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MINISYMPOSIUM

Magnetoencephalography

Erin Simon Schwartz · J. Christopher Edgar · William C. Gaetz · Timothy P. L. Roberts

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Abstract Although magnetoencephalography (MEG) may not be familiar to many pediatric radiologists, it is an increasingly available neuroimaging technique both for evaluating normal and abnormal intracranial neural activity and for functional mapping. By providing spatial, temporal, and time-frequency spectral information, MEG affords patients with epilepsy, intracranial neoplasia, and vascular malformations an opportunity for a sensitive and accurate non-invasive preoperative evaluation. This technique can optimize selection of surgical candidates as well as increase confidence in preoperative counseling and prognosis. Research applications that appear promising for near-future clinical translation include the evaluation of children with autism spectrum disorder, traumatic brain injury, and schizophrenia.

Keywords Magnetoencephalography · Epilepsy · Functional imaging · Children

Introduction

Magnetoencephalography (MEG) is a non-invasive neuroimaging method that measures electromagnetic neural activity with excellent temporal and good spatial resolution. MEG is increasingly utilized for the clinical assessment of neurosurgical candidates (e.g., children with epilepsy, brain tumor, or arteriovenous malformations) requiring presurgical mapping of eloquent cortex as well as the identification of zone(s) of abnormal interictal activity (i.e. presumptive epileptogenic zones) in patients with seizure disorders [1–7].

E. S. Schwartz · J. C. Edgar · W. C. Gaetz · T. P. L. Roberts
Lurie Family Foundations MEG Imaging Center,
Department of Radiology, The Children's Hospital of Philadelphia,
Philadelphia, PA, USA

E. S. Schwartz (✉)
Department of Radiology,
The Children's Hospital of Philadelphia,
34th Street and Civic Center Boulevard,
Philadelphia, PA 19104-4399, USA
e-mail: simon@email.chop.edu

Basic physics and theoretical considerations

Unlike electroencephalographic (EEG) signals, which originate primarily from volume-conducted extracellular activity, MEG signals arise from intracellular postsynaptic currents that flow from dendrites to the soma [8, 9]. Human folded cortical geometry includes both sulci and gyri and, as such, cortical pyramidal cells exhibit one of three principal geometries: tangential, perpendicular, or oblique to the cortical surface. This distinction is important, as the orientation of the cortical source (primarily the orientation of the pyramidal cells) determines whether a magnetic field is externally observed. MEG is most sensitive to tangentially oriented cortical sources, along the walls of a sulcus, and least sensitive to cortical activity from radially oriented cortical sources such as on the crown of a gyrus [10].

As the magnetic fields generated by neural activity are exceedingly weak (on the order of 10 fT–1 pT; roughly 10 million times smaller than Earth's magnetic field), special technology has been developed to record magnetic fields associated with neural activity. Specifically, magnetic fields generated by the neuronal currents induce an electric current within a detection coil. The coil is coupled to a superconducting quantum interference device (SQUID), which produces a proportional voltage output. To detect the tiny magnetic fields generated by neural activity,

detection coils and sensors are maintained at superconducting temperatures, achieved by surrounding the sensors in liquid helium, with the entire apparatus enclosed within an insulated dewar (Fig. 1). Thus, unlike EEG, MEG sensors cannot be placed directly on the patient's head. In the most recent generation of MEG systems, several hundred coil/SQUID sensors are distributed in the helmet of the dewar, giving whole-brain coverage. Because the sensitive MEG sensors cannot discriminate sources of magnetic activity, MEG examinations must be performed in a highly shielded room to prevent contamination by external magnetic fields (e.g., elevators, electrical lines, etc.).

The depth of a cortical source is a contributing factor in measurement, with the magnetic field of a (neuronal) electrical current dipole predicted by the inverse square law, rapidly decreasing in magnitude with distance. As such, MEG systems are designed so that the sensors are as close as possible to the adult head (given the physical constraints of dewar design) in order to record a strong signal. Because an infant's head is smaller than an adult's, the MEG sensors of conventional systems (designed to accommodate the majority of potential patients) are at a greater distance from the child's head, compromising sensitivity. Research is under way into the development of MEG systems for pediatric populations (particularly neonates, infants, and toddlers) [11]. For neonates, MEG might be superior to EEG, as the fontanels and calvarial sutures can significantly distort EEG but not MEG signals [12, 13]. In addition, in both adults and children, new source localization methods in conjunction with dense whole-brain detector arrays and sophisticated experimental manipulation might allow for assessment of relatively deep cortex, such as that within the hippocampus [14, 15], amygdala [16, 17], and cerebellum [18, 19].

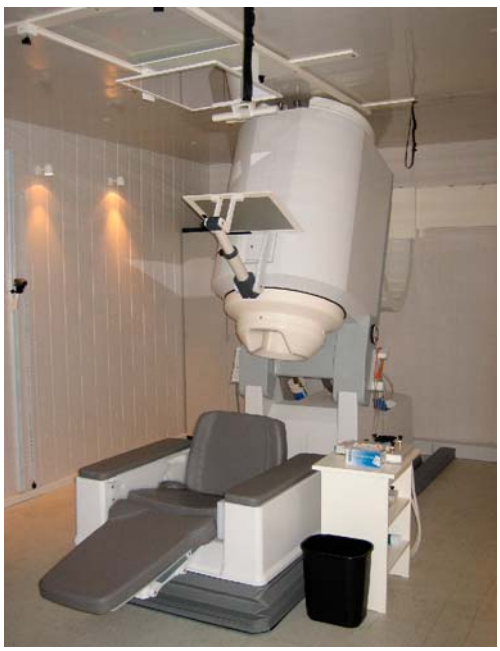

Fig. 1 CHOP's 275-channel whole-head MEG system in its magnetically shielded room

Interpretation of the activity detected at the MEG sensors is dependent on a method of source modeling to determine its location. Source modeling is most valuable when localization results are displayed in an anatomical context. This is typically accomplished by "fusing" the localization determined by MEG with the cross-sectional anatomy provided by MRI, which requires a method of co-registering "MEG space" and "MRI space." To achieve this, head position locating coils are generally placed over nasion and left and right preauricular positions, allowing definition of the three-dimensional space relating the MEG sensors to the patient's head and the MRI data. Head position and motion are monitored in real time, and post-processing algorithms are used to correct for reasonable degrees of head movement during the examination. Historically, the single equivalent current dipole (ECD) model has been the most widely adopted source analysis method. Standard ECD fitting procedures use a model in which the magnetic field pattern at the relevant sensors is forward-modeled as though it were generated by a point source current dipole embedded within a spherical, homogeneously conducting medium [8]. The dipole modeling algorithm uses iterative minimization procedures to determine the spatial position, orientation, and strength of the hypothetical current dipole that best accounts, in a statistical sense, for the magnetic field actually measured by the array of sensors within the specified time window.

An emerging alternative approach to source localization involves the use of rastered spatial filter, or "beamformer," methods. Although the mathematics of this approach is beyond the scope of this article, the net result is to virtually interrogate any chosen point in the brain to reveal its electrical activity time course. This process can be repeated for multiple points, effectively allowing scanning of a volume of voxels covering the entire brain. The voxel (virtual electrode) time courses can then be described in terms of an appropriate statistical attribute to yield a single value for each voxel, which can be colorized and visualized as a statistical parametric map overlay, rather analogous to typical functional MRI (fMRI). The statistical measure can be as simple as a mean amplitude or intensity, or a standard deviation; it can be spectrally restricted to a chosen frequency band (e.g., alpha: 8–13 Hz); or it can describe more complex features of the time-domain signal, such as spikiness, reflected in excess kurtosis (increasingly used to explore interictal epileptogenic activity). Beamforming can also be used in a differential mode to compute the difference in activity during brief latency windows

(~100–500 ms) surrounding stimulus delivery and/or task performance.

The key feature of such beamforming methods is that they allow construction of images, with functionally relevant neural activity portrayed as a color overlay on anatomic MRI. Furthermore, beamforming algorithms can be tailored to separate temporally overlapping activity arising from discrete spatial sources, which has the beneficial application of removing contaminant artifact sources such as muscle, eye-blink, and cardiac electrical activity. While these physiological sources are generally more pronounced in the pediatric population than in adults (due to patient size and compliance), other forms of artifact are also more commonly encountered in the younger population but can be similarly addressed with beamforming. These include artifact from dental braces, permanent retainers, palate expanders, and piercings.

Clinical MEG data acquisition

For the majority of clinical examinations, passive recording of spontaneous electromagnetic activity is performed to identify abnormal interictal discharges in patients with epilepsy. MEG has been shown to significantly contribute to the management of these patients by determining whether the abnormal interictal activity is focal or multifocal, and identifying the patients who are more likely to benefit from resective surgery [20–23]. MEG is also commonly used to guide intracranial electrode placement in patients undergoing seizure surgery [3, 24, 25].

Additionally, MEG is often used in clinical practice for identification of eloquent functional cortex in relation to structural lesions or regions of abnormal electrical activity. Motor, somatosensory, auditory, visual and language areas are often investigated [7, 26–28], particularly in the pediatric population, where the potential for cortical reorganization might diminish the value of predictions based on neuroanatomy alone.

Recording of spontaneous interictal activity requires no stimulus, and a conventional approach is to collect data while subjects passively relax, seated or supine, typically recording for 30–60 min. When the data are collected, the spontaneous MEG (and sometimes simultaneously recorded EEG) data are reviewed to identify characteristic sharp and spike and slow wave activity, as well as abnormal delta (1–4 Hz) and theta (5–8 Hz) slow waves.

It is increasingly believed that modeling the onset of abnormal interictal activity, rather than the peak of the activity, has a higher likelihood of identifying the focus of origin, rather than a region to which it has rapidly spread. Multiple dipole models can be valuable when multiple areas of simultaneous or near-simultaneous activity are suspected [29].

In addition to dipole source localization, more automated approaches to localizing seizure foci are increasingly implemented. As previously detailed, the beamformer approach can estimate the time-activity profiles of every voxel in the entire brain [30]. This method can be used to identify epileptiform activity; the time-activity profile at each voxel is analyzed for the presence of significant spikiness during the course of the recording. Brain areas with significant spikiness (e.g., putative epileptogenic regions) are registered to the structural MR of the patient and overlaid as statistical parameters, calibrated to depict significance (Fig. 2). Each imaged voxel can thus be

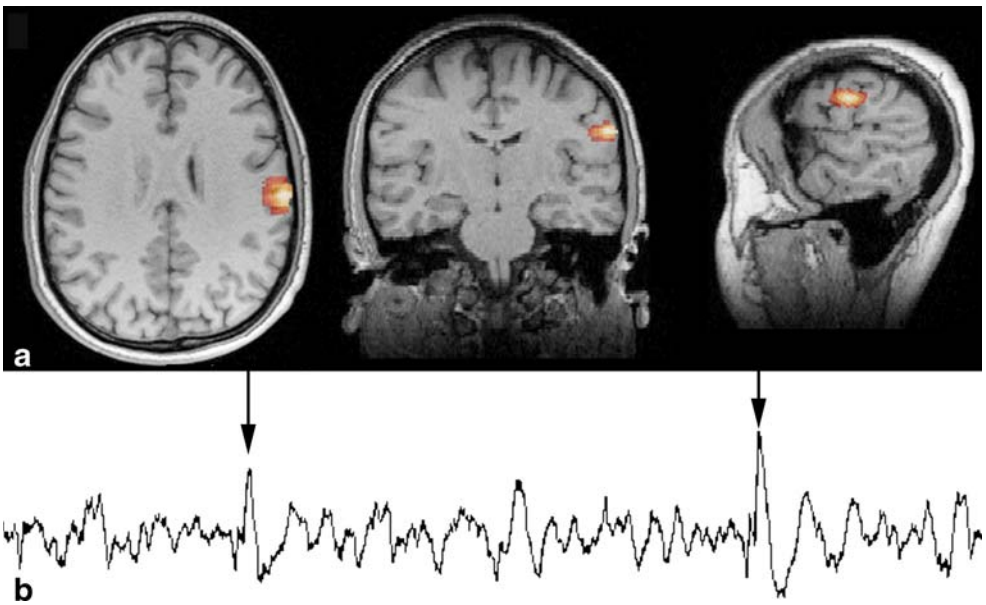

Fig. 2 Epilepsy. **a** MEG SAMg2 data superimposed on volumetric T1-weighted MP-RAGE gradient echo. **b** 10 s of a time activity curve from a synthetic depth electrode, created at the point of peak activity. Note the transient, abnormal sharp activity (*arrows*)

interrogated in the time-domain to reveal its underlying electrical activity, in the form of a "virtual electrode" time course, much akin to that recorded with invasively implanted intracranial electrodes (but synthesized entirely from a non-invasive, extracranial recording).

Evoked fields and mapping

In addition to recording spontaneous activity, MEG can also be collected while sensory stimuli are presented (auditory tones, visual images, tactile stimuli, etc.). These could be purely passive tasks or could incorporate a response to stimulus presentation (a recordable motor or verbal response, for example). MEG data can be time-locked to the stimulus presentation and/or patient response. The response to a single stimulus is weak, so an averaged response to many stimuli is required, creating the event-related field (ERF). Usually, more than 100 stimuli are presented in each condition to obtain an ERF with a signal-to-noise ratio (SNR) adequate for accurate localization. This typically takes between 2 and 5 min per stimulus type. In the sections below, methods commonly used to record and localize functional areas are detailed.

Somatosensory representation mapping

Somatosensory evoked fields (SEFs) are obtained via the application of a tactile stimulus (typically electrical or pneumatic) to a focal region of skin. Nerves commonly studied include the median and tibial, but tactile stimuli can be applied to nearly every region of the body to generate an SEF. MEG somatosensory activity at 20 ms post-stimulus (referred to as the N20m) reflects activity in the primary somatosensory cortex, along the posterior bank of the central sulcus [31–34]. The N20m SEF is usually quite focal, allowing successful modeling with a single source [33, 35], although beamforming can also be valuable for localization, particularly in the setting of artifact from a metallic implant, such as a vagal nerve stimulator (VNS) [28].

To obtain SEFs during a typical MEG exam, stimuli are presented to the anesthetized patient via an electrical device (placed over the appropriate nerve), using a pulse of ~0.2 ms duration with sufficient current to obtain a muscular response, or to the awake patient via pneumatic stimulation, where a pulse of compressed air is delivered to the skin in clinically relevant regions. By mapping multiple digits, toes, and the lip (with pneumatic stimulation), it is possible to accurately determine the individual somatosensory homunculus for a given patient. From this, the localization of the central sulcus and presumed location of motor cortex in the precentral gyrus can be inferred. MEG methods to identify primary sensory areas have been validated against intraoperative direct cortical stimulation and are widely used in clinical practice [36–39].

Motor mapping

Accurate identification of primary motor cortex is important for surgical planning when structural lesions or regions of abnormal interictal activity appear to involve perirolandic areas. Mapping of motor activity is more complex and challenging than mapping somatosensory function, as motor tasks require patient compliance to produce well-controlled motor responses. Additionally, the typical motor response is more complicated than the typical somatosensory response, as even a relatively simple motor task (such as the self-paced button press) produces a cascade of movement-related cortical activity, involving planning, movement and proprioception. In particular, prior to the button press, low-frequency motor cortical activity is observed hundreds of milliseconds prior to movement onset (commonly called the readiness field [RF]) [40]. The RF shows an abrupt increase in transient cortical power, peaking at the approximate time of movement onset. This peak has been termed the "motor field" (MF). The peak MF source has been localized to the MI cortex hand area in recent studies involving healthy adult [41] and pediatric clinical populations [7]. Directly following movement, a series of movement-evoked fields (MEFs) components has been reported (e.g., MEFI at ~50 ms, MEFII ~100 ms). The MEFI likely represents a volley of movement-related sensory activity and has been localized to the postcentral gyrus [41], whereas the MEFII has been localized to related but not identical areas of the precentral gyrus. This re-activation of motor cortex might reflect the continued expression of ongoing motor control (antagonist to the original movement), or possibly a motor activation arising from sensory proprioception, as has been observed in primates [42].

Movement studies in pediatric clinical populations routinely exhibit considerably poorer SNR than adult populations, largely due to an increased distance from the MEG sensors to the cortical source [43], as well as an increase in low-frequency noise sources from inadvertent movements of the eyes and face during MEG recording. Given these limitations, beamformer source localization approaches are preferred over dipole modeling in pediatric populations, as motor-directed corticospinal activity can be separated from the expected movement-related sensory activity, as well as interference from correlated noise [28].

The change in the magnitude of beta band (15–30 Hz) activity—directly in relation to cortical motor function—can be examined using the differential beamformer method [44]. Specifically, by comparing beta-band activity during a

window surrounding the button press with beta-band activity during a baseline period, regions showing a significant decrease in beta activity (event-related desynchronization, ERD) can be localized to primary motor cortex. Localization of beta ERD (identifying primary motor cortex) can be overlaid on the patient's MRI along with the corticospinal fiber trajectories generated from diffusion tensor imaging (DTI) (Fig. 3), thus providing clinical information about the association between primary motor areas and tumors/lesions.

Language lateralization and localization

Accuracy in the lateralization and localization of language function is often of great importance to the neurologist and neurosurgeon when considering frontal lobe and/or temporal lobe procedures. Although the invasive Wada test is currently the gold standard [45], MEG might allow a non-invasive alternative [26]. A variety of functional language paradigms, similar to those used in fMRI, are commonly utilized. These include verb generation, stem completion, picture naming, and word recall tasks [27, 46]

Analogous to motor mapping, ERD associated with neuronal activity can be used to probe language function. When presenting stimuli (such as pictures or words), subsequent ERD can be identified in time-windows when language-related activity is presumed to be occurring and then be compared to a baseline period, using the differential beamforming approach. Voxels displaying statistically significant ERD can then be overlaid on the structural MRI to identify the neural substrates of language function. As various paradigms probe different aspects of language function, the precise time-window of maximum language-related activity might also vary and activity might in fact be best assessed by selecting a time-window "just prior to completion of the task" rather than "just following stimulus presentation." In general terms, selection of sequential latency windows allows serial depiction of language-related activity across time and can be considered to map the dynamic network in space and time.

Common clinical scenarios

MEG is clinically indicated for presurgical mapping of eloquent functional cortex and for the identification of the source(s) of abnormal epileptiform interictal activity. MEG has been shown to play several roles in the preoperative assessment of patients with medically refractory epilepsy. In cases where alternative imaging modalities, including ictal EEG and MRI, are not clearly localizing, MEG can help determine whether the origin of the discharges is focal (offering a potential surgical candidacy), multifocal (still potentially allowing for a surgical approach), or generalized (typically precluding surgery). If surgery is deemed possible, MEG data might allow for reduced coverage phase II intracranial electrode grid placement. Information on the functional organization of the patient's brain obtained through MEG functional mapping can guide presurgical counseling and prognosticating by identifying the relationship between the apparent ictal onset zone and eloquent cortex, even in cases where cortical reorganization is suspected to have occurred.

Case examples

Case 1: A 17-year-old right-handed boy was referred for medically refractory epilepsy. An extensive work-up prior to his referral to our institution included brain MRI, which raised the concern for left mesial temporal sclerosis; scalp EEG, which suggested a right frontal lobe seizure onset; and positron emission scanning, which reported hypometabolism in the "inferior and lateral aspect of the right frontal lobe."

MEG consistently localized abnormal interictal activity to the anterior aspect of the right inferior frontal gyrus

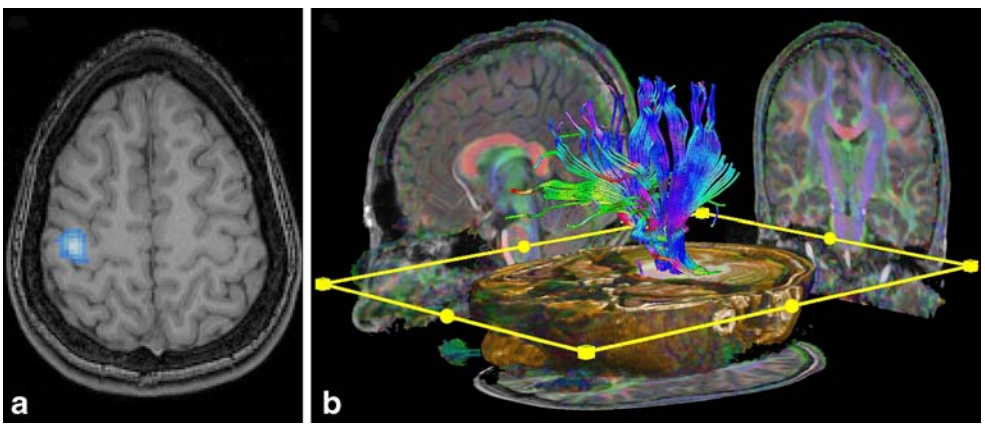

Fig. 3 Motor mapping. **a** Results from a self-paced motor task superimposed on the volumetric T1-weighted MP-RAGE gradient echo show ERD in the right precentral gyrus from the left index finger activity. **b** Trajectories generated from correlative diffusion tensor imaging with directionality color-coded 3-D display of the corticospinal tracts in the same patient

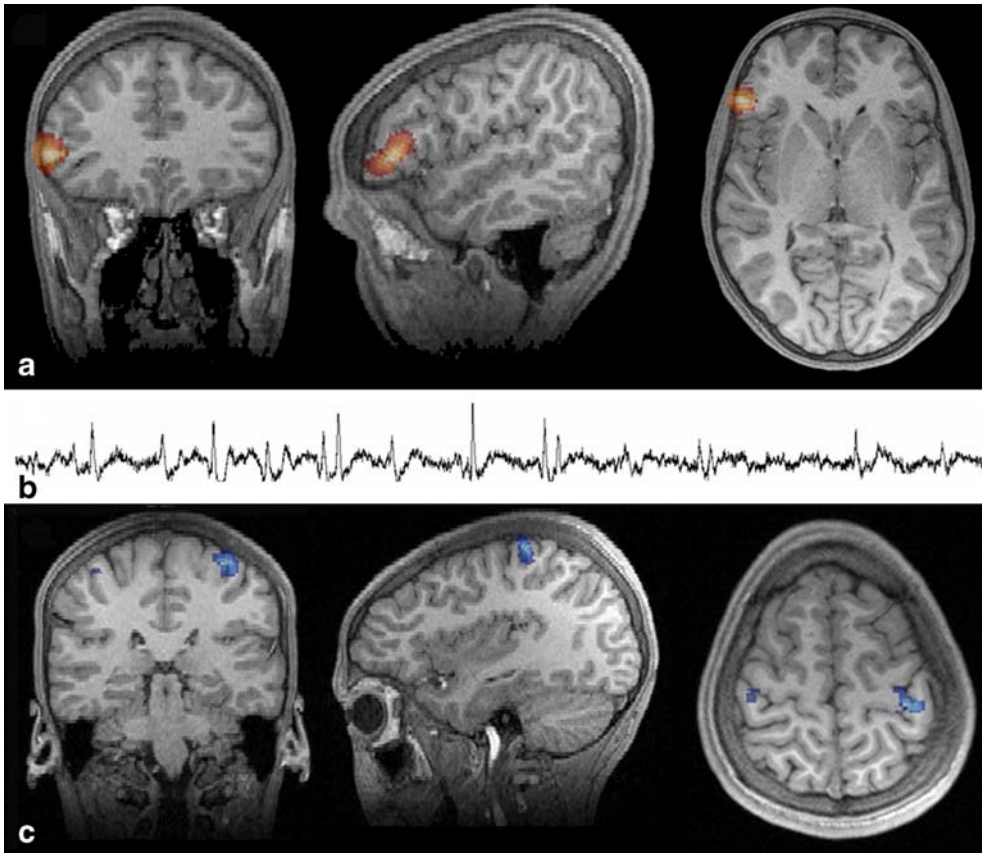

Fig. 4 Case 1. **a** The yellow/red region superimposed on the volumetric T1-W MP-RAGE gradient echo brain MRI indicates the focal epileptogenic zone in the right inferior frontal gyrus. **b** Approximately 10 s of time activity from a synthetic depth electrode (created at the point of peak activity defined in **a**) shows very frequent abnormal spike activity. **c** The blue regions superimposed on the volumetric brain MRI indicate the regions of beta-band sensorimotor ERD from a right index finger button-press motor task. Although the majority of the ERD is in the left precentral gyrus, bilateral ERD is present, as is commonly seen in young adults

(Fig. 4). No significant abnormal activity was seen outside this region. Functional language and motor mapping demonstrated that the epileptogenic zone was far removed from eloquent cortex, confirming surgical candidacy.

A brief period of intracranial grid placement confirmed the MEG findings and a tailored anterior right frontal lobectomy was performed. The boy remains seizure-free.

Case 2: An 8-year-old ambidextrous girl was referred for evaluation of medically refractory epilepsy. She was known to have extensive left hemispheric polymicrogyria and volume loss, believed to be the result of an in utero insult, which resulted in a mild right hemiparesis. Scalp EEG showed multifocal generalized discharges, predominately arising from the left hemisphere. It was hoped that her major functional regions had reorganized to the right hemisphere given the early onset of the injury, potentially making her a candidate for an extensive left-side resection or hemispherectomy.

MEG revealed a cluster of abnormal interictal activity in the left posterior temporal-occipital-parietal junction region but no other abnormal activity in the left hemisphere (Fig. 5).

Extensive functional mapping did demonstrate reorganization of the primary motor region subserving the right index finger to the right precentral gyrus, immediately adjacent to the orthotopic mapping of the left index finger; however, the somatosensory localization for the right hand remained in the left hemisphere. Additionally, the functional centers for language appeared to reside in the left hemisphere, although a small amount of ERD was seen in the right posterior temporal lobe, as has commonly been our experience in patients who are left-hemispheric-dominant for language. Importantly, her expressive language center was partially overlapping with the regions of abnormal interictal activity. The left hemispheric dominance for language was also present on fMRI, and the combination of the data from the MEG and fMRI exams eliminated the need for invasive Wada testing.

With only partial reorganization, the girl was not deemed a strong surgical candidate, as significant func-

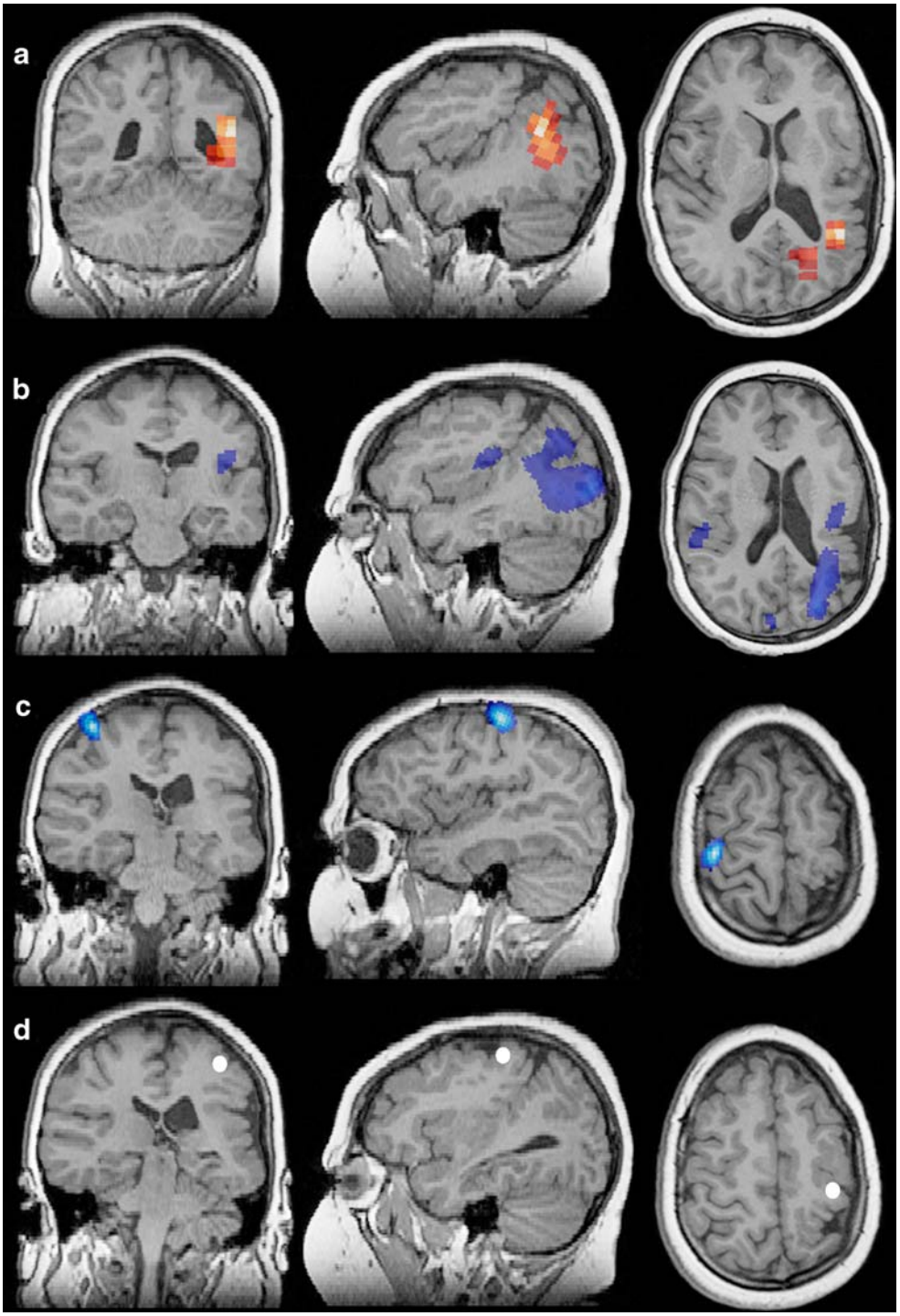

Fig. 5 Case 2. **a** The yellow/red region superimposed on the volumetric T1-W MP-RAGE gradient echo brain MRI shows one cluster of left hemispheric interictal epileptiform activity. The images also show portions of the extensive left hemispheric polymicrogyria and ventricular dysmorphism. **b** The blue region superimposed on the brain MRI indicates beta-band ERD from a language task, showing that language areas are in close proximity to the region of interictal epileptiform activity. Some bilateral language ERD was seen. **c** The blue region superimposed on the MRI shows significant beta-band ERD in the right posterior frontal lobe from a right index finger motor task, indicating trans-hemispheric functional reorganization. **d** The site of the ECD from somatosensory testing of the right index finger (*white dot*) shows more orthotopic representation, albeit within the markedly dysmorphic perirolandic region

tional deficits would be expected. Placement of VNS is being considered.

Research applications

In contrast to conventional cross-sectional imaging, MEG offers insight into the time course of activity throughout the brain, and when using analysis methods such as beamforming that examine neural activity in a specific frequency range, five-dimensional descriptions of brain function can be obtained (space, time, frequency). With such capabilities, insight into pathologic conditions characterized by abnormal neuronal activity and communication/connectivity is possible, even in the absence of so-called structural lesions. As such, MEG might open up imaging-based approaches to neuropsychiatric and developmental disorders currently underserved by conventional radiologic techniques.

Areas of research of particular interest to the pediatric clinical community that exploit the strengths of MEG include traumatic brain injury (TBI), autism spectrum disorder (ASD), and schizophrenia. The roles of MEG in each disorder differ. For TBI, a focus of research is the objective confirmation of brain injury, especially in children with mild head trauma, via detection and localization of focal abnormal slow-wave (delta band) rhythmic activity. For schizophrenia, a focus of research is the detection of early neural markers that predict subsequent development of the disease and that are associated with clinical measures (e.g., attention impairment). For ASD, it might be toward a neurobiological understanding of the auditory abnormalities typically observed in ASD, with a view to improve characterization/subtyping in the tremendously heterogeneous group of individuals diagnosed with ASD.

To provide a somewhat more detailed example, ASD is characterized by a triad of behavioral phenotypes, including impaired social interaction, impaired language and communication, and stereotypical or repetitive behaviors. With emerging data pointing to a prevalence of as high as 1:150, ASDs are receiving increased attention. A striking feature of ASD is the heterogeneity in severity in each of the above symptoms across the autism spectrum. The genetic profiles of ASDs are thought be complex, with diagnosis based on intensive observational assessments from a specially trained clinician. Treatments remain elusive.

Recent data using MEG to study auditory processing in children with ASD suggest a delay in the latency of auditory-evoked fields, which might distinguish children with ASD from typically developing peers. Using paradigms that probe detection of syllable change, distinguishing between ASD children with milder versus more severe language impairment, appears possible. Ongoing MEG studies using more complex linguistic stimuli are being conducted with the hope of further identifying subpopulations of children within the autism spectrum. It is hoped that such biomarkers of ASD result in improved characterization (subtyping) of individual patients, leading to better stratification for emerging treatments, as well as providing the potential for earlier diagnosis as well as novel and tailored therapeutic approaches.

MEG billing and authorization

Current commercially available MEG systems are FDA approved, and there are three category I CPT codes for MEG:

95965—MEG recording and analysis; for spontaneous brain magnetic activity (e.g., epileptic cerebral cortex localization)

95966—for evoked magnetic fields; single modality (e.g., sensory, motor, language, or visual cortex localization)

95967—(to be used in conjunction with 95966) for evoked magnetic fields; each additional modality (e.g., sensory, motor, language, or visual cortex localization) (list separately in addition to code for primary procedure)

Interpretation of the epilepsy recording and the function mapping is optimized by a team of physicians and PhDs, combining their expertise in clinical medicine, neuroanatomy, physics and electrophysiology. Of note, the time spent by the PhD preparing the clinical interpretation of an MEG is incorporated into the technical component of the charge.

While some third-party payers still consider MEG to be investigational, a large number in the United States approve payment for MEG as part of a pre-neurosurgical evaluation. A letter of medical necessity from the referring physician, noting the individual history of refractory epilepsy despite anti-epileptic medications, or the close proximity of the brain tumor to the precentral gyrus, and the role of MEG in the patient's treatment, is often beneficial in securing authorization for an individual referred for MEG.

Conclusion

MEG provides a sensitive and accurate evaluation of brain electrical activity, providing spatial, temporal, and spectral information. Work continues in improving the spatial localization achievable with MEG. Future work is needed to develop more quantitative approaches to identifying abnormal brain activity and its clinical relevance. Primary clinical applications include localization of epileptogenic foci and presurgical mapping of eloquent cortex. Research applications that are promising for near-future clinical applications include the evaluation of children with ASD, TBI, and schizophrenia.

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