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PASSIVE AND ACTIVE MARKERS OF CORTICAL EXCITABILITY IN EPILEPSY

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Key points:

- Advances in computation and engineering have enabled the development of novel quantitative biomarkers of cortical excitability in epilepsy
- We discuss developments in passive (recorded in the resting state of the EEG) and active (stimulation-induced) biomarkers of excitability
- Several barriers must be overcome to permit translation of these biomarkers to clinical practice

ABSTRACT

EEG has been the primary diagnostic tool in clinical epilepsy for nearly a century. Its review is performed using qualitative clinical methods that have changed little over time. However, the intersection of higher resolution digital EEG and analytical tools developed in the last decade invites a re-exploration of relevant methodology. In addition to the established spatial and temporal markers of spikes and high frequency oscillations, novel markers involving advanced post-processing and active probing of the interictal EEG are gaining ground. This review provides an overview of the EEG-based passive and active markers of cortical excitability in epilepsy and of the techniques developed to facilitate their identification. Several different emerging tools are discussed in the context of specific EEG applications and the barriers we must overcome to translate these tools into clinical practice.

ABBREVIATIONS

Antiseizure medication (ASM); cortico-cortical evoked potentials (CCEPs); intraoperative electrocorticography (ECoG); electromyography (EMG); epileptogenic zone (EZ); functional magnetic resonance imaging (fMRI); high-frequency oscillations (HFO); intracranial electroencephalography (iEEG); motor-evoked potential (MEP); non-rapid eye movement (NREM); transcranial magnetic stimulation (TMS); TMS-evoked potential (TEP)

1. Introduction

EEG has been one of the primary diagnostic tools for epilepsy since 1924, when Hans Berger first recorded human EEG. By the 1950's, clinicians had identified several patterns that correlated with epilepsy: spikes, sharp waves, seizures, etc. Identifying these patterns by eye became the art of the epilepsy specialist, which has continued to be handed down to each subsequent generation as the *de facto* standard of care. The decades that have followed have seen remarkable changes in technology and analytical tools, yet these new tools remain largely unused by clinicians. One of the primary goals of the ICTALS community is to translate these new tools into epilepsy care.

The 2022 ICTALS meeting presented several emerging techniques to identify epileptic abnormalities. In this article, we present several strategies under development to identify brain cortex that is likely to be epileptic. These strategies focus on the concept of identifying cortical excitability using tools that are not available to clinicians in their current clinical practice. After presenting an overview of these techniques, we turn our focus to several key questions that must be addressed to allow these techniques to be utilized by clinicians. We limit our scope to biomarkers to identify epileptic cortex rather than biomarkers for seizure prediction, which are discussed in a separate manuscript in this issue[1].

2. Cortical excitability

Cortical excitability can be measured as the varying cortical response to a fixed stimulation, repeated serially. While this is possible non-invasively (transcranial magnetic stimulation, TMS) and invasively during intracranial EEG (iEEG) investigations, cortical excitability is mostly inferred from the passive observation of interictal epileptiform discharges (spikes, sharp-waves, high-frequency oscillations: HFO, etc.). These discharges tend to occur frequently, multiple times per day or hour, and have long been used as markers of epilepsy, both to confirm diagnosis and to localize epileptic brain tissue. Mechanistically, these discharges are thought to reflect abnormal firing of a group of neurons[2–4], a phenomenon often referred to as “hyperexcitability” or “hypersynchronicity” in the epilepsy literature. Given that the categories referred to by the latter terminology elude clear cut-offs (e.g., When is the brain too synchronized?[5]), we will here simply use the term “cortical excitability”, a property of an ensemble of neurons, which individually have their own neuronal excitability. Importantly, the degree of cortical excitability can vary both in space, with focal epileptic tissue being more excitable, and in time, delineating “at risk” periods as well as brain states (**Table 1**).

3. Passive markers of excitability

3.1 Spikes

Critics say that the time of spikes has come and gone, but recent advances in engineering have given spikes new relevance. Interictal spikes (here we include ‘sharp waves’ and other epileptiform discharges seen with standard EEG electrodes) are brief paroxysmal discharges, facilitated by cortical excitability. Spikes are an attractive biomarker of epileptic regions for surgical planning. The shared excitability underlying both spikes and seizures has led some to suggest that we think of spikes as mini-seizures, providing insight into the same disordered process that leads to seizures[6]. Spikes occur much more frequently than seizures, and — unlike seizures — we don’t need to wean antiseizure medication (ASM) or monitor patients in the Epilepsy Monitoring Unit to induce spikes. In the 1950s and 1960s, the epilepsy community relied heavily on spikes to guide surgery. When neurosurgeons like Penfield and Rasmussen performed open resections for epilepsy using intraoperative electrocorticography (ECoG), they would resect tissue until the spikes went away, reporting good outcomes with this approach[7].

Later in the 20th century, spikes fell out of favor. Rasmussen noted that some patients became seizure-free despite leaving behind cortex with spikes. Clinicians increasingly saw cases of spike-seizure discordance, including patients with bitemporal spikes rendered seizure-free with a unilateral temporal lobectomy[8]. This led to the belief that the “epileptogenic zone” (EZ), the cortex we must remove to stop seizures, is typically a subset of the "irritative zone", the cortex that generates spikes[6]. Epileptologists and surgeons lamented the fact that there was no way to distinguish the spikes that needed to be resected from the innocent spikes that are better left alone. As a result, spikes now play a limited role in pre-surgical evaluation for drug-resistant epilepsy. The current belief that spikes localize near the EZ, but are non-specific, suggests that they are ripe for data mining[9]. The useful information is there if we can learn how to decode it.

New tools have enhanced our ability to analyze spikes. Modern data storage now allows us to save the entirety of the days-to-weeks-long scalp or intracranial EEG (iEEG) recording at high sampling rates. Powerful computers can more quickly mine large amounts of interictal data. Sophisticated algorithms detect spikes as accurately as clinicians at speeds impossible for humans[10–12]. These advances allow us to do what the human eye cannot: We can summarize the relative frequency of spikes in different brain regions, and how they change over time[13]; we can measure the precise timing of when a spike reaches different electrodes (**Fig. 1**)[14–17]; and we can compare spike morphology across space and time[4].

Applying these tools has taught us that not all spikes are equal as surgical biomarkers. Combining analysis of time-varying spike rates with automated sleep staging demonstrated that spikes in non-rapid eye movement (NREM) sleep are more frequent and better localize seizure generators than spikes occurring in wakefulness[18,19] . Also, the earliest spike in a spike train better localizes the seizure onset zone than the later spikes[20]. Combining EEG with functional magnetic resonance imaging (fMRI) reveals the area of maximal hemodynamic response to spikes, which also corresponds to the seizure onset zone[21]. Spikes with co-occurring HFOs have different single-neuron correlates than spikes without HFOs, and these HFO-spikes better localize the seizure onset zone[4]. We can now do what Rasmussen could not: we can say *which* spikes are informative of the EZ.

Within the limitations of retrospective studies, quantitative spike data appears to localize the EZ as well as clinical designations of the seizure onset zone[18]. These advances in spike research are concurrent with increasing recognition of the limits of seizure data. For instance, chronic iEEG has revealed that independent bilateral seizures are common, and it often takes longer to record the first contralateral seizure than is feasible in the hospital setting[22]. Together, these results argue that spikes should be more than just ancillary data in surgical planning. The advances in engineering presented at ICTALS are elevating spikes to the same level as seizures.

3.2 High-frequency oscillations

Research over the last years has shown HFOs to be a specific interictal biomarker of epileptic tissue in various patient cohorts, be it in pre-surgical iEEG to help assess the EZ[23–25] (**Fig. 2**), intraoperative ECoG[26], or non-invasive scalp EEG[27–33]. Each modality addresses different clinical questions. For example, HFOs in non-invasive recordings hold promise for their widespread application in measuring seizure propensity, disease severity, and treatment response[27], thus improving prognostication of the disease state. These studies suggest that HFO-based information may improve current electrophysiological practice, which relies on the detection of seizures and interictal spikes. However, multiple studies challenge the overly optimistic view that HFOs can identify epileptogenic tissue using only a few minutes of interictal slow-wave sleep data[24,34–38]. To meet these challenges, strategies have been proposed on how to validate biomarkers based on HFOs[39,40].

However, one aspect that has hindered the acceptance of HFOs is the inconsistency in not just how HFOs are analyzed but also in what goals we expect them to accomplish. For example, whether HFOs can be used intraoperatively to adjust resection boundaries[34] is a different question than whether HFOs can predict surgery outcome[41]. Part of the confusion is that HFOs themselves are not a biomarker: Part of a biomarker's definition is the specific clinical context, and HFOs are an electrographic element that may be useful in multiple clinical contexts. Even just considering

HFOs measured during interictal periods of iEEG, at least three potential biomarkers may be considered: a diagnostic biomarker of the EZ (here defined as the cortical region necessary and sufficient for seizure initiation), a prognostic biomarker of surgery outcome, or a diagnostic biomarker of seizure onset zone. Of these three, only the latter two can be validated, as the EZ cannot be directly and objectively assessed. It can be argued that a biomarker of seizure onset zone is not needed, as it already is determined by standard clinical procedures and there is need to find unique information to improve outcomes, not merely the same information that often fails. Each HFO-based biomarker may have different optimal choices for data collection, HFO detection and analysis, and biomarker validation. Thus, as applies for all markers of cortical excitability, future progress will be facilitated by clearly demarcating which biomarker is being discussed in each paper and presentation. This will help preventing results from one HFO-based biomarker being falsely attributed to a different HFO-based biomarker.

A few other issues are worth noting. 1) HFO-based biomarkers should be validated against the measure appropriate for the specific biomarker. In some cases, this may require studies at the group level and use of surrogate benchmarks like the seizure onset zone or HFO defined by human experts. 2) Data collection and processing standards need to be developed for each biomarker. If interictal, intracranial data is used, we recommend analyzing multi-day recordings in order to account for temporal variability[24,35,38,42]. Many labs choose segments of slow wave sleep for HFO analysis[42–44], while others report HFO detection also at other states of vigilance[35,45]. The low amplitude and high frequency of HFOs compared to spikes makes it challenging to distinguish HFOs from artifacts. This requires appropriate hardware and highly standardized processing and detection standards. 3) HFOs should be detected by an automated algorithm, mitigating the influence of human bias and variability, while facilitating reproducible results and eliminating the prohibitive time constraints of human marking. Several software packages perform fast HFO detection[46–50]. 4) It should be recognized that HFOs can be produced by physiological processes, and there is yet no consensus about how to identify a pathological versus physiological HFO. Development of methods that can disambiguate pathological from physiological HFOs is expected to greatly enhance HFO-based biomarkers. For clinical application, the focus should be on detecting HFOs that serve the intended purpose of the HFO, for example as a biomarker for seizure outcome prediction. Here it is not the morphology of the single HFO that defines its predictive power[46] but rather the consistent appearance of HFOs over time[24,38] or the association of an HFO with an interictal epileptic discharge[28,38]. 5) Sharing benchmark datasets[24] or multicenter studies[36,42] serve to validate HFO detectors. 6) Hardware with sufficiently high sampling rate and low noise level must become widely available. Solving these issues will pave the way for HFO detection systems with CE/FDA approval, which is a prerequisite for the broad application of HFO as a biomarker in epilepsy.

3.3 Interictal background EEG

Beyond clear-cut discrete epileptic events such as spikes and HFOs, it is possible that the ongoing brain activity recorded in the interictal EEG is altered in epileptic parenchyma. One quantitative and objective computational approach is to measure EEG bandpower, although other approaches have been considered[51]. The idea behind studying EEG bandpower is that abnormal cortical excitability is expected to have some spectral signature that deviates from normal spectral properties of a brain region. By quantifying this deviation, or abnormality, we capture abnormal cortical excitability.

The normal spectral properties of different brain regions have been consistently described for decades. Indeed, properties on various modalities such as scalp EEG and MEG show prominent patterns, or gradients including strong posterior alpha power, and high temporal delta power [see Markello[52] for most recent maps]. Past and recent work using intracranial EEG were able to reproduce those maps in a normative mapping approach (**Fig. 3A**), where only “normal” interictal recording channels far away from the EZ were used[53–56]. Furthermore, Taylor *et al.*[55] reported that comparing a new patient's interictal data to this normative map yields patient-specific abnormalities that can localize the epileptogenic tissue. Finally, in preliminary data, we also demonstrate that this approach can be applied over long timescales to highlight abnormal cortical excitability as a function of brain regions and time (**Fig. 3B**), thus opening the possibility to timed interventions in the future. The utility of the described and similar computational approaches remains to be demonstrated in large multi-center studies retrospectively and prospectively, ideally with community-defined assessment approaches and outcome measures.

4. Active markers of excitability

The idea to actively "probe" the epileptic brain and gauge its dynamical properties is not new[57,58], but much work remains to be done to determine the true potential of this approach. Tools to probe cortical excitability include non-invasive TMS and direct cortical stimulation.

TMS coupled with electromyography (EMG) can evaluate the excitability of the cortico-spinal tracts (through motor-evoked potentials, MEPs), whereas TMS coupled with EEG can evaluate the excitability within one lobe (e.g., frontal) or between lobes (e.g., fronto-parietal though TMS-evoked potentials, TEPs). This macroscopic view has confirmed that neuro-active drugs, including benzodiazepines, other ASMs, and antipsychotics can broadly alter cortical excitability[59,60].

Direct cortical stimulations are discussed in depth in another article in this special issue entitled "Stimulation to probe, excite, and inhibit the epileptic brain" but are succinctly mentioned here to contrast them with passive markers of epilepsy. Cortico-Cortical Evoked Potentials (CCEPs) evoked by single-pulse electrical stimulation of the cortex via intracranial electrodes offer a more refined spatial resolution at the level of individual gyri and sulci and of specific long-range connections. This mesoscopic view could in theory enable a more precise delineation of epileptic tissue, based on putatively enhanced excitability. Whether CCEPs to mild stimulations are increased within the EZ is yet unclear, despite a number of reports postulating this view[61–64]. Advanced analyses of CCEPs include characterizing them as short oscillatory perturbations. Theory-based approaches have characterized CCEPs in terms of complexity and resonance properties of the underlying cortex[65].

In the epileptic parenchyma, another phenomenon was found 20 years ago: in addition to eliciting CCEPs, stronger single-pulse stimulations can elicit delayed, epileptiform responses, an induced spike. Despite a landmark publication[66], and a few replications[67], this finding has not gained much traction in clinical practice, and the question of whether it applies more broadly to delineating epileptic cortex remains open.

On the other hand, seizure induction protocols have now been adopted by a number of hospitals. Here, a train of pulses is applied over a few seconds to entrain the cortex into a triggered seizure, and confirm its expected, patient-typical clinical correlates[68]. The ability to trigger a seizure at the suspected seizure-onset zone and not in other cortices contributes to the localizing value of actively probing the epileptic brain.

The advantage of direct cortical stimulation over TMS is clear from a spatial resolution perspective. However, an untapped diagnostic advantage is that of repeated stimulations that can offer nearly continuous probing of the epileptic brain (e.g., every 10-20 seconds). Indeed, beyond its therapeutic use in deep or responsive neurostimulation, repeated brain stimulation may open the path to true active monitoring of the time-varying function of a given circuit. Given recent advances in understanding pharmacoresistant epilepsy as cycles of enhanced seizure likelihood[69,70], monitoring cortical excitability may identify at-risk phases.

5. Network analysis

Epilepsy is increasingly viewed as a brain network disorder[71–73], which makes visual inspection of iEEG data to identify epileptogenic regions challenging. As such, several studies have described computational approaches to view iEEG recordings from a network perspective and aim to offer fast and objective measures of epileptogenicity[74,75].

One approach is to apply network-based measures to capture pairwise dependencies in the iEEG window of interest. Specifically, correlation or coherence between each pair of iEEG channels is computed and organized into an adjacency matrix, on which summary statistics are derived including degree distribution and variants of nodal centrality[76–85]. Such network-based measures have shed insights into the role of the EZ in the iEEG network, but researchers recognize that many different networks (adjacency matrices) can have identical summary statistics. Additionally, as iEEG sampling is not spatially uniform, and together with the brain's complex morphology, network "hubs" may arise through higher spatial sampling or in areas of dense gray matter tissue. Finally, the sampling of the brain via iEEG is patient-specific, making direct comparisons of network properties across patients challenging. Wang et al.[86] have thus proposed spatial normalizations and normative approaches (as in the above case of bandpower abnormality), which have recently shown some success[56].

Another approach to studying epileptic networks is to assume that the iEEG recordings are observations of a dynamic networked "system". These recordings are then used to perform "system identification" to create a generative model that can produce the observed iEEG data. The model parameters describe internal properties of the system including bandwidth, stability, controllability, connectivity, fragility, and system gain[87]. One recent study introduced the notion of "sources" and "sinks" where sources are brain regions that significantly influence sink regions, and that between seizures the EZ are sinks (**Fig. 4**)[88]. Sources and sinks are quantified by dynamic model parameters. Transfer functions and directed transfer functions[65,89–92] (to name a few) and linear time varying models[88,93] are two classes of dynamic models proposed to assist in localizing the EZ.

6. Epilepsy biomarkers. Questions and controversies

Epilepsy biomarkers are defined as objectively measurable characteristics of a normal or pathological process that can be measured and used to provide actionable clinical information, for example, to predict epilepsy development (epileptogenesis) or to monitor seizure propensity (ictogenesis). By identifying these biomarkers, we may be able to predict epilepsy development, to identify the tissue capable of generating spontaneous seizures, to measure disease progression, and to prognosticate pharmacoresistance[94]. Although epilepsy is characterized by the presence of seizures, their occurrence alone does not necessarily satisfy the criteria for epilepsy diagnosis, since single seizures as the result of an acute brain insult are no rarity. Therefore, there is an urgent need for additional, more valid epilepsy markers, to allow for the identification and differentiation of epilepsy. EEG is the most accessible and established modality in epilepsy diagnostics and signal changes, even in the absence of seizures, have been related to distinct disease states. Since no EEG biomarker has proven reliable in detecting and predicting epilepsy so far, it is imperative to develop novel approaches to extract more advanced biomarkers from the EEG signal.

Biomarker research has rapidly evolved in the last decades and rigorous standards have been defined to facilitate the development of tools deriving from and dedicated to a specific clinical context. Biomarker performance should be judged depending on standards of statistical verification and validation conferring clinical utility. Biomarker research should also follow the new Biomarkers, EndpointS, and other Tools (BEST) guidelines with a standardized description and a defined context-of-use[95]. While most studies measure biomarkers retrospectively, in clinical data collected and stored for later research use, it is clear that these conditions do not suffice to determine clinical usefulness. As described above in the HFO section, choice of biomarker has significant implications to rigor, reproducibility, and translation. Biomarkers should be easily, accurately, and reproducibly detectable but may be specific for a certain time window, condition, or syndrome. Furthermore, it cannot be ruled out that a single biomarker will prove insufficient and multiple biomarkers will be required to secure a reliable detection or prediction[1].

How do we translate new epilepsy biomarkers into clinical practice? First, we must validate proposed biomarkers in large external datasets, which will require improved methods of data-sharing, or federated approaches to sharing code across centers[96,97]. Next, one approach to translation is to build an easy-to-use tool for clinicians to predict important clinical outcomes, such as the 5-SENSE score, which incorporates scalp EEG-spikes and other features to predict focality of the seizure onset zone[98]. We can also package quantitative algorithms into submodules of commonly-used commercial software, putting sophisticated techniques into the hands of the clinicians. We may ultimately need prospective, randomized controlled trials, testing whether incorporating these biomarkers into surgical decision-making improves outcomes[34]. Recent advances in translational work have given hope in the quest for EEG-based epilepsy biomarkers. Now we need to put the tools for mining them in the hands of epileptologists, and overcome the last barriers to translation by implementing technical advances in clinical practice. We need to persuade policy-makers that these "fancier tools" are needed and that the extra cost/work/devices are worth it for the benefit of our patients. Another barrier to overcome is the “black box problem”, which is met with skepticism by most clinicians. Earning their trust will require demonstrating clinical benefit in human trials and possibly also providing some physiological insight and/or normative values from the outputs of these tools, rather than simply presenting an abstract result.

7. CONCLUSION

Novel EEG-based passive and active markers of cortical excitability, as identified by emerging techniques, have the potential to open new avenues in epilepsy diagnosis and treatment and ultimately revolutionize patient care. Given the recent technological advances, this multidisciplinary area of research is currently located in the spotlight of human neuroscience. Further prospective, large-scale research is clearly needed to answer open questions and pave the way for the transfer of these biomarkers from research to clinical practice and implement them to the benefit of individual patients.

AUTHOR CONTRIBUTIONS

All authors were responsible for both writing the original draft and critically revising the draft (GR, BW, SG, JS, SS, YW, MB, WS, EC). WS was also responsible for conceptualization of the manuscript. GR, WS, and EC were also responsible for supervision of the project.

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CONFLICT OF INTEREST

SG and WS have a licensing agreement with Natus Medical, Inc. WS has a consulting agreement with Neuronostics, Inc. BW is a co-founder of Beacon Biosignals and receives royalties for authoring Pocket Neurology from Wolters Kluwer and Atlas of Intensive Care Quantitative EEG by Demos Medical. MB is a shareholder of Epios SA, a medical device company based in Geneva, Switzerland. EC has a consulting agreement with Epiminder. The remaining authors report no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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FIGURE LEGEND

Fig. 1: Quantitative analysis reveals the latency of spike detection across electrodes.

Fig. 2: An interictal epileptic discharge (blue) recorded in human epileptic hippocampus and associated with an HFO (red, bandpass filtered 80-500 Hz and shifted by 200 µV) on its rising flank.

Fig. 3: Normative bandpower maps and abnormality mapping in an example patient. A: iEEG normative bandpower maps in five frequency bands derived from over 200 patients and over 21,000 electrode contacts[55]. B: iEEG bandpower abnormality for an example patient calculated as a function of brain region and time. Bandpower abnormality is persistently higher in the resected tissue; the patient was seizure free after surgery. However, bandpower abnormality can also fluctuate, for example in the midtemporal area in a circadian rhythm.

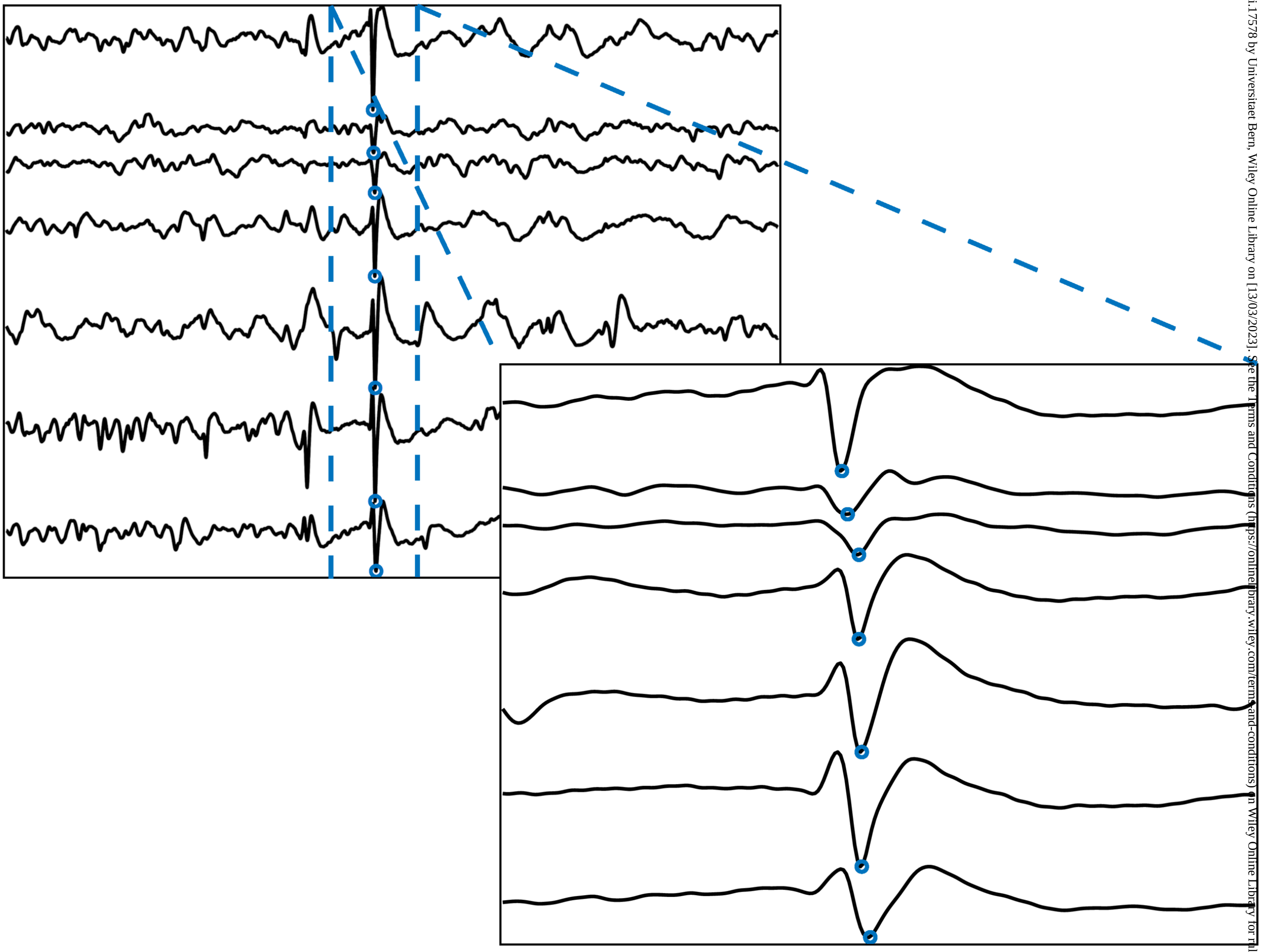
Fig. 4: Network analysis deriving from invasive EEG recordings. EEG recordings are used to build a dynamic network model which provide edge weights defined by dynamic influence, which then can be used

to compute the source-sink index (ranging from 0-1), which then can be displayed as a heat map overlayed on the patient's implantation map. Red regions correspond to hypothesized epileptogenic zone.

TABLES

	Passive			**Active**	
	Spikes	**HFOs**	**Background EEG**	**Single pulse**	**Train of pulses**
Current use	Clinical evaluation of the irritative zone for surgical planning		Research	Research	Trigger clinical seizures for surgical planning
What is measured	Visual identification of spikes Spike quantity and network	Visual identification of HFOs HFO quantity and network	Spectral measures Connectivity measures	CCEP amplitude Triggered epileptiform responses Connectivity measures	Visual identification of seizure onset
What is localized	Spike zone	HFO zone	Not established	Not established	Seizure onset zone
Monitoring over time	Strong modulation by brain states: frequency, amplitude, and propagation variable across sleep-wake, circadian and multidien cycles.			Not established	Not established
Modulation by ASMs	Expected decrease	Expected decrease	Not established	Expected decrease in excitability	Expected increase in seizure threshold

Table 1: Overview of passive and active markers of cortical excitability. ASM: Antiseizure medication; HFO: high-frequency oscillations; CCEPs: cortico-cortical evoked potentials



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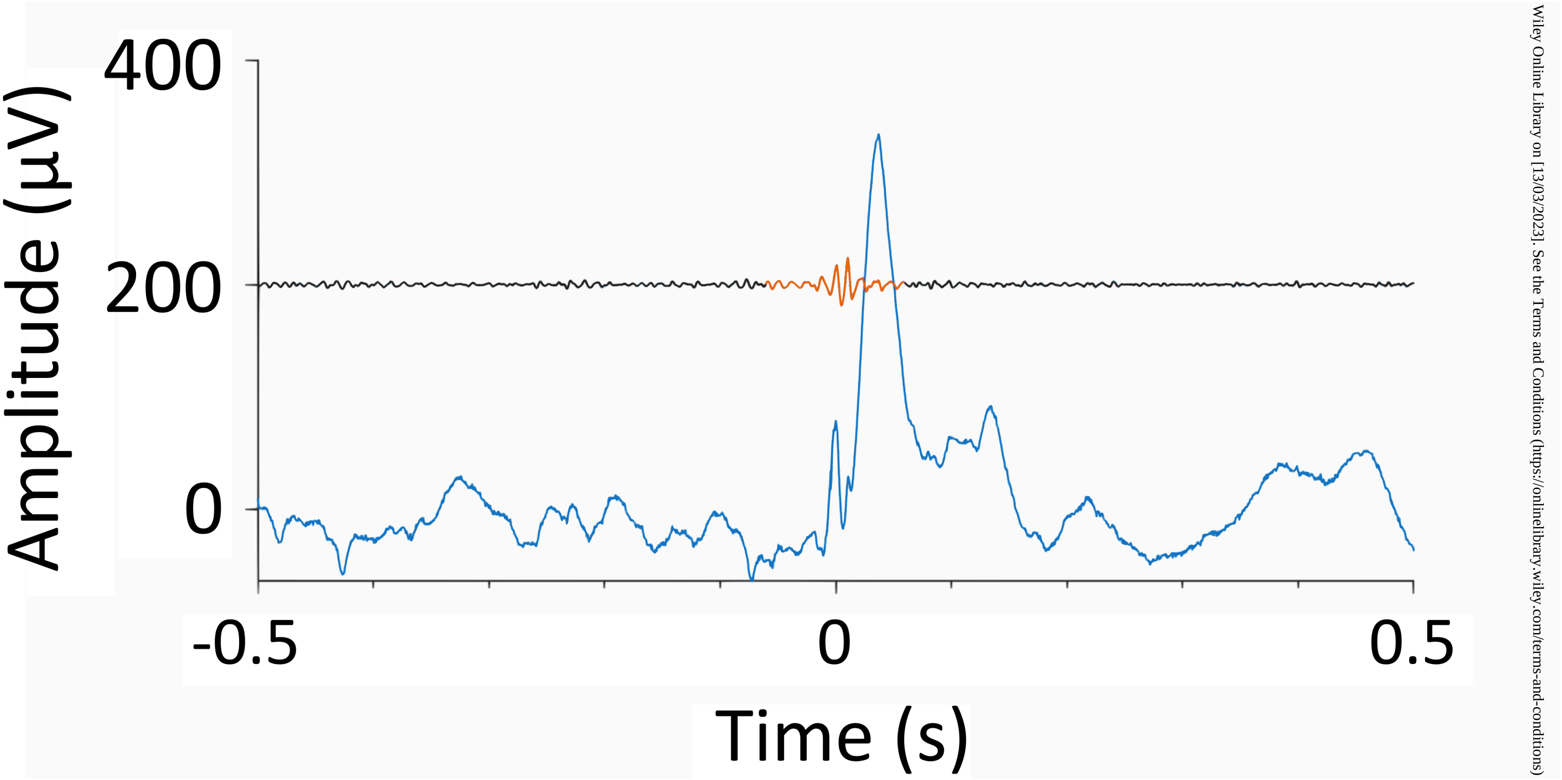

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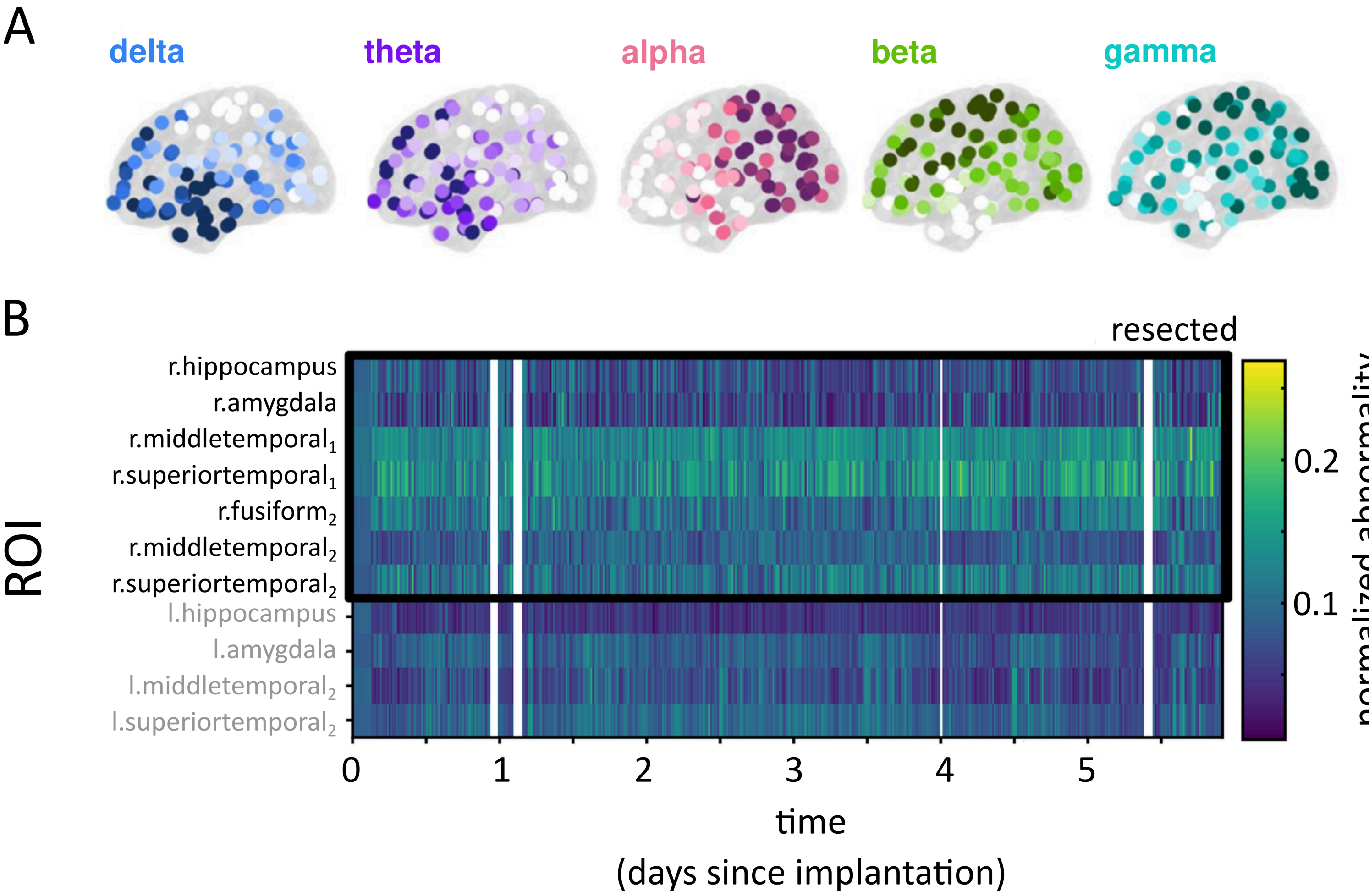

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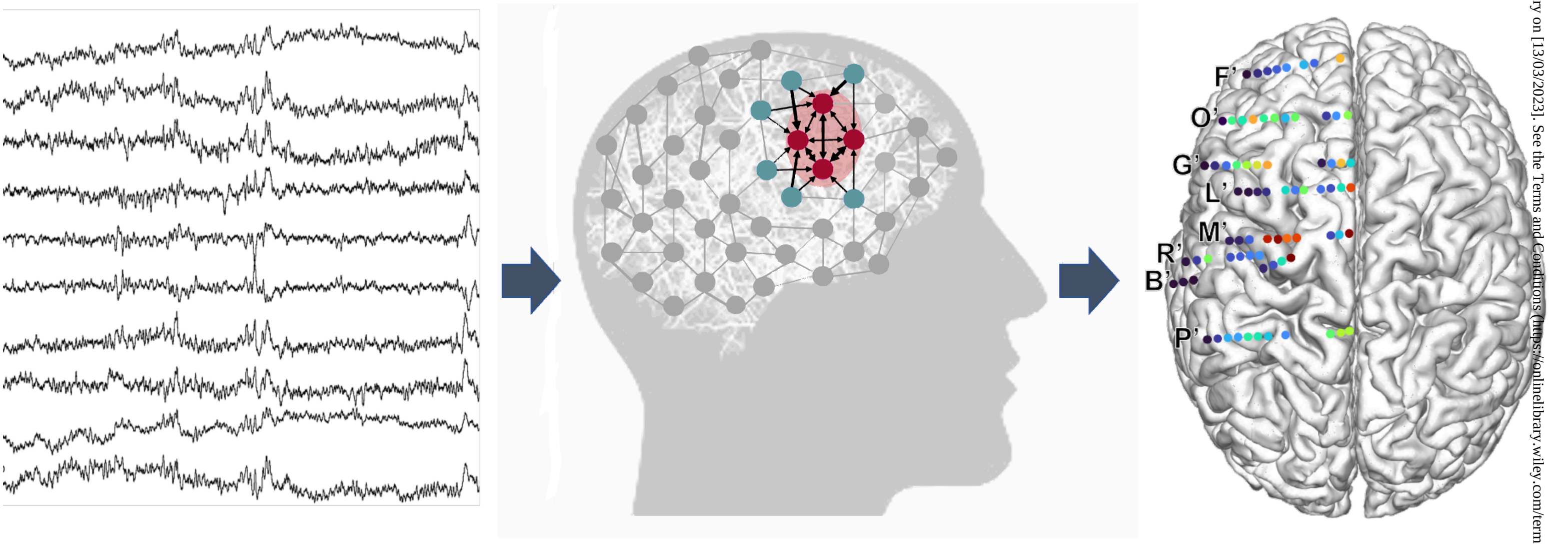

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