Seizure: European Journal of Epilepsy 83 (2020) 70–75

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Review

Redefining the role of Magnetoencephalography in refractory epilepsy

Umesh Vivekananda [1]

Department of Clinical and Experimental Epilepsy, Institute of Neurology, Queen Square, UCL, WC1N 3BG, United Kingdom

ARTICLE INFO

Keywords:
magnetoencephalography
electroencephalograph
source localisation
OPMs

ABSTRACT

Magnetoencephalography (MEG) possesses a number of features, including excellent spatiotemporal resolution, that lend itself to the functional imaging of epileptic activity. However its current use is restricted to specific scenarios, namely in the diagnosis refractory focal epilepsies where electroencephalography (EEG) has been inconclusive. This review highlights the recent progress of MEG within epilepsy, including advances in the technique itself such as simultaneous EEG/MEG and intracranial EEG/MEG recording and room temperature MEG recording using optically pumped magnetometers, as well as improved post processing of the data during interictal and ictal activity for accurate source localisation of the epileptogenic focus. These advances should broaden the scope of MEG as an important part of epilepsy diagnostics in the future.

1. Introduction

A mainstay in epilepsy diagnostics over the last century has been the electroencephalogram or EEG. Simply explained, EEG records electrical currents reflecting synchronous neuronal activity attributable to the brain surface, and can identify abnormal activity related to epilepsy with good temporal resolution. Another non-invasive neurophysiological approach to epilepsy diagnosis has been Magnetoencephalography or MEG, that measures fluxes in the magnetic field caused by the same brain electrical activity with excellent spatial and temporal resolution. Indeed a number of studies have supported the complementary use of scalp EEG and MEG for a number of reasons [1–4]. The first is related to overcoming the inverse problem, i.e. determining where a source would have to be located to generate the fields actually observed at the scalp. Key advantages of MEG over EEG would be its immunity to signal distortion as a result of highly variable conductances from scalp and skull. Modern MEG scanners, which utilise around 300 sensors for whole head coverage, confers superior spatial resolution of 3-4 cm^2 for epileptogenic activity detection compared with 6 cm^2 for EEG [5]. Finally MEG is sensitive to tangentially oriented sources i.e. parallel to the scalp, whereas EEG is more sensitive to radially orientated sources i.e. perpendicular to the scalp.

However the use of MEG has been limited to specific epilepsy scenarios, mainly within epilepsy surgery evaluation, i.e. the surgical resection of the epileptogenic focus. It certainly has value in this area; one large study of 1000 consecutive cases of refractory focal epilepsy demonstrated that MEG provided additional information to existing presurgical methods (including scalp EEG, single photon emission computed tomography (SPECT) and MRI) in 32% of cases, and complete magnetoencephalography resection was associated with significantly higher chances to achieve seizure freedom in the short and long-term [6]. MEG has been used to inform invasive intracranial electroencephalography planning, viewed as the gold standard for precise localisation of the epileptogenic zone, in up to a third of patients [7] with patients having a significantly higher chance of being seizure-free when intracranial EEG completely sampled the area identified by magnetoencephalography as compared to those with incomplete or no sampling of magnetoencephalography results [8]. So why has MEG not had the impact predicted by early clinical evaluation? There appear to be a number of reasons, primarily being the associated cost and space required to run MEG systems; traditional MEG uses superconducting quantum interference device (SQUID) sensors that are necessarily cryogenically cooled in a large liquid helium dewar, and recordings can only occur in a magnetically shielded room. Consequently there is limited availability to MEG scanners (currently there are 10 scanners in the UK). Another limitation is the restrictive nature of recording; patients are required to have their head fixed in a limited selection of MEG helmet sizes with any motion of the head relative to the sensors e.g. during a seizure, affecting MEG signal quality. This means that MEG recording sessions are usually brief (1-2 hours) when compared to EEG

E-mail address: u.vivekananda@ucl.ac.uk.

[1] Dr Umesh Vivekananda is this year's winner of the 2020 ILAE British Chapter Clinician Scientist Gowers Award. Dr Vivekananda is a neurology academic clinical lecturer at UCL/National Hospital for Neurology and Neurosurgery. His research interests include the use of Magnetoencephalography in epilepsy, and a multimodal approach to understand cognition in refractory epilepsy.

https://doi.org/10.1016/j.seizure.2020.10.010
Received 30 September 2020; Accepted 10 October 2020
Available online 17 October 2020

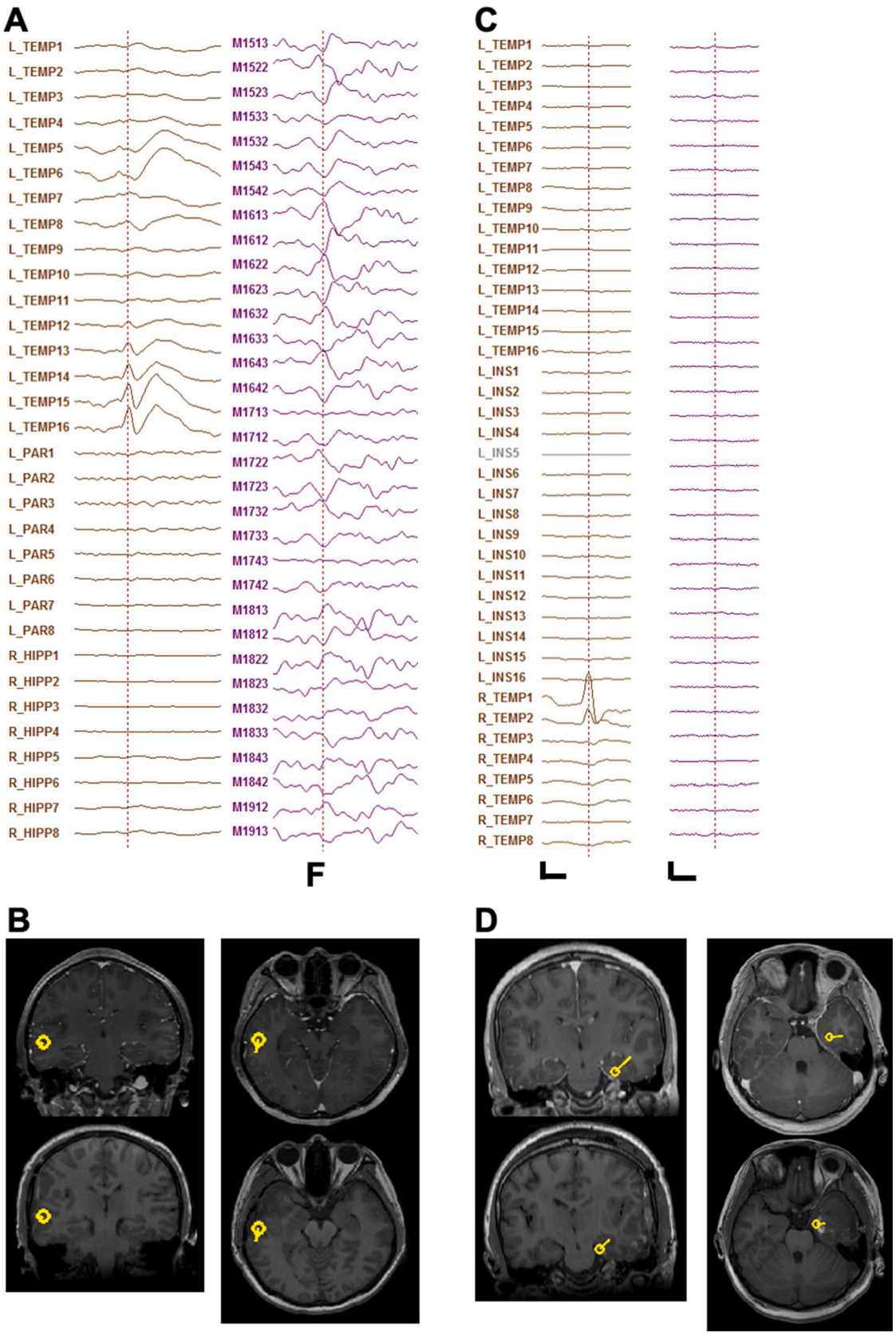

Fig. 1. Combined SEEG-MEG recording. A. Average IED recorded with SEEG (left) and MEG (right) from a patient with a superficial epileptogenic focus B. Coronal and sagittal image from same patient of average MEG dipole (top) and post resection (bottom). C. Average IED recorded with SEEG (left) and MEG (right) for a deep epileptogenic focus; scale bar 300μV/500 fT and 0.2 s. D. Coronal and sagittal image from same patient of average MEG dipole (top) and post resection (bottom) (Adapted from [25]).

telemetry that can last several days.

This essay focuses on advances within traditional SQUID MEG recording and post-processing of data, which has looked to overcome these limitations, as well as novel forms of MEG recording that may translate MEG into a more widely available clinical investigation.

2.1. Epileptogenic source localisation using MEG

Localising electrophysiological activity in epilepsy using MEG is either based on interictal activity, usually in the form of interictal epileptic discharges (IEDs) and high frequency oscillations (HFOs), or ictal activity. However as already mentioned, with relatively short recording times, the likelihood of capturing seizures is around 10% [9]. Methods for source localisation include single equivalent current dipole (SECD), limited constrained minimum variance (LCMV) beamformer, low-resolution brain electromagnetic tomography (LORETA) and minimum norm estimation (MNE). For SECD, IEDs are visually identified on MEG recording and the location, orientation, and strength of dipole sources that best fit the measured magnetic fields are calculated. Propagation of the IED can be observed at several time points along the spike upslope up to the peak of the global field power [10]. This creates a cluster of dipoles that represent each individual spike, which can then be represented on individual MRI anatomy. Cluster 'tightness', the presence of several dipoles within a sublobar region or even adjacent gyri, has implications on seizure freedom post epilepsy surgery if removed [8]. In comparison to dipole methods that estimate source distributions within reconstructed data, a LCMV beamformer estimates the activity for a source at a given location (typically a point source) while simultaneously suppressing the contributions from all other sources. As such this method may provide additional value when spikes are not clearly discernible on the sensors and support ECD localizations when dipoles are scattered [11].

MEG detection rate for IEDs is approximately 70%, with deep sources such as the mesial temporal lobe, a region commonly associated with refractory epilepsy, being poorly detected with MEG [12,13]. Indeed, diagnostic accuracy has been reported to be significantly higher in extra-temporal lobe epilepsy (diagnostic odds ratio of 4.4 versus 41.6 for temporal lobe) [14]. This is likely because spatial resolution decreases rapidly as a function of the depth of the epileptic generators, making source estimation challenging. To overcome this, beamforming with spatial filtering has been applied to detect hippocampal IED previously not visualised in the raw MEG trace [15], and trials of combined SEEG-MEG techniques which will be discussed later.

HFOs, between 80-200 Hz, are increasingly being recognized as EEG biomarkers for epileptogenicity [16]. MEG provides the spatiotemporal resolution required to accurately identify such activity. One study of 52 medically refractory epilepsy patients reported that concordance rate of high frequency oscillations sources with the presumed epileptogenic zone and the resected cortex were 75.0% and 78.8%, respectively, superior to standard dipole fitting methods. Moreover congruence between high frequency oscillation sources and resected cortex, predicted an 82.4% probability of achieving seizure freedom up to two years post resection, far greater than the 50% success rate currently seen post surgery [17]

MEG recording of ictal activity has proved more elusive. The largest study to date on 44 patients who had recorded MEG ictal activity, reported that even then single equivalent current dipole analysis was only possible in 29 patients (66%), due to poor dipolar ictal patterns, no MEG changes, and movement artifact [18]. Interestingly, using a MNE method over a narrow frequency band at seizure onset was more predictive than SECD for sustained seizure freedom post surgery. Again HFO detection during the periictal state can be useful in evaluating the seizure onset zone [19]. The effect of movement artifact on MEG signal can be a significant limitation, especially when recording hyperdynamic seizures. One approach to limit such disturbance on MEG signal would be to apply post-processing techniques to the data recorded such as spatiotemporal signal space separation (tSSS) or movement correction i.e. reconstructing sensor level MEG signals in the reference head position [20].

2.2. Combined EEG/MEG studies

Most clinical MEG centres perform simultaneous time locked scalp EEG and MEG, in order to validate abnormal MEG responses as being epileptiform in nature, rather than artefact. However the majority of combined recording use low density EEG coverage (<64 electrodes), thereby missing an inferior electrode array to view the basal and inner surfaces of the frontal, temporal and occipital lobes. One study addressed this by recording simultaneous high density EEG and MEG in 13 patients, and reported that independent electrographic source localisation (ESL) and magnetoencephalographic source localisation (MSL) was superior to combined MESL for accuracy in determining the epileptogenic zone (EZ). Interestingly focussing on the early phase of interictal and ictal activity (first latency 90% explained variance) was more sensitive in accurately localising the EZ than mid-phase (involving the positive peak of spike) or late phase (negative peak) [21].

As described earlier MEG and SEEG performed at different timepoints (typically separated by a number of months) have been compared, demonstrating that concordance between both modalities in identifying epileptiform activity was associated with a higher chance of seizure freedom post surgical resection [8,22]. However these studies would be limited by variability in brain anatomy, disease status and medications taken between recordings. Only a few single case studies up to now have attempted to perform simultaneous SEEG-MEG recording, mainly due to the technical challenge it poses [23,24]. The potential benefit of such recordings would be to combine both modalities, with MEG providing whole brain information, and SEEG providing information on deep sources with high signal to noise ratio. One recent study performed simultaneous SEEG-MEG in a case series of 14 patients with a range of focal refractory epilepsies, broadly divided in patients with a superficial epileptogenic focus ($n = 7$) and with a deep epileptogenic focus ($n = 7$). IED were compared for frequency and source localisation between both modalities and related to post epilepsy surgery outcome where possible. It reported that for superficial sources there was no significant difference between SEEG and MEG in detecting IED ($p = 0.135$) (Fig. 1A) but SEEG was significantly better at detecting deep spikes ($p = 0.002$) (Fig. 1C), with no IED visibly identified in MEG for four patients. To assess source localisation an average MEG dipole was calculated for IED and compared to SEEG source localisation. MEG dipole location was consistent with entire SEEG study findings in all superficial cases, and its removal during surgery was associated with 12 month seizure freedom in 6 out of 7 cases (Fig. 1B). Interestingly, in the four patients with deep sources where no IED was visible, an MEG dipole was fitted to SEEG interictal activity triggered average, and found that average MEG activity informed by identified SEEG spikes still accurately localised deep source activity, which has not been demonstrated in epilepsy before. Moreover surgical resection of the consequent average MEG dipole predicted seizure freedom (Fig. 1D) [25]. This finding using a distributed inverse method is consistent with the recent observation that SEEG informed deep brain MEG activity can be detected using independent component analysis (ICA) [31], thereby potentially overcoming a perceived limitation of MEG in imaging deep brain activity.

2.3. Optically Pumped Magnetoencephalography (OP-MEG) in Epilepsy

As already mentioned, main limitations of traditional MEG scanning that uses SQUID sensors include the restrictive nature of scanning and the impact of head motion on MEG signal. To overcome this, a novel form of MEG has been developed using quantum sensors (optically-pumped magnetometers or OPMs) that do not rely on superconducting technology but on the transmission of laser light through a vapour of spin-polarised rubidium atoms. Crucially, OPM sensors can be worn

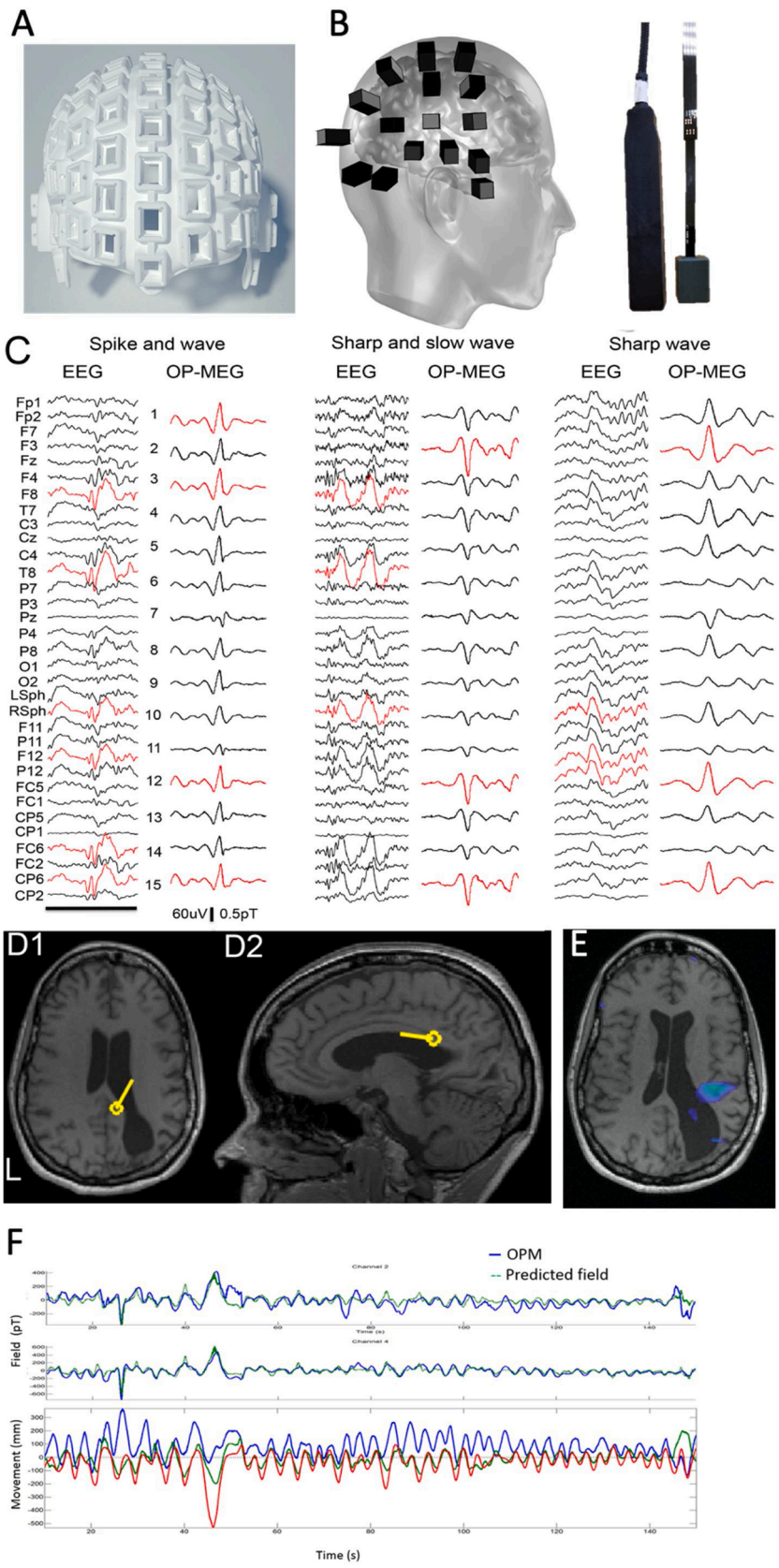

Fig. 2. Use of OP-MEG in epilepsy. A. Example of a 3D scanner cast B. Distribution of 15 OPM sensors in relation to patient's head (left) and comparative sizes of first and second generation OPMs (right) C. Examples of interictal epileptiform activity recorded from the patient using scalp EEG and OP-MEG D. Source localisation of average interictal activity using MEG dipole within patient space E. Source localisation using beamformer method on separate patient visit F. Example of motion tracking predicting changes in local magnetic field (Adapted from [27]).

directly on the head, allowing the subject to move within a magnetically shielded environment whilst being scanned. Indeed, OPM sensors are placed just 6 mm from the scalp surface by comparison to roughly 3-4 cm in cryogenic MEG, meaning the magnetic field strengths measured due to cortical sources are typically 4 times greater in adults [26]. The first use of OP-MEG in a patient with refractory epilepsy with a right posterior quadrant focus was reported recently [27]. 15 OPM sensors were positioned over that quadrant using a 3D printed scanner helmet (Fig. 2A,B) informed by an anatomical 3 T MRI scan. Forms of abnormal interictal activity previously seen on clinical EEG were detectable with OP-MEG (spikes, sharp and slow waves, polyspikes, spike and waves) demonstrating similar morphology (Fig. 2C), and produced consistent localisation of IED activity (Fig. 2D,E). Since this first reported case study, optically tracking of the OPM sensors have also been incorporated as the subject moves, thereby providing the ability predict the field changes due to head movement, in order to regress patient motion artefact away from the MEG signal (Fig. 2F). Importantly as OP-MEG permits the patient to move naturally while recording, long term OP-MEG recording akin to EEG telemetry is now a possibility, especially useful when considering paediatric epilepsy cases.

2.4. Use of MEG in mapping eloquent cortex

An important aspect of epilepsy surgery workup is defining eloquent brain pathways that are important for speech, motor function, and memory and how they may be affected by potential surgery. Methods to attain this information include the intracarotid amobarbital test or Wada; however it is a demanding and invasive test that serves to lateralise but not localise function. Alternative advanced non-invasive techniques to map function are functional MRI, that identify variations in magnetic resonance signalling associated with altered blood oxygenation level-dependency (BOLD) as the brain engages in an activity i.e. response to a cognitive task [28] and more latterly MEG [29]. Language mapping has also been performed with OP-MEG using a validated verb generation test in naturally moving healthy adults, showing that at a sensor and source level, a lateralising beta band (15–30 Hz) desynchronization could reliably be detected in all subjects [30]. This suggests a future role for combined epileptogenic source localisation and eloquent cortex mapping using OP-MEG in epilepsy subjects.

In conclusion, due to its inherent properties such as excellent spatiotemporal resolution and immunity to signal distortion from skull, MEG has been used as a non-invasive investigation in limited epilepsy scenarios, namely refractory focal epilepsy surgery cases, to provide complementary information to scalp EEG in defining the epileptogenic focus. However more widespread use of MEG has been stymied by limitations such as a restrictive recording environment, signal disturbance due to subject motion, and high maintenance costs. With advances in processing of MEG data, development of simultaneous EEG-MEG and SEEG-MEG recording, and more recently the replacement of SQUID sensors with OPMs, translation of MEG into a more clinically available tool for a range of epilepsy diagnostics is now a real possibility.

Funding

UV is funded by Epilepsy Research UK, NIHR, MRC and Academy of Medical Sciences.

Declaration of Competing Interest

The author has no conflicts of interest to disclose.

References

[1] Lin YY, Shih YH, Hsieh JC, Yu HY Yiu CH, Wong TT, Yeh TC, Kwan SY, Ho LT, Yen DJ, Wu ZA, Chang MS. Magnetoencephalographic yield of interictal spikes in temporal lobe epilepsy. Comparison with scalp EEG recordings. NeuroImage 2003; 19:1115–26.
[2] Scheler G, Fischer MJM, Genow A, Hummel C, Rampp S, Paulini A, Hopfengärtner R, Kaltenhäuser M, Stefan H. Spatial relationship of source localizations in patients with focal epilepsy: Comparison of MEG and EEG with a three spherical shells and a boundary element volume conductor model. Hum Brain Mapp 2007;28:315–22.
[3] Wennberg R, Valiante T, Cheyne D. EEG and MEG in mesial temporal lobe epilepsy: Where do the spikes really come from? Clin Neurophysiol 2011;122:1295–313.
[4] Pellegrino G, Hedrich T, Chowdhury RA, Hall JA, Dubeau F, Lina J-M, Kobayashi E, Grova C. Clinical yield of magnetoencephalography distributed source imaging in epilepsy: A comparison with equivalent current dipole method. Hum Brain Mapp 2018;39:218–31.
[5] Oishi M, Otsubo H, Kameyama S, Morota N, Masuda H, Kitayama M, Tanaka R. Epileptic spikes: magnetoencephalography versus simultaneous electrocorticography. Epilepsia 2002;43:1390–5.
[6] Rampp S, Stefan H, Wu X, Kaltenhäuser M, Maess B, Schmitt FC, Wolters CH, Hamer H, Kasper BS, Schwab S, Doerfler A, Blümcke I, Rössler K, Buchfelder M. Magnetoencephalography for epileptic focus localization in a series of 1000 cases. Brain J Neurol 2019;142:3059–71.
[7] Sutherling WW, Mamelak AN, Thyerlei D, Maleeva T, Minazad Y, Philpott L, Lopez N. Influence of magnetic source imaging for planning intracranial EEG in epilepsy. Neurology 2008;71:990–6.
[8] Murakami H, Wang ZI, Marashly A, Krishnan B, Prayson RA, Kakisaka Y, Mosher JC, Bulacio J, Gonzalez-Martinez JA, Bingaman WE, Najm IM, Burgess RC, Alexopoulos AV. Correlating magnetoencephalography to stereo-electroencephalography in patients undergoing epilepsy surgery. Brain 2016;139: 2935–47.
[9] Burgess RC. Clinical MEG passes another milestone. Brain 2019;142:2897–900.
[10] Lantz G, Spinelli L, Seeck M, de Peralta Menendez RG, Sottas CC, Michel CM. Propagation of interictal epileptiform activity can lead to erroneous source localizations: a 128-channel EEG mapping study. J Clin Neurophysiol Off Publ Am Electroencephalogr Soc 2003;20:311–9.
[11] Hall MBH, Nissen IA, van Straaten ECW, Furlong PL, Witton C, Foley E, Seri S, Hillebrand A. An evaluation of kurtosis beamforming in magnetoencephalography to localize the epileptogenic zone in drug resistant epilepsy patients. Clin Neurophysiol 2018;129:1221–9.
[12] Guy CN, Walker S, Alarcon G, Binnie CD, Chesterman P, Fenwick P, Smith S. MEG and EEG in epilepsy: is there a difference? Physiol Meas 1993;14(Suppl 4A): A99–102.
[13] Stephen JM, Ranken DM, Aine CJ, Weisend MP, Shih JJ. Differentiability of Simulated MEG Hippocampal, Medial Temporal and Neocortical Temporal Epileptic Spike Activity. J Clin Neurophysiol 2005;22:388–401.
[14] Stefan H, Hummel C, Scheler G, Genow A, Druschky K, Tilz C, Kaltenhäuser M, Hopfengärtner R, Buchfelder M, Romstöck J. Magnetic brain source imaging of focal epileptic activity: a synopsis of 455 cases. Brain J Neurol 2003;126: 2396–405.
[15] Hillebrand A, Nissen IA, Ris-Hilgersom I, Sijsma NCG, Ronner HE, van Dijk BW, Stam CJ. Detecting epileptiform activity from deeper brain regions in spatially filtered MEG data. Clin Neurophysiol 2016;127:2766–9.
[16] Jacobs J, LeVan P, Chander R, Hall J, Dubeau F, Gotman J. Interictal high-frequency oscillations (80-500 Hz) are an indicator of seizure onset areas independent of spikes in the human epileptic brain. Epilepsia 2008;49:1893–907.
[17] Velmurugan J, Nagarajan SS, Mariyappa N, Mundlamuri RC, Raghavendra K, Bharath RD, Saini J, Arivazhagan A, Rajeswaran J, Mahadevan A, Malla BR, Satishchandra P, Sinha S. Magnetoencephalography imaging of high frequency oscillations strengthens presurgical localization and outcome prediction. Brain 2019;142:3514–29.
[18] Alkawadri R, Burgess RC, Kakisaka Y, Mosher JC, Alexopoulos AV. Assessment of the Utility of Ictal Magnetoencephalography in the Localization of the Epileptic Seizure Onset Zone. JAMA Neurol 2018;75:1264–72.
[19] Velmurugan J, Nagarajan SS, Mariyappa N, Ravi SG, Thennarasu K, Mundlamuri RC, Raghavendra K, Bharath RD, Saini J, Arivazhagan A, Rajan J, Mahadevan A, Rao MB, Satishchandra P, Sinha S. Magnetoencephalographic imaging of ictal high-frequency oscillations (80-200 Hz) in pharmacologically resistant focal epilepsy. Epilepsia 2018;59:190–202.
[20] Nenonen J, Nurminen J, Kičić D, Bikmullina R, Lioumis P, Jousmäki V, Taulu S, Parkkonen L, Putaala M, Kähkönen S. Validation of head movement correction and spatiotemporal signal space separation in magnetoencephalography. Clin Neurophysiol 2012;123:2180–91.
[21] Plummer C, Vogrin SJ, Woods WP, Murphy MA, Cook MJ, Liley DTJ. Interictal and ictal source localization for epilepsy surgery using high-density EEG with MEG: a prospective long-term study. Brain 2019;142:932–51.
[22] Knowlton RC. Can Magnetoencephalography Aid Epilepsy Surgery? Epilepsy Curr 2008;8:1–5.
[23] Gavaret M, Dubarry A-S, Carron R, Bartolomei F, Trébuchon A, Bénar C-G. Simultaneous SEEG-MEG-EEG recordings Overcome the SEEG limited spatial sampling. Epilepsy Res 2016;128:68–72.
[24] Badier JM, Dubarry AS, Gavaret M, Chen S, Trébuchon AS, Marquis P, Régis J, Bartolomei F, Bénar CG, Carron R. Technical solutions for simultaneous MEG and SEEG recordings: towards routine clinical use. Physiol Meas 2017;38:N118–27.
[25] Vivekananda U, Cao C, Liu W, Zhang J, Rugg-Gunn F, Walker M, Litvak V, Sun B, Zhan S. The use of simultaneous SEEG and MEG in localising seizure onset zone. medRxiv 2020. 2020.01.31.20019505.
[26] Boto E, Meyer SS, Shah V, Alem O, Knappe S, Kruger P, Fromhold TM, Lim M, Glover PM, Morris PG, Bowtell R, Barnes GR, Brookes MJ. A new generation of

magnetoencephalography: Room temperature measurements using optically-pumped magnetometers. NeuroImage 2017;149:404–14.
[27] Vivekananda U, Mellor S, Tierney TM, Holmes N, Boto E, Leggett J, Roberts G, Hill RM, Litvak V, Brookes MJ, Bowtell R, Barnes GR, Walker MC. Optically pumped magnetoencephalography in epilepsy. Ann Clin Transl Neurol 2020;7:397–401.
[28] Collinge S, Prendergast G, Mayers ST, Marshall D, Siddell P, Neilly E, Ferrie CD, Vadlamani G, Macmullen-Price J, Warren DJ, Zaman A, Chumas P, Goodden J, MCHJ Morrall. Pre-surgical mapping of eloquent cortex for paediatric epilepsy surgery candidates: Evidence from a review of advanced functional neuroimaging. Seizure 2017;52:136–46.
[29] Verrotti A, Pizzella V, Trotta D, Madonna L, Chiarelli F, Romani GL. Magnetoencephalography in pediatric neurology and in epileptic syndromes. Pediatr Neurol 2003;28:253–61.
[30] Tierney TM, Holmes N, Meyer SS, Boto E, Roberts G, Leggett J, Buck S, Duque-Muñoz L, Litvak V, Bestmann S, Baldeweg T, Bowtell R, Brookes MJ, Barnes GR. Cognitive neuroscience using wearable magnetometer arrays: Non-invasive assessment of language function. NeuroImage 2018;181:513–20.
[31] Pizzo F, Roehri N, Villalon SM, Trébuchon A, Chen S, Lagarde S, Carron R, Gavaret M, Giusiano B, McGonigal A, Bartolomei F, Badier JM, Bénar CG. Deep brain activities can be detected with magnetoencephalography. Nat Commun 2019;10:1–13.