HISTORICAL REVIEW

A History of Diagnostic Investigations in Epilepsy Surgery

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ABSTRACT: Epilepsy surgery has progressed significantly in the last 150 years. Functional brain maps allowed for the localization of epileptogenic lesions based on seizure patterns, allowing surgeons like McEwan and Horsely to treat epilepsy surgically. Berger's electroencephalogram marked the first modality directly identifying epileptic abnormalities. Penfield and Jasper collaborated, as neurosurgeon and neurologist, to use EEG for surgery. Meanwhile, Wada developed the amobarbital test, improving the protection of language and memory. Talairach and Bancaud pioneered invasive monitoring of deep brain activity with stereoelectroencephalography before the computer age made CT and MRI possible. Looking forward, AI and robotics hold promise for further improving outcomes.

RÉSUMÉ : Historique des modalités diagnostiques dans la chirurgie de l'épilepsie. La chirurgie de l'épilepsie a progressé de manière notable au cours des 150 dernières années. La cartographie fonctionnelle du cerveau a ainsi permis la localisation de lésions épileptogènes en fonction du type de crise convulsive, ce qui a permis à des chirurgiens comme McEwan et Horsely de traiter l'épilepsie au moyen d'interventions chirurgicales. L'électroencéphalogramme de Berger a constitué la première modalité d'identification directe des anomalies épileptiques. De leur côté, Penfield et Jasper, respectivement neurochirurgien et neurologue, sont connus pour avoir collaboré dans l'utilisation de l'électroencéphalographie (EEG) lors d'interventions chirurgicales. À l'aide de l'amobarbital sodique, Wada a quant à lui développé un test grâce auquel on a pu améliorer la protection des capacités langagières et mémorielles des patients. S'appuyant sur la stéréo-électroencéphalographie, Talairach et Bancaud ont été par ailleurs les pionniers de la surveillance invasive de l'activité cérébrale profonde, et ce, avant que l'ère de l'informatique ne rende possible les examens de tomodensitométrie et d'IRM. Enfin, si l'on se tourne vers l'avenir, l'intelligence artificielle et la robotique constituent des domaines prometteurs en vue d'une amélioration des traitements offerts.

Keywords: Diagnostic investigations, Epilepsy surgery, History of neurosurgery

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INTRODUCTION

An estimated 50 million people are affected by epilepsy worldwide, accounting for 0.5%–1% of the global disease burden. The World Health Organization (WHO) describes epilepsy as a chronic disease characterized by recurrent seizures. These can include movements of part or all the body and may be associated with loss of consciousness, memory deficits, or loss of other bodily functions.[1] The financial impact of epilepsy includes the cost of caring for and treating patients as well as their lost productivity. Beyond this, epilepsy has significant biopsychosocial sequelae including mental illness, social stigma, and seizure-related injuries.[2]

Seizures and epilepsy have confounded and mystified humanity throughout history, with the earliest descriptions dating back to Mesopotamian tablets from 2000 B.C.[3] In the ensuing centuries, various etiologies were proposed, from curses by moon goddesses to the divine price of genius. It was not until 400 BC that epilepsy was recognized as a disease of the brain by Hippocrates.[3] From this point forth, myth and superstition were intermingled with inquiry and hypothesis. Through the millennia, various remedies were recommended for seizures, ranging from diet restrictions and poultices to significantly more ritualistic practices like utilizing the blood of gladiators. Moreover, invasive procedures such as trephination and rudimentary cautery were attempted.[3]

The introduction of scientific inquiry into clinical medicine during the 19th century led to important improvements in our knowledge of neuroanatomy. Pioneering work by anatomists and psychiatrists such as Broca, Wernicke, and Brodmann led to the mapping of brain function to structure.[4–6] These advances were concordant with improvements in the management of seizures and epilepsy. Sir Charles Locock reported the efficacy of potassium bromide as an anticonvulsant in 1857.[7] Subsequent advances by McEwan, Horsely, Cushing, and Penfield helped define the role of neurosurgeons in the treatment of epilepsy.[4]

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In the past 150 years, knowledge of seizure pathophysiology and the available therapeutic options have expanded immensely. Moreover, there is a clear recognition that a significant subset of patients suffering from epilepsy benefits from surgical procedures. The success of such surgeries depends on diligent pre-operative workup and lesion localization. Here, we focus on the evolution of diagnostic investigations for epilepsy surgery over the past century. In addition to their clinical significance, the rapid improvement of these techniques is a great testament to the power of collaboration between physicists, engineers, and physicians.

The Localization Problem

An important determinant of success in any surgical procedure for epilepsy is the ability to identify the epileptogenic zone. In the late 19th and early 20th centuries, McEwan, Cushing, and Penfield used transient electrical disturbances to the cortex during surgery to map brain function to anatomy.[5] This neuroanatomical knowledge continues to be used and improved by neurologists and neurosurgeons to localize neurological findings. By observing pre-ictal auras, the physical manifestations of a seizure, and post-ictal deficits, it is possible to infer the location of seizure origin.

However, localization by seizure pattern alone is quite limited because the seizure focus can only be attributed to a general area of the human brain. Moreover, due to the spreading nature of seizures, it can often be difficult to elucidate where the initial source of a seizure is, as the first noticeable clinical signs and symptoms may occur further along the path of spread. These limitations made the development of various modalities, including electroencephalography and brain imaging, necessary.

Brain Electrical Activity and the Electroencephalogram

The development of the electroencephalogram (EEG) began with Richard Caton's recording of electrical current variations on the exposed cortex of rabbits and monkeys in 1875.[8] Several decades later, Hans Berger (Figure 1) published his first report of the human scalp electroencephalogram (EEG) and described alpha and beta waves. Interestingly, Berger also performed the first electrocorticography (ECoG) a year later.[8–11] Despite Berger's early breakthroughs, his findings would remain relatively unknown due to his protective nature and his publishing in psychiatric journals, as opposed to better known physiological journals at the time.[12,13] Berger's work would ultimately be confirmed, circulated, and expanded upon by the likes of Edgar D Adrian in England and Hallowell Davis in the USA. These neurophysiologists were able to capture the rhythms described by Berger and build upon his recording technology to solidify the EEG as a viable method for studying brain activity.[8]

Through Davis, the EEG came to the attention of neurologists, William Lennox and Frederic Gibbs, who saw its potential for characterizing epilepsy.[8] In 1934, Lennox, Erna Gibbs, and Frederic Gibbs were the first to record two patients with absence seizures and observe 3Hz spike and wave complexes in Davis' laboratory.[14,15] This was a monumental moment, marking the clinical significance of the EEG while also providing evidence-based insight into the mechanics of seizures. The Lennox–Gibbs team would go on to describe other EEG patterns for different seizure subtypes in the following years.[16,17]

Figure 1: *Hans Berger circa 1920, father of electroencephalography. Unknown author, public domain, available at https://commons.wikimedia.org/wiki/File:HansBerger_Univ_Jena.jpeg.*

Scalp EEG has proven to be a powerful tool, both in research and clinical practice. With it, true seizures can be identified and characterized much more accurately than with clinical signs alone. EEG provides the ability to capture a seizure's focus and spread in real time and can be performed safely for an extended period of time. However, there may be significant noise in the signal detected by scalp EEG due to the presence of bone and tissue layers. Moreover, while the electrodes do characterize seizure spread, they mostly pick up activity on the surface of the brain, limiting EEG's value in describing epileptogenic foci located in deeper structures. Hence, while EEG remains an invaluable tool, other investigative modalities are necessary.

Lateralizing Speech and Memory

The advent of EEG, along with advances in anesthesia and surgical technique, ushered an era of greater effectiveness and safety, establishing epilepsy surgery as a viable treatment option by the mid-20th century. However, challenges remained, including the localization of language and memory centers, which could be dominant in different hemispheres between patients. This information was necessary to inform whether a resection could cause significant impairment of language and memory after surgery. Enter the Wada test, named after Japanese Canadian neurologist, Juhn Wada (Figure 2): a method for lateralizing language and memory centers in the brain prior to epilepsy surgery.

During the Wada test, sodium amytal is injected into the internal carotid arteries while the patient is awake. In modern practice, this is often done through a catheter from the femoral artery. The barbiturate sedates the hemisphere ipsilateral to the injected carotid and blocks its function while the contralateral hemisphere is still active. Once the injection is complete, the patient is asked to perform tasks that test language and memory. If these are impaired, it can be inferred that the dominant language or memory center was in the injected hemisphere. During the test, the patient is monitored with EEG to follow the effects of the injection and check for overflow of the barbiturate into the contralateral hemisphere (Figure 3).[18]

As a young physician in post-war Japan, Dr. Wada worked in Hokkaido Imperial University Hospital's Neurology and

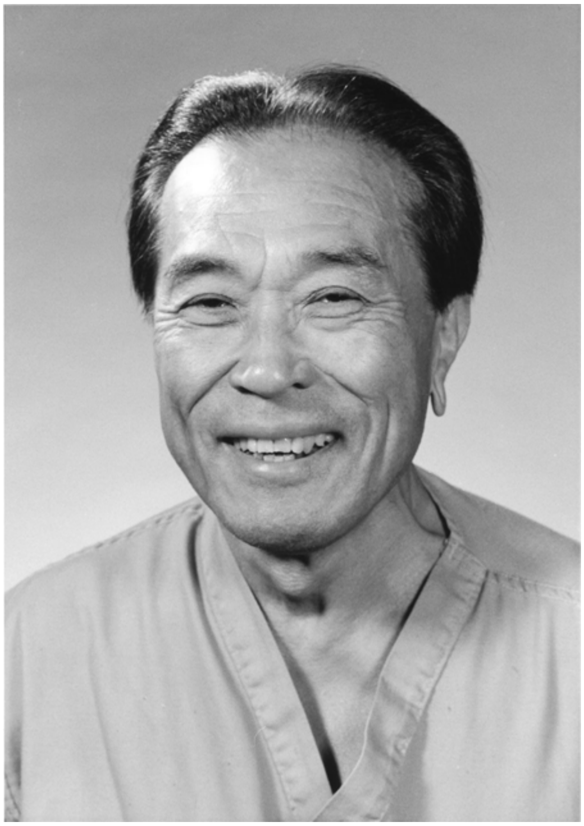

Figure 2: *Juhn A. Wada circa 1995, Japanese Canadian neurologist and inventor of the sodium amytal test. Photo courtesy of University of British Columbia Archives (44.1/3071).*

Psychiatry department. His initial interest was in preventing the poverty of speech associated with repeated bilateral frontal electric shock (ES) therapy. To ameliorate these effects, Wada wanted to limit shocks to one hemisphere but his initial attempts at unilateral ES failed due to the occurrence of generalized seizures. Hence, he proposed "deactivating" the contralateral hemisphere during ES using sodium amytal, a technique he employed in 1948, albeit under significantly different circumstances. In his memoir, Wada recalls a young man presenting in refractory status epilepticus, with stereotyped seizures in his paretic right foot which repeatedly generalized. With the exhaustion of other therapies and the serendipitous availability of sodium amytal, Dr. Wada elected to attempt a left carotid injection of sodium amytal. What followed was an arrest of the seizure as well as transient hemiparesis and a profound mute state. From this, Dr. Wada was able to extrapolate that he had deactivated the patient's language centers, which in this case were housed in the left hemisphere. This was a breakthrough in language localization.[19,20]

In 1955, Dr. Wada took a sabbatical to the Montreal Neurological Institute (MNI).[19,20] It was at the MNI that he presented his test to the world. This was in the form of a collaborative study and report with Theodore Rasmussen, Penfield's successor at the MNI. In their seminal paper, Wada and Rasmussen[21] described sodium amytal injections in 8 monkeys and then presented 20 human cases. The test would initially only be used in left-handed and ambidextrous individuals, given the possibility of a right-sided language center in these cases.[18] Dr. Wada spent 18 productive months at the MNI prior to moving to and settling in Vancouver, British Columbia, where he continued his contributions to epilepsy.[22]

At the same time, there was a growing understanding of the temporal lobes' role in memory function. A key player in elucidating this understanding was the now renowned British-Canadian neuropsychologist, Brenda Milner. Milner had worked with Penfield, alongside her mentor Donald Hebb, studying the effects of temporal lobe resections for epilepsy on higher cognitive functions like memory. Of note was her work with the famous epilepsy patient, HM, in highlighting the association between the hippocampus and memory acquisition.[23] Milner had

Figure 3: *Juhn Wada performing a sodium amytal test by injecting the left carotid artery of a patient. EEG electrodes are in place to assess for the overflow of barbiturate into the contralateral hemisphere. Photo courtesy of University of British Columbia Archives (41.1/2160).*

already shown that temporal lobe resections could lead to impaired memory function in patients whose contralateral memory structures were previously damaged.[24] It was in this context that Rasmussen enlisted her help in refining the Wada test to localize memory function in addition to language. Together they developed methods for testing for amnesia despite aphasia during sodium amytal injections. By testing memory acquisition during hemispheric deactivation through the Wada test, their methodology assessed whether a patient could retain adequate memory function after epilepsy surgery. This multidisciplinary collaboration would shape the Wada test into its modern form.[25]

Despite its elegance, the Wada test has limitations with regard to morbidity, variability between patients, and issues with reliability.[26] Rapid improvements in imaging and the development of advanced modalities such as functional magnetic resonance imaging (fMRI) obviate the need for Wada testing to lateralize language. However, this test continues to be used in a subset of patients awaiting temporal lobectomy.

NEURORADIOLOGY

The discovery of radiation and its application within medicine is one of the great collaborative efforts of physics and medicine. Several decades after Roentgen's pioneering use of X-rays, Walter Dandy and Egaz Moniz developed pneumoencephalograms and angiography, thus, establishing neuroradiology. The utility of neuroimaging investigations increased considerably with the advances in computer science. In 1971, Hounsfield obtained the first computed tomography (CT) scan from a living human brain, showing a tumor which was promptly resected.[27] Concurrently, many physicists and engineers were attempting to use nuclear magnetic resonance (NMR) signals to distinguish tumors from regular tissue. Research by Damadian, Lauterbur, and Mansfield led to the development of a clinically useful NMR machine in 1978; magnetic resonance imaging (MRI) was born.[27–31]

By the mid-90s, MRI would prove itself to be the best imaging study to detect parenchymal brain pathologies. Acquired images clearly demonstrated focal lesions such as tumors, cavernous malformations, tubers, and nodules. Moreover, clinicians were able to detect more subtle abnormalities like hippocampal sclerosis and cortical dysplasia, the prevalence and significance of which had previously been underestimated.[27] Ongoing developments in MR imaging allowed neuroradiologists to interrogate brain perfusion and oxygenation in real time. This was the basis for various functional imaging techniques, the most relevant of which is functional MRI (fMRI) developed by Seigi Ogawa in 1990.[32] This type of imaging is mostly used in the context of mapping language and memory lateralization prior to epilepsy surgery.

Currently, MR imaging plays a central role in disease diagnosis and surgical planning of many conditions, including epilepsy. Two other non-invasive imaging techniques of note in epilepsy are positron emission tomography (PET) and single photon emission computed tomography (SPECT). Before the advent of fMRI, it had been observed intraoperatively that seizures result in hyper-perfusion of the affected brain area. The use of radioactive tracers in the blood (^{133}Xe) later demonstrated that there was also hypoperfusion and hypometabolism associated with these areas interictally. PET scans rely upon the differential uptake of radioactively tagged metabolites ictally and interictally. These scans are most commonly performed using fluorodeoxyglucose (^{18}F-tagged radionuclide) and help identify seizure foci in MRI-negative patients and highlight broader areas than EEG.[27]

SPECT, developed in the 80s, uses the blood flow paradigm to assess areas affected by epilepsy and may help localize an epileptogenic zone. Modern SPECT uses the radiotracer 99mTc-hexamethyl propylene amine oxime (99mTc-HMPAO) which deposits in brain areas in correlation with blood flow. Ictal SPECT requires the radiotracer to be injected during (or soon after) seizure activity but the images may be acquired hours later. This is possible because the radiotracer embeds based on the blood flow pattern during the seizure. Given the complications associated with acquiring an image while a patient is seizing, the advantages of this method are clear. The ictal scan is often compared with and subtracted from baseline SPECT for greater contrast.[27]

The diagnostic investigations discussed thus far have revolutionized surgical decision-making for patients with epilepsy; however, some cases require more direct tests. EEG has limited spatial resolution, especially for deeper foci, while imaging studies may show multiple abnormalities and only propose candidate epileptogenic zones. Hence, there has been considerable interest in refining techniques that directly record from the cortex or deeper structures such as electrocorticography (ECoG) or stereoelectroencephalography (SEEG).

INVASIVE TESTS

An early solution to the artifact problem in EEG recordings from the scalp was to place electrode arrays on the cortex. The first such recording is attributed to Hans Berger, the father of electroencephalography, who made recordings from the cortex of a patient undergoing surgery.[8] However, Berger's studies were not widely reported or recognized, as previously discussed.[8,33,34] Nevertheless, in 1934, Hans Altenburger and Otfrid Foerster reported electrocorticography from 30 intracranial EEG recordings. This would be the first time a seizure pattern would be captured and described using invasive methods, complementing Lenox and the Gibbs' capture with scalp EEG that same year.[35] Beyond his work with ECoG, Foerster was a prolific neuroscientist, mentoring and collaborating with a significant number of neurologists and neurosurgeons who visited him in Breslau, now Wroclaw, Poland. One such visitor was neurosurgeon, Wilder Penfield (Figure 4) in 1928. The pair collaborated on surgical treatment of epilepsy, laying the groundwork for Penfield's future endeavors.[36,37]

Penfield would continue his work on epilepsy surgery at the MNI in close collaboration with neurologist, Hebert Jasper. In 1939, the pair were the first to use ECoG in conjunction with electrical cortical stimulation during a procedure. This was to localize an epileptogenic area secondary to previous head trauma. ECoG was also used after the resection to detect any remaining epileptogenic tissue.[38,39] This case also involved the first instance of extraoperative invasive EEG recordings prior to an operation. Single-lead epidural electrodes were placed over both temporal lobes through burr holes and data were gathered for 3 days prior to the surgery. The idea to monitor epilepsy invasively over days was quite prescient and subdural grids continue to play an important role in pre-surgical investigations. Using this

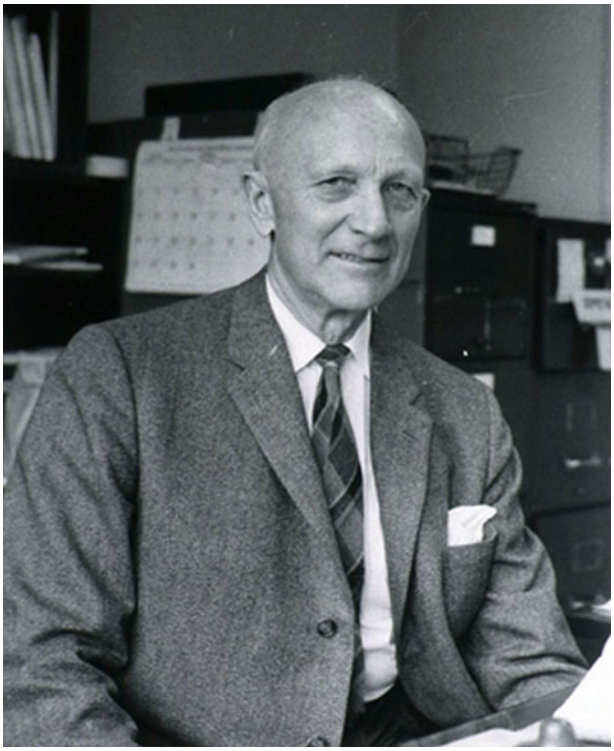

Figure 4: Wilder G. Penfield circa 1958, a pioneering neurosurgeon in epilepsy surgery. United States National Library of Medicine, public domain, available at https://commons.wikimedia.org/wiki/File:Wilder_Graves_Penfield.jpg.

methodology in the subsequent years, Penfield and Jasper would shape epilepsy surgery for decades to come.[33]

Electrocorticography is an exceptionally powerful tool when localizing and characterizing neocortical lesions. However, it has limitations when lesions are in deeper structures since electrical potentials can follow variable paths at seizure onset before reaching the brain surface. The Gibbs group was one of the first to attempt detecting seizure production and propagation from deeper structures in 1949. They designed a needle electrode 2.5 mm in diameter, similar to a standard ventricular needle, with 8 silver rings, 2mm in length separated by insulating material. As electrodes needed to be guided very precisely, they modified stereotaxy devices which had been designed by Horsely and Clarke. However, determining the exact target for each electrode within the brain remained a challenge. Hence, Hayne, Belinson, and Gibbs developed approximate coordinates for brain structures based on external landmarks using averaged coordinates from three fixed cadaver heads.[40] In this way, recordings of deep structures including the thalamus, caudate, and putamen were reported, albeit with questionable accuracy. Later, the French neurosurgeon, Jean Talairach, developed a system using structural landmarks found on the pneumoencephalogram, such as the ventricular system, to provide individually optimized pathways for the exploration of deep structures.[41,42] He also went on to collaborate with neurologist, Jean Bancaud, to advance stereotactic techniques in the treatment of epilepsy, coining the term “stereoelectroencephalography”. The pair quickly came to realize the potential for SEEG, which allowed neurologists to assess seizure progression in three dimensions.[43] Furthermore, the implanted electrodes could remain in situ for days which provided greater spatial resolution of epileptogenic zones.[44]

Despite its advantages, SEEG does have limitations, such as lower electrode density to cover the cortex and taxing administration, given the number of electrodes that need to be implanted. Hence, ECoG became the more widely used modality in North America, branching from Penfield and Jasper’s efforts and popularized by the likes of Lüders, Wyler, and Ojemann in the USA.[45,46] In parallel, SEEG’s influence grew in Europe at centers like St Anne Hospital in Paris, Grenoble, Milan, and later at the MNI.[47]

This division in preference would continue for several decades until the arrival of high-resolution imaging, advanced computing, and robotics, which have resulted in a dramatic shift over the past decade. For one, evidence is beginning to show that SEEG is safer with regard to infection risk and hemorrhage compared to ECoG via subdural electrodes.[48] Image-guided intraoperative neuro-navigation has also facilitated surgical planning and made this technique more accessible.[47] Most recently, with advances in robotics and artificial intelligence, assistant robots including the Neuromate (Renishaw Inc.) and ROSA (Zimmer Biomet) have entered the field. These machines can streamline the implantation process and make SEEG significantly less time-consuming.[49] With this safety, precision, and efficiency, an increasing number of centers across North America are now offering SEEG.[50]

CONCLUSIONS

The past century has witnessed numerous advances in the diagnosis and treatment of patients with epilepsy. The exact processes of aberrant neuronal firing and network propagation are yet to be fully elucidated. However, the management of patients with epilepsy has benefitted from a commitment to research and a uniquely intradisciplinary approach to care. Improved knowledge of neuroanatomy and neuroscience has led to important insights into the pathophysiology of epilepsy and aborting seizures. Consequently, the compendium of medications that treat various seizure subtypes continues to grow and newer medications are better tolerated by patients with epilepsy. Moreover, fundamental discoveries in physics, engineering, and medicine have led to the innovations of pioneers like Berger, Penfield, and Wada. The early diagnostic tests have been expanded upon and the advent of computer science has allowed significant improvements in imaging. Together, these modalities have been leveraged to increase the safety and efficacy of surgical resections. Ongoing collaborations between scientists and clinicians, as well as the rapid incorporation of novel technologies such as robotics and artificial intelligence, portend a bright future for patients undergoing epilepsy surgery.

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DISCLOSURES

The authors have no conflicts of interest to declare.

STATEMENT OF AUTHORSHIP

KH completed the literature review for this article. KH and MF drafted the manuscript. NS, YA, and GJR provided guidance, reviewed the article, and suggested edits that were incorporated.

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