Electric and Magnetic Source Imaging of Epileptic Activity

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Summary

Electroencephalography (EEG) plays a central role in confirming the diagnosis of epilepsy and in characterizing the electro-clinical epilepsy syndrome. Additionally, EEG and magnetoencephalography (MEG) can be used to image the functional activity of the brain with millisecond resolution. Recent progresses in recording systems now allow easily measuring the electromagnetic field generated by cerebral activity using hundreds of sensors spread all over the scalp. Together with these advances in hardware, modern analytic methods that take into consideration the cerebral anatomy of individual patients and account for the involvement of distributed cortical areas have greatly increased the spatial accuracy of electric and magnetic source imaging. These techniques are most useful in the evaluation of patients with drug-resistant focal seizures who are potential candidates for epilepsy surgery. Localizing the source of interictal epileptic spikes recorded by high-density EEG or MEG is a reliable marker of the epileptogenic zone, the brain region whose resection leads to seizure freedom. The accuracy of electric and magnetic source imaging seems higher than that of positron electron tomography (PET) or single-photon emission computed tomography (SPECT) and is on par with that of structural magnetic resonance imaging. Electromagnetic source imaging is also increasingly used to define the neural networks involved in epileptogenesis. Electromagnetic source imaging should be part of the presurgical evaluation of all patients considering epilepsy surgery.

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Key words: Electroencephalography, magnetoencephalography, functional neuroimaging, epilepsy

Imagerie de source électrique et magnétique de l'activité épileptique

L'électroencéphalographie (EEG) joue un rôle central pour confirmer un diagnostic d'épilepsie et pour caractériser le syndrome épileptique électro-clinique. L'EEG et la magnétoencéphalographie (MEG) peuvent également être utilisées pour localiser l'activité fonctionnelle du cerveau avec une résolution temporelle de l'ordre de la milliseconde. Il est maintenant facile d'enregistrer le champ électromagnétique généré par l'activité cérébrale au moyen de centaines de senseurs répartis sur l'ensemble du scalp. En plus de ces progrès techniques, les méthodes d'analyse modernes, qui incluent l'anatomie cérébrale de chaque patient et qui tiennent compte de l'activité de régions cérébrales étendues, ont nettement amélioré la précision spatiale de l'imagerie de source électrique et magnétique. Ces techniques sont très utiles dans le contexte de l'évaluation de patients souffrant d'épilepsie focale pharmaco-résistante candidats à la chirurgie de l'épilepsie. La localisation de la source des pointes intericales épileptiques est un marqueur fiable de la zone épileptogène, dont la résection supprime les crises épileptiques. La précision de l'imagerie de source électromagnétique semble meilleure que celle de la tomographie par émission de positrons (PET) ou de la tomographie d'émission monophotonique (SPECT) et égale à celle de l'imagerie par résonance magnétique. De plus, l'imagerie de source électromagnétique permet de délimiter les réseaux neuraux qui participent à la génération des crises épileptiques. L'imagerie de source électromagnétique devrait faire partie du bilan préopératoire de tout patient candidat à une chirurgie de l'épilepsie.

Mots clés : Electroencéphalographie, magnétoencéphalographie, neuroimagerie fonctionnelle, épilepsie

Elektrische und magnetische Quellenlokalisation der epileptischen Aktivität

Die Elektroenzephalographie (EEG) spielt eine zentrale Rolle um eine Epilepsie zu diagnostizieren und das epileptische Syndrom zu charakterisieren. Das EEG und die Magnetoenzephalographie (MEG) können die Aktivität des Gehirnes darstellen und zwar mit einer Präzision von Millisekunden. Heuzutage kann man das durch die Hirnaktivität generierte elektromagnetische Feld mit Hunderten von Sensoren auf dem ganzen Kopf relativ einfach registrieren. Neben diesen technischen Fortschritten erlauben moderne Analysemethoden die Darstellung der elektrischen Aktivität von breiten kortikalen Regionen unter Berücksichtigung der individuellen Hirnanatomie, so dass die spatiale Auflösung der elektrischen und magnetischen Bildgebung deutlich verbessert ist. Diese Techniken sind sehr hilfreich in der prächirurgischen Evaluation von Patienten mit pharmako-resistenter Epilepsie. Die Quellenlokalisierung der interiktalen Spitzenpotenziale ist ein zuverlässiger Marker der epileptogenen Zone, deren Resektion zur Anfallsfreiheit führt. Die Präzision der elektromagnetischen Quellenbildgebung scheint höher zu sein als die von nuklearmedizinischen Methoden (PET/SPECT) und gleich gut wie jene der strukturellen Kernspintomographie. Ausserdem kann die Quellenlokalisation die epileptischen neuronalen Netzwerke darstellen, welche zur epileptischen Aktivität beitragen. Die elektromagnetische Quellenbildgebung sollte für alle prächirurgisch evaluierten Patienten eine Routineuntersuchung werden.

Schlüsselwörter: Elektroenzephalographie, EEG, Magnetoenzephalographie, funktionnelle Bildgebung, Epilepsie

EEG and MEG: From Epileptic Focus to Brain Networks

What are electroencephalography (EEG) and magnetoencephalography (MEG) doing in a collection of reviews devoted to advanced imaging in epilepsy? After all, EEG produces squiggly lines (at least to the uninitiated), not pictures of the brain. What's more, one of the first things that residents embarking on clinical neurophysiology training are told is that EEG traces do not simply reflect the activity of the brain area lying directly under the corresponding electrode. So how could EEG ever be expected to localize epileptic activity with the high spatial resolution reached by legitimate neuroimaging methods such as MRI? Then again, if functional neuroimaging using EEG were at all possible, it would be a highly valuable method in epilepsy thanks to its millisecond temporal resolution – several orders of magnitude better than functional MRI.

MEG records the magnetic fields produced by neural activity that diffuse out of the head (whereas EEG measures the electric potential at the scalp surface). Because these magnetic fields are very small (approximately eight orders of magnitude smaller than the magnetic field of the earth), high amplification and strict shielding from outside interference are required. MEG systems are thus large machines that take up a dedicated shielded room. MEG and EEG are sensitive to different physical features of neural activity, and the two techniques can therefore bring complementary information. The relative strengths and weaknesses of each modality will be discussed throughout the article.

Here, we recapitulate how electromagnetic neuroimaging using EEG (Electric Source Imaging, ESI) and Magnetic Source Imaging (MSI) has in fact become a reality in recent years, thanks to developments both in hardware (recording systems) and software (analytic approaches), and how it can crucially inform clinical practice in epilepsy [1, 2].

How Does Electromagnetic Neuroimaging Work?

The inverse problem

Why is it actually difficult to localize the neural generators of EEG signals recorded at the surface of the head (the so-called inverse problem)? The physics of electromagnetism state that any given configuration of the voltage field at the surface of the head could theoretically be generated by an infinite number of configurations of the potential generators. Not all of these configurations are biologically or medically realistic, however, and the practical approach to solving the inverse problem is therefore to set constraints on what the potential solution may be.

The source space

One of these constraints relies on our knowledge of where epileptic EEG signals are generated, i.e. by neurons in the cortex [3]: the generators of any given surface voltage field should therefore lie in the cortical grey matter (including the hippocampus and amygdala), but not in the basal ganglia or thalamus and certainly not in the white matter or the cerebral ventricles. Feeding the patient's own brain anatomy into the inverse solution improves the accuracy of ESI by taking into account individual anatomical variations as well as existing cerebral lesions or malformations [4, 5].

Dipoles vs. distributions

Another constraint concerns the number of sources: some inverse solutions limit the numbers of generators to one or a few point-like sources (i.e. equivalent dipoles), while others attempt to estimate cerebral activity at thousands of points distributed within the brain volume (distributed solutions). Equivalent dipole modelling has intuitive appeal in the context of epilepsy: we like to think of interictal spikes as being generated by a single, well-delineated patch of cortex. The reality is more complex, however: spikes are often generated within a spatially widespread epileptic network, and propagation from the initial source of the spike to other parts of the network happens within milliseconds of its onset [6, 7]. Moreover, dipole localisation is artificially in the "centre of mass" of the region that it represents. Therefore, the orientation of the dipole is as important as its localisation in interpreting such source analysis, and distance measurements between a dipole and a lesion or an intracranial electrode do not really make sense. Distributed inverse solutions are therefore needed if we want to take into consideration the whole epileptogenic network. Multiple algorithms for distributed inverse solutions have been developed, each incorporating specific a priori mathematical and biophysical assumptions. They have been the subject of several recent reviews that detail these points [2, 8 - 11].

Number and position of the sensors

An important factor in determining how well ESI/MSI performs is how precisely and completely the electromagnetic field is sampled at the head surface. Using EEG, increasing the number of electrodes from a standard, 31-electrode montage to 123 electrodes significantly improves the localization of interictal spikes [12]. It is also crucial to sample the electric field below the top of the ears, as routine EEG montages that totally ignore this region cause generators in the inferior and medial temporal lobes to be significantly displaced upwards [13]. Recently developed EEG caps with more than 200 sensors can now easily be applied in minutes, making high-density EEG readily available in the clinical neurophysiology laboratory. Appropriately-sized caps are also available for infants and children. High density of sensors is made particularly relevant by the fact that the ratio between skull and brain conductivity has recently been shown to be higher than previously estimated (1:20 instead of 1:80) [14], so that a high spatial sampling of scalp EEG is definitely more than oversampling of a field smoothened by its passage through the skull. This is naturally even truer in children who show higher skull conductivity than adults. Current MEG systems comprise around 300 sensors to record and image neuronal activity using the same analytic principles that apply to ESI.

Methodological differences between ESI and MSI

Magnetoencephalography and electroencephalography both measure cerebral activity in real time, but since they measure different physical properties of this activity, there are differences in their sensitivity to different configurations of neural generators. Magnetic fields diffuse across the skull and scalp with essentially no distortion, whereas electrical potentials are distorted by variations of skull thickness, cranial foramina, previous craniotomies, etc. [15]. Thus, there is no such thing as a "breach rhythm" in MEG. Also for this reason, MSI is often claimed to be more accurate than ESI in detecting superficial, neocortical sources [16]. However, MEG is only sensitive to the activity of neurons oriented tangentially (i.e. parallel to the skull surface and the MEG sensors, as found in sulcal banks) and not to that of radially-oriented neurons (as found in gyral crowns and fundi). By contrast, EEG is able to record the activity of neurons regardless of their orientation [17]. Another clinically important difference is that MEG is less sensitive to deep sources than EEG [11]. Finally, MEG sensors are affixed to the machine and not to the patient's head, which makes MEG exquisitely sensitive to patient motion. As a result, MEG is impractical for recordings longer than a couple of hours or sleep studies and in young children or non-cooperative patients.

What Can ESI and MSI Image in Epilepsy?

Since ESI is based on the exact same signal as the routine EEG, everything that is recorded by EEG can be subjected to ESI. This ranges from normal spontaneous brain rhythms [18] through sensory-evoked and event-related activity [19] to epileptic activity.

At the EEG and Epilepsy unit of Geneva University Hospitals, we systematically perform high-density EEG recordings as part of the non-invasive evaluation of adult and paediatric patients considered for epilepsy surgery. Our approach to ESI is illustrated in **Figure 1**.

ESI/MSI of interictal spikes

Most studies of ESI and MSI in epilepsy to date focused on localising interictal spikes rather than on seizures. The justification for this lies in their respective nature: spikes can be averaged together in order to improve the signal-to-noise ratio, are usually more frequent than seizures, and their spatiotemporal dynamics are simpler [20]. As previously mentioned, however, interictal spikes do not remain confined to a single neuronal population in a single cortical patch; rather, they propagate within milliseconds to involve cortical areas away from the initial generator [6]. The temporal resolution of EEG and MEG allows disentangling the generation of a spike from its propagation. In order to im-

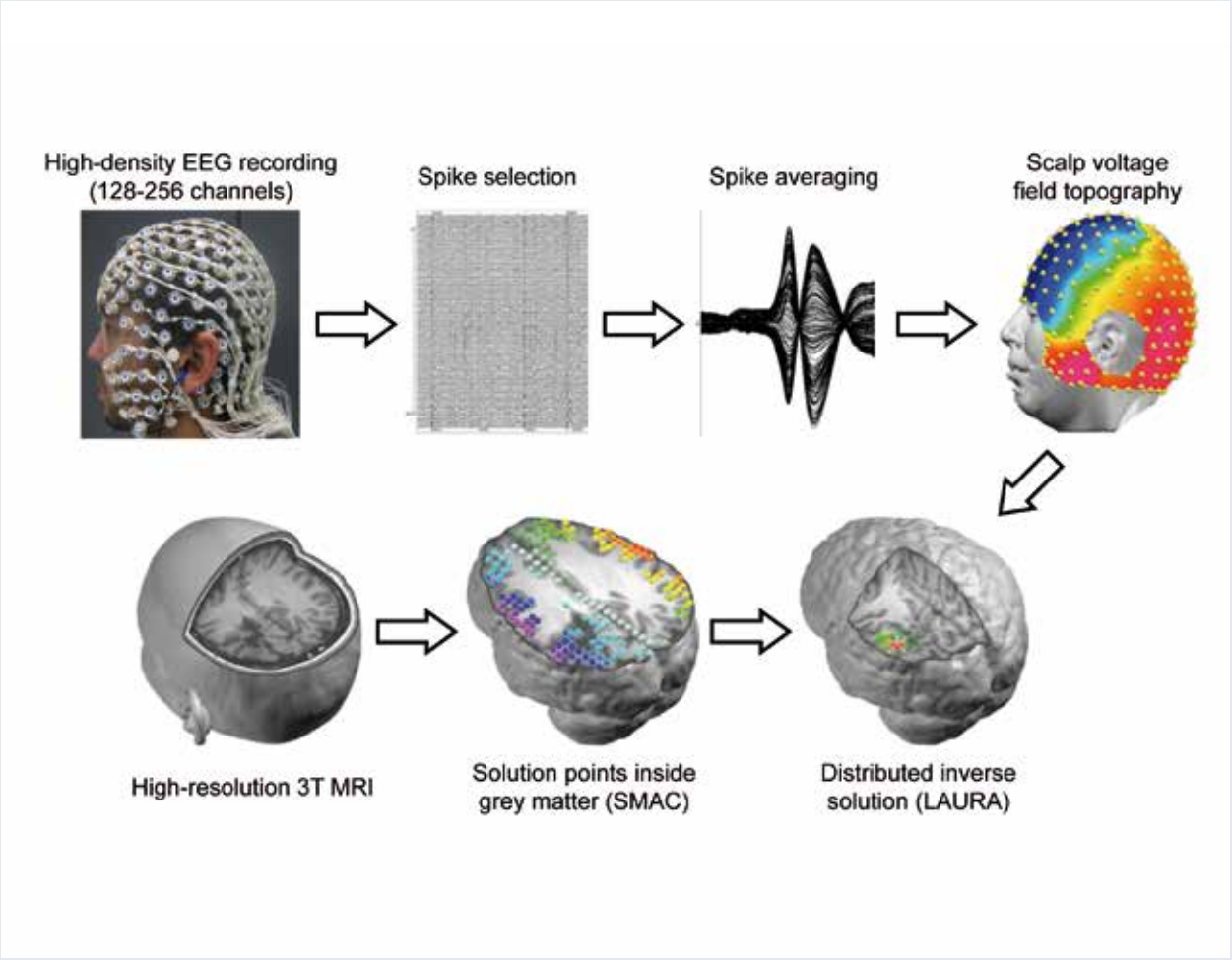

Figure 1: Electric Source Imaging of interictal epileptic spikes. Upper line: high-density EEG is recorded. Spikes are identified by visual analysis and averaged together to improve the signal-to-noise ratio. The topography of the voltage field on the scalp is mapped. Lower line: the patient's own high-resolution MRI is used to define the source space for the inverse solution algorithm (Spherical Model with Anatomical Constraints, SMAC; [4]). A distributed inverse solution (Local AUtoRegressive Average, LAURA; [21]) is used to localize the source of the surface voltage field.

age the initial generators of a spike, it is recommended to perform the ESI around the middle of the upslope of the spike rather than at its peak [7].

ESI/MSI of seizure onsets

Ictal activity can also be localized by ESI [22 - 24]. The procedure is generally applied during the very first seconds around the ictal onset, both because we are more interested in localizing the cortical area where a seizure begins than its potentially multiple and widespread propagation areas, and also because EMG artefacts due to motor activity during the seizure often obscure the EEG so much as to make ESI impossible after a few seconds. Although adequate validation of its accuracy and clinical usefulness is yet lacking, ictal-onset ESI may well find a place in the arsenal of clinical neurophysiologists. High-density EEG caps that allow recording for longer than 24 hours, including while sleeping, will likely increase the number of seizures that are captured and amenable to ESI.

Imaging the ictal onset using MSI has also been reported in a few cases where seizures were serendipitously captured during an MEG recording [25]. However, as mentioned above, MEG machines are very sensitive to motion of the patient. Therefore, anything more than minor motor activity during a seizure will interrupt the recording.

How Accurate Is ESI/MSI?

Here, we focus on clinically relevant measurements of accuracy in the context of epilepsy and leave aside modelling approaches and experimental studies performed in other contexts. Ideally, assessing the accuracy of ESI in epilepsy should be performed by measurin

how far the ESI/MSI lands from the actual epileptic focus (measurement error). This prompts two questions: first, what exactly is an epileptic focus? Second, how do we know for sure where this focus is in the brain, i.e. what is our gold standard to compare ESI against?

In the zone

An approach to defining the "epileptic focus" involves identifying several interrelated, but not necessarily overlapping, zones participating in the electroclinical picture of epilepsy [26]. Of these zones, the epileptogenic zone, a theoretical construct defined by the cortical area whose complete resection is necessary to free the patient from seizures, is the one that we want to localize. However, the epileptogenic zone cannot be delineated preoperatively, and other zones therefore need to be used as surrogates. These include the irritative zone, the cortical area that produces interictal spikes, defined most precisely by intracranial EEG; the ictal onset zone, from where seizures originate, studied by intra-cranial EEG (and also by ictal single-photon emission computed tomography, SPECT); and the epileptogenic lesion, the morphological abnormality (when present) that generates the seizures, revealed by MRI. If there is a single MRI lesion that may plausibly cause the epilepsy (e.g. unilateral hippocampal sclerosis or focal cortical dysplasia), then it is a good approximation to the epileptogenic zone [27]. In cases where there are either no lesion or multiple lesions on the MRI, however, the seizure onset zone is generally thought to be the better surrogate [28].

Irritative zone and seizure onset zone

It becomes clear that ESI/MSI of interictal spikes in fact attempts to localize the irritative zone, and that the clinical usefulness of this technique depends both on its absolute accuracy and on the value of the irritative zone as a surrogate for the seizure onset and epileptogenic zones. A few studies have shown that the irritative zone indeed often co-localises with the seizure onset zone [29 - 31] (**Figure 2A**). In fact, resecting the cortical areas that lie outside the margins of the seizure onset zone but display irritative activity has been associated with a more favourable post-operative outcome [32]. Of course, there are cases when there is an extended or multifocal irritative zone, not all of which participate in seizure generation (so-called secondary irritative zone [33]) (**Figure 2B**). The results of ESI/MSI, like those of any investigation, must therefore always be integrated within the patient's overall clinical, neurophysiological and radiological picture, in order to assess its reliability in estimating the epileptogenic zone.

Accuracy of ESI/MSI with respect to intracranial EEG

Few studies have assessed the accuracy of ESI or MSI in large groups of patients with diverse epilepsy types using intracranial EEG as a gold standard. Co-localization at a sub-lobar level is often reported as a criterion for accuracy rather than absolute measurement error; sub-lobar borders are defined partly arbitrarily according to anatomical landmarks, and sub-lobar regions can differ widely in size and shape. Using MSI, Agirre-Arrizubieta et al. [34] reported concordant localization in 90% of lateral temporal spikes, 80% of interhemispheric and peri-central spikes, 60% of superior frontal spikes, 40% of orbitofrontal spikes, and 0% of medial temporal spikes. Knowlton et al. [35] found the concordance between MSI and the seizure onset zone to be about 80% in patients with lateral temporal lobe epilepsy and 45% in those with medial temporal lobe or extratemporal lobe epilepsy. The same group found that the performance of MSI was on average similar to that of PET and ictal SPECT [36]. Overall, findings from these studies suggest that MSI performs better when the epileptic focus is not in the medial temporal lobe, likely because of the difficulties of MEG in recording the activity of deep-seated brain structures [11].

Accuracy of ESI/MSI with respect to resection and post-operative outcome

Another approach to assessing the accuracy of ESI is to compare its result with the resected brain volume as a function of post-operative outcome: ESI is deemed accurate if it falls within the resection and if the patient is subsequently seizure-free. This approach makes sense in the clinical context of epilepsy surgery; its main drawback is that the resection will always include normal brain tissue (sometimes a considerable volume of it) surrounding the epileptogenic zone, and that the ESI may well lie centimetres away from the epileptogenic zone and still be included in the resection. In the largest study on the performance of ESI in epilepsy surgery so far, performed by the EEG and epilepsy unit of Geneva University Hospitals, the sensitivity of ESI was 84% and its specificity 88% [37]. The accuracy of ESI was further highlighted by the finding that it performed at least as well, and often better, than the more established structural MRI, PET and SPECT. Importantly, ESI performed as well for patients with temporal lobe epilepsy as it did for patients with extratemporal lobe epilepsy [37]. That study also underlined the importance of an adequate sampling of the scalp electrical potential field: when ESI was performed on the standard, 32-channel EEG recordings instead of the 128- or 256-channel high-density EEG systems, the accuracy of ESI fell significantly (sensitivity and specificity around 60%).

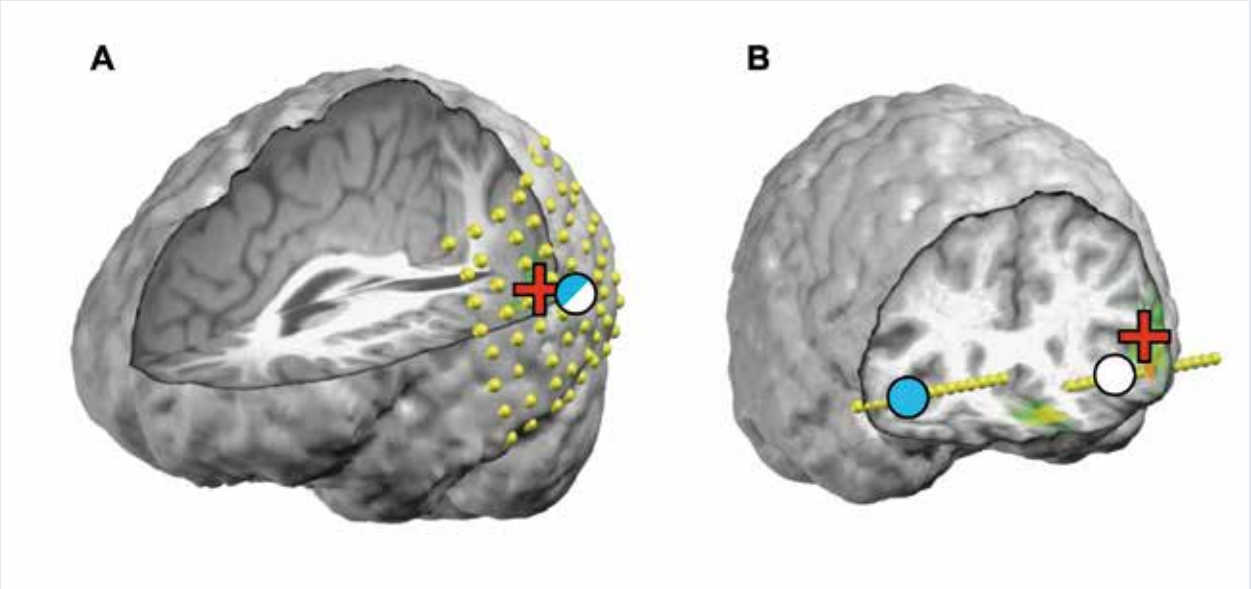

Figure 2: Accuracy of ESI of interictal spikes with intracranial EEG as the gold standard
A: Successful localization of the irritative zone and of the seizure onset zone. In this 15-year-old female patient with tuberous sclerosis, the ESI maximum (red cross) of interictal spikes pointed towards the left angular gyrus. Intracranial EEG showed that both spikes and seizures were generated in the left inferior parietal lobule. The white and blue circle shows the intracranial electrode nearest the ESI maximum that was involved in both the irritative and seizure onset zones.
B: Successful localization of the irritative zone, but unsuccessful localization of the seizure onset zone. This 51-year-old female patient had previously undergone a right frontal resection for a focal cortical dysplasia, which had failed to bring seizure freedom. She had bilateral independent frontal interictal abnormalities. Ictal scalp video-EEG suggested that the seizures still originated from the anterior right hemisphere, but PET and SPECT were non-contributive, and neuropsychological testing found deficits of verbal memory, suggesting left-sided temporal dysfunction. During the high-density EEG, only left-sided spikes were recorded. Intracranial EEG with bilateral frontal and temporal stereotaxic electrodes was therefore performed. The ESI maximum (red cross) lay close to the left frontal irritative zone revealed by intracranial EEG (white circle). All seizures, however, originated from the right frontal lobe (blue circle). In this case, consideration of the electro-clinical pattern and other imaging tools strongly suggest that the spike recorded for ESI is not representative of the seizure onset and the epileptogenic zone. This underlies the importance of integrating ESI with other clinical and imaging data.

Influence of ESI/MSI on surgical planning

The influence of ESI or MSI results on the strategy for implanting intracranial electrodes has been assessed in two MEG studies where the implantation strategy was established twice for each patient: first after reviewing the results of all investigations except MSI, and then again after showing the results of MSI [38, 39]. MSI led to changes in the implantation strategy in 23% to 33% of cases, indicating that this technique brings non-redundant information to a significant proportion of patients who have already undergone multiple non-invasive testing modalities. Findings of a positive association between the inclusion of the ESI or MSI result in the resection and seizure freedom ([37]; see also [40 - 42]) also suggest that the results of ESI or MSI should be taken into account when defining the strategy for resective surgery.

So which one is better: ESI or MSI?

This remains a controversial issue. The ultimate test, where the accuracy of ESI and MSI would be compared against each other using simultaneously recorded interictal spikes, with similar numbers of sensors and head coverage, and with simultaneously acquired intracranial EEG data as the gold standard, has yet to be published. In the interim, most of the attempts at comparing the two techniques suffer from shortcomings that limit the strength of the conclusions that can be drawn from them [11]. For instance, comparing high-density MEG systems against (at most) moderate-resolution EEG recordings artificially tips the balance in favour of MEG [43, 44]. In any case, more importantly than establishing which technique beats the other, it would be more beneficial for patients considering epilepsy surgery to ensure that at least one of the techniques (with state-of-the-art, clinically validated acquisition and analysis strategies) is available to them.

From Source Localisation to Network Analysis

As stated above, the precise localisation of the generators of epileptic activity is of particular relevance for patients who are candidates for epilepsy surgery. However, despite the fact that a very focal cortical resection can lead to seizure freedom, consistent results of several studies using different mapping techniques strongly support the concept that epilepsy is a condition generated by abnormal brain networks and affecting large-scale brain networks, rather than the result of a very focal unique dysfunctional patch of cortex. Scalp EEG [45], intracranial EEG [33], MEG [46], functional MRI [47] and simultaneous EEG-fMRI [48] have all revealed large-scale often bi-hemispheric functional alterations in relation to epileptic activity. Structural imaging such as tractography [49] or cortical volume studies [50] also support this network-based approach. The understanding of such network dysfunctions requires not only to localise the affected network nodes, but also to characterise the interdependencies and flow of information within the network. This can be done with several methods of "functional connectivity". The temporal resolution of EEG and MEG makes them particularly adapted to study the fast-changing dynamics of the connectivity between the network sources. Granger

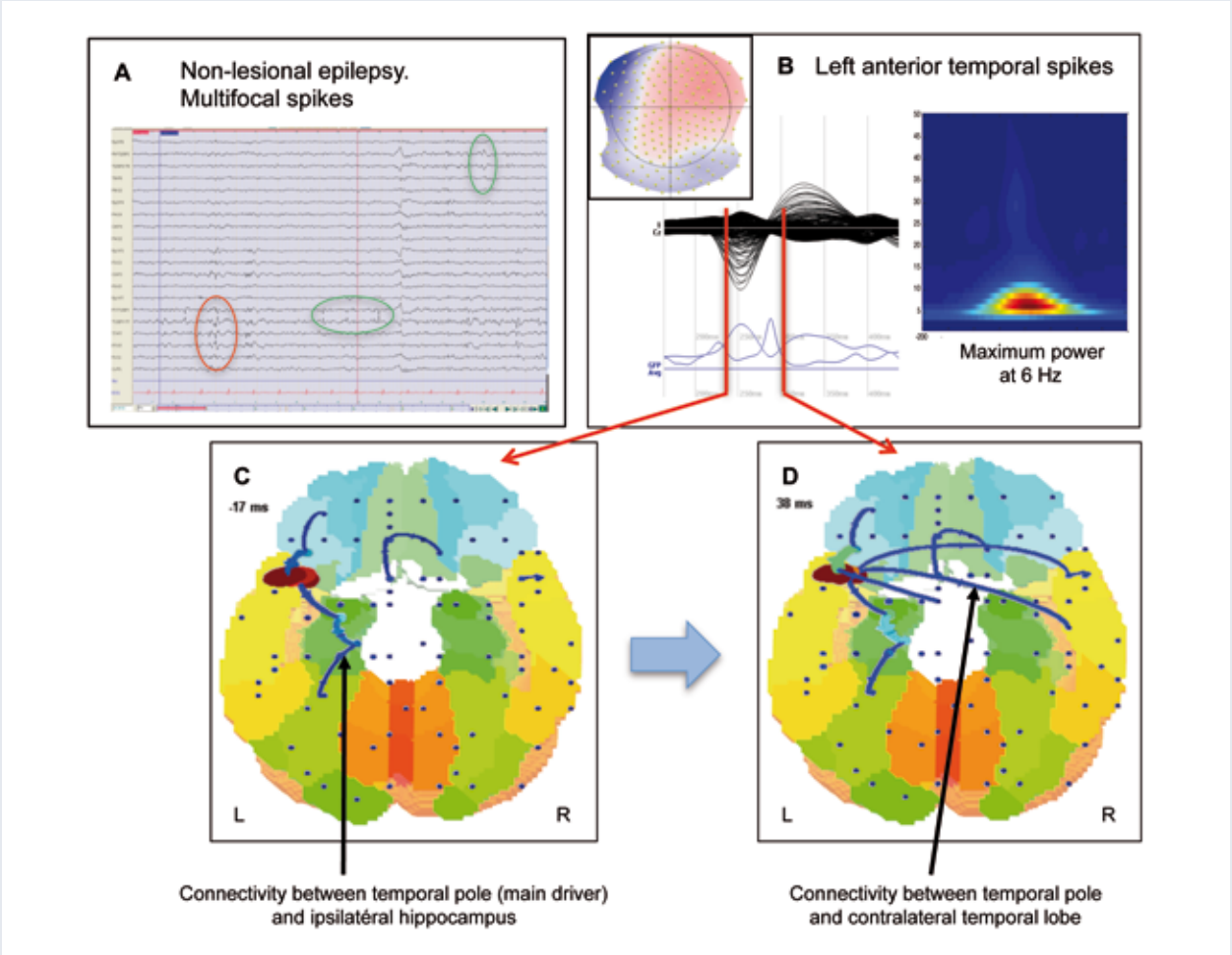

Figure 3: Directed connectivity in a patient with temporal lobe epilepsy using high-density EEG.
A: Temporally independent spikes in the left anterior temporal (red), left posterior temporal and right temporal regions (green).
B: The averaged left anterior temporal spike and the corresponding scalp voltage topography are calculated. The frequency with maximal power (6Hz) is identified. The directed brain connectivity related to the interictal activity can then be estimated for this major frequency for 82 cortical regions based on an atlas (shown in C and D). The connectivity calculation is time-varying so that changes of the connectivity across time during the epileptic spike can be investigated, given the high temporal resolution of EEG.
C: Transverse view of the regions of interest at the level of the temporal lobe. At spike onset, the main outflow of information (dark red spot) estimated by connectivity analysis is in the temporal pole (red spot) and has strong connections (arrows) with the anterior and posterior temporal medial structures.
D: At a later time point there is strong connectivity with the contralateral temporal lobe.
The region of highest outflow was resected and the patient is seizure-free without spike on the post-operative EEG. The connectivity pattern could explain the multifocality of the interictal spikes.

causality allows inferring the causal relationships between the signals of two regions by looking at how much the signal of one region can be reliably predicted knowing the previous values of the other signal (i.e. how much transfer of information, or directed causality, is occurring between the two regions). This approach has been applied to MEG data in a small case series of patients with focal epilepsy and found that the regions contributing most to the outflow of neuro-electrical information were concordant with the epileptogenic regions [46]. Moreover, connectivity between affected regions seems to be related to disease duration [51]. We are currently developing and using functional connectivity analysis of high density EEG and ESI to map the major sources of information ("outflow" = epileptogenic zone ?) and their connectivity in focal epilepsy, which will provide additional information for managing surgical candidates, particularly when multifocal epileptic activity is recorded on the scalp (**Figure 3**).

Why Is ESI/MSI Not Universal? Overcoming Barriers to Their Use in Clinical Routine

Given the accuracy of ESI and MSI and their proven usefulness in the workup of candidates for epilepsy surgery, one may wonder why these techniques have not yet been routinely adopted. We suspect that there are several potential barriers to this, all of which can be remediated. First, the clinicians who routinely work with epileptic patients need to be aware of the techniques and of the potential clinical benefits that they can bring to the patients. However, ESI and MSI still lie on the margin of the curriculum of clinical neurophysiology residents or EEG technicians. This could be remediated by integrating ESI and MSI in the teaching curriculum. Second, learning how to perform ESI or MSI analysis requires adequate training so that the technique can yield its full potential. Appropriately trained personnel can process high-density EEG or MEG recordings and generate ESI or MSI in one to two hours, a relatively small temporal investment given the potential clinical benefits. Fourth, the cost of the equipment may be more of an issue for MEG, where the machine, its environment and the support team cost several million dollars, while the price of acquiring and maintaining a high-density EEG system is at least one order of magnitude lower, which makes it readily affordable for most hospitals in the Western world.

To conclude, integrating ESI or MSI in the routine non-invasive workup of candidates for epilepsy surgery is feasible and is likely to provide significantly higher accuracy in the delineation of the suspected epileptogenic zone, and ultimately meaningful improvement in clinical outcomes.

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