

## An Update on Promising Diagnostic and Therapeutic Interventions in Epilepsy

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### Abstract

There have been many developments in the management of patients with epilepsy ranging from diagnostic modalities to pharmacological and non-pharmacological interventions. This review discusses several advances which the authors believe will have a significant impact on how such patients will be managed in the coming years.

Electroencephalography [EEG] remains the main diagnostic tool in the evaluation of patients with seizure disorders. The novel discovery of high frequency EEG oscillations introduces new concepts of epileptogenicity. Also, techniques that couple EEG with imaging data will be discussed.

The early intervention to abort seizures using a method that is easily administered by paramedic staff in the field has been shown to result in more rapid seizure cessation we elaborate on the pre-hospital management. Epilepsy surgery which has revolutionized the treatment of medically refractory patients is invasive and often resective in nature. We discuss the emerging science of neurostimulation as an alternative and potentially similarly efficacious technique.

**Keywords:** Epilepsy; Therapeutic; Diagnostic; EEG; fMRI; SISCOM; Benzodiazepine

### Introduction

The last decade has seen a significant number of advances in the research of epilepsy, many of which have achieved clinical relevance. Further developments are still in progress, both in the diagnosis and the treatment of patients with epilepsy. This article describes those that are felt to make a significant clinical impact in the decade to come.

### Diagnostic Advances

#### Functional MRI (fMRI)

When deciding if a patient is suitable for epilepsy surgery it is important to determine whether removal of a potentially epileptogenic area will have deleterious effects on cortical function, particularly language and memory. In some centers fMRI has now replaced intra-carotid sodium amobarbital [Wada] testing to predict cortical dominance. It works by measuring changes in blood oxygen dependent levels [BOLD] and provides a surrogate of neuronal activity [1-3]. Not only has fMRI been shown to be more accurate, especially in terms of possible verbal and naming deficits compared to Wada testing [4-10], but it can also be used to determine cortical function in patients with disrupted brain architecture. Localization of eloquent areas remains important and being able to distinguish between primary and secondary motor areas [11-16] is crucial if the resection zone is within the motor strip. Similarly, visual deficits can be predicted by generating retinotopic maps with fMRI [17,18].

There are however some disadvantages, particularly as fMRI requires the patient to be able to perform certain tasks in order to generate activation maps, which is not always possible in young children or those with cognitive dysfunction. In such cases the Wada test is more useful to determine language dominance. The significance of language maps generated with fMRI also remains uncertain as language centers often extend beyond Broca's and Wernicke's area [19-27] and in some cases critical areas remain quiescent. Avoiding aphasia therefore cannot be predicted in all surgical patients [28-31].

#### Simultaneous electroencephalography and fMRI (EEG-fMRI)

Accurate identification of the epileptogenic zone is pivotal in determining a successful outcome from epilepsy surgery in patients with intractable seizures. In such cases, scalp or non-invasive EEG monitoring does not provide sufficient accuracy in localization and intracerebral EEG is required. Placement of intracerebral electrodes however presents its own problems. Not only is it invasive and costly, but it only allows a small area of cortex to be monitored and therefore pre-operative assessment with other imaging modalities which augment accurate placement is vital.

Functional magnetic resonance imaging [fMRI] provides a useful non-invasive means of identifying potentially epileptogenic generators in patients with focal epilepsy who may benefit from surgery [32, 33-35]. When fMRI is performed simultaneously with scalp EEG, it enables identification of epileptogenic networks, their boundaries and potentially the location of epileptogenic generators [32-35].

By studying global neuronal activity, fMRI allows detailed analysis of epileptogenic networks in generalized seizures and areas surrounding a focal interictal event beyond that which is normally achieved with standard neurophysiological recordings [36-39]. fMRI is particularly useful in patients with malformations of cortical development [40] and has the potential to determine the effects of epileptogenic lesions on cognitive processes [41]. In some patients focal areas of deactivation are observed in areas contralateral to regions displaying interictal activity, although the significance of this remains uncertain [42]. BOLD signal

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is also affected pharmacologically due to changes in cerebral blood flow and therefore may also have a role in the future assessment of anti-epileptic drugs [32].

Despite the advantages of being non-invasive and providing information over the whole brain, EEG-fMRI cannot reliably distinguish between irritative and epileptogenic zones, or the effects of seizure propagation, which can be assessed with intracranial electrodes. In addition, the epileptogenic zone is not always identified as was demonstrated in two large studies in which only half of patients with focal seizures exhibited discharges during the 10-60 minute recording [34,35].

### **Subtraction ictal SPECT co-registered to MRI (SISCOM)**

The epileptogenic zone often resides within the anterior or mesial temporal lobe, and when removed may result in 70% of patients becoming seizure free. A significant proportion of patients however fail surgery. In some cases this is due to non-diagnostic MRI or inconclusive histology and in others, the occurrence of extra-temporal seizures [43,44]. 20% of patients with intractable seizures fail initial surgery, although the outcome does improve when repeated [44,45].

The inability of fMRI to identify with certainty all areas of pathological foci has led to the development of more eloquent diagnostic tools. One such method, known as SISCOM [subtraction ictal SPECT co-registered to MRI] combines functional data acquired from single photon emission CT [SPECT] and anatomical detail acquired by MRI. Changes in neuronal activity correlate with cerebral blood flow and can be measured following administration of a radiotracer. Areas of hyperperfusion can therefore be used to identify the epileptogenic focus or if there is seizure propagation, reveal distal sites. By combining this functional data with MRI, SPECT becomes a highly discriminative tool when planning surgery, especially if MRI alone is unable to identify the epileptogenic focus. Sometimes MRI reveals a large lesion, which cannot be fully removed and SISCOM allows a more targeted approach [46]. In cases of initial surgical failure, SISCOM can be used to determine cortical electrode placement to increase accuracy if further surgery is contemplated [47,48].

Several studies indicate that the use of pre-operative SISCOM improves outcome in patients with temporal and extra-temporal disease [49,50]. This is particularly apparent when supported by EEG or PET evidence of a localized epileptogenic zone [51,52].

SISCOM is expensive and not indicated in all patients, particularly those with simple cases of hippocampal sclerosis. It can however prove invaluable in more complex cases, especially in patients with cortical dysplasia when the epileptogenic zone may extend beyond the lesion visualized on MRI.

### **High frequency oscillations**

Fast electroencephalographic [EEG] activity greater than 80 Hz frequency have been termed high-frequency oscillations [HFOs]. These were originally detected via microelectrodes positioned in the hippocampus, entorhinal cortex and subiculum of patients with mesial temporal lobe epilepsy who were undergoing intracranial EEG as part of pre-surgical evaluations [53-55]. These were noted during wakeful immobility and slow-wave sleep [56]. HFOs recorded from human brains closely resembled ripple oscillations found in nonprimate hippocampi. HFOs in the 80-200 Hz range are termed 'ripples' and 200-600 Hz 'fast ripples' [57-59].

Physiologically, ripples represent summated inhibitory post-

synaptic potentials arising from presumed interneurons and are believed to play a role in the imprinting of episodic memory that occurs as a result of the synchronization of neuronal activity [57].

Pathological HFOs are thought to represent the field potentials of population spikes from clusters of abnormal synchronous burst-firing neurons within epileptogenic tissue [60]. From the identification of its pathological role a decade ago, the body of knowledge surrounding HFOs in patients with epilepsy has grown significantly as electrophysiological equipment capable of recording at these high frequencies has become more readily available [61-69]. Furthermore, HFOs have been observed in intracranial EEG recorded using conventional macroelectrodes which obviates the need for special amplification and analytical tools that are required when studying microelectrode recordings [70-73]. In patients with focal epilepsy, generators of HFO may be recorded from regions as small as 1 mm<sup>3</sup> using microelectrodes and in the range of 1 or a few cm<sup>3</sup> using macroelectrodes [53-55, 74-76]. However, it does not appear that the nature of the HFOs recorded by the different electrode is entirely similar. Pathological HFOs were initially believed to be restricted to the fast ripple frequency spectra but this has since been acknowledged to be an oversimplification [77]. Fast ripples can be recorded from normal neocortex and ripples have been found in epileptic dentate gyrus where physiological HFOs do not occur [78].

Approximately one third of patients with focal epilepsy will prove to be medically refractory [78]. Intuitively, the removal of the epileptogenic tissue in these patients will potentially have a curative result. Invasive methods are used to delineate these areas in great detail [79,80]. Yet, removal of the seizure onset zone (SOZ) does not always equate to seizure freedom [81-84].

Studies have shown that HFOs may be markers of epileptogenicity [72]. Irrespective of the underlying epileptogenic lesion and its boundaries, HFOs appear to be closely associated with the SOZ [85]. Whilst the majority of the HFOs occur within the SOZ as identified using standard methods [intracranial EEG], they have also been observed in adjacent tissue [86,87]. Failure to remove these HFO laden areas which are outside the SOZ has been associated with poorer surgical outcomes [88]. It is a more robust marker than traditional EEG spikes, following the discovery that reductions in anticonvulsant medication results in an increase in the number of HFOs recorded [89]. The combination of the two electrographical features indicates that neurons in that particular vicinity are capable of generating hypersynchronous action potentials and are potentially highly epileptogenic.

More recently, interictal HFOs have been successfully recorded using standard scalp EEG electrodes after careful separation from EMG artifact [90,91]. This holds promising future applications particularly as non-invasive biomarkers for epileptogenic brain regions [61-63,65,90]. At present further studies are required to be able to definitively differentiate pathological and physiological HFOs. Automated detection systems are currently being designed to relieve the laborious efforts undertaken to manually mark HFOs which currently can only be performed on several minutes of carefully selected EEG epochs [92].

### **Continuous Electroencephalography (CEEG)**

Continuous EEG monitoring is now being advocated in the intensive care, particularly patients with underlying seizure disorders. Seizures occur commonly in structural brain insults and encephalopathic states [93]. Between 11-55% of patients in the neurological intensive care unit may experience seizures. [94]. More than 90% of these are nonconvulsive in nature and are associated

with higher mortality and morbidity rates [94,95]. EEG has the dual advantage of providing excellent temporal resolution [up to 2 ms] and sufficient spatial resolution that allows brain abnormalities to be regionalized [94]. With the application of Fast Fourier Transformation digital EEG signals from prolonged recordings can be condensed into user-friendly graphical quantitative trends that potentially may be used by non-electroencephalographers. These commercially available modes of display include compressed spectral array, density spectral array, bispectral index and power values [96-102].

Recent developments involve the use of EEG outside the setting of seizure disorder. Research is ongoing in the ability of EEG to detect neuronal dysfunction that occurs as a result of disturbances of brain perfusion. EEG detects changes in cerebral perfusion prior to the point of irreversible damage and this provides a window of opportunity to perform further investigations to corroborate the findings or to very closely monitor the patient clinically and institute changes in management [103]. Increasing research has taken place in the use of CEEG in patients with subarachnoid hemorrhage, a major complication of which is delayed cerebral ischemia [DCI]. This is a clinical phenomenon of vasospasm-related hypoperfusion and occurs in 22-40% of patients, resulting in morbidity and mortality rates of up to 30 % [104-106].

Alterations in CEEG can precede clinical change by more than 24 hours. In recent studies, a single measurable CEEG parameter improved the ability to predict the progress of patients with SAH a day in advance by detecting EEG changes at the pre-clinical stage [107]. This ultra-early detection suggests that in a proportion of patients, the therapeutic window of intervention to prevent permanent neurological damage may extend beyond 24 hours.

## Therapeutic Advances

### Pre-hospital management of seizures

The management of epilepsy has continued to evolve in the last two years beyond the use of anti-epileptic medication, which continues to be the mainstay of treatment. Paradigm shifts in the approach to pre-hospital treatment of continuous seizures have gained attention with recent evidence suggesting that intramuscular [IM] benzodiazepine administration may be equally effective as the intravenous [IV] route. This review serves to highlight these recent developments in this ever-changing field.

Early termination of prolonged seizures and status epilepticus using IV benzodiazepines has been shown to improve patient outcomes. The Pre-hospital Treatment of Status Epilepticus trial compared intravenously administered diazepam, lorazepam, and placebo given by paramedics to treat subjects with prolonged convulsive seizures and established that benzodiazepines were an effective pre-hospital treatment for seizure control as compared with placebo [108].

A meta-analysis of several small trials studying the use of non-intravenous midazolam in the hospital setting compared favorably with intravenous diazepam in the treatment of status epilepticus [109]. Although intravenous lorazepam is the preferred benzodiazepine for aborting seizures in the emergency department, practical issues such as obtaining rapid IV access may preclude its use in the field. Furthermore, lorazepam has a short shelf life with poor stability when it is not refrigerated [110]. Pharmacodynamic and pharmacokinetic studies have shown that IM midazolam is rapidly absorbed. For these reasons, some emergency medical services have advocated the use of

IM benzodiazepines such as midazolam to achieve a faster and more consistent administration with the aim of rapid cessation of seizure activity [111].

The recently concluded Rapid Anticonvulsant Medication Prior to Arrival Trial [RAMPART] established that intramuscular midazolam is safe and as efficacious as intravenous lorazepam for pre-hospital seizure abortion in children and adults [112]. This was a randomized, double blind, phase 3, non-inferiority clinical trial that involved 1023 participants. Adults and children with an estimated body weight of more than 40kg received either 10mg of intramuscular midazolam followed by intravenous placebo, or intramuscular placebo followed by 4mg of intravenous lorazepam. In children with an estimated weight of 13 to 40kg, the active treatment was 5mg of intramuscular midazolam or 2mg of intravenous lorazepam. The intramuscular medications were administered via a pre-manufactured auto-injector, which reduced delays in drug administration when compared to the intravenous route (1.2 versus 4.8 minutes respectively). 73.4% of patients who received IM midazolam were seizure-free on arrival at the Emergency Room compared to 63.4% who received IV lorazepam (95% CI 4.0 to 16.1, p=0.001 for non-inferiority and superiority). Interestingly, the proportion of subjects admitted was significant lower and the proportion discharged from the emergency department was significantly higher in the IM group than in the IV group. However, for patients who required hospital admission, the length of stay did not differ significantly between the two groups. This study provides initial evidence that the pre-hospital administration of IM midazolam by paramedics to abort seizures is an effective, practical and safe alternative to the IV route. Successful early termination of seizures in the field improves patient outcomes and may reduce hospital admission rates.

### Neurostimulation techniques

Patients who are medically refractory to multiple trials of antiepileptic medication should be assessed for their suitability to undergo epilepsy surgery. In the appropriately selected patients, this may be a curative intervention whilst in other cases, palliative insofar as reducing the number of seizures whilst not being able to achieve complete seizure freedom [113].

However, not all patients will be surgical candidates. In some, epileptiform foci may be multifocal, bilateral, or located in a highly eloquent and functionally important region of the brain. For such patients, novel procedures such as neurostimulation and highly localized ablative therapy are emerging as viable therapeutic strategies.

**Vagal Nerve stimulation (VNS):** Although the precise mechanism of action is unknown, it has been shown from various studies dating back to the 1930s that stimulation of the vagus nerve was able to modulate EEG changes. Subsequent development in this field has resulted in an FDA-approved scheduled closed loop system of continuous high frequency stimulation which is believed to cause desynchronization of EEG, changes in sleep architecture and the ability to suppress interictal epileptiform discharges [114-116]. It is also possible that the stimulation of the vagus nerve is itself inhibitory causing a rise in gamma-aminobutyric acid [GABA] levels [114]. It has proven to be efficacious in seizure reduction of partial and to a lesser extent, generalized epilepsies, with 40% of patients enjoying a 50% reduction in seizure frequency [117-122].

From a practical point of view, the VNS device is similar to a cardiac pacemaker in that it involves the subcutaneous or submuscular implantation of a generator which is then attached to leads that wrap around the left vagus nerve in the neck [120]. A craniotomy is not

required. Due to the lateralized functions of the vagal system, the right vagus nerve is avoided in order to minimize the potential cardio-vagal effects [114]. In experienced hands, the effects of this technique are minimal, usually associated with a mild cough on stimulation and hoarseness of voice.

**Thalamic stimulation:** The thalamus has long been thought of as a central relay station in the brain and with its close connections to the mesial temporal structures via the thalamocortical and mammillothalamic tracts, may be a potential target in the modulation of epileptic activity [123,124]. Indeed, this has been studied extensively in animals. Recently, a large blinded controlled study was undertaken which corroborates the results of animal studies [125-128]. The SANTE trial reported a 38% seizure reduction in patients who underwent active stimulation. At 2 years 60% of patients had their seizure frequency reduced by half, with 9% even attaining seizure freedom [129].

**Hippocampal stimulation:** Another intuitively attractive target would be the hippocampus which is intricately involved in seizure propagation, particularly in the temporal lobe epilepsies. Although small scale animal studies have been performed, they are preliminary and larger scale and longer term clinical trials assessing efficacy and safety have yet to be performed. Its usage should be reserved until controlled clinical studies of stimulation of the mesial temporal structures are performed [130,131].

**Responsive neurostimulation:** A routine pre-surgical assessment prior to resective epilepsy surgery involves the implantation of electrodes at the region of interest in the brain to further delineate the epileptogenic focus that is recorded from the scalp. Further to this, electrical stimulation via these electrodes is occasionally applied in awake patients to map the eloquent areas of the brain. It is also possible to identify the sites that may trigger electrographical after-discharges when stimulated. These have the potential to evolve into frank ictal activity.

Subsequently it was discovered that delivery of a short burst of 50 Hz stimulation via the same electrodes into these regions could ameliorate the occurrence of these after-discharges, hence potentially terminating this electrical precursor to a full-blown ictal event [132,133]. The Responsive Neurostimulation System [RNS] has been evaluated in multi-center controlled clinical trials as an adjunctive modality for use in adults with refractory partial seizures [134]. Leads are connected to a neurostimulation device [implanted in the skull] that detects electrographic seizures with electrocorticography. Patient specific electrographical ictal patterns are identified. Using this data, the system is therefore able to detect aberrant electrographical activity and subsequently deliver high frequency stimulation into the epileptogenic tissue in order to abort the discharges. This modality is especially suitable in the treatment of epilepsy with seizure onset in eloquent areas which are not resectable in an operation, as the stimuli do not disrupt cortical function [135].

### Stereoelectroencephalography aided thermocoagulation

Using the same platform of pre-surgical electrode implantation phase of the assessment of patients with medically refractory epilepsy, stereoelectroencephalography guided thermocoagulation is a novel method that is being studied [136,137]. Once the responsible foci of epileptogenesis have been identified, these areas are ablated using a radiofrequency generator. This allows the targeted and individualized removal of tissue or at least a disconnection of the epileptic network to prevent seizure propagation. This modality appears to be safe and had demonstrated a 50% seizure reduction rate in 48.7% of patient who

underwent this procedure [138]. Whilst less invasive than conventional surgery, it has not been proven to be as efficacious [139,141]. However this procedure is comparable to other palliative therapeutic procedures [142,143]. This technique does not preclude the patient from being considered for epilepsy surgery later on if this is deemed appropriate.

### Magnetic resonance-guided laser ablation for epilepsy

In patients who have a lesion visible on MRI that is clearly the focus of epileptogenic activity without the need to undergo invasive monitoring, an MRI-guided ablative laser resection may be a therapeutic option. Magnetic Resonance-guided laser ablation has been used for tumor resection, and even with limited imaging feedback has been proven to be very safe [144-146]. Recently, the FDA cleared the first MRI-guided laser interstitial thermal therapy allowing for real-time thermal monitoring and feedback over the amount of energy delivered via the laser. Laser energy could be delivered while observing the damage calculated from real-time thermal images, greatly increasing the precision. In a limited study of 5 patients, all remained seizure-free at least 2 to 13 months post-procedure. All subjects in the study had deeply seated epileptogenic zones and would have required transcortical corridors through normal brain [or extensive dissection of it] to complete their removal. This shows that guided laser resection may reduce morbidity in patients who required re-operations for surgical failure require extensive dissection of scarred brain from the dura, or have multifocal epilepsy that would require more than one craniotomy to affect a cure [147,148].

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