hari et al., 1998), and differential emphasis of mouth vs. hand area in speech vs. nonspeech production (Salmelin & Sams 2011). The neuronal generation mechanisms of this rhythm are under keen scrutiny (Jones et al., 2009).

Analysis of coherence between the surface electromyogram and brain signals opened a new line of research (for a review, see Salenius and Hari, 2003). This corticamuscular coherence manifested as salient coherence peaks at around 20 Hz (Conway et al., 1995) or 40 Hz (Salenius et al., 1996), with the cortex leading the muscle (Salenius et al., 1997). The coherence was abnormal in unmedicated Parkinsonian patients (Salenius et al., 2002). Subsequent choices of the peripheral reference signals include a continuous record of finger location (Gross et al., 2002), hand speed (Jerbi et al., 2007), and accelerometer measures of hand movement (Bourguignon et al., 2011).

Activity in the gamma range (> 30 Hz) has received much interest ever since stimulus-dependent interareal coherence at ~40 Hz was observed in cat visual cortex (Gray et al., 1989). Gamma activity—especially > 60 Hz—has been promoted as an efficient measure of neural activation (Jensen et al., 2007; Ulhaisa et al., 2011). Intracranial recordings show sustained, task-relevant gamma activity both locally (Tallon-Baudry et al., 2001) and widely across the cortex (Jerbi et al., 2009). However, gamma appears to be markedly harder to pick up with MEG (Dalal et al., 2009), with the exception of visual-cortex gamma activity elicited by large, attention-capturing visual stimuli (Hoogenboom et al., 2006; Muthukumaraswamy et al., 2009). An interplay between gamma and theta (4–7 Hz) MEG activity has been taken to reflect encoding and retrieval of short-term (Fuentemilla et al., 2010) and long-term memories (Osipova et al., 2006).

The systematic suppression of the parieto-occipital 10–Hz activity with attention directed to different parts of the visual field (Brahmamisharif et al., 2010) might prove to be useful for brain–computer interfaces.

MEG in the 2000s—cognition and connectivity, training and development

MEG user base has been expanding rapidly since the turn of the century, with a simultaneous shift of focus to higher cognitive function—as such as language and social interaction—as well as to brain development, its disorders, and cortical correlates of cognitive training.

Language function

The 1990s saw the identification of the MEG correlate of the extensively-studied N400 EEG response that is triggered by semantically incongruent sentence-ending words (Kutas and Hillyard, 1980); MEG displayed a salient N400m in the left superior temporal cortex

practitioners at that time, the new findings were often accepted only after EEG source analysis had been performed. For example, the generation of the auditory 100–ms response (Fig. 1) in the supratemporal auditory cortex (Hari et al., 1980) was widely accepted only after the source analysis of corresponding auditory evoked potentials half a decade later (Scherg and von Cramon, 1985). Similarly, the tangential source of the 20–ms somatosensory response N20 (N20m) within the sulcal wall of the primary somatosensory cortex SI (Wood et al., 1985) was accepted after a long delay as it was in contrast to the EEG-based view (for reviews, see Hari and Forss, 1999; Kakigi et al., 2000).

Nevertheless, MEG started to demonstrate its unique power. For example, MEG successfully differentiated between responses generated in the primary (SI) vs. secondary (SII) somatosensory cortices based on response timing, locations and directions of source current (Hari et al., 1983b; Teszner et al., 1983); positron-emission tomography description of the human SII followed a decade later (Burton et al., 1993). The SI/SII discrimination, and possible SI–SII interaction (Simöes et al., 2003), is central for understanding disorders of the cortical somatosensory network (Forss et al., 2001). MEG’s sensitivity to tangential currents also allowed to demonstrate cortical representation for acute dental pain within the SII region (Hari et al., 1983c).

Other pioneering observations in the 1980s include, e.g., the first recordings of the tonotopic organization of the auditory cortex (Romani et al., 1982), the somatotopic organization of the primary somatosensory (Hari et al., 1984b; Okada et al., 1984) and motor (hand vs. foot) (Deecke et al., 1982; Hari et al., 1983a) cortices, a decade later accompanied by observations of the retinotopic organization of the visual cortex (Ahlfors et al., 1992; Aine et al., 1996). Recordings of auditory cortical responses addressed topics such as the effect of interstimulus interval (Hari et al., 1982) and the concept of “lifetime” of the auditory trace (Lu et al., 1992), as well as the effect of attention (Hari et al., 1989) and stimulus changes (Hari et al., 1984a) on the auditory cortex (for reviews, see Hari, 1990; Nätänen et al., 1994).

The careful groundwork laid in the 1980s, although focused on rather local cortical processing, has been frequently revisited with the increasingly available whole-scalp MEG systems.
While word reading activates multiple areas in both hemispheres, stimulus manipulation indicated specific functional roles for a subset of them, such as visual feature analysis at ~100 ms in the occipital cortex and letter-string analysis ~150 ms in the left occipitotemporal cortex (Tarkiainen et al., 1999); access to phonology was proposed to engage the left inferior frontal cortex within 100 ms (Wheat et al., 2010). During speech perception, activation is mainly concentrated to the superior temporal cortex, reflecting at 50–100 ms sensitivity to speech-specific acoustic–phonetic features (Obleser et al., 2004) and at ~150 ms differentiation between phonological categories (Näätänen et al., 1997; Phillips et al., 2000); frontal activation is found in specific paradigms (Pulvermüller and Shtyrov, 2009), especially when the subject is prepared to later repeat the word (Biermann-Ruben et al., 2005).

The cortical sequences of auditory and visual word processing converge in the superior temporal cortex (Marinkovic et al., 2003), with the left-hemisphere activation at 250–450 ms reflecting lexical-semantic analysis in both sensory modalities (Vartiainen et al., 2009).

Natural language processing is also starting to be accessed with MEG. Tracking of the phase pattern of 4–8-Hz MEG signal from the auditory cortex allowed to discriminate between spoken sentences, and suggested speech segmentation in ~200-ms windows, at the level of syllables (Luo and Poeppel, 2007).

Language production, difficult to study with EEG because of the wide-spread artifacts due to mouth and tongue movement, is better tractable with MEG. The first language production paradigms described the cortical sequence of picture naming (Levelt et al., 1998; Salmelin et al., 1994), and more recent studies have sought to

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**Fig. 2.** Cortical dynamics of silent reading. The colored patches represent the group-level anatomically constrained MNE model and the dots individual ECD models. The curves display the mean time course of activation per area. Activation advances from visual feature analysis in the occipital midline (~100 ms) to letter-string analysis in the left inferior occipitotemporal cortex (~150 ms) and further to activation of the left superior temporal cortex, reflecting lexical-semantic processing (and also phonological and syntactic processing). Modified from Salmelin et al. (2000a) and Vartiainen et al. (2011).

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**Fig. 3.** Measurement of “corticovocal coherence” between the listener’s brain signals and the speaker’s fundamental frequency as monitored with an accelerometer over the speaker’s throat. **Left:** 3-dimensional accelerometer signals and their envelope filtered through 0.1–1 Hz. **Right:** Group-level coherence map (across 10 subjects) computed at 0.5 Hz, mainly related to phrasing of the reader’s voice. Modified from Bourguignon et al. (in press).
The importance of multimodal interactions—e.g., audiovisual (Rajj et al., 2000), auditory-tactile (Gobbele et al., 2003), visuoauditory (Kim et al., 2007)—is emphasized in naturalistic environments. Eye tracking may help to focus MEG analysis to the moments when specific parts of the visual scene are being attended to (Hirvenkari et al., 2010).

Interareal connectivity

Dynamic Imaging of Coherent Sources, DICS (Gross et al., 2001), an analysis method based on frequency-domain beamforming, was initially applied to characterization of the cortico-thalamo-cerebellar network controlling slow finger movements (Gross et al., 2002) (Fig. 4). DICS allows estimation of all-to-all connectivity across the cortex, without a specific seed region (Kujala et al., 2008), and it has been used to describe, e.g., cortico-cortical connectivity during continuous reading (Kujala et al., 2007).

An MNE-based coherence analysis successfully tracked slow cortico-cortical connectivity in hand movements (Jjerbi et al., 2007). Because of its linearity, coherence is well suited for reaching from MEG sensors to the source level. The resulting networks can be characterized further, e.g., with causality measures that estimate whether one signal is likely to drive the other (Kujala et al., 2007). Other proposed methods include Dynamic Causal Modeling (Kiebel et al., 2009), mutual information (Joannides et al., 2000), estimation of metrics based on graph theory (Stam et al., 2009) or a small-world framework (Bassett et al., 2009). So far, the last two methods have been applied primarily on sensor-level MEG data; however, a recent study on working-memory networks combined MNE source-level and graph-theoretical descriptions (Palva et al., 2010).

In coherence estimation, even activity in brain areas that are fairly far removed from the sensors, such as the thalamus and the cerebellum, may become detectable due to the selective enhancement of the signals from those areas (Gross et al., 2002; Schnitzler and Gross, 2005). However, also artificial commonalities may be accentuated, particularly at the sensor level (Schoffelen and Gross, 2009).

Connectivity patterns corresponding to the fMRI-derived ‘resting-state networks’ (for a review, see Raichle, 2010) are less apparent in MEG/EEG analyses, probably due to the multitude of relevant frequencies (Mantini et al., 2007) and the fast dynamics of MEG/EEG. Recently, independent component analysis (ICA) has been used for characterization of functional connectivity in resting-state MEG data (Hväärinen et al., 2010); a recent MEG study, applying both beamformers and ICA, reported patterns highly similar to those seen with fMRI (Brookes et al., 2011).

Training and development

Brain imaging is increasingly used to assess neural effects of cognitive training. In language training (re-learning) of chronic anomic patients, behavioral improvements were accompanied by changes in cortical dynamics (Cornelissen et al., 2003). In healthy subjects, learning new names for unfamiliar pictured items resulted in enhanced involvement of the left temporal and frontal cortices in naming (Hulten et al., 2009), and the change of activation by 1 week post-training predicted how well the individual remembered the names 10 months later (Hulten et al., 2010). Spoken word-forms of an (artificial) foreign language were integrated rapidly and successfully into existing lexical and conceptual memory networks (Dobel et al., 2010).

Development, even during the prenatal period, can be studied with the totally noninvasive MEG. Fetal auditory MEG responses were first found, at 34–35 weeks gestation, to sounds delivered through the mother's abdominal wall (Blum et al., 1985) and have since then been recorded with increasing sophistication and success (Draganova et al., 2005; Waki et al., 1996). Discriminative responses to speech sounds have been recorded in neonates and infants (Draganova et al., 2005; Imada et al., 2006). Evoked response latencies become shorter and their polarities change during infancy (somatosensory responses Lauronen et al., 2006) and childhood (auditory responses Paetel et al., 1995); obvious causes include myelination of neural pathways and maturation of transmitter systems. Already in 7-year-old children, the neural sequence of word reading is remarkably similar to that in adults, although still notably delayed (Parviainen et al., 2006). The auditory system, however, seems to remain malleable even when visual language processing already looks largely adult-like (Parviainen et al., 2011).
Brain disorders and clinical use of MEG

Epilepsy, stroke, chronic pain and preoperative localization

Since the early 1980s, MEG has proved its usefulness in identifying epileptic foci and differentiating between primary vs. mirror foci (Barth et al., 1982; Fischer et al., 2005; Hari et al., 1993; Nakasato et al., 1994; Paetau et al., 1991). Although an MEG assessment of epileptic phenomena has been slow to develop into a routine procedure, reports already exist—including hundreds of epileptic patients—on the benefits of MEG in the presurgical evaluation of epileptic foci (Stefan et al., 2003) and in aiding the decision on the most informative placement of intracranial electrodes (Knowlton et al., 2009).

MEG shows promise in monitoring of stroke recovery (Forss et al., 2011; Rossiini et al., 2007), especially since modified vasomotor reactivity in stroke easily affects the BOLD hemodynamic response but leaves the MEG signal intact (Rossini et al., 2004).

Clinical research of chronic pain may benefit from the possibility to differentiate between cortical representations of the first and second pain (Ploner et al., 2002) and to selectively stimulate the thin, slowly conducting C-fibers and the faster conducting Aδ-fibers (Kaligi et al., 2003; Raji et al., 2004). In patients suffering from complex regional pain syndrome, both the extent of the somatosensory cortical representation of the painful hand and the reactivity of motor-cortex rhythms are altered (Juottonen et al., 2002). Long-term follow-up recordings of such patients have demonstrated spread of the disorder from one hemisphere to the other (Forss et al., 2005).

The sensorimotor strip can be reliably indentified preoperatively either by means of evoked fields or cortex–muscle coherence (Mäkelä et al., 2001). MEG paradigms of language lateralization that could replace the highly invasive and complication-prone Wada test have been developed (e.g., Papanicolau et al., 2004), and the work continues (for reviews, see Pirmoradi et al., 2010; Salmelin, 2007).

Dyslexia and stuttering

In adult dyslexics, cortical processing in both reading and speech perception starts to differ from the normal pattern at the stage of the earliest language-sensitive processing (Helenius et al., 1999b; Parviainen et al., 2005), with a marked delay by lexical–semantic processing, particularly in reading (Helenius et al., 1999a, 2002). The left occipitotemporal dysfunction for written words was marked delay by lexical-semantic processing. For example, the suppression of auditory responses to words out loud, as infants and patients; even artifacts caused by deep brain stimulation can be efficiently suppressed (Airaksinen et al., 2011).

Timing of cortical activation also seems to play a role in other developmental language disorders, such as stuttering. When reading words out loud, fluent speakers first activated the left inferior frontal and then (pre)motor cortex but this sequence was reversed in stuttersers, suggesting that they initiated motor programs before articulatory planning. Abnormalities emerged in activations involved in overt speech production rather than core linguistic processes (Salmelin et al., 2000b).

Multimodal imaging

With an implicit assumption that the MEG and fMRI measures reflect the same neural activation, the two methods have been used, e.g., to characterize the cortical organization of the auditory “what” and “where” pathways (Ahlveninen et al., 2006; Brunetti et al., 2005) and the time course related to itch (Mochizuki et al., 2009).

Direct comparison of MEG responses and BOLD fMRI of low-level sensory and motor processing has suggested similarity of activated areas (Korvenoja et al., 1999; Sharon et al., 2007). In the SI cortex, the best correspondence between the two measures, for varying interstimulus intervals, was found by squaring the MEG waveforms over the entire stimulus train (Nangini et al., 2009).

However, any differences between the methods are more likely to manifest in complex cognitive processing. Attention to faces vs. houses indicated different functional effects in fMRI and MEG within 200 ms after stimulus onset but similar effects in later time windows (Furey et al., 2006). In three recent studies of language processing, with the same subjects and the same exact paradigm in MEG and fMRI, action vs. object naming revealed largely similar overall activation patterns and stimulus effects in both imaging modalities (Liljestroom et al., 2009) but speech perception indicated differences in the hemispheric balance (Renvall et al., 2012) and, in reading, marked functional differences appeared in the left occipitotemporal, superior temporal (MEG emphasis) and inferior frontal cortex (fMRI emphasis) (Vartiainen et al., 2011).

Modulation of rhythmic background activity, in various frequency bands, can show reasonable spatial agreement with BOLD fMRI (Jerbi et al., 2009; McDonald et al., 2010; Singh et al., 2002). However, systematic evidence of such a relationship—and correspondence of stimulus/task effects—directly at the level of the (whole) brain, from independently analyzed MEG and fMRI data sets is crucially needed. It is still unclear which of the multiple MEG/EEG features might best correspond to BOLD fMRI functionality, and under which conditions.

From the neuroscience point of view, consistent differences between the methods, ideally indicative of sensitivity to specific aspects of neural processing, would be far more interesting and informative than merely plugging fMRI locations to MEG analysis and extracting a time course. Interareal connectivity may well provide a framework for bringing together apparently (partly) separate MEG and fMRI activation patterns (Salmelin and Kujala, 2006). Both MEG and fMRI have reached the level of maturity where we can—and should—ask how the different measures may best be exploited, alone and together, as informative probes of cognitive processes and their disorders.

MEG: quo vadis?

With present-day neuromagnetometers, it is possible to expand the frequency range of interest from infra-slow fluctuations (Leistner et al., 2009) up to very high-frequency (about 600 Hz) oscillations (Curio et al., 1994; Hashimoto et al., 1996). Continuous head-position monitoring and novel artifact suppression methods (Taulu et al., 2004) facilitate recordings from poorly cooperative subjects, such as infants and patients; even artifacts caused by deep brain stimulation can be efficiently suppressed (Airaksinen et al., 2011).

The future MEG studies, building on the solid work of the first four decades of MEG research, aim for an increasingly comprehensive view of brain function, especially as regards its dynamics. The studies will explore the added value of combined MEG–fMRI recordings, proceed to increasingly real-life–like experimental designs and multisensory stimulation, and exploit new, efficient computational methods, such as decoding of task- and stimulus-specific neural patterns (Chan et al., 2011; Toda et al., 2011; Koskinen et al., in press). Reaching to the genetics of MEG signals also represents a promising line of ongoing and future studies.

Timing matters from behavior to sensory and cognitive functions, from infancy to adulthood and aging, and from health to various disorders, with many intermingled time scales (Hari et al., 2010). MEG, after its long journey that started in physics laboratories, is now available to address these time-sensitive issues of human brain function.

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