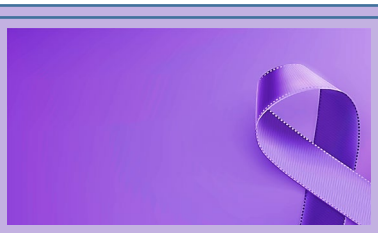

EPILEPSY

Vol. 1 | Issue 5 | 2022

Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "EPILEPSY Newsletter'' which contains latest and interesting news in the field of Neuropsychiatry.

This issue contains:

EPILEPSY
Vol. 1 | Issue 5 | 2022

Combining multiple neuroimaging modalities to identify the epileptogenic zone in MR-negative epilepsy

About 70% of epileptic patients receiving pharmaceutical treatment are seizure-free and have a notable improvement in quality of life. For the remaining, medically refractory patients, surgical surgery became the preferred course of treatment. However, a typical clinical MRI evaluation in 20% to 40% of surgery candidates fails to detect any obvious abnormalities or only detects equivocal abnormalities; these patients are referred to be MR-negative.[1] The accurate location and delineation of EZ are crucial for the outcome of epilepsy surgery. The location is determined by carefully examining the aura, seizure semiology, interictal epileptiform discharge (IED) distribution, ictal video-EEG, and high-quality 3T MRI; additional techniques and approaches may also be used. The goal was to identify the ideal mix of multimodal imaging techniques (IMs) for locating the epileptogenic zone (EZ) in patients with drug-resistant epilepsy who had MR-negative epilepsy.[2]

The study focuses on epileptic imaging techniques (IMs) that may be utilised to detect the EZ as well as their benefits in the diagnosis of individuals with drug-resistant epilepsy who have MR-negative epilepsy. 25 patients with MR-negative medication resistance were enrolled in the research. The patient population was divided into two subgroups: the first category, which included 12 patients, was determined by successful surgery using ILAE 1 or 2, and the second subgroup, which included 13 patients, was determined by epileptogenic histological findings (FCD or hippocampal sclerosis).

Establishing a fundamental battery of IMs for assessing patients with MR-negative status was one of the study's goals. By assessing the mutual resemblance of the approaches and the precision of the EZ localization, the study was able to minimise the overall battery. • Goal 2: To assess the accuracy of each IM in the basic battery as confirmed by EZ resection. Determine the best IM combination for localising EZ in patients who do not have MR imaging.

According to the similarity clustering, seventeen distinct clusters (about half of all techniques) representing the complete general battery (N=38) were identified. The fundamental battery's individual IM differences are statistically significant, with a p value of 0.006. The following order was produced after sorting all IMs according to their mean Predictive Index: SISCOM, PETai, ASLai, ReHo, GMV, Tick*, PETc, ESI-HD, and ASLhc are listed in that order. Using

the Helmert contrast, the statistical differences between the neighbouring procedures in the sorted list were compared. The decrease in accuracy occurs at the 14th junction, which is significantly less accurate than the previous 13 consecutive approaches (with p=0.02). The first 13 consecutive methods were not significantly different. (Fig. 1)

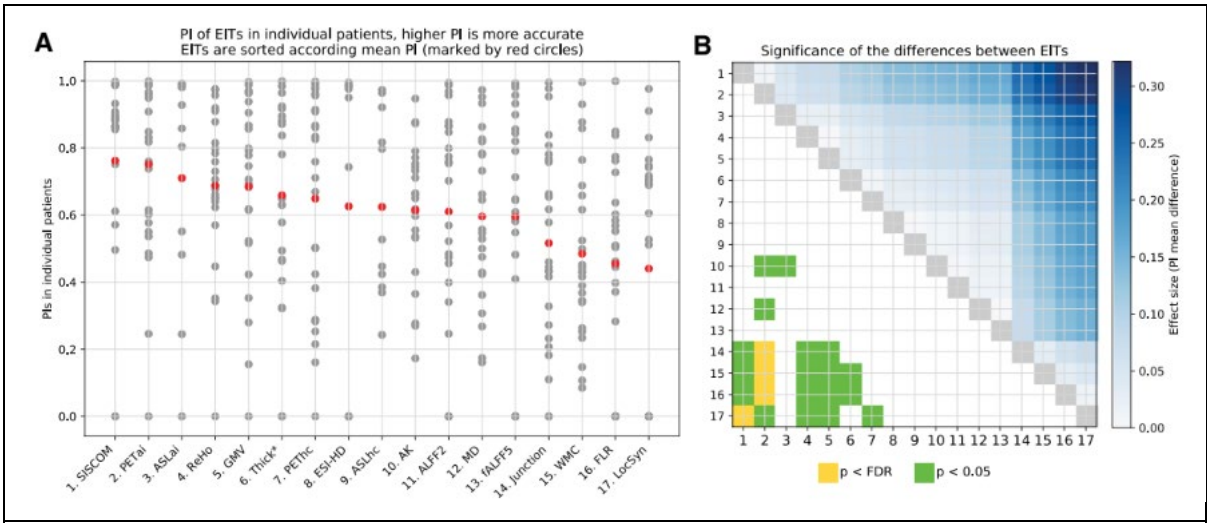

Fig 1: Mean Predictive Index of individual neuroimaging techniques (IMs).

After surgery, 15 patients in the study group had FCD, which was discovered. Hippocampal sclerosis was found in 5 individuals, unsuspected by MRI, and in 4 patients with negative histological findings who had successful surgical outcomes. The IMs employed in this study combine both established techniques and more recent ones for image development. Traditional techniques include tried-and-true techniques like FDG-PET and SISCOM. These techniques' clinical usefulness has been established. There are still certain individuals, though, for whom these conventional approaches are ineffective, and even obtaining them can be challenging (for example, due to the necessity of radiotracer application or application at the beginning of a seizure). From this perspective, it makes sense to concentrate on the creation of innovative procedures based on MRI and HD-EEG postprocessing.[3]

The neuroimaging of epileptic patients who do not have MR imaging can make use of a large number of IMs based on MRI, SPECT, and PET post-processing. Following reconstructive surgery, we compared various IMs in patients and suggested an ideal multimodal mix of IMs for therapeutic use. Based on our findings, we advise using SISCOM, PETai, ASLai, ReHo, GMV, Tick*, PETc, ESI-HD, ASLhc, AK, ALFF2, MD, and fALFF5 in combination with sophisticated MRI methods in clinical settings for patients with MR-negative epilepsy.

EPILEPSY
Vol. 1 | Issue 5 | 2022

Reference:

1. Bartoňová M, Bartoň M, Říha P, Vojtíšek L, Brázdil M, Rektor I. The benefit of the diffusion kurtosis imaging in presurgical evaluation in patients with focal MR-negative epilepsy. Sci Rep. 2021 Jul 9;11(1):14208.
2. Říha P, Doležalová I, Mareček R, Lamoš M, Bartoňová M, Kojan M, Mikl M, Gajdoš M, Vojtíšek L, Bartoň M, Strýček O, Pail M, Brázdil M, Rektor I. Multimodal combination of neuroimaging methods for localizing the epileptogenic zone in MR-negative epilepsy. Sci Rep. 2022 Sep 7;12(1):15158.
3. Mareček R, Říha P, Bartoňová M, Kojan M, Lamoš M, Gajdoš M, Vojtíšek L, Mikl M, Bartoň M, Doležalová I, Pail M, Strýček O, Pažourková M, Brázdil M, Rektor I. Automated fusion of multimodal imaging data for identifying epileptogenic lesions in patients with inconclusive magnetic resonance imaging. Hum Brain Mapp. 2021 Jun 15;42(9):2921-2930.

A study on cortical sleep spindles in epilepsy patients during interictal hippocampal epileptiform discharges

The consolidation of memories depends on sleep. According to two-stage accounts, during non-rapid-eye-movement (NREM) sleep, memory traces are gradually transferred from the hippocampus to the neocortex. The connections between the thalamocortical spindles and the hippocampus ripples are assumed to be the mechanism behind this information transfer. 1 Patients with temporal lobe epilepsies frequently have memory problems. Memory impairment is known to be a result of hippocampal interictal epileptic discharges (hIEDs), which are thought to be epileptic exaggerations of sharp wave-ripples (SWRs), but the underlying cause is unknown. Memory consolidation depends on the precise timing of hippocampal SWRs and corticothalamic spindles during sleep. Furthermore, earlier research suggested that hIEDs cause neocortical spindlelike oscillation. In the current work, we sought to evaluate how hIEDs affected neocortical spindles. 2

The study examined the foramen ovale (FO) electrode spindle characteristics (duration, amplitude, and frequency) of 21 epilepsy patients throughout the course of a full night of sleep. Based on their temporal association to hIEDs found on the FO electrodes, scalp sleep spindles were divided into different categories. The spindles that coincided with hIEDs, the spindles that were "caused" by hIEDs, and the spindles that did not co-occur with hIEDs were divided into three groups.

The study discovered that spindles that co-occurred with hIEDs had altered characteristics in all examined variables, including longer duration (mean SD), higher amplitude (3.4 3.2 V), and a shift in frequency range toward higher frequencies in the 13–15 Hz range. Additionally, spindles caused by hIEDs shared the same oscillatory characteristics as spindles that were not related to hIEDs in time. Clear temporal coherence between hIEDs and spindles was found in more than half of the individuals, however the coupling's direction varied from patient to patient.

Table 1: Sleep spindle characteristics at each electrode

Characteristic	F3, mean + SD	F4, mean + SD	P3, mean SD	P4, mean + SD
Density, /min	6.76 + 3.56	6.24 + 3.91	7.08 + 4.01	5.92 4.52
Duration, ms	837 + 291	832 + 98	829 + 224	817 + 107
Maximal amplitude, V	43.16 9.813	42.91 10.022	39.43 + 11.813	38.76 + 13. 041
Frequency, Hz	12.276 + 2.977	12.601 + .924	13.240 + 5.207	13.556 + 1.039

This study was the first to document variations in spindle properties brought on by hIEDs in people. Spindles that also happened to be associated with hIEDs lasted longer, had a larger amplitude, and their frequency range changed upward. Previous research using data from both humans and animals suggested that hIEDs can cause spindles in the frontal areas even when the subject is awake. We also examined the spindles that were preceded by hIEDs within a 1-s time window to further investigate this effect. We discovered that these induced spindles shared statistical similarities with spindles that did not exhibit a temporal link to hIEDs and lacked the same difference. 2

According to Ujma PP et al., there isn't strong evidence linking different spindle types to various laminar profiles, which suggests that they are produced in cortical and thalamic circuits with cortical innervation patterns that are identical. A more likely proposed mechanism for causing functional variations across spindle subtypes is local neural activation.

The study looked at how hippocampal IEDs affected neocortical spindle activity and discovered that spindle changes only occurred when hIEDs and spindles cooccurred. We suggest that this is a sign of a pathogenic process, in which IEDs may directly affect the formation of spindles. It might indicate a potential method by which IEDs impair memory functions and offer a potential therapeutic target for treating memory problems in epilepsy.

Reference:

1. Ngo HV, Fell J, Staresina B. Sleep spindles mediate hippocampal-neocortical coupling during long-duration ripples. Elife. 2020 Jul 13;9:e57011.
2. Sákovics A, Csukly G, Borbély C, Virág M, Kelemen A, Bódizs R, Erőss L, Fabó D. Prolongation of cortical sleep spindles during hippocampal interictal epileptiform discharges in epilepsy patients. Epilepsia. 2022 Sep;63(9):2256-2268.
3. Ujma PP, Hajnal B, Bódizs R, Gombos F, Erőss L, Wittner L, et al. The laminar profile of sleep spindles in humans. Neuroimage. 2021;226:117587.

The location of epileptogenicity in temporal lobe epilepsy with hippocampal sclerosis is indicated by a higher phase-amplitude connection between ripple and slow oscillations.

The most prevalent type of focal (partial) epilepsy in adults is temporal lobe epilepsy (TLE). Hippocampal sclerosis (HS) is the most prevalent neuropathological signature in TLE patients, and seizures in TLE-HS patients are often resistant to pharmacological treatment. Additionally, cognitive impairment and mental comorbidities are common in TLE-HS patients.[1] In order to measure the degree of epileptogenicity in patients with mesial temporal lobe epilepsy (TLE) with hippocampal sclerosis, the study evaluated the diagnostic value of the frequency of high-frequency oscillations and the modulation index (MI) from intraoperative electrocorticography (ioECoG) (HS). Temporal lobe epilepsy is the most typical kind of focal (partial) epilepsy in adults (TLE). The most common neuropathological hallmark in TLE patients is hippocampal sclerosis (HS), and seizures in TLE-HS patients frequently resist pharmaceutical treatment. Additionally, TLE-HS patients frequently have mental comorbidities and cognitive impairment.[1]

The study assessed the diagnostic utility of the frequency of high-frequency oscillations and the modulation index (MI) from intraoperative electrocorticography (ioECoG) in patients with mesial temporal lobe epilepsy (TLE) with hippocampal sclerosis (HS).[2]

In the group with poor seizure outcomes, ripple incidence rates in the hippocampus, LTL pre-SelAH, and LTL post-SelAH increased. The most telling sign of a bad outcome was the MIRipples/3-4 Hz from the LTL pre-SelAH.

The area with epileptogenicity was well delineated using the intraoperative occurrence rate of ripples, MIRipples/3-4 Hz, and MIFRs/3-4 Hz. The pre-SelAH hippocampus and LTL (pre- and post-SelAH) in the group with poor outcomes had a greater incidence rate of ripples from ioECoG, but not the pre-SelAH amygdala. Pre-SelAH, MIRipples/3-4 Hz and MIFRs/3-4 Hz were high in all areas, and they stayed high in the MIRipples/3-4 Hz post-SelAH LTL.(Fig.1)

EPILEPSY
Vol. 1 | Issue 5 | 2022

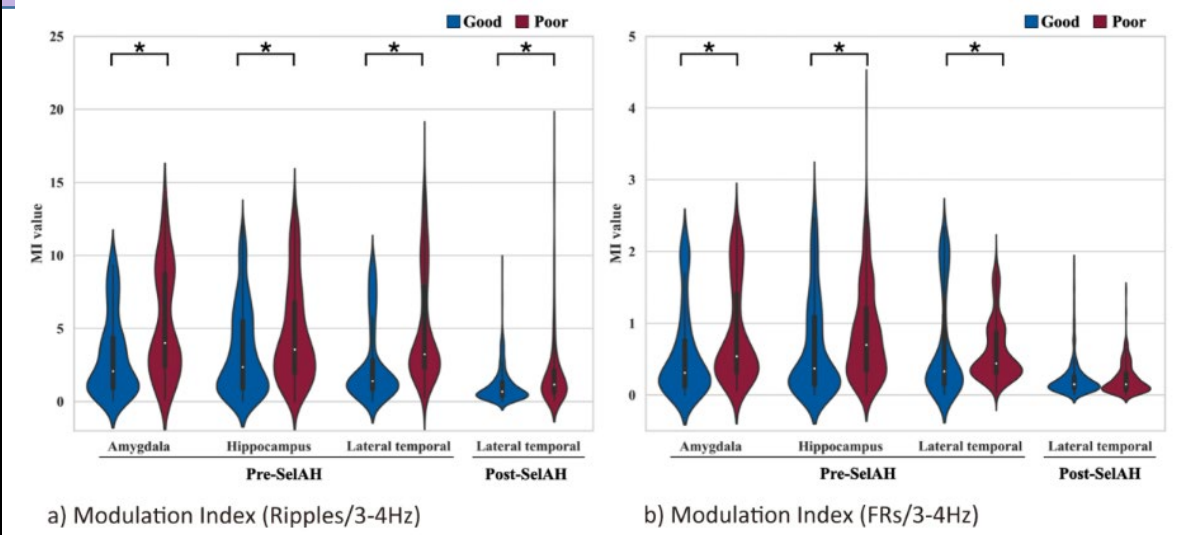

Fig 1.: Modulation index of high-frequency oscillations in regions of interest before and after selective amygdala hippocampectomy.

Ripple power connected to seizure evolution increased and spread with fluctuations, as demonstrated by Hashimoto H et al. The oscillations associated with the fluctuations may be a representation of the typical neurophysiological processing involved in seizure onset.

In TLE patients with poor seizure outcomes after SelAH, a high incidence rate of ripples and MIRipples/3-4 Hz from the LTL demonstrated widespread epileptogenicity. Our findings imply that the distribution of epileptogenicity in TLE with HS can be determined by analysing the frequency of HFOs and MIHFOs/3-4 Hz from ioECoG, particularly from the LTL.

Reference:

1. Xiao W, Yang Z, Yan X, Feng L, Long L, Tu T, Deng N, Chen W, Xiao B, Long H, Zeng Y. iTRAQ-Based Proteomic Analysis of Dentate Gyrus in Temporal Lobe Epilepsy With Hippocampal Sclerosis. Front Neurol. 2021 Jan 25;11:626013.
2. Tamrakar S, Iimura Y, Suzuki H, Mitsuhashi T, Ueda T, Nishioka K, Karagiozov K, Nakajima M, Miao Y, Tanaka T, Sugano H. Higher phase-amplitude coupling between ripple and slow oscillations indicates the distribution of epileptogenicity in temporal lobe epilepsy with hippocampal sclerosis. Seizure. 2022 Aug;100:1-7.
3. Hashimoto H, Khoo HM, Yanagisawa T, Tani N, Oshino S, Kishima H, Hirata M. Phase-amplitude coupling of ripple activities during seizure evolution with theta phase. Clin Neurophysiol. 2021 Jun;132(6):1243-1253.

EPILEPSY
Vol. 1 | Issue 5 | 2022

A case study on a 59-Year-Old Man with Thymoma and Constitutional Symptoms, Seizures, and Multifocal CNS Lesions

Thymoma patients that develop a paraneoplastic syndrome do so in about 50% of cases.[1] The most typical form is in myasthenia gravis. More and more publications in recent years have detailed examples of thymoma complicated with autoimmune encephalitis (AE).[2] Data on A 59-Year-Old Man With Thymoma with Constitutional Symptoms, Seizures, and Multifocal CNS Lesions were provided in this case study.[3]

A 59-year-old guy initially showed in with a numbing episode in his left arm. A thymoma was unintentionally found and removed during workup. His left arm's symptoms were explained by a heart pathology. He started losing weight and being anorexic a month later, and had one generalised tonic-clonic seizure after that. A toxic and metabolic screening as well as a brain MRI were unremarkable parts of the workup. After beginning treatment with an anti-seizure drug, he did well for two years until his symptoms returned. Multiple cortical T2/FLAIR hyperintense lesions were visible on a second MRI of the brain without any enhancement or diffusion restriction. Additional testing included a spine MRI, a CT scan of the chest, abdomen, and pelvis, CSF tests, and autoimmune/paraneoplastic panels in the blood and CSF, all of which came out negative. (Fig.1) Antibodies to the striatum, acetylcholine receptor (AChR) binding antibodies, and AChR modifying antibodies were all detected in the serum. After receiving high dosage steroids and a plasma exchange, his symptoms disappeared, and he has been stable on mycophenolate mofetil ever since.

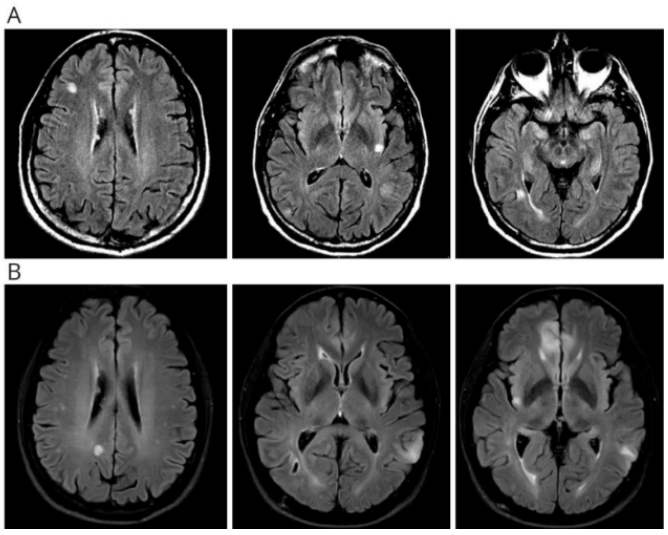

Fig 1: MRI brain, selected axial T2 FLAIR sequences.

Various autoantibodies against antigens of the nervous system can be detected in thymoma patients. The most frequently found antibodies are those linked to myasthenia gravis, while they can also exist in people who don't exhibit symptoms of a condition of the neuromuscular junction. Although AChR antibodies are frequently detected in TAPE patients, they may not always be harmful. Although they are frequently observed in TAPE, neuronal surface antibodies linked to autoimmune encephalitis are not necessary for the diagnosis. Additionally, it is possible to find intracellular antibodies like CRMP5, GAD-65, and ANNA-1.[4]

The diagnostic strategy for this unusual presentation was covered in this article, along with critical aspects of the clinical presentation, the right workup, relevant differential diagnoses, and important considerations for patient care.

Reference:

1. Zhao J, Bhatnagar V, Ding L, et al. A systematic review of paraneoplastic syndromes associated with thymoma: Treatment modalities, recurrence, and outcomes in resected cases. J Thorac Cardiovasc Surg. Jul 2020;160(1):306-314 e14. doi:10.1016/j.jtcvs.2019.11.052
2. Yao Y, Li X, Lin J, Zhang X, Wang H. Thymoma-associated autoimmune encephalitis with positive Titin antibodies: A case report. J Neuroimmunol. 2021 Sep 15;358:577670.
3. Stopschinski BE, Fredrich S, Vernino S, Phillips L, Blackburn KM. Clinical Reasoning: A 59-Year-Old Man With Thymoma and Constitutional Symptoms, Seizures, and Multifocal CNS Lesions. Neurology. 2022 Sep 30:10.1212/WNL.0000000000201381.
4. 4. Liu H, Edson RS. Thymoma associated paraneoplastic encephalitis (TAPE), a potential cause of limbic encephalitis. BMJ Case Rep. Aug 30 2019;12(8)doi:10.1136/bcr-2019-230709