

Clinical neurophysiology is one of the lesser known medical beasts, small enough to pass unnoticed, yet diverse enough to throw up surprises. EMG and EEG form its backbone, but what of the less well understood branches that are continually evolving and moving in new directions? This new series takes us on a tour of some of these exciting new avenues, ably guided by some of the experts responsible for shaping them. The aim of each article is to provide an

overview of a new technique and discuss its role in clinical practice, both now and in the future. In this exciting series we are starting with a discussion of magnetoencephalography (MEG) by Fergus Rugg-Gunn. In future issues we can look forward to hearing about electrotonus, fMRI-EEG, single pulse electrical stimulation and other techniques – words which at present may carry no meaning for some readers, but all will be revealed in the fullness of time.



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Magnetoencephalography – Current Use and Future Applications

Magnetoencephalography (MEG) is a non-invasive neurophysiological technique that measures the magnetic fields generated by intracellular neuronal currents in the brain. The recorded magnetic field pattern is analysed to determine the localisation of either spontaneous, for example epileptic, or evoked, for example, somatosensory, neuronal activity. The resulting map of magnetic dipoles is typically superimposed on a co-registered MRI scan to facilitate accurate neuroanatomical localisation.

The first MEG recordings of cortical activity took place in 1968 using a single channel biomagnetometer. Data from a large number of recordings was averaged to elucidate normal resting alpha activity. In the late 1970's, a number of important advances, including the construction of specially shielded rooms to reduce interference from ambient electromagnetic noise, the development of gradiometers which measure magnetic field gradients rather than the actual field and the introduction of superconducting quantum interference devices (SQUIDs) greatly improved the sensitivity of MEG. These innovations permitted, for the first time, the detection of spontaneous and evoked neuronal activity (Figure 1).

More recently, whole head magnetometers comprising up to 275 sensors have been developed which through more extensive spatial coverage produce greater accuracy of dipole localisation and spatiotemporal propagation within an acceptable time period.

The magnetic fields detected by MEG originate from dipolar intracellular currents associated with dendritic inhibitory and excitatory post-synaptic potentials within sulcal pyramidal neurons orientated tangentially with the cortical surface. MEG is insensitive to radially orientated neurons located on the gyral crown, which comprise approximately one third of cortical neurons, and which dominate the EEG. The magnitude of the magnetic fields produced from about 10^4 – 10^5 synchronous potentials, typical for an evoked auditory or somatosensory response, is in the order of 100 femtotesla, with

epileptic activity in the region of 1-2 picotesla (Figure 2).

MEG has high temporal resolution, in the milliseconds range, which is comparable to EEG, and favourable to functional MRI which has a temporal resolution of several seconds. Modern multi-channel, whole-head MEG systems possess good spatial resolution; in the order of <5mm localisation error, with a mean scattering of source localisations of 10mm for neocortical generators, compared to a mean scattering of 20mm for EEG. In addition, magnetic fields are less distorted by the resistive properties of the skull and scalp and retain localisation accuracy following craniotomy and resective surgery. MEG is, however, an expensive investigative tool with a modern multichannel whole-head magnetometer, shielded room, liquid helium and computer hardware costing in the region of £1.5 million. This is beyond the reach of all but the most dedicated specialist units.

Clinical Applications

Epilepsy

The clinical potential of MEG was first demonstrated in studies of patients with epilepsy with the detection and localisation of, for example, rolandic spikes using single channel detectors. Currently, the main application of MEG in epilepsy is the characterisation of epileptic foci through the source localisation of interictal epileptiform activity,¹ although, infrequently, ictal abnormalities are recorded by chance. The sensitivity of MEG for the identification of interictal epileptiform discharges, typically spikes, is approximately 50-70%, with 89% localisation accuracy, using standard equivalent current dipole source localisation techniques (Figure 3). This is possibly further enhanced by using advanced analysis methods such as dynamic source modelling. MEG has been reported to be of superior localising accuracy to scalp EEG and of equivalent accuracy to invasive EEG recordings in predicting the epileptogenic zone in patients undergoing presurgical evaluation. In 41

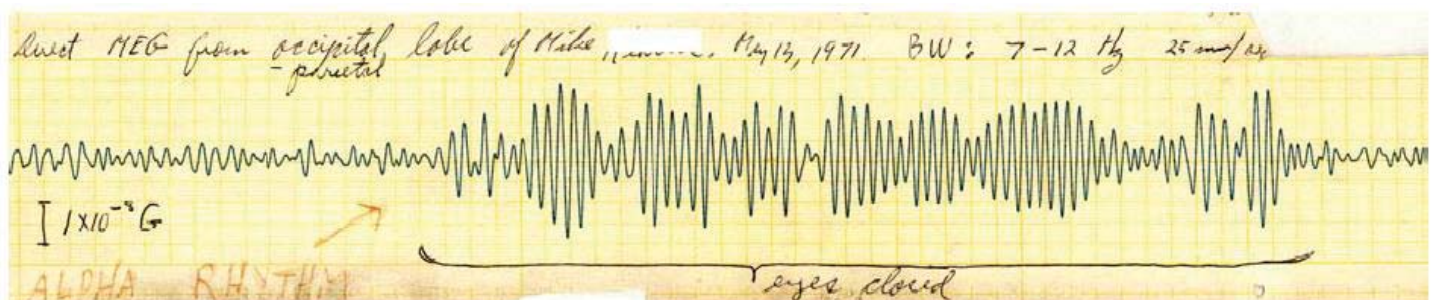


Fergus Rugg-Gunn qualified from St Thomas's Medical School in 1994, and completed basic medical training in London and Oxford. He obtained a PhD with the Epilepsy Group at Queen Square on advanced MRI techniques. SpR training in neurology was undertaken in London and most recently he has re-joined the Epilepsy Group at Queen Square following completion of specialist training. His interests are MEG, in particular localisation of epileptiform activity and neural synchrony, advanced MRI sequences, such as diffusion tensor imaging, and SUDEP and cardiac arrhythmias in epilepsy.

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Figure 1: Single channel MEG recording of normal alpha rhythm.



patients with focal epilepsy who underwent pre-surgical evaluation the localisation accuracy, as determined by the location of surgical resection and post-operative seizure outcome, of interictal MEG was 56% compared to 54% for invasive EEG monitoring. Within this group, MEG exhibited a bias towards patients with extratemporal lobe epilepsy (65.5%).² This is most likely due to the improved signal to noise ratio from neocortical generators rather than deep sources. Furthermore, it has been shown that the localisation of interictal MEG dipoles correlate with ictal-onset zones as defined by intracranial EEG and complete resection of these areas predicts good post-operative seizure outcome.³ At the present time, the information derived from MEG is complementary to data acquired from other investigations including MRI, PET and scalp and invasive EEG recordings, and, in future, may be used to guide surgical resection or more commonly, inform placement of intracranial electrodes in patients with complex refractory focal epilepsy.

Mapping of eloquent cortex

MEG has been used to map somatosensory, motor, auditory and visual specific cortex (Figure 4). The localising data from MEG may be combined with fMRI and tractography and utilised in pre-surgical planning in patients with lesions, such as tumours, adjacent to or within eloquent cortex. More recently, language mapping has been implemented and compared with intra-operative direct cortical stimulation and sodium amytal (Wada) testing.⁴ MEG and sodium amytal data showed concordance in 87% of patients suggesting that MEG may be suitable for assessing hemispheric dominance for language. Functional MRI may also be used to map language function non-invasively and shows good concordance with MEG localisation.⁵ In contrast to fMRI however, MEG possesses high temporal resolution and can therefore be used to characterise the propagation of cortical activation during language tasks.

MEG has also been used to investigate inter- and intra-hemispheric functional reorganisation of language areas in patients undergoing left anterior temporal lobe resection (ATLR). In a small study of 12 patients with refractory left temporal lobe epilepsy, patients with atypical (bilateral) hemispheric dominance preoperatively were more likely than patients with typical (left hemisphere) dominance to show evidence of increased right hemisphere participation in language functions after surgery. Patients with left hemispheric dominance preoperatively were more likely to show intrahemispheric changes involving a slight inferior shift of the putative location of Wernicke's area.⁶ There is a paucity of MEG studies that evaluate memory function in normal subjects, and memory dysfunction in patients with conditions such as temporal lobe epilepsy or Alzheimer's disease.⁷ The spatiotemporal characterisation of memory function is an important goal in, for example, the presurgical evaluation of patients with refractory epilepsy as a major concern is the potential negative effect of ATLR on memory function.

Cognitive impairment

Abnormalities of both spontaneous activity and evoked responses have been identified in patients with cognitive impairment using MEG. These studies have focused on determining the relationship between cognitive impairment and MEG abnormalities and have shown, for example, deficits in preconscious auditory processing, decreased coherence in all frequency bands and an increase in the low frequency magnetic power over the frontal and central areas.⁸ More recently, in patients

Figure 2: Spectrum of magnetic field strength

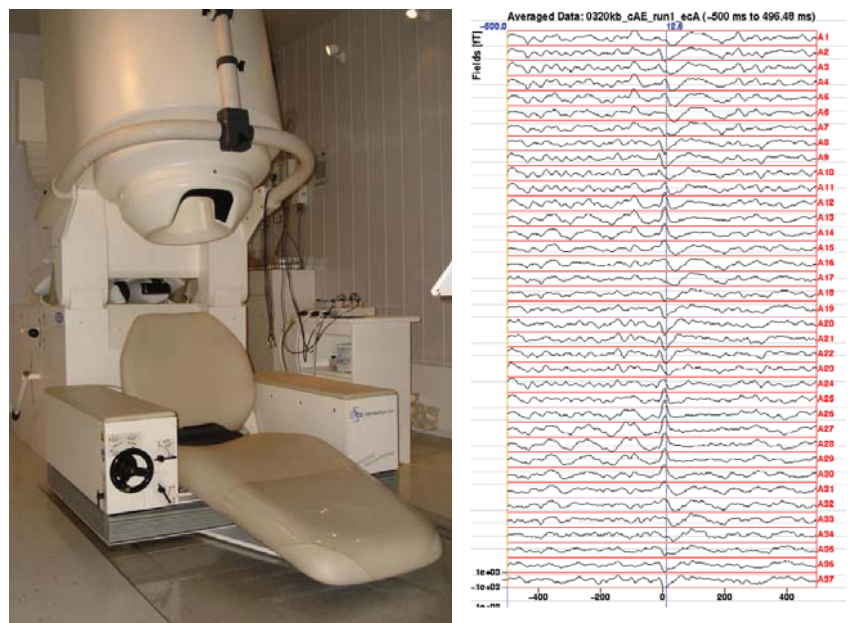
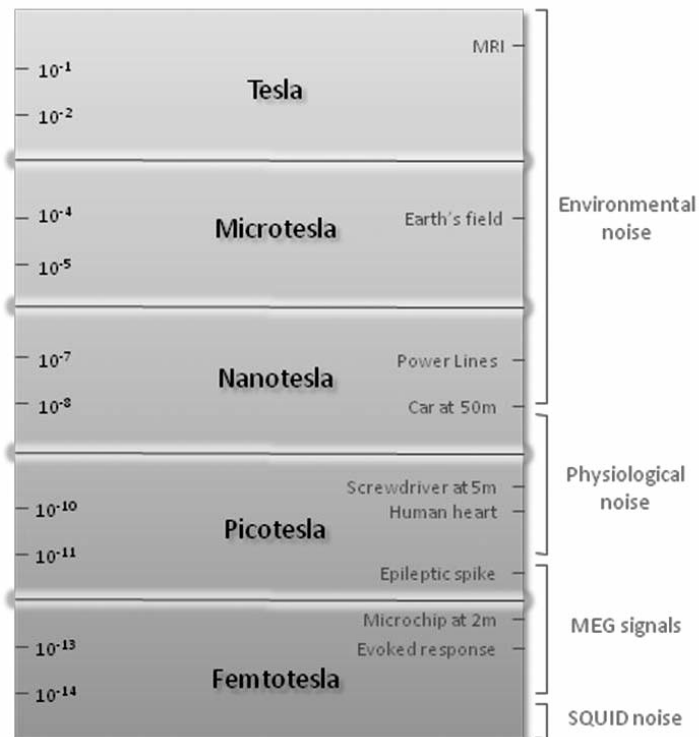
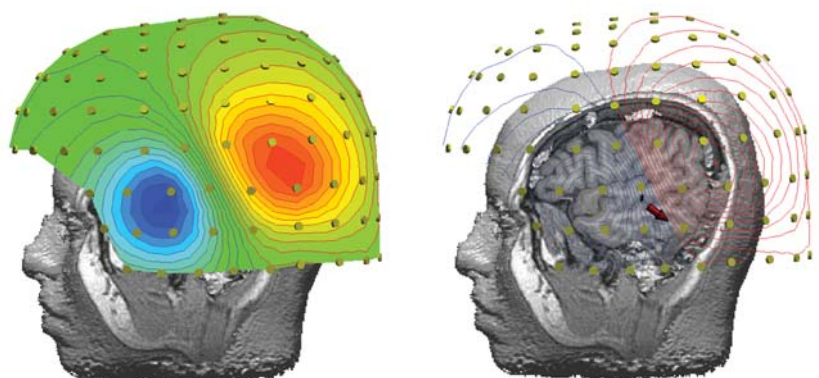


Figure 3: (Above left) Typical MEG suite showing dewar containing liquid helium and 275 recording sensors. (Above right) Recording from the first 37 MEG channels showing interictal epileptiform discharge (blue line) in a patient with focal epilepsy. (Below) Source localisation is then performed and overlaid on MR images for anatomical characterisation (red arrow).



with Alzheimer's disease, a significant correlation between the relative volume of the left hippocampus and degree of left temporal slow wave activity was seen.⁹ Furthermore, left temporoparietal slow-wave activity covaried with a functional status scale whereas right temporal slow-wave activity varied with cognitive performance.¹⁰ The degree of activation within the left temporal lobe during a simple memory paradigm correlated with left hippocampal volume in patients with Alzheimer's disease, but not in healthy control subjects or elderly patients with chronic depression and normal cognition suggesting that MEG may be of diagnostic value.⁷ It has recently been shown that slow-wave activity may be present in some patients with subjective cognitive impairment only,¹¹ although this is not universally accepted. The functional significance of slow-wave activity in this patient group is presently unclear and future MEG studies are needed to determine whether focal slow wave activity is a specific early functional marker of AD and mild cognitive impairment or a consequence of general neuropathology.

Stroke

MEG is particularly suited to studies of stroke due to the high spatial and temporal resolution, whole-head coverage and insensitivity of cerebral generators to surrounding abnormal tissue and inconsistent neurovascular coupling that may affect investigations reliant on a haemodynamic response, such as fMRI. The earliest studies to evaluate MEG in stroke focused on the effects of cortical ischaemic lesions on the spatiotemporal propagation of somatosensory responses,¹² in particular the sequential activation of primary and secondary cortical regions. More recent studies have evaluated the possibility of "plastic" reorganisation of eloquent cortical regions following stroke. Typically, following a stroke, the MEG evoked response to, for example, somatosensory stimulation of the hand, is delayed, more widely dispersed and there is evidence of involvement of brain areas outside normal boundaries in the affected hemisphere.¹³ MEG recordings of evoked responses have prognostic value. Patients with minimal cortical response on MEG testing immediately following acute stroke exhibit little functional recovery and those that show a typical response pattern recover more completely. In patients with partial activation of normal cortical regions there is frequently recruitment of atypical brain areas during somatosensory, motor or language tasks.¹⁴ Despite the involvement of other regions, this pattern of brain activation is inefficient and functional recovery is typically incomplete. A number of rehabilitative strategies have been developed, for example, intense peripheral somatosensory stimulation, immobilisation of the intact side and transcortical magnetic stimulation which may encourage further cortical plasticity and aid recovery. MEG is well suited to inform on the underlying mechanisms of rehabilitative interventions and this may, in turn, facilitate targeted therapy for individual patient populations.

Headache

There have been a number of small series studies exploring the utility of MEG in migraine. MEG field shifts and desynchronisation of alpha band activity (7-13Hz) were seen within the occipital cortex during migrainous visual auras in patients with classical migraine, consistent with cortical spreading depression.¹⁵ Cortical hyperexcitability, determined by analysing MEG recordings during somatosensory stimulation, was demonstrated in patients with migraine compared to control subjects,¹⁶ consistent with earlier reports of augmented visual evoked responses in this patient group. Furthermore, the degree of hyperexcitability correlated with the severity of migraine and was diminished by migraine prophylaxis with sodium valproate.¹⁷ It may, therefore, be possible to use MEG derived markers of cortical excitability to provide surrogate evidence of the efficacy of migraine preventatives.

Multiple sclerosis

Desynchronisation within the alpha band range was also seen in patients with relapsing-remitting multiple sclerosis (MS). Interhemispheric coherence, reflecting the synchronisation between the cerebral hemispheres, was reduced in patients with MS when compared to control subjects, most likely as a result of demyelination and secondary axonal degeneration.¹⁸ Abnormal cortical activity with an excess of slow and beta waves adjacent to subcortical white matter lesions has been identified in a small series of patients with MS,

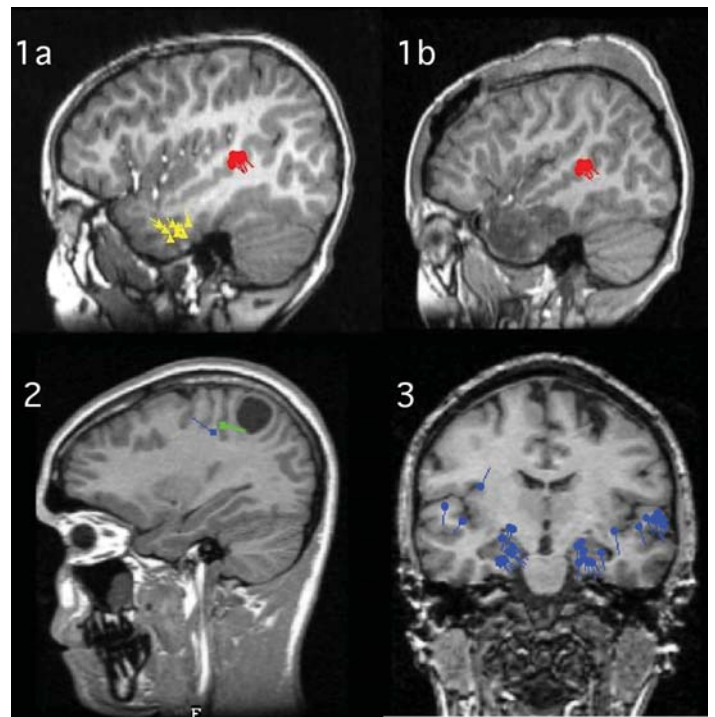


Figure 4: MEG evoked responses. 1a: pre-operative MRI with superimposed MEG derived localisation of interictal epileptiform activity (yellow triangles) and receptive language areas (red circles) in a patient with focal epilepsy undergoing pre-surgical evaluation. 1b: post-operative MRI from the same patient showing the margins of anterior temporal lobe resection and intact receptive language regions. 2: source localisation of somatosensory (green) and motor (blue) activation in a patient with a cystic parietal lobe lesion. 4: MEG-derived profiles of activation during a simultaneous auditory and visual memory task in a healthy control subject. (Images courtesy of Dr E Castillo, Division of Clinical Neurosciences, Houston).

although the significance of this remains unclear.¹⁹ It is possible that neurophysiological parameters may provide a more sensitive marker of disease progression and treatment response than current imaging techniques such as MRI.

Future direction

MEG is an established and clinically useful technique in the investigation of patients with epilepsy. In particular, the source localisation of epileptic spikes has been validated with intracranial EEG recordings and post-operative outcome data and paradigms for the activation of somatosensory, motor and receptive language regions are reproducible and robust. The demonstration that MEG could obviate the requirement for intracranial EEG recordings or reliably guide the placement of intracranial EEG electrodes in more complex cases would be a significant advance in the presurgical evaluation of patients with drug resistant focal epilepsy. Epileptic spikes are typically seen in only 50% of interictal MEG recordings of 30-60 minutes duration. It is important therefore, to develop techniques to localise the epileptogenic zone in patients without overt interictal epileptic activity using, for example, slow waves, fast oscillations and local hypersynchrony. Paradigms for the characterisation of memory function are not yet fully established and are limited by both technical and physiological factors. Nevertheless, this is an important goal, particularly in patients with dementia for early diagnosis and treatment response or in patients undergoing epilepsy surgery. In the case of temporal lobe epilepsy surgery, the ability to localise eloquent cerebral regions and map neural networks involved in memory may lead to a more targeted / individualised surgical approach and may be able to predict and avoid post-operative memory decline.

Oscillatory synchronous rhythms are thought to coordinate large-scale neural networks, thereby influencing the perception, representation and long-term coding of information. MEG is ideally suited to explore synchrony as neither fMRI nor standard EEG are able to fully characterise the dynamic interaction between cortical regions due to limitations in temporal and spatial resolution respectively. Synchrony

