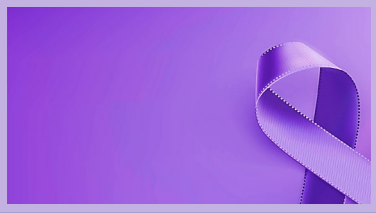

EPILEPSY

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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:

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Imaging of Epilepsy and Its Comorbidities Using Artificial Intelligence

The sudden aberrant discharge of brain neurons causes epilepsy, a central nervous system (neurological) condition. Annotating and tagging/detection of severe seizure occurrences on an annual basis has become a difficult and time-consuming task. As a result, there is a need to more efficiently automate the process of recognising epileptiform patterns, which has led to the creation of several artificial intelligence (AI)-based models. Artificial intelligence (AI) refers to the simulation of human intelligence processes by computers, particularly computer systems. AI is defined as the study or construction of "limited" intelligent agents that can detect and understand their surroundings and take appropriate action to maximise their chances of attaining the desired goals.[1]

The aim of this study was to show how artificial intelligence (AI) has been applied to neuroimaging in epilepsy patients to improve clinical diagnosis classification, treatment outcome prediction, and cognitive comorbidity understanding. The strengths and weaknesses of existing AI research were also reviewed, as well as the necessity for future studies employing big datasets to evaluate the reproducibility and generalizability of present findings, as well as studies to test the clinical value of AI approaches.

Machine learning (ML) and deep learning (DL), two subfields of AI, are commonly used interchangeably yet have different meanings. While ML is more data-driven, uses statistical models, and relies on human interaction, DL employs numerous layers of neural networks, which reduces the need for human intervention.[2] In patients with temporal lobe epilepsy (TLE) and hippocampal sclerosis, ML algorithms utilising multimodal MRI have been proven to lateralize hippocampus disease in recent years (HS). The efficacy of ML and DL algorithms using structural MRI and diffusion MRI (dMRI) to categorise controls vs patients with TLE with HS and MRI-negative TLE was studied in a recent ENIGMA-Epilepsy study.

The accuracy of structural MRI and dMRI-based models was comparable in this investigation, and models for TLE-HS were more accurate than those for MRInegative TLE.

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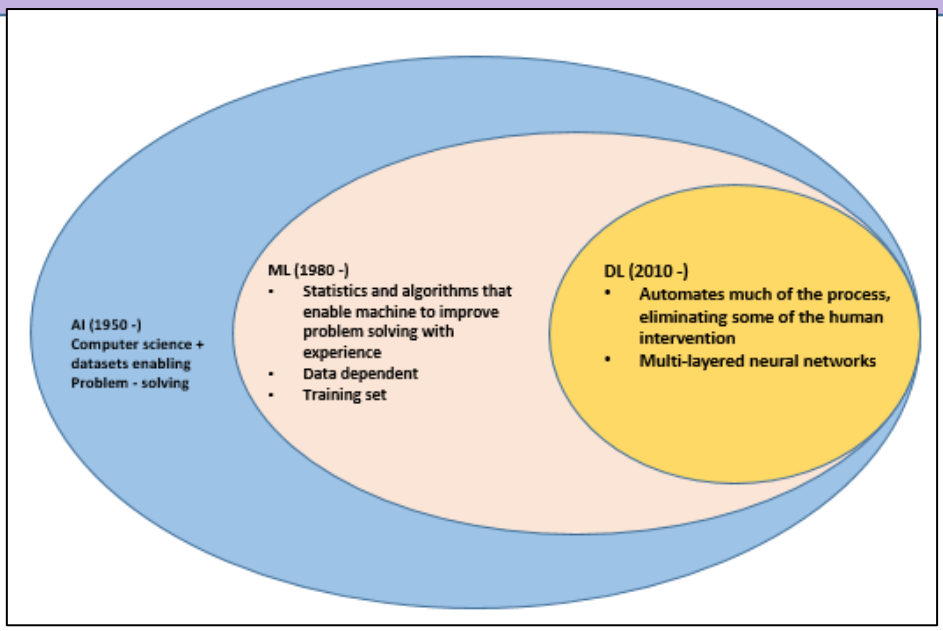

Concepts about artificial intelligence, machine learning, and deep learning.

While automatic quantification methods may not yet be able to match the abilities of imaging professionals to visually evaluate MRIs in all instances, AI algorithms and tools provide valuable support and may become critical when such expertise is unavailable. Although certain AI technologies have already been integrated into clinical care for epilepsy, doctors and AI experts must continue to collaborate closely in order for newer ML and DL approaches to be adapted for clinical usage.[3,2] Gill RS et al demonstrated that utilising multimodal MRI data, DL could reliably identify previous MRI-negative focal cortical dysplasia (FCD) lesions, implying that DL has promise in assisting non-expert physicians with this difficult diagnosis.[4]

Artificial intelligence (AI), particularly machine learning (ML) and deep learning (DL), has been applied to neuroimaging data to predict clinical diagnosis, or clinical phenotyping from imaging, as well as predict response to antiseizure medicines. Patients with juvenile myoclonic epilepsy, for example, may be identified using dMRI measurements and connectome profiles, which can also be used to distinguish patients with focal epilepsy from healthy controls. However, because these investigations are scarce, larger studies with external datasets are required to determine the reproducibility and generalizability of current findings.[5]

The use of AI to analyse neuroimaging data to better identify cognitive comorbidities in epilepsy is still in its early stages, with only a few studies published to date. Only one study employed multimodal imaging to assess cognitive impairment. The majority of studies used

whole-brain dMRI or resting-state functional MRI (rsfMRI) to classify cognitive impairment. Machine learning has been used in four research to classify or predict language impairments, three studies to predict IQ, two studies to predict memory, and one study to predict embodied cognition (actionconcept deficiencies) in epilepsy. Although most studies have focused on adults with TLE, investigations with children with epilepsy and people with other epilepsy syndromes are beginning to emerge.[6,5]

In conclusion, studies using artificial intelligence to characterise the neural substrates of cognitive impairment in epilepsy have revealed new information about the vast extent of network dysfunction that underpins cognitive comorbidities, and they align with research that challenges region-specific theories of cognitive dysfunction. These studies used whole-brain analyses to reduce the dimensionality of imaging data and enhance prediction accuracy by using feature selection algorithms. No research, however, have employed large, external datasets to assess the results' repeatability and generalizability. Furthermore, no research has used AI to predict cognitive outcomes after epilepsy surgery or to assess the likelihood of cognitive decline over time. As a result, the use of AI in cognitive networks in epilepsy is still in its early stages, and its clinical relevance has yet to be determined.[5]

Artificial intelligence (AI), particularly machine learning (ML) and deep learning (DL), has been applied to neuroimaging data to predict clinical diagnosis, or clinical phenotyping from imaging, as well as predict response to antiseizure medicines

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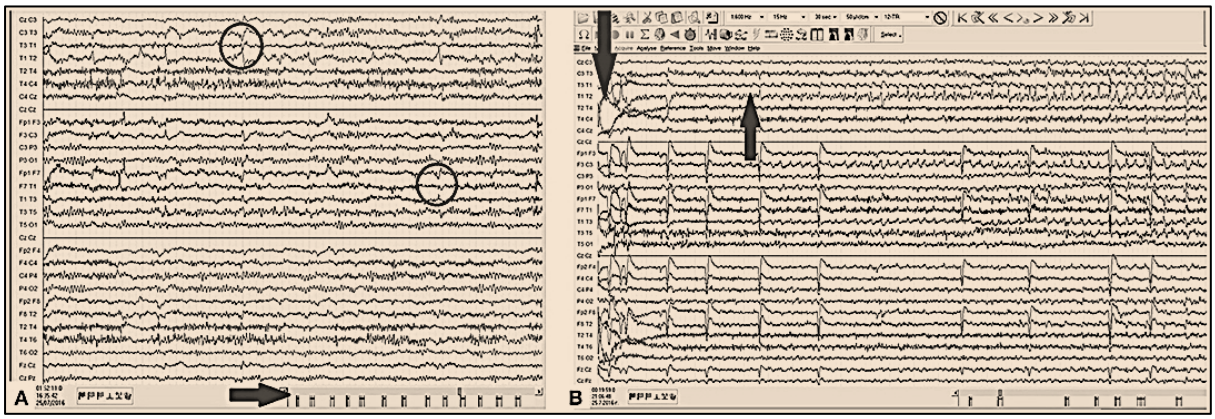
Multisystem Autoimmune and Overlapping GAD65-Antibody-Associated Neurological Disorders with a Beneficial Effect of Epilepsy Surgery: A Case Report

Glutamic acid decarboxylase (GAD) is an intracellular enzyme whose physiologic purpose is to decarboxylate glutamate into gamma-aminobutyric acid (GABA), the central nervous system's principal inhibitory neurotransmitter.[1] GAD65 and GAD67 are two isoforms of this enzyme that are broadly distributed throughout the central nervous system, pancreas, and other organs. Antibodies against GAD65, but less frequently against GAD67, can be seen in patients with neurological symptoms. Stiff-person syndrome (SPS), cerebellar ataxia (CA), ocular movement dysfunction, and myelitis are some of the neurological phenotypes of anti-GAD65-related neurological illness that have been identified. Those with seizures in the context of encephalitis, as well as patients with chronic epileptic syndromes without clinical or MRI signs of current CNS inflammation, were shown to have anti-GAD65 antibodies (Abs).[2] As the clinical range of GAD- spectrum disorder (SD) has broadened and their overlapping symptomatology has become increasingly apparent, a slew of confusing clinical links, diagnostic snags, and pathogenetic pathways have surfaced. Only patients with typical GAD-SD neurological syndromes have very high GAD antibody titers directed at different epitopes. GAD antibody titers directed at different epitopes are seen in 80 percent of patients with diabetes mellitus-1 (DM-1), and up to 30 percent of patients with GAD-SD also have DM-1.[3]

Case presentation:

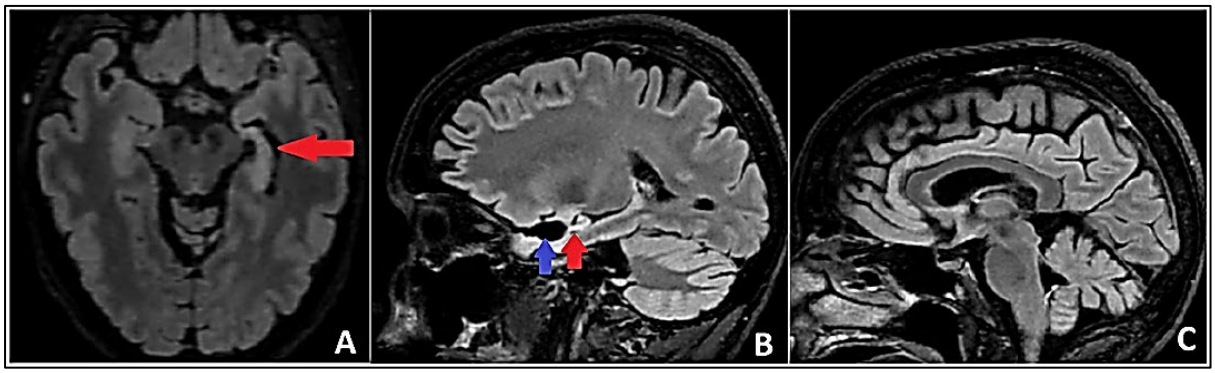
A 40-year-old patient came in for a presurgical examination because of epileptic episodes. Previously, the patient had been operated on for autoimmune Hashitoxicosis at the age of 30 and was being treated with 100 g L-thyroxin. The patient was diagnosed with HLA-B27-negative ankylosing spondylitis (AS) at the age of 34. Six bilateral tonic-clonic seizures in sleep began the epilepsy at the age of 35. After a few months, focal seizures with retained or reduced awareness began, at first only a few per month, but eventually becoming weekly and clustered. Motion stoppage, eye closure, vocal automatisms, and a flushed face was noticed. Several anti-seizure medicines (ASDs) were found to be ineffective or had significant side effects. As a result, lamotrigine (LTG) and low-dose clonazepam were used as treatments (CZP). Electroencephalograms (EEGs) were taken as usual. More than 150 seizures were

documented during a three-day video-EEG monitoring session. They lasted 40–60 seconds and were accompanied by a left temporal ictal alteration in initial attenuation and rhythmic epileptiform discharge. Verbal memory loss was confirmed by neuropsychological testing. An autoimmune aetiology based on the patient's clinical history, appearance, and examination results was suspected.



(A) EEG in wakefulness with left temporal sharp- and spike-wave (SW) complexes with maximum and phase reversal on T1-T3 (red arrow). **(B)** Ictal EEG epoch from the clinical seizure onset (red arrow) demonstrating the evolution of the left temporal ictal discharge

Although a control brain MRI demonstrated no advancement of mesiotemporal abnormalities, fluorodeoxyglucose-positron emission tomography (FDG-PET) revealed limited hypermetabolism in the left amygdala, which the patient linked to an ictal experience during the examination. The patient was diagnosed with DM1 a year later, then five years later when the patient presented with increasing CA, which was controlled with surgery.



(A) Axial FLAIR MRI with left HS (red arrow). **(B)** Sagittal FLAIR MRI scan demonstrating the postoperative defect (blue arrow) and the left HS (red arrow). **(C)** Sagittal FLAIR MRI without obvious signs of cerebellar and brainstem atrophy.

In this example, a very high GAD-Ab titer was identified in both serum and CSF, with the recognised abnormal level by ELISA being >1,000 IU/ml and the serum level being substantially higher than the CSF level. Despite the fact that the serum GAD-Ab titer reduced dramatically after the first IV MPR trial, the disease course did not follow this Ab-reduction, as extremely frequent debilitating seizures persisted and two other GAD-related diseases (DM1 and CA) occurred subsequently. Patients with delayed diagnosis of GAD-associated epilepsy were found to be ASD-resistant and not responsive to immunotherapy, according to Makela MK et al. The cornerstone of management in such complex instances is "the interplay between AEDs and immunotherapy," which was further confounded in our patient by the eventual emergence of DM1 and CA. In each situation, the treatment strategy must be tailored to the person, and epilepsy surgery cannot be ruled out as a therapy option. This is an example of a difficult clinical circumstance in which personalised and very selective epilepsy surgery could be an effective therapy option for reducing seizure frequency and improving quality of life.[3,4]

This study showed the importance of early and aggressive immunotherapy in severe GAD-TLE patients, as well as the potential benefit of epilepsy surgery in select GAD-TLE patients.

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Therapeutic Challenge in a Case of Refractory Cluster Seizures

Epilepsy is one of the most frequent major neurological disorders, accounting for 1% of global disease burden in terms of disability-adjusted life years, or the number of person years lost due to impairment and premature death. About 30-40% of patients with epilepsy have seizures that are uncontrolled by medication in countries where effective diagnosis and treatment are available. As a result, medically refractory epilepsy is a major public health concern. Patients are diagnosed with refractory epilepsy if they continue to have disabling seizures despite adequate trials of two antiseizure medicines, either alone or in combination. Patients should be referred to multidisciplinary epilepsy facilities at this time, where specialised diagnostic testing can be performed to identify whether they are pharmacoresistant and, if so, alternative medications can be offered.[1]Epilepsy surgery is the preferred treatment for drug-resistant epilepsy, however determining the best time for surgery is difficult and case-specific. In terms of seizure independence after surgery, focal cortical dysplasia type 2b (FCD type 2b) offers the greatest prognosis; however, there is little data on the treatment of explosive onset FCD.[2]

A 4-year-old child with explosive onset FCD was treated with electrocorticography (ECoG) guided focal excision and obtained total seizure independence.

Case Presentation:

A 5-year-old child had continuous cluster seizures for two weeks. Patient parents described brief incidents lasting around 10 seconds in which the child had up rolling of eyelids, tonic extension of both hands forward, and giggling. The general physical exam, as well as the systemic and neurological exams, were unremarkable. A video electroencephalogram (EEG) was used to examine patient and record occurrences. The interictal record (IED) revealed spike and wave discharges, as well as rhythmic rapid activity, primarily in the left frontal lobe (F3>Fz>Fp1). Two electrographic seizures were documented along with four routine clinical episodes. A magnetic resonance imaging (MRI) brain epilepsy protocol was carried out based on this electroclinical theory. In the left middle frontal gyrus, MRI revealed an aberrant gyral pattern with cortical thickening and blurring of the grey white matter junction. Interictal positron emission tomography indicated left anterior frontal hypometabolism, which was confirmed by an interictal positron emission tomography. The patient's development quotient

(DQ) was >85 because the patient did not respond to anti-epileptic medicines (AEDs) (normal). The poor response to AEDs and immunomodulation, as well as the lack of data on extremely early surgery, were obstacles. Neuronavigation craniotomy was planned to centre over the lesion under AXIEM (Medtronic Stealth station S7). ECoG utilising a four-channel strip electrode exhibited the most spikes near the lesion's edges. Also, a depth electrode put into the sulcus revealed spikes well localising the location for resection. The lesion was completely excised along the boundaries of the dysplastic, thickened, greyish gyri that extended to the depth of the sulcus. The spikes that were detected before resection were completely silent in post-resection ECoG from the edges and walls of the resection cavity. The patient has not had a seizure in 32 months and has been off anti-epileptic medication for the past three months.The most prevalent cause of refractory focal epilepsy is focal cortical dysplasia, and surgical excision is the only way for patients to be seizure-free.

The current case presented a decision-making problem since epilepsy surgery in the early stages of refractory epilepsy is a difficult decision to make for both the epilepsy team and the patient's family. The superiority of surgery over medicinal management has led to choose it over an uncertain waiting in which the patient is subjected to a daily flurry of seizures.[3] Terra VC, et al. showed that targeted excision of focal cortical dysplasia (FCD) lesions for intractable epilepsy can be accomplished safely in children with good seizure outcomes and minimal complication rates. All patients with FCD and refractory epilepsy should seek epilepsy surgery.[4] Isler C, et al found that surgical intervention in patients improves seizure outcomes, resulting in a higher quality of life. There are clear variations between the FCD type 1 and type 2 groups, which may help with medicinal and surgical care of this diseases.[5]

Surgical resection is feasible and effective in the early phase of FCD clinical presentation

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The Association between Post-Traumatic Epilepsy and 1-Year Outcomes After Traumatic Brain Injury

Traumatic brain injury (TBI) is described as a change in brain function or other signs of brain pathology caused by an external force. Mild TBI (which includes concussion) to moderate and severe TBI.[1] Posttraumatic epilepsy (PTE) occurs when patients with a TBI develop late symptomatic seizures, usually more than 7 days after the injury.[2] Brain trauma epilepsy is difficult to manage with medical therapy, and it is the cause of epilepsy in about 5% of patients sent to specialised epilepsy centres. After a TBI, patients with PTE have been shown to have poor mental health outcomes. Despite the existence of prospective data on the incidence and risk factors of PTE, few research has looked at how PTE is linked to overall TBI outcomes.[3]

The goal of this study was to examine the prevalence, risk factors, and relationship between self-reported PTE and functional outcomes as well as self-reported somatic, cognitive, and psychological problems in a large, prospectively collected TBI cohort.

As part of the Transforming Research and Clinical Knowledge in Traumatic Brain Injury project, this multicenter prospective cohort study identified individuals with TBI to one of 18 participating levels. Patients with TBI, people who had extracranial orthopaedic injuries (orthopaedic controls), and people who had no reported injuries were all observed for a year. TBI Common Data Elements were used to collect demographic, imaging, and clinical data. The National Institute of Neurological Disorders and Stroke Epilepsy Screening Questionnaire was used to determine the prevalence of self-reported PTE (NINDS-ESQ). The Glasgow Outcome Scale Extended, Rivermead Cognitive Metric (RCM; developed from the Rivermead Post Concussion Symptoms Questionnaire), and the Brief Symptom Inventory-18 were used to measure the primary outcomes (BSI).

Of 3044, 3296 participants met the study's inclusion criteria, and 1885 of them (mean [SD] age, 41.3 [17.1] years; 1241 [65.8%] men and 644 [34.2%] women) had follow-up information

at 12 months, including 1493 patients with TBI, 182 orthopaedic controls, 210 uninjured friend controls, and 41 patients with TBI (2.8%) and no controls had positive PTE screening results. A positive PTE screening result was linked with a higher presenting Glasgow Coma Scale score (8.1 [4.8] vs. 13.5 [3.3]; P< .001) and abnormal acute head imaging results as compared to a negative PTE screening result (risk ratio, 6.42 [95% CI, 2.71-15.22]). Patients with TBI and positive PTE screening results had significantly lower Glasgow Outcome Scale Extended scores (mean [SD], 6.1 [1.7] vs 4.7 [1.5]; P =.002), higher BSI scores (mean [SD], 50.2 [10.7] vs 58.6 [10.8]; P =.02), and higher RCM scores (mean [SD], 3.1 [2.6] vs 5.3 [1.9]; P =.002) at 12 months.

	Full sample						3:1 Propensity-matched sample[a]					
	Self-reported PTE diagnosis, No. (%)		Unadjusted difference (SE)	*P* value[b]	*P* value[c]	*P* value[d]	Self-reported PTE diagnosis, No. (%)		Unadjusted difference (SE)	*P* value[b]	*P* value[c]	*P* value[d]
	Negative	Positive					Negative	Positive				
GOSE (TBI)[e]												
Mean (SD)	7.0 (1.2)	4.6 (1.5)	−2.4 (0.2)	<.001	<.001	<.001	6.1 (1.7)	4.7 (1.5)	−1.4 (0.4)	<.001	<.001	<.001
3	34 (2)	16 (39)	NA	NA	NA	NA	10 (13)	11 (35)	NA	NA	NA	NA
4	22 (2)	2 (5)	NA	NA	NA	NA	4 (5)	2 (6)	NA	NA	NA	NA
5	106 (8)	10 (24)	NA	NA	NA	NA	12 (16)	7 (23)	NA	NA	NA	NA
6	231 (17)	9 (22)	NA	NA	NA	NA	14 (18)	7 (23)	NA	NA	NA	NA
7	363 (26)	3 (7)	NA	NA	NA	NA	14 (18)	3 (10)	NA	NA	NA	NA
8	620 (45)	1 (2)	NA	NA	NA	NA	22 (29)	1 (3)	NA	NA	NA	NA
BSI (GSI t-score), mean (SD)[f]	49.0 (11.5)	56.0 (11.5)	7.0 (2.4)	.007	.017	.017	50.2 (10.7)	58.6 (10.8)	8.4 (3.0)	.01	.02	.02
Rivermead (cognitive), mean (SD)[f,g]	2.8 (2.6)	4.9 (2.0)	2.1 (2.1)	<.001	.001	.001	3.1 (2.6)	5.3 (1.9)	2.2 (2.2)	.001	.001	.002

12-Month Outcome Analysis According to Self-Report Group

This cohort study reports on the NINDS-initial ESQ's validation in the TRACK-TBI cohort, confirms that the risk factors for PTE and overall incidence were comparable to previous studies, and uses the large, prospectively collected cohort to investigate the associations of self-reported PTE with poor functional outcomes and persistent posttraumatic symptoms.[3]

In this study (a proxy for PTE), the percentages of self-reported diagnosis were 0.9 percent for GCS scores 13 to 15, 5.3 percent for GCS scores 9 to 12, and 12.2 percent for GCS scores 3 to 8. These findings are in line with the findings of Annegers et al.[4] Bunshik T et al conducted a retrospective analysis on a TBI Model Systems cohort and discovered differences in some quality of life metrics between PTE and non-PTE groups, but no correlation with self-reported cognitive variables.[5] The follow-up rate following TBI in this study was quite low compared to other illness processes, which is one of the study's shortcomings. The poor incidence of

follow-up following TBI, particularly in big level 1 trauma centres, was expected and should not be used to skew the rate of PTE in the described patient cohort.[3]

The incidence of PTE after a TBI was 2.7 percent at 12 months following injury, according to this cohort study based on a screening questionnaire. Because PTE is linked to poor outcomes, doctors should be on the lookout for it after a TBI and seek antiepileptogenic therapy if necessary.

After a TBI, the incidence of self-reported PTE was found to be 2.8 percent, and it was found to be associated with undesirable outcomes. These findings emphasise the importance of effective antiepileptogenic therapy following a TBI.

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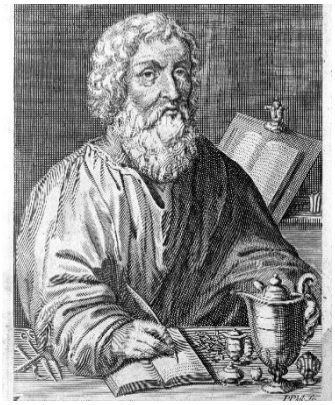

Hippocrates, a Greek philosopher (460-377 BC) was the first person to think that epilepsy starts in the brain. Almost 2500 years ago, Hippocrates wrote the first book about epilepsy. He concluded that the cause of epilepsy was excessive phlegm leading to abnormal brain consistency.