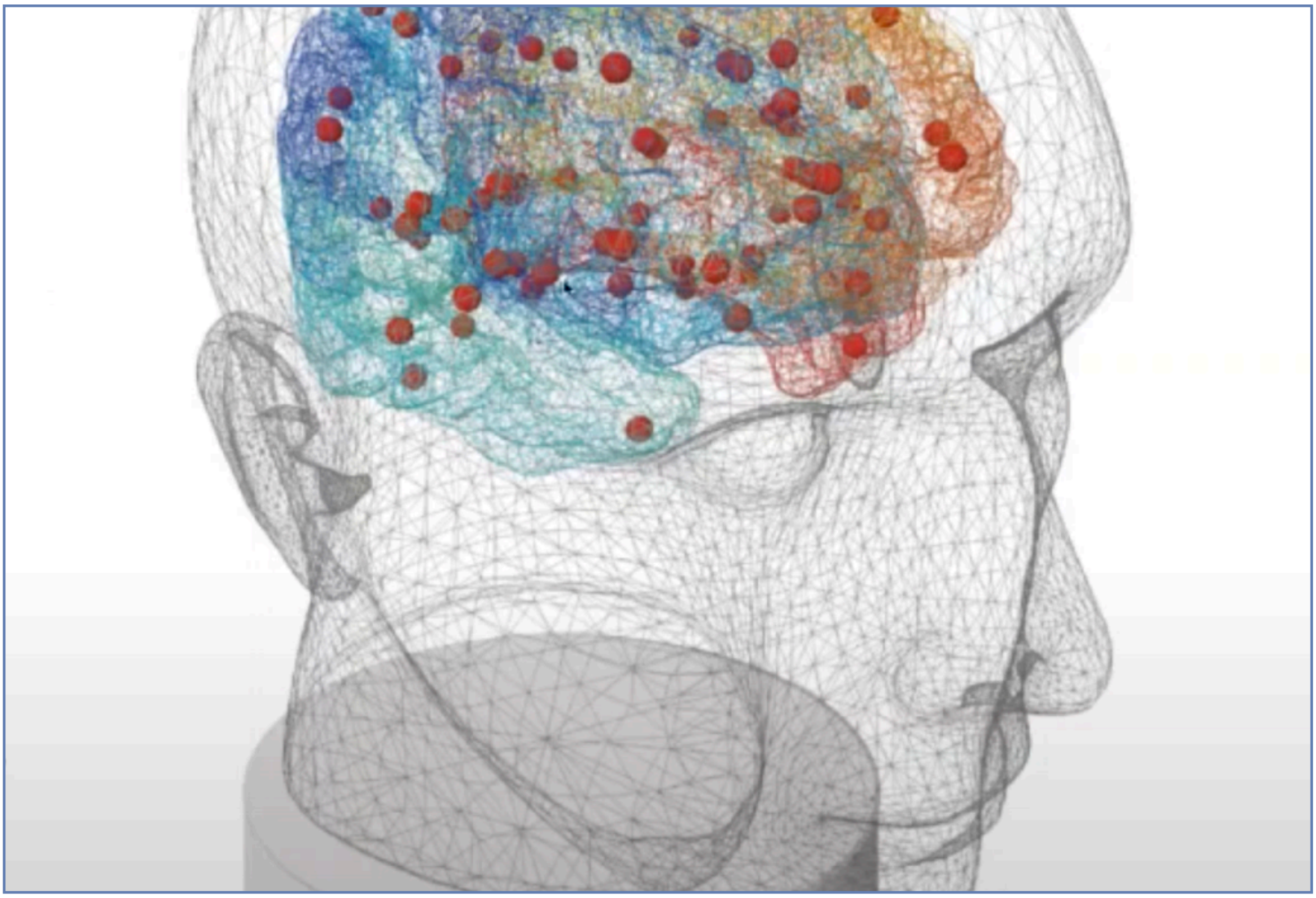

Image: Presentation of HBP Virtual Epileptic Patient - Prof. Viktor Jirsa.
Spanish Innovation Community - Human Brain Project.

HBP Innovation Market Analysis Series

VEP Market Review: A strategic analysis for the management and exploitation of technology

UNIVERSIDAD POLITÉCNICA DE MADRID
POLITÉCNICA

Human Brain Project

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November 2020, V2

Human Brain Project
UPM
Innovation Team

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ACKNOWLEDGMENTS

This study has been directed by the Innovation Team of Universidad Politécnica de Madrid (UPM) within the task 8.5 of SGA3.

With special thanks to the Human Brain Project, for providing a space for collaboration and knowledge generation that inspires neuroscientific continuity and multidisciplinary teams in developing research and solutions for the future. Also, to the Virtual Epileptic Patient Team, for their kind support in providing us with the latest and most accurate information possible, enriching the present analysis.

This work has been funded by the EC under grant 945539 (HBP SGA3).

Project Number	945539	Project Title	HBP SGA3

Document Title:	VEP Market Review
Document File Name:	VEP Exploitation Analysis
WP(s) / Task(s)	WP8, T8.5
WP Objective (s):	WPO8.1
Output(s)	OP8.19
Dissemination Level:	PU = Public
Delivery Date:	November, 2020
Author (s)	Teris DURAN, Gonzalo LEON, Guillermo VELASCO, Bryan STRANGE (P68)
Compiled by:	Gonzalo LEON, Guillermo VELASCO (P68)
Abstract:	The Virtual Epileptic Patient is a technology of next introduction in the healthcare industry worldwide, as a diagnostic evaluation tool for those patients with refractory epilepsy, susceptible to surgical intervention. The model has the ability to identify the Epileptogenic Zones and Propagation Zones. As a project developed within the Human Brain Project, it is desired in SGA3 to assess the exploitation of this technology and its achievement to the market, mainly. Three levels of drivers associated to the model are analyzed, factors that will be key to its eventual expansion in the industry, in order to create strategies according to different demands and introduction priorities. This review also analyses some of the virtues and weaknesses of the VEP model against its eventual application in the healthcare industry, contrasted with doctors, specialists and also with the creators of the model. Furthermore, regarding technological trends and characteristics, possible links are proposed for other developments and collaborations in new related areas. Finally, a roadmap is developed that frames the actions and possible tasks to follow in medium and long term, which will be subject to continuous updates.
Keywords:	Epilepsy disorder, personalised brain network models, market analysis, strategic planning, VEP technology roadmap.
Target Users/ Readers:	Non-experts interested in large-scale brain networks; Investors interested in neurotechnologies and epilepsy; Experts looking for research and/or industrial actors in the field.

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Image: Viktor Jirsa, Director of the INSERM Institut de Neurosciences des Systèmes at Aix-Marseille-Université and Fabrice Bartolomei, Clinical Coordinator and Neurologist.
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Globally, neurotechnologies face the continuous challenge of being differentiated to the rhythm of a constant technical transformation and its adaptation to needs of the human being, on a precise and demanding context by the healthcare industry. Likewise, an avalanche of constant information is translated into new data that requires with impetus the opportunity to provide an increasingly personalized medicine for the patient. From this perspective, challenges are being made to understand the extent to which innovations that have emerged around the human brain and the diseases that afflict it are responding effectively.

This continuous technological redefinition has deserved to address the intrinsic problem to be solved in relation to diagnoses in refractory epilepsy, starting from different critical angles of specialization in medicine and engineering, mainly. However, for technologies with a relevant degree of maturity for their introduction to the market, the roles to be played by both exploitation and commercialization characterize a particular framework of action that is mostly undetermined by the obstacles described throughout this report; and whose singular intention is precisely to consider them in technology transfer plans. In this sense, the present study analyzes the evolution of VEP from its conception and its current level of development, considering the potential user and the industry it favors, nuanced by an opinion matrix by some leading doctors and researchers inside and outside its creator team.

To this end, this research has been organized into four parts. *The first part* addresses the existence of VEP that emerge as a powerful virtual tool to improve the diagnosis of refractory epilepsy, as a necessary phase to understand its usefulness to those who are outside it and adapted mostly to a market angle, without undermining to attribute the medical conceptualization that concerns it. This addresses not only the context of epilepsy disorder in the current era but also the opinions of experts in the field, which ultimately contribute to its technical effectiveness, as well as promising and future related studies. *The second part* aims to define the achievements of VEP both in the international medical community and patient diagnoses, in addition to new derivative studies such as BVEP that highlight its attributes; allowing us to analyze why it is competitive in the global context against other similar technologies. To achieve a more complete and integrated vision of this innovation, the obstacles to be faced and good practices are described through its drivers, as well as a SWOT analysis in order to facilitate its commercial and non-commercial exploitation through a start-up

All this leads us to the *third part* of the report in which the structure of the roadmap is constructed as part of its strategic planning, identifying possible medium and long term applications through related studies in neuroscience and which promptly require applications such as VEP to improve their approaches, or what has been defined in this study as possible *strategic aspects of innovation*, mentioned below: Optogenetics, deep brain stimulation or DBS, neural tissue engineering or NTE, smart wearable technology for seizure prediction and personalized recording of EEG brain waves, as well as the application for the diagnosis of other neurodegenerative diseases such Alzheimer's. Each aspect is concisely described in this study to justify the contribution of the VEP mechanism in these areas. The last and *fourth part*, regarding the exploitation of the technology, some guidelines and recommendations are suggested.

PART I. CURRENT POSITION OF THE VEP

Brain modelling relies on two basics concepts related to large-scale brain networks: On the one hand, the structural connectivity understood as the set of connections in the different brain areas; and on the other hand, the functional connectivity, which comprises the set of relationships that are established between two areas of the brain and according to the metrics that the specialist determines for the model (Hansen et al., 2014).

In this sense, one of the various challenges faced by neuroscience -including VEP- has been to try to simulate brain states in the face of non-stationary dynamics or non-stationary time series that are unpredictable.

The VEP
A multimodal tool that provides significant prediction tailored to each patient's brain parameters.

The Virtual Epileptic Patient, or VEP, is **a non-invasive technique, through which the formations of the brain are reconstructed in a three-dimensional scheme, applying a modeling in which neural groups are reflected in nodes**. Using an application called Epileptor (Jirsa et al., 2016), with downloaded variables and slow processes to combine the connectomes of the patient's brain and their reconstructed white matters, this model is composed by five variables that work in three times states -from the fastest to the slowest-. These replicate discharge models, for example, in a crisis corresponds to the fastest discharge, while in slower processes there is a variation in energy concentrations and tissue oxygenation; through mathematical equations and reflecting the possible changes between variables that affect the spread of the seizures.

Three key ideas about the VEP:
- Custom neural network model.
- Exploration and prediction of epileptogenic zones.
- Greater accuracy with high-performance software.

Through this high-dimensional modeling, clinical hypotheses can be established about the anomalies identified mainly by the Magnetic Resonance Imaging (MRI) and Diffusion Magnetic Resonance Imaging (dMRI) to the network, **demonstrating the evolution of the areas that trigger epilepsy, identifying possible Epileptic Zones (EZ), as well as Propagation Zones (PZ) in the absence of epilepsy.** Specific data is also collected for each patient in preoperative stages, evaluating the possible medical history: Neurological and neuropsychological exams, Electroencephalograms (EEG), Video-EEG, Positron Emission Tomography (PET), Stereoelectroencephalography (SEEG), Magnetoencephalography (MEG), Ictal ESPECT; therefore, based on the hypothesis, the specialists can set parameters (Ibíd. 2016). Then, they make an evaluation of the model obtained through the simulation adjusted to the mathematical analyses and with customizable data for each patient according to the clinical observations, allowing to map affected or seizures-free areas.

The key concepts to be considered are highlighted, summarizing most of the information presented.

Also, complementary ideas are included to enrich the context.

However, there are conditions that can be missed by the magnetic resonance. Although it is undoubtedly useful for certain pathologies, there may be some exceptions, for example, when there might be no visible lesions on the MRI[1]. In this sense, constitutes an opportunity for the application of the VEP model, because it recreates at a macro level the brain connections based on non-invasive models from empirical patient data, as indicated by the creators, they allow the

[1] 25% of surgical patients with focal epilepsy reflect non-injury MRIs. Jeha et al., 2007 mentioned by Jirsa et al., 2016.

Structural and anatomic connectivity: Set of all existing connections between brain areas.
Functional connectivity: Set of relationships between two areas, depending of the chosen metrics.

construction and testing of medical hypotheses inherent in web-based mechanism.

Therefore, highlighting the functionality of VEP, brain modelling relies on two basics concepts related to large-scale brain networks (Jirsa et al., 2014): On the one hand, the structural connectivity understood as the set of connections in the different brain areas; and on the other hand, the functional connectivity, which comprises the set of relationships that are established between two areas of the brain and according to the metrics that the specialist determines for the model. In this sense, one of the various challenges faced by neuroscience -including VEP- has been to try to simulate brain states in the face of non-stationary dynamics or non-stationary time series that are unpredictable; however, they comment that by covering a macro connectivity it allows reducing the imperfections of the simulation. In relation to the BVEP the functional connectivity is the most accurate to defining parameters for diseases such as epilepsy and Alzheimer, according to the experts.

Biomarkers Biological substances, characteristics or images that provide an indication of the biological state of an organism. (NIH, 2001)

In this sense, **the effectiveness of the simulations has led to ask neuroscientists to refine and question the metrics that are applicable to these models.** Biomarkers have been applied for more than five years to VEP with high statistical significance (Ibíd.), allowing a more accurate prediction, despite the fact to be more accurately at a group level rather than individually -for each patient-, precisely because on the basis of what has been said before about the intrinsic difficulty of non-stationary brain states.

Currently, at a conference promoted by HBP, the expert explains that in order to evaluate the patient's behavior **is necessary to address the large-scale brain networks, while the functional aspect tends to be explained at the micro-circuit level, in other words, more specific for possible surgical interventions**. Therefore, the expert explains that the next challenge lies on the electrophysiological evaluations, whose variability oscillates, naturally, according to each area within the same brain structure, which can generate interpretations of pathological and non-physiological conditions or vice versa, adding also that the definition and prediction of the metrics will fall on the experience of the clinician at a more specific level and consistent with previous analysis. Nevertheless, this has not been an obstacle to reflect the evolution of the areas involved in the epileptogenic seizures known as the PZ and EZ.

To date, specialists continue to obtain the most accurate and reliable data taken from the preoperative stages, including medical history, neurological and neuropsychological examinations, as well as the above-mentioned diagnostic imaging results; with this, more personalized biomarkers are defined and tested, in order to make predictions that favor patients' interventions both at the surgical level and in their subsequent therapies. One of the solutions that its creator team has been working on, is the application of **Hamiltonian Monte Carlo model, recently published in another scientific article: The Bayesian Virtual Epileptic Patient (BVEP).**

BVEP
A framework that combines probabilistic programming languages and the personalized brain network modeling to reflect the evolution of the seizures.

This mechanism achieves greater accuracy in the parameters, which would translate into more reliable predictions, and also reflect the evolution of the disorder being a way to validation for the clinician, based on the TheVirtualBrain. For this purpose (Hashemi et al., 2020) applied conditional probability models within the machine learning field, particularly the Hamiltonian Monte Carlo algorithm, which has allowed a greater approximation given the dimensions and metrics considered, they point out (Ibíd., 2020): "This class of sampling algorithms provides efficient convergence and exploration of parameter space even in very high-dimensional spaces that may exhibit strong correlations", argue that **the probabilistic programming languages on which they rely -STAN y PyMC3- allow to reduce the randomness of correlated parameters**, resulting in two aspects: NUTS y ADVI.

80%
The success rate of BVEP, comparable to a clinical expert team.

Therefore, throughout their study, the experts explain how to apply the BVEP and obtain a viable validation mechanism for the clinician, arguing that "based on existing but limited statistics the range of error is comparable to a clinical expert team, approximately 80% of success rate", optimistic results to be an evaluation that is also complemented by the experience of medical specialists.

On the other hand, in order to provide continuity to the clinical trial in this last phase of validation, the Fenix infrastructure has provided IT services through the project ICEI[2], considering that the simulations have to be tested periodically. However, the trial is led by the EPINOV

[2] Integrated by five European supercomputing centers: BSC (Spain), CEA (France), CINECA (Italy), CSCS (Switzerland) and JSC (Germany). More at: https://fenix-ri.eu/about-fenix

and partners[3] for surgical interventions of those patients with refractory epilepsy, distributed in 13 hospitals over a period of 4 years, which would ultimately allow the results of the model to be validated. In the case of hospitals, clinics, research centers and other institutions in the EU that require the use of the VEP and BVEP, **no additional IT resources are needed to run the simulations, according to the creator team, workstation is suitable for clinical treatment**. For those countries outside the EU that may have limited IT resources or neuroimaging evaluations, they can also contact the UPM Innovation Team to help refer these requests to the experts of the VEP.

EPILEPSY AND THE VEP

The etymology of the word Epilepsy comes from the Greek *epilepsia, epilépsis.*, and the verb *epilambanin*, to take, because it is sudden[4]. It is a **disorder that affects 1% of the world population** (Schmidth and Shorvon, 2016), which manifests not only seizures but physical and psychological consequences that impact the life of the affected person, altering their personality, self-esteem, neurological deficits, intellectual impairment and other neurological conditions that also accompany seizures.

Jacksonian seizures
The term was used in 1870 by the French neurologist Jean Martin Charcot, describing seizures as a symptom involving an occasional, an excessive and disorderly discharge of the nerve tissue on muscles. This theory made it possible to redefine the concept of discharges in the cortex, which until then was considered inexcitable, and three years later defined their nature in the grey matter. (Med Hist Supp., 2007)

With impressive progress at the scientific and medical level, significant therapeutic improvements and approaches to the dynamics of this condition have been achieved, with increasingly advanced technologies for diagnosis and treatment. However, the emergence of new neurological health conditions and disorders has, according to the authors, eclipsed part of the investigations related to the disease, recognizing that beyond the enormous amounts of money invested over the last few decades to find progress on it, the most impressive improvements have been the changes that society has made in favor of solidarity with those affected, reducing the stigma that existed around this condition and opening doors to integrate them socially.

[3] Assistance Publique - Hôpitaux de Marseille (AP-HM), the French National Centre for Scientific Research (CNRS), the Institut national de la santé et de la recherche médicale (INSERM), l'Université d'Aix-Marseille and les Hospices Civils de Lyon (HCL) .

[4] In antiquity it had several meanings, as *morbus caducus, morbus sacer, morbus comitialis*. Bicheteau et al., 1856.

Approximately **20 different types of drugs** have been used to inhibit seizures since the first medication was applied in treatment and at least half have been discontinued in the last 20 years. (Page et al., 2018)

Although **medications can decrease the seizures, the disorder can continue progress along with the side effects of treatments that also affect the quality of life of patients**. Surgical interventions can slow down the attacks by showing a partial improvement, but they can lead to new consequences or risks that the patients may present after overcoming the surgery; nevertheless, the number of seizures and deterioration of the patient's life is such that, in certain cases these interventions are preferable according to specialists, especially for those urgent cases related to refractory epilepsy.

With a much more critical view, other experts (Page et al., 2018) also analyse some advances on current procedures, stating that an understanding of the urgency of timely diagnosis for patients with epilepsy has been achieved, but no significant progress has been made in more than 30 years. They argue that, although numerous technological applications have been developed to improve treatments, **many of them fail to be integrated due to the workload that it implies for the specialists and do not comply with the purpose for which they were created**; suggesting that the effectiveness of interventions supported by these applications should also be accompanied by changes in the current diagnostics.

Hans Berger, the creator of the EEG, makes the first record of brain activity evaluating an absence seizure. (Brigo et al., 2018)

Undoubtedly, the creation of the electroencephalogram EEG in the 19th century and its application in human brain studies marked a major advance in the history of medicine and research on the disorder. In this regard (Panteliadis et al., 2017), explain that reflected changes in brain waves could be studied, conceptualizing their typology and differentiating them initially in: Generalized tonic-clonic seizures[5], *minor epilepsy* (currently called absence seizures) and focal seizures[6]. Nevertheless, the EEG as diagnostic test has certain limitations and in some cases does not reflect the neuronal electrical discharges, to define what might or might not be an epileptic seizure[7], because the disorder shows and unknown area between a seizure and a non-convulsive state epileptic (Goselink et al., 2019). When a seizure is not evident as it usually is, what they call interictal anomalies[8], can

[5] They are severe seizures derived from others of primary or secondary type, accompanied by a high rate of morbidity and mortality. Hammond, 2016

[6] Absence seizures, although less severe, usually present generalized discharges in the EEG with an approximate duration of 10 s, and may occur tens or hundreds of times a day (Brigo et al., 2018). In contrast, focal seizures are generally evident in motor cortical regions. Reif et al., 2016

[7] Defined as "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain". Fisher et al., 2005

[8] Refers to the time interval between two episodes of acute or ictal. Clínica Universidad de Navarra, 2020

also be classified as one -depending on the manifestation- can occur when there are no symptoms or without a significant alteration in the EEG of the interictal state. This analysis could verify one of the virtues of the VEP explained in later sections.

Consequently, the specialists also determine that there is an element that distinguishes the disorders of epilepsy such as paroxysmal depolarization shift (PDS), as a manifestation of the cells leading to a hyper-excitable state. The normal activity of the cell is altered by very abrupt and repetitive electrical movements that are reflected in violent contractions of the muscles, as well as the alteration of sensitivity, consciousness and the mind. Indicating that these triggering processes limit the inhibitory processes of the brain and activate other neuronal networks at the same time, producing a propagation effect. Although experiments have been carried out through microscopes on different sections of the brain and on some animals, the conditions under which they start or end remain unknown.

Paroxysmal depolarization shift (PDS): Term in medicine that denotes this exaltation of certain neurons fo the epileptic focus, the cause being the predominance of excitatory neurotransmission left over by the inhibitor. (Laso, 2020)

Therefore, identifying the cause that triggers the epilepsy disorder is still complex for experts, because the manifestation of the seizures usually integrates multifactorial processes and also depends on genetic elements or activated by various alterations - severe brain injuries, tumours, sleep deprivation, alcohol, stress, among others -; hence it is not usual to attribute it to a single cause. The definition of epilepsy according to the Spanish Federation of Epilepsy (FEDE) states: "**Epilepsy is a disorder resulting from the abnormal functioning of a group of neurons (nerve cells) that occurs sporadically in a particular area of the brain. It manifests itself in the form of recurrent seizures which may or may not be convulsive, as in the case of *epileptic absences***".

Causes of epilepsy are grouped into 5 areas: **genetic, structural, metabolic, immune-related,** or **infection.** (Wirrell, 2020)

In this regard, according to Vakharia et al., 2018, surgery is recommended for urgent cases involving refractory epilepsy. In a study published by Wieve et al., 2001, mentioned by Vakharia et al., 2018, of a group of 80 patients who volunteered to participate in the study, almost half were randomly referred for drug treatment while the rest underwent surgery. The result published in the original article by Wieve et al., 2001, shows that the latter group of patients (36) maintained a better post-operative quality of life compared to those who were treated with medicines (40). Of the 36 patients, 4 had adverse effects as a result of these interventions: One presented a mild bilateral thalamic infarction, in another patient the wound became infected, in the other two there was a deficiency in verbal memory, affecting their job for one year. They also point out (Ibid.) that 55% of these patients who underwent surgery, presented asymptomatic defects in relation to the upper visual field.

In the European Region, almost 200.000 patients might benefit from surgical treatment of epilepsy. (WHO, 2011)

Additionally, in a survey of 20 epilepsy surveillance units in Europe, it was explained that approximately 26.7 patients with refractory focal epilepsy are operated every year per center[9] (Markoula et al., 2020). Likewise, it is not to be ignored the percentage of patients who demand to be re-admitted because of post-surgical sequelae, **readmission which involves not only a new risk for the patient but also the investment of considerable resources by the health system**. In other countries as the United States[10], for example, in a study of 10 indexes of surgical admissions, it is determined that about 11% of patients were re-admitted within 30 days (Kwon et al., 2019) mostly due to the recurrence of epileptic seizures, which also implies a significant annual cost to the Centers for Medicare and Medicaid Services (CMS)[11].

Added to this perspective, the average time it takes to finally do a surgery on patients with refractory epilepsy in that country is 20 years (Engel et al., 2012) suggesting a significant impairment in the cognitive and physical capacity of those affected during those years. Although the study was published 8 years ago, none of the patients in the medical control group showed a complete absence of seizures in the following two years, nor did the surgical group (11 de 15); while the sequelae attributable to this group -memory impairment, transitory neurological deficit by MRIs, in some cases- was also not highly determinant given the size of the sample.

Prognostic factors for outcomes of epilepsy surgery: Histopathological diagnosis, age at surgery and duration of epilepsy. (Lamberink et al., 2020)

However, in Europe, a new study (Lamberink et al., 2020) that evaluates to 9.147 patients of 37 centers after 5 years from the surgery, a correlation was found for the first time between seizures in the long term, the consequences of the drugs, age and duration; so, among some conclusions, **the percentage of patients free of disabling seizures decreased by 72% the first year to 66% after 5**

[9] 57 surveys were sent to EMUs in different parts of Europe, of which 20 centers completed the questionnaire. Markoula, 2020

[10] 3 million people suffer from epilepsy in the United States, representing 1.2% of the population. Zack and Kobau, 2017

[11] 17.4 billion dollars a year, penalizing those hospitals with high readmission rates. Kwon et al., 2019

years from the surgery, related to the variables mentioned above. This new perspective suggests a sightly optimistic evolution of the results of the interventions in Europe, given the suspicion of the appearance of post-surgical sequelae both immediately after the intervention and in subsequent years. For example, in another similar study (Baud et al., 2018) in which two groups of patients were compared after 15 years of surgery in 16 centers in Europe, in addition to noticing an average increase from 31 to 50 operations every two years, the improvement in seizures went from 66.7% to 70.9%, respectively. This panorama suggests persisting in the perfection of the interventions, considering the impact on these patients dealing with epileptic seizures on a daily basis, the psychological, labor and social repercussions inherent to the condition; and a cohesive effort from the medical sector.

Drug-resistant epilepsy (DRE): 30% of patients. (WHO, 2019)

On the other hand, the percentage of drug-resistant patients differs between studies, it is estimated that **30% of epilepsy patients are drug-resistant and require surgical treatment**. In this context, Dr. Antonio Gil-Nagel, Neurologist, an expert in epilepsy from the Hospital Ruber International in Madrid, explains that, if two drugs do not control seizures, it is recommended to consider surgery, according to the International League Against Epilepsy (ILAE). He indicates that neurologists sometimes do not consider surgery as an option and invites to redefine these perceptions by searching and analyzing the origins of these assumptions, referring to studies such as Schiller and Najjar (2008), authors that evaluate the probability that an epilepsy can be controlled with different medications.

The expert explains how the first drug administered controls the seizures up to 61.8%, however, for those patients who were not able to control them with the first drug, they try a second one reaching a control of up to 41.7%. From these response groups or, in other words, from those patients who were not able to control the seizures with one or two drugs, 3-6 different are given with a control of up to 16.6%; while for the fourth group that did not achieve crisis control with any of the above drugs, up to a 7-8 or ninth treatment can be given. **Therefore, the doctor suggests reconsidering or evaluating a possible surgery for those groups of patients who do not respond adequately to the first groups.**

Image: EBRAINS

These details are significant as they give an idea of the degree of affectation involved in surgical interventions, the relevance it acquires

Nonconvulsive Status Epilepticus (NCSE):
A State of continuous seizure activity for at least 30 minutes, with cognitive or behavioral changes. (Sutter et al., 2012)

as advances in neurology progress and the need to create instruments or technologies that improve the accuracy of these operations. Despite the difficult perception in choosing -both for the doctor and the patient- an intervention, recovery to lead a normal life seems to be the answer to this type of refractory focal epilepsy[12].

It should be noted that **one of the variants of the epilepsy disorder and another concern of specialists, is the Nonconvulsive Status Epilepticus (NCSE)**[13]. Its diagnosis is difficult for doctors (Gómez et al., 2012), is a condition that increases with age, there are no differences between genders, and even affect between 2 and 20 cases per 100,000 inhabitants each year and accounts for between 5% and 49% of all epileptic states. When It comes to generalized NCSE, there is also an alteration in the patient's level of consciousness. In a conference shared by the Colombian Neurological Institute, Dr. Castaño (2014) offers an interesting insight about this condition, explaining that the region of the brain that triggers the muscle contractions is very small and the epileptic focus may be in another region in the brain. The symptoms can be very disguised, like sweating or discomfort in other areas of the body, different from the typical symptoms of crisis; that may indeed imply one. The doctor points out that it should be considered at the same time: Changes in consciousness behavior (low Glascow scale[14]), history of seizures, and EEG variations; in a given time range, which according to official sources is 30 minutes, although this time is under discussion. When it is of a generalized type, it is possible to evidence the type of alteration of the level of consciousness that the specialists identify through the GCS.

Despite advances and sophistication of neuroimaging techniques, it may happen that the EEG do not show an episode of NCSE at the time, without implying that the patient is not suffering from it. For this purpose, preventive monitoring is conducted that can vary from 12 to 48 hours depending on the GCS (Castaño, 2014), mentioned that in other study conducted on 570 patients with altered

[12] A randomized trial of surgery for frontal lobe epilepsy showed 64% seizure freedom, and a later study of surgery also showed 85% seizure freedom. Vakharia et al., 2018.

[13] The clinical classification of the subtypes are the NCSE with coma and without coma, the latter can be generalized -typical absence status, atypical absence status, myoclonic absence status- and focal -without impairment of consciousness-, aphasic status, with impaired consciousness, unknown whether focal or generalized and autonomic SE. Baykan, 2016.

[14] The Glasgow Coma Scale (GCS) is a scale used in neurology to identify a person's degree of consciousness, using three parameters: verbal, ocular and motor response. Elsevier, 2017.

consciousness, revealed that 10% of the patients were diagnosed with a NCSE, concluding that patients who are not in a coma should have their EEG monitored between 12 and 24 hours and those who show more severe symptoms between 24 and 48 hours and identify the crisis[15]. Also, other specialists suggests that they can detect the etiology with other neuroimaging tests (Baykan, 2016).

Image: Viktor Jirsa and Fabrice Bartolomei. EBRAINS

This analysis could confirm one of the virtues of the VEP software. Precisely, if for an EEG it is complex to evidence a crisis, if there is no order of continuous monitoring for the patient, the software takes part of these results and could lead to limited simulations. This concern was consulted with the scientists who created the model, and they argue that it is indeed a limitation of the EEG, however, **the VEP is supported by other diagnostic evaluations**, points Jirsa: "Given that EEG is currently the best explorations available, it even underlines the utility of VEP, which combines EEG, but also MRI, SEEG, fMRI".

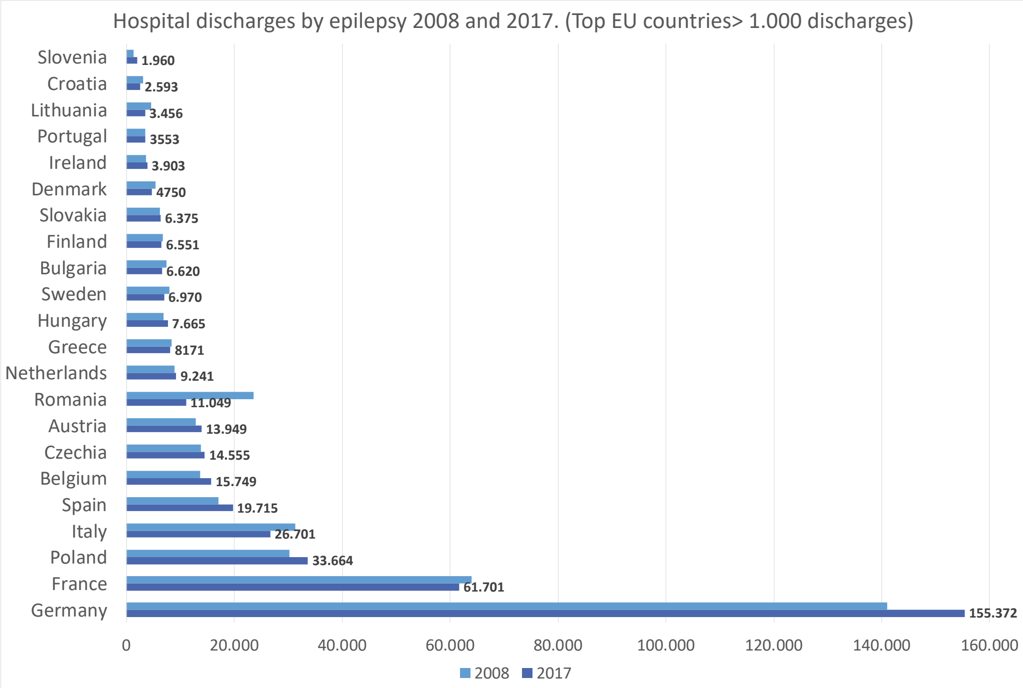
INTRODUCTION TO MARKET ANALYSIS

6 million people are diagnosed with epilepsy in **Europe**, 400.000 new cases each year: 1 every minute.

More than **50 million people worldwide suffer from epilepsy and 5 million new cases are registered annually** (WHO, 2019). Only in Europe, 6 million people are diagnosed, resulting in 400 thousand new cases every year, that is, one every minute (Baulac et al., 2015). In addition, they explain that, coupled with high rates of misdiagnosis, the quality of health services differs markedly between EU countries, with a considerable cost over GDP of 0.2% annual[16]. The following studies also helps to explain, for example, the significant differences found between hospital admissions for epilepsy in some EU countries between 2008 and 2017, as shown in the illustration below:

[15] Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Claassen et al., 2004.

[16] 20 billion euros per year. Baulac et al. (2015).

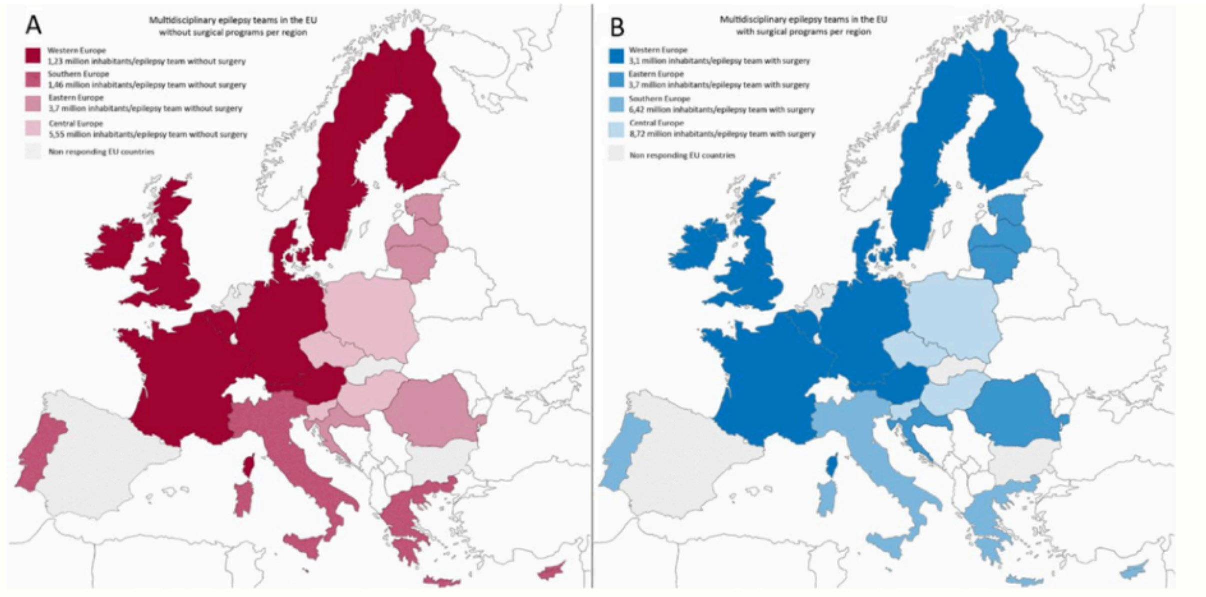


Data: Eurostat (2020).

Additionally, **the difference in the quality of health services between the different countries of the EU favors the displacement and migration of those affected and their families, in the search for better diagnoses and results.** This international demand requires robustness of the health system, as well as social commitment to reach those patients who for various reasons do not follow a treatment, whose represent the 30% of those affected in the European region according to studies (Baulac et al., 2015). Another interesting study (Zelano et al., 2019), determines the characteristics of health care, personnel and resources for the diagnosis of the disease, taken from a survey initially conducted in 2003 of European countries called the European Epilepsy Services Inventory (EESI), in other words, they updated the study by noticing significant differences in these segments between different European countries and others considered by the International League Against Epilepsy (ILAE). According to the answers obtained by the countries, they were grouped into four regions (Western, Southern, Eastern and Central Europe[17]).

30% of patients with epilepsy in Europe do not follow a treatment.

[17] Countries that responded to the survey by region: Western (France, Germany, Belgium, Austria, Denmark, Sweden, Finland, UK, Ireland) -Spain, Netherlands did not provide data specifically for this study-. Eastern (Romania, Croatia, Lithuania, Latvia, Estonia). Southern (Italy, Greece, Cyprus, Portugal, Malta). Central (Czech Republic, Slovenia, Poland, Hungary).



Regional density of multidisciplinary epilepsy teams without (A) and with (B) surgical programs in the responding European Union (EU) countries. Zelano et al., 2018.

These contributions are relevant to the VEP model, as they also provide a clearer idea of the number of specialists who could make use of the tool and their population ratio, as well as the disease trends in certain countries in the region, and can be introduced with more defined priority levels. The survey indicates that the average number of epilepsy related specialists in the EU per million inhabitants is: Neurologists (79), neurosurgeons (15), neurophysiologists (6), pediatricians (173), pediatric neurologists (6), psychiatrists (146), pediatrics psychiatrists (17), general practitioners (679), internists (312) and geriatricians (19). The figure shows which countries have multidisciplinary programs in epilepsy surgery, **those countries with more intense colour have team programmes in epilepsy surgery (Western Europe), the remaining regions have at least one country without a programme.**

The authors comment that a team with epilepsy surgery programmes would correspond to 9 million inhabitants for all ILAE chapters[18]. Although there has been a general increase in the number of epilepsy-related specialists since 2003, the programmes of epilepsy surgery teams per population are not enough, so it can be considered to introduce VEP with higher priority in those Southern, Central and Eastern European countries with less equipment per inhabitant and make the surgical procedure more accesible for these patients.

[18]120 National Chapters, are the associate members of the organization at the global level, it tends to be one chapter per country. ILAE (2020).

Standardized mortality ratio (SMR) and **standardized incidence ratio (SIR)** are used to compare rates of certain diseases with a reference sample

Regarding the risk of death associated with the disease, studies such as (Thurman et al., 2016) mentioned by Beghi (2020), explain that **the standardized mortality ratios[19] are high for those patients under 50 years of age with structural/metabolic epilepsy who do not respond to treatment.** Deaths are mainly related to sudden epilepsy death (SUDEP), epilepticus status (SE), fall death and suicide; addressing the analysis of these rates in both high-income countries (HIC) and lower middle-income countries (LMICs). In this segment, Beghi (2020) points out the comparison of ratios in two studies (Thurman et al., 2016; Levira et al., 2017), explaining that the results of *standardized mortality ratio* (SMR) as far as premature death is concerned, it ranges from 1.6 to 3.0 for HICs; while for LMIC the index is 19.8 respectively. In a similar study for 2013, the average annual death rate from epilepsy as a primary cause for the Latin America region was 5.87 (ratio of 1.04 per 100,000 inhabitants)[20].

As for the LMIC countries, **medical care in epilepsy -as in other brain diseases- faces important challenges due to the limited technical, economic and human resources needed to cover the care of the affected population.** On the one hand, the high cost of access to private medicine in inflationary economies or in countries in conflict, coupled with the lack of hospitals specializing in epilepsy and/or with the technical equipment available and, on the other hand, by the availability of resources on the part of these patients that can assume the medical tests and certain surgical operations, leading to partial diagnoses and treatments. Another determining factor is the cost to centers in these countries of acquiring medical technologies and qualified personnel, including the lack of epilepsy programmes that can reach more disadvantaged populations, as well as the lack of support for health personnel to access technical knowledge and specific skills that undoubtedly require the investment of resources.

Considering that 80% of people with epilepsy reside in LMICs[21], there is critical concern about the increasing trend in these countries of neurological disorders and the non lack of specialized centers, resources and doctors working under minimal conditions. Here WHO (2017, pp. 35) states: "Neurological disorders are six times higher in low-and middle-income countries compared to high-income

[19] The SMR or SIR determine the number of observed deaths and the number of expected deaths by age and gender, for example of a general population. Kelsey, 2017.

[20] PAHO, 2013.

[21] WHO, 2019.

countries, largely due to epilepsy (14 times higher)", they also reflect the marked differences in the number of specialists related to the disorder per 100,000 inhabitants such as neurologists, neurosurgeons and pediatric neurologists; the average indicated by the WHO for the 114 countries in the study (3.1), Europe (9), Western Pacific (3.7), South East Asia (0.3) and Africa (0.1). The differences with respect to the average in the study are more drastic: 0.2 per 100,000 inhabitants in LMIC and 1.24 per 100,000 inhabitants in HIC, **reflecting a disturbing lack of adult and child neurosurgeons mainly in African and South East Asian countries.**

Image: Unsplash,/@hush52.

In other regions such as Latin America, the treatment picture for epilepsy disorder suggests no less concern. In a report published by PAHO (2013), there were around 94 surgical services in 16 of the 25 countries surveyed in the study, and in addition, although 84% of the countries in the region claimed to have specialized diagnostic teams such as the EEG, 88% CAT[22] and 76% MRI; are diagnostic tests which, for economic reasons, availability and geographical location (mostly in the capitals), are limited to the number of people affected. The average per specialist in Latin America according to the study is 1.18 neurologists and 0.78 neurosurgeons per 100,000 inhabitants, with a conservative increase in the number of specialists compared to the previous 2017 study (0.43).

5 million people are diagnosed with epilepsy in **Latin America**, and more than half do not receive treatment. (OPS, 2018)

It is clear that **if one third of the centers specialized in epilepsy surgery are located in the capital cities of Latin America (36%), the VEP model can be introduced there.** For example, of the 94 epilepsy surgery centers in the countries studied, they were mostly concentrated in South America with 76 centers, it was also estimated that about 258 patients were surgically intervened annually, mostly in that geographical area. There is another factor to consider and that is, as the VEP depends on diagnostic evaluation studies such as the SEEG for a more accurate diagnosis, there are low-income countries that do not have this equipment -even some do not have access to medicines because they are not available or are expensive-.

It may be a possible limitation to distribute the VEP software if the introduction of the parameters in the model for a better diagnosis requires this evaluation, at least in the first years of technological development. However, if partnerships with specialists agencies with

[22] Computed Tomography (CT or CAT) as a noninvasive diagnostic imaging procedure with X-rays, for the identification of lesions or diseases, with data on brain tissue and structure. Johns Hopkins Medicine, 2020.

In Asia, nearly **23 million people suffer from epilepsy,** 65% of whom live without up-to-date treatment, due to an insufficient numbers of specialised doctors. (Trinka et al., 2018)

active programmes to support these regions are assessed, the tool could be more accessible. Other studies (Watila et al., 2019) explain that in regions such as Latin America and Asia epilepsy surgeries have progressed, as well as an increasing trend in their execution in countries such as India, China and Brazil; although they are still concentrated in large cities with the exception of sub-Saharan African countries[23].

INTERNATIONAL PATENT APPLICATION

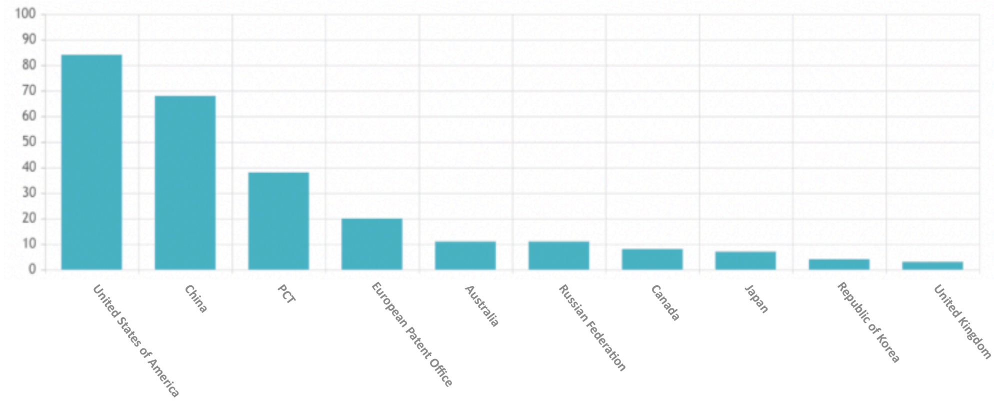
Another element in this area involves a strategy of protection through an international patent application, its applicants are: **L'Aix-Marseille Université (AMU), Centre National de la Recherche Scientifique (CNRS), Institut National de la Santé et de la Recherche Médicale (INSERM) and the Assistance Publique – Hôpitaux de Marseille (AP-HM)**[24]. The patent for the VEP was applied for at the World Intellectual Property Organization (WIPO) with a filing date of July 2016. It is described as a method to modulate epileptogenicity in a patient's brain, under the following international classification A61B 5/0476, A61B 5/00 y G06F 19/00, respectively.

The International Patent Classification (IPC) within the Strasbourg Agreement of 1971, allows uniform framework and search tool for patent documents.

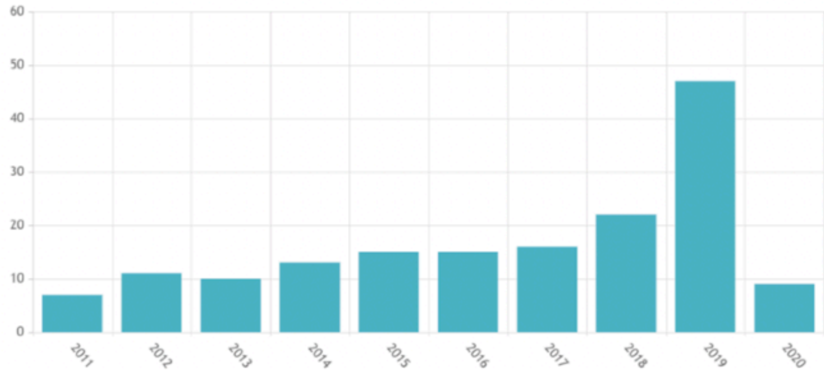
In general terms, the WIPO classification (2020) suggests eight large thematic groups ordered in alphabetical order: The first group relates to human needs (letter A), followed by a numerical format (61 in this case for being related to the medical aspect), and within this value, a subgroup (B) related specifically to "Diagnostics, Surgery, Identification". Number 5 is related to measurement for diagnostic purposes and 04 as a subclass, on bioelectrical signals of the human body and its parts; while for the group G06F and G06N comprises "Electrical Digital Data Processing" and G06N "Computer systems based on specific computational models", in this sense the search has been based on "IC: A61B5/04 AND AB: EPILEPTIC". Under this classification and following the advanced search criteria recommended by the WIPO portal some 259 related patents were detected from 2011 to 2020, as shown in the following images:

[23] In countries such as Congo, there are no surgical treatments for epilepsy, due to the absence of medical and research staff. Ntsambi et al., 2015.

[24] Application dated July 18, 2016. Patentscope (2020), see reference: PCT/IB2016/001164.



Patents applications related to the VEP, major countries. Data from WIPO (2020)



Patents applications related to the VEP, (2011-2020). Data from WIPO (2020)

The Patent Cooperation Treaty (PCT) administered by the WIPO, as an international system that encompasses acts and procedures, however, each designated State is the one that finally grants or denies the application. (OEPM, 2016)

According to the Spanish Patent and Trademark Office, OEPM (2016), the Patent Cooperation Treaty (PCT) includes applications for protection of a single invention in the states associated with the Treaty, which they call "international application" and are kept in the chart since many of them are also related to the VEP. Most of its applicants are located in the United States, companies such as Neuropace, Flint Hills Scientific, Cyberonics, Brain Sentinel and Medtronic; as well as recognized research institutes such as the MIT and the University of Pennsylvania.

In China, other related patents were applied by Hangzhou Dianzi University, Beihang University, Beijing University, Peking University, as well as institutes such as Harbin and Shenzhen University, specialized in these fields. The European Patent Office also includes the company Brain Sentinel, which is in this segment since one of its strategies was to acquire a Danish company called Italcare AS, including their intellectual property, providing a practical example of the M&A strategies that healthcare companies are taking to enter new markets and can be considered for future model VEP opportunities.

OUTSTANDING TECHNOLOGIES RELATED TO THE VEP MODEL

DARPA stablished in 1958 originally as Advanced Research Projects Agency (ARPA), after the launch of the USSR' satellite Sputnik. (DARPA, 2020)

In the United States, DARPA programs, *Systems-Based Neurotechnology for Emerging Therapies* o SUBNETS and *Nonsurgical Neural Interfaces,* have conducted experiments within national regulatory standards with patients suffering from epilepsy or Parkinson's, with implanted electrodes that record brain activity and emit signals to certain areas of the brain or "microstimulations", correcting moods and symptoms (Sanchez and Miranda, 2019) explain that they are obtaining positive results in the recovery of memories by stimulating areas of the hippocampus, with a project called REMIND, in conjunction with the University of Pennsylvania.

The limitations are diverse, but starting from the fact that they are invasive, expensive technologies and are currently aimed at people with greater urgency in this field, comment that it left them with a concern about how to apply these benefits or make these advances more accessible to defense personnel. For this purpose, that have designed a remarkable **neural interface called N3, which works in a non-invasive way**, with the opportunity to maneuver through a portable neural device that can read and write signals from the brain.

Therefore, they continue to work on non-invasive experiments through the stimulation of peripheral nerves that act at a neurochemical level by stimulating the neuronal connections and making learning more efficient. It is clear that neuroscience still has the great challenge of being able to provide these long-term solutions in a less invasive and accessible way for all types of public, since part of the challenges, they argue, has to do with overcoming the physical limitations that slow down the receptivity of signals such as bones and skin, as well as employing algorithms that define neural electrical signals. Other ambitious projects are also developing **brain-machine interfaces with chips that can be implanted in the brain with wireless technology unlike other types of electrodes**, and consists in three main components: Ultra-fine polymer probes, a neurosurgical robot and custom high-density electronics (Musk, 2019).

Brain Machine Interface (BMI) means that allow the communication between brain tissue to machines, currently with bidirectional scheme: 'write-in' signals to the brain and 'readout' signals. (Andersen et al., 2004)

It is increasingly common to find initiatives from technology centers and medical companies worldwide and companies marketing devices related to the brain-machine interface, at a non-invasive level, those

As it is known in neuroscience, there are five types of brain waves. **Gamma** (concentration), **beta** (active, busy mind), **alpha** (passive, reflective attention), theta (deep relaxation, sleepiness), and **delta** (during sleep). (Abhang et al., 2016)

that are placed on the head and **allow the record of biological signals, to improve attention, directing the brain towards states of relaxation with alpha waves**, increasing proactivity across frequencies, and assessing dynamics within games, marketing, health and work performance, while others developments have the impressive potential to rebuild images observed or imagined previously by the user, using the EEG-based BCIs systems (Rashkov et al., 2019) the latter are also part of a Russian company that already markets such brain-controlled devices, as well as the design of human-looking robots. Universities globally are also taking a step forward in the development of this type of technology such as drones controlled by brain waves (University of Florida, 2015).

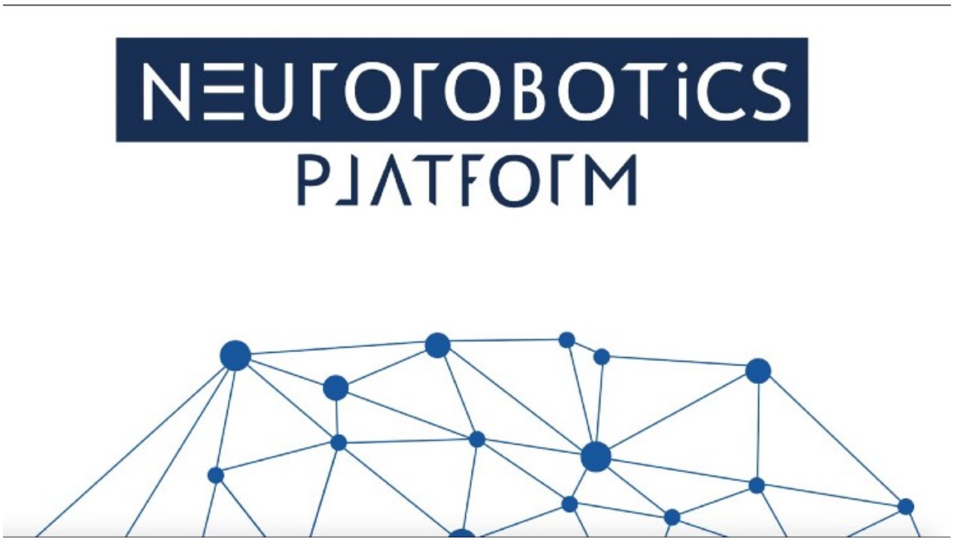
Additionally, other studies **related to technology applied to the patient with epilepsy** (Sinha et al., 2017) in the United States, explain the methodology for predicting the result of surgical interventions in patients with focal epilepsy through computer models. In this case they created a prediction model based on the patient's data specifically of the epileptogenic cerebral cortex, identifying the matrix of neuronal connectivity coming from the electroencephalograms and applying them to their simulation, which they explain has the same particularity of switching from a "bi-stable" state to a model in which seizures manifest themselves. In this way, they test in the model a possible resection of these areas, reflecting improvements in the results of the simulation, being able to verify them with the real situation of the patient, finding an approximation with 81.3% accuracy. It is relevant that also with the method they can evaluate alternatives in terms of resection of areas and results, they can even evaluate the consequences of eliminating areas of the brain to reduce seizures and compare more effective interventions.

On the other hand, from another perspective related to neuroimaging companies, there are projects initiatives that join the field of artificial intelligence, data storage and cloud imaging, as well as the processing of this information using MRI images and clinical evaluation of the patient (Puch, S., 2018; Prčkovska et al., 2018), through medical image processing algorithms, the use of the cloud and a collaborative platform contribute to improving the diagnosis of neurodegenerative diseases. They respond to **segmented solutions and an agile marketing strategy, based on the needs of the pharmaceutical sector with a customized user interface and report**

visibility; as well as other solutions to hospitals and research institutions for virtual assessments through their models.

Other similar technologies have been developed as devices or wearables for the prediction of epileptic seizures and being marketed for over a thousand euros, for example, during sleep (Arends et al., 2018), although with certain limitations in terms of inaccuracy in some of their equipment (Ryvlin et al., 2020) due to false crisis warnings or lower sensitivity, being effective for a certain group of affected people; so it is urgent to continue the development of machine learning for these technologies.

Also, the **University of Sydney supported by Microsoft** (Low, 2019) is developing these devices with greater precision, with the clear goal of alerting when a crisis is going to be evident and the patient can receive preventive care. Therefore, these devices or wearables can be an alternative development for the VEP and, although it does not imply being a patentable discovery, it is a possibility to move some of its functionalities over new devices. For example, those patients who are authorized to drive, even if they are granted permission after one year of absence of crisis, without loss of consciousness and with medical authorization, can serve as potential protection; as well as children or older adults who may warn about these seizures and are in places where they may suffer severe falls and impacts.



Video: The Human Brain Project. Source: Fortiss

PART II. TOWARDS A FULLY EXPLOITABLE VEP

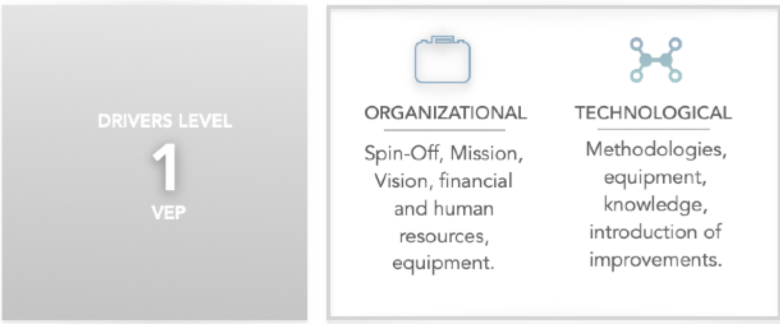
"In VEP models we can take advantage of pathology and patient specific constraints on model structure and priors that enable clinically useful estimations"
(Jirsa et al., 2017)

In this second part we look at the current context of the VEP, with a path that starts from its competitive advantage through a SWOT matrix contrasted with the opinions of medical specialists in epilepsy, to the influential factors that allow or hinder the development of this technology in the market and to facilitate commercial and non-commercial exploitation through a start-up.

DRIVERS RELATED TO THE VEP AND THE HEALTHCARE INDUSTRY

Drivers are influential elements, those factors with sufficient capacity to exert force towards the success or failure of the VEP model in the industry so, in fact, they have a global scope. **According to the direct or indirect influence they may have on the technology, they are grouped into three levels for the present study**: The first level is closely linked to the model, starting from the ideal structure to bring the tool in practice to the market and the technical or operational aspects. Second level drivers have an intermediate influence, they include internal and external mechanisms of technology, while third level drivers are related to external macro factors, which determine both the introduction of VEP model and market success as its life cycle; as shown below:

LEVEL I DRIVERS



The following is a detailed description of the drivers involved in VEP model, mainly from a *technological and organizational* point of view:

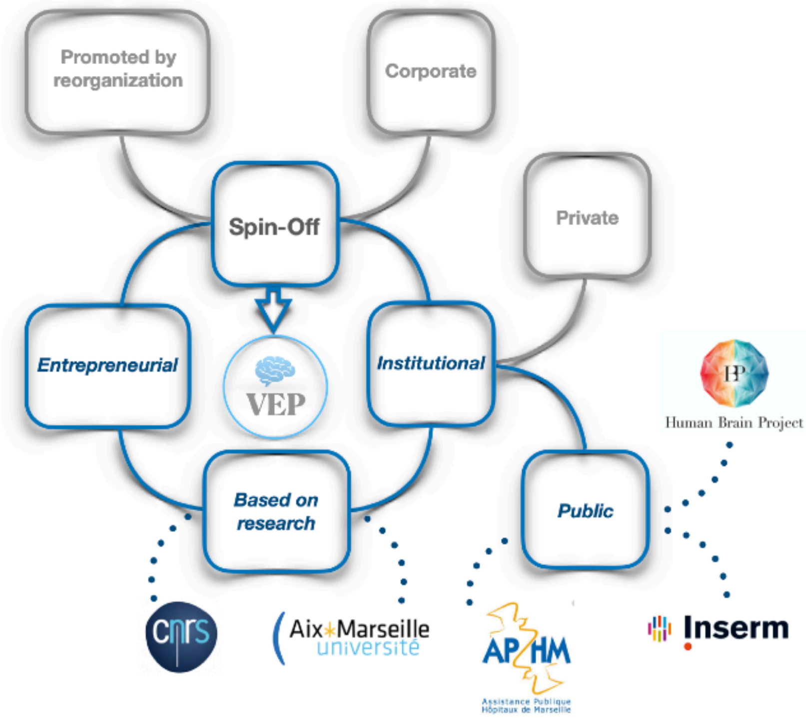
In relation to the ***organizational driver***, the creation of a spin-off is initially proposed in France, with the intention of replicating the model in other countries. In this context, Storey and Tether (1998) mentioned by Hidalgo, León and Pavón (2013) explain: "New

EPINOV
Composed of high-performance computing cluster, TVB, Meg, MRI systems, epileptic patient unit expert in SEEG, and ECRIN-certified data management center. (Dassault Systèmes, 2020)

technology-based companies NTBC are those whose activity requires the generation or intensive use of technologies, some of them not fully mature, for the generation of new products, processes or services" (pp. 471). This implies that given the nature of the innovations that are generated by research groups, the need arises to create organizations capable of promoting cutting-edge technologies or with an important technical level, with the capacity to generate useful solutions, they face the challenge of successfully reaching the market without a defined legal framework. For the case study, an institutional-type spin-off[25] and it is originated from the public sector with financial and intangible assets support from the Human Brain Project (HBP). As a support strategy, a project has been launched called **Improving EPilepsy surgery management and progNOsis using Virtual epileptic patient software (EPINOV), with participation distributed among the HBP, AMU, CNRS and AP-HM**.

A second category which classifies spin-offs according to Tubke (2005) starts from the motivation in their creation, if they are promoted from the parent company or, on the contrary, as an initiative of the entrepreneurs. If it is promoted by the research team, it is called an **Entrepreneurial Type Spin-Off** -a case can arise in which the parent company does not agree with the creation of a legal figure and does not provide any type of support, or a conflict of interest arises-, while if it is initially promoted by the parent company, it would be a Restructuring Driven Spin-Off. For the purposes of the study and in accordance with the meetings conceived during this phase of the project, it is understood that the initiative comes from the creator team to materialize the innovations derived from VEP, so besides being an Institutional, it is an Entrepreneur type. In relation to the case study, the subcategory is related to the nature of **Research Based Spin-Off**, in order to transfer the results of a research and experimentation process to a market structure. This classification can be seen in a simplified way in the following illustration inspired by Tubke, highlighting in blue what characterizes current VEP software:

[25] Six types of institutional spin-off exist, those promoted by the public sector. The typology varies according to their founders (if they are employees of the university or civil servants), the ownership of the technology license (university or public institute), it may or may not include a student as one of its founders, if it starts its activity in a technology park or incubator, companies in which the public body has held a stake in the capital, as well as those companies promoted by public institutions to offer a service through one of their units. Hidalgo, León and Pavón (2013).



Basic structure of the VEP Spin-Off.

In regard to the strategy of technology exploitation (Hidalgo, León and Pavón, 2013) suggests two basic options that can be adopted: A Dissemination Policy and an Industrial Property based Protection Policy. On the VEP model a direct exploitation of technology has taken place, i.e. a strategy of protection through industrial and intellectual property has been established: the patent application is submitted at an international level and various specialised articles on the software are also published.

Another reflection considered by the authors in this aspect is that when it comes to process technologies and not products that are useful to end users, the option of incorporating technology into an organisation's products can be considered. In this sense, it is understood that VEP software will be used mainly by medical specialists, radiologists and engineers. Therefore, some evaluations were carried out together with the research team on the possibility of the software to be moved to other areas and applications. **It can be considered to distribute the software through licenses and to put freemium more specific functionalities, like the *VirtualBrainCloud* or access to more complex data.**

The VirtualBrainCloud
As a cloud-based platform for biomedical research and clinical decision-making. (VirtualBrainCloud, 2020)

In relation to **technical drivers,** the VEP depends of several elements among which the pre-surgical evaluations mainly of the fMRI, SEEG,

Biobanks
Have the power to build patient data repositories, digitizing personalized and identical avatars of each patient, allowing AI to perform simulations and progression of diseases. (ESR, 2019)

EEG and the patient's clinical history in order to establish the most accurate approximations per individual. Computer equipment or information technology (IT) systems by health centers which process and manage large amounts of data based on medical services and examinations, in this case as a means for the VEP to also store the information and be available to medical staff. The platform on which it operates is *TheVirtualBrain*[26], for running simulations on the dynamics of the brain's neural networks over different periods of time through analytical tools with time series and functions, mainly. However, it should be considered, **the software is still undergoing clinical evaluation and expects to receive the first official results in 2022 and to be formally completed in 2024 with almost 400 participants**[27].

As regards data storage, a structure on which the model also depends, it is managed through its own database in which the fundamental values of the project are assigned, while the most complete data is stored in a software of the HDF Group with the capacity to store large and unlimited amounts of data, as well as being able to exchange projects between users who use the VEP. However, as it is planned to use the tool in health centers, patient data will be transferred to third parties to optimise diagnoses, obviously maintaining control and policies on data processing, providing them with records to authorise their transfer and ensuring that they are used for diagnostic and treatment purposes[28].

FENIX RESEARCH INFRASTRUCTURE

Nevertheless, HBP has created the infrastructure "Federated Exascale Network for data Integration and eXchange" (FENIX) providing cloud computing services, large-scale storage -this infrastructure was created by a project called -Interactive Computing e-Infrastructure o ICEI- composed of a consortium of five supercomputing centers in Europe as BSC (Spain), CEA (France), CINECA (Italy), CSCS (Switzerland) y FZJ/JSC (Germany); so all outputs will probably be derived to this new infrastructure.

[26] Jirsa et al., 2016.

[27] NIMH, 2018.

[28] The General Data Protection Regulation is maintained throughout the EU, with national bodies responsible for its enforcement. European Commission, 2020.

VEP technical drivers

LEVEL II DRIVERS

In this section we will analyse the drivers of the VEP in the strategic, educational, collaborative and ethical fields:

In the strategic area, applying part of Lichtenthaler's (2010) contributions to the VEP, it is possible to start from a market analysis related to work, that is, evaluating different markets in which one can enter, whose visibility is generated from the dynamics of collaboration and alliances with other organizations, which can bring technology closer to other business areas. Therefore, by executing a strategy of licensing the use of the VEP, an important step of technology transfer is being opened up in commercial terms together with an openness of vision in the health field, immersing itself in the challenge of being applied to improve the diagnosis of other neurodegenerative diseases such as Alzheimer's, expanding the market target. To complement the characteristic elements of the market, the following table shows a strategic picture of the software, inspired by the analysis of the structure suggested by the MIT (2013):

INDUSTRY	MEDICAL VISUALISATION
FINAL USER	Neurologists. Neurosurgeons, Radiologists, Engineers, Medical students, Patients.
APPLICATION	- Neurosurgical planning for epilepsy - Diagnosis.
BENEFITS	- Reduction of the time in surgical intervention. - Precise and personalised brain model. - EZ and PZ simulator. - Personalised medicine. - Allows the establishment of precise hypotheses based on the EZ and PZ. - It contributes to the precision of surgical operations. - It allows to reflect certain congenital malformations found in the EEG. - Non-invasive. - Flexible in its application, it allows to adapt to specific needs and parameters.
LEAD CUSTOMERS	- Hospitals. - Clinics. - Epilepsy research centers. - Universities and medical training centers. - Distributors of medical equipment. - Manufacturer of neurofeedback equipment. - Diagnostic imaging system companies. - Neurosurgical planning software companies.
MARKET CHARACTERISTICS	- Growing trend in digital diagnostic services. - Highly qualified and expensive personnel. - High standards in surgical procedures. - Demanding in clinical data protection. - Increased need for surgical procedures.
PARTNERS/ PARTICIPANTS	- Human Brain Project (HBP). - Aix-Marseille University (AMU). - Centre National de la Recherche Scientifique (CNRS). - General Hospital Marseille (AP-HM).
MARKET SIZE (APPROXIMATE CENTERS)	- Surgical centers and hospitals with epilepsy surgical units, in numerical order (see references below*): America: 289. Latin America (84): Argentina (13), Bolivia (1), Brazil (25), Chile (6), Colombia (4), Costa Rica (1), Cuba (1), Dominican Republic (1), Ecuador (2), El Salvador (2), Guatemala (2), Honduras (1), Peru (1), Uruguay (1), Venezuela (23). North America (205): Canada (3), Mexico (10), United States (192). Asia: 168. China (32), HK (3), India (39 for the year 2017 and an estimated by 60 by 2020), Indonesia (1), Japan (43), Korea (17), Malaysia (1), Nepal (1), Philippines (4), Taiwan (3), Thailand (3).

	Europe: 100. Austria (4), Belgium (4), Bulgaria (1), Czechia (4), Denmark (1), Estonia (1), Finland (2), France (13), Germany (9), Greece (1), Hungary (3), Italy (2), Ireland (1), Lithuania (1), Netherlands (2), Norway (2), Poland (3), Portugal (6), Romania (1), Spain (10), Sweden (6), United Kingdom (23). (Iceland, Malta, Latvia, Slovakia, Slovenia without surgical programmes in epilepsy, require international collaboration). Africa: ≥ 18 Burkina Faso (1), Cameroon (2), Egypt (1), Kenya (2), Morocco (4), Niger (1), South Africa (3), Tanzania (1), Tunisia (1), Uganda (1), Zimbabwe (1). Oceania: ≥ 6 Australia (4), New Zealand (2).
DIRECT COMPETITOR	- None identified so far.
RELATIONSHIP/ DEPENDENCE OF TECHNOLOGICAL TRENDS	- Virtual brain simulators, computer models. - Software to predict results of possible surgical interventions in patients. - Software for surgical planning in epilepsy. - Wireless electrical impulse recording devices with EEG technology. - Implanted electrodes and microstimulations or Deep Brain Stimulation (DBS) techniques. - Image processing algorithms. - Technological devices in graphene for early crisis prediction (soon to be introduced in the international market).
PLATFORM	- Epileptor. - TheVirtualBrain. - Windows, Mac, Linux.

Segmentation for the VEP.

*America: PAHO, 2013. Venezuela had high figures in epilepsy surgical centers for the last updated report. Nevertheless, given the crisis of the last few years, its health system is at minimum operating levels, with a lack of most of the medicines and supplies necessary for the treatment and intervention of neurodegenerative diseases. Asia: Rathore and Radhakrishnan, 2017; Trinka et al., 2019. Europe: Jedrzejczak et al., 2013; Schijns et al., 2015; Alceepilepsia., 2016; García de Sola., 2015; Neligan, 2013; European Reference Network- EpiCare (2020) with information by country to be updated. Africa: Kissani et al., 2013; Khiari et al., 2009; ILAE, 2020; WHO, 2002; Maiga, 2016; Callixte et al., 2013; WHO, 2019. There is no single report with overall figures for Africa, so the consultation is done by country and according to official reports, which are still to be updated. Oceania: Shih et al., 2018; Healthpoint, 2019.

End Users
those who will use the technology
Lead Customers
those who would pay for it

In this context, some of the factors to be considered in the segmentation of the market related to VEP can be simplified. **Different potential customers were identified**, on the one hand, those who will make use of the technology -*End Users*- (medical specialists, engineers, radiologists, medical students) and on the other hand, those who would pay for it -*Lead Customers*- (Hospitals, clinics, epilepsy research centers, etc). Each one requires marketing strategies tailored to their needs, naturally for the case of End Users their needs will differ in terms of location, professional experience, learning methodology, requirement in their diagnoses, to mention a few aspects.

For the *Lead Customers*, the need is determined mostly in handling a vanguard technology, new knowledge and introduction of specialized equipment in surgical interventions, besides a differentiation in their professional services. In the case of centers specialized in medical technologies related to epilepsy, universities, congresses and symposia in this area, through quality training with certifications for the professionals. Equally important, the characteristics of the market in which the VEP will be developed follow a trend in developing intangible assets as far as the health sector is concerned. Certainly, they vary within the structures of the health organizations and start from professional licenses, certificates of need or CONs[29], relations with patients, patent registration, agreements of different nature regarding services, suppliers, among others (Jelonek and Chluski, 2014).

VEP opportunity: There is an ongoing discussion about the **future of the radiologist's profession** given the advent of machine learning in AI, which requires these specialists to **obtain skills** that interact with these new developments (Hardy, et al, 2020).

However, with regard to the context of the neurological sector specifically for the treatment of epilepsy, those related to licensing agreements for the use of software packages and equipment are involved, as they are the Information Technologies (IT) that operate within their organizational structures, for example, the system for recording patient data, image results and additional medical examinations. Therefore, the advance of digital platforms constitutes a competitive structure of health organizations, allowing the improvement of diagnostic services and the commitment of qualified personnel. In other words, **the VEP model offers a novel alternative as an intangible asset and a new skill for qualified human capital**,

[29] In the United States, a Certificate of Need (CON) must be requested for certain technologies and products in the healthcare field. It is also a regulatory mechanism that can restrict the entry of various competitors into certain healthcare environments. National Conference of State Legislatures (2020).

in addition to being a technological tool that adds value to the services offered by the medical sector.

With regard to the exact size of the entire market, it is complex to determine in this study, since the long-term interest is to move it to a global scope, an approach has been made with epilepsy surgical centers as part of the main market. However, there is research and certain data related to epilepsy - data that is very dispersed and possibly limited because it is related to the field of health and, therefore, the privacy of patients - that helps to have a rough idea by geographical area, which is why, identifying the *End Users* and *Lead Customers*, an an approximate idea of its size can be obtained.

Although **mental illnesses** are not considered to be the main cause of the death in other adults, there is still an increase in the mortality due to them and a decrease in the rest of the illnesses considered to be the main ones: of the circulatory system, cancer and respiratory illnesses (Abellán and Ayala, 2017).

For example, it is clear that there is a **growing trend in epilepsy surgery especially in Latin America and Asia, and in general, there is an increase in neurodegenerative diseases related to the elderly**, also accentuated in Europe. It is imperative to collaborate with the LMICs that have the highest concentration of people with epilepsy (i.e 80% of those affected) even with the disjunctive of presenting fewer medical personnel and appropriate facilities for the interventions, unlike the more advanced countries.

Image: Neurology Department in India. Fortis (2019).

As for the number of centers specialized in epilepsy surgery beyond Europe and for possible insertion of the VEP, for example, in **India**, only two are operational in major cities, taking 50% of the 420 surgeries per year (Watila et al., 2019). However, in another study (Rathore and Radhakrishnan, 2017) 39 epilepsy surgery centers were identified, confirming the theory of Watila et al. (2019), the two centers that have taken more operations to the year are in New Delhi and Kerala, nevertheless, it is necessary to delimit that they have more time of being founded (1995 and 1997 respectively), they also foresee that by this year 2020 they will amount to about 60 surgical centers. As for the **United States**, the following were recorded in 2012, about 170 epilepsy centers, including also hospital neurology services, being some 221,000 Americans who come to these centers at least once a year (part of the one million refractory epilepsy patients in the country, (Gumnit et al., 2012) in conjunction with the National Association of Epilepsy Centers or NAEC. By the 2019, the NAEC (2019) already had some 192 level 4 epilepsy centers, 54 level 2 centers and were considering granting accreditation for 10 new centers.

> "In some **EBRAINS** Facility Hubs there will be highly specialized equipment and in other cases, users could remotely access to facilities and work from anywhere". (León, 2020)

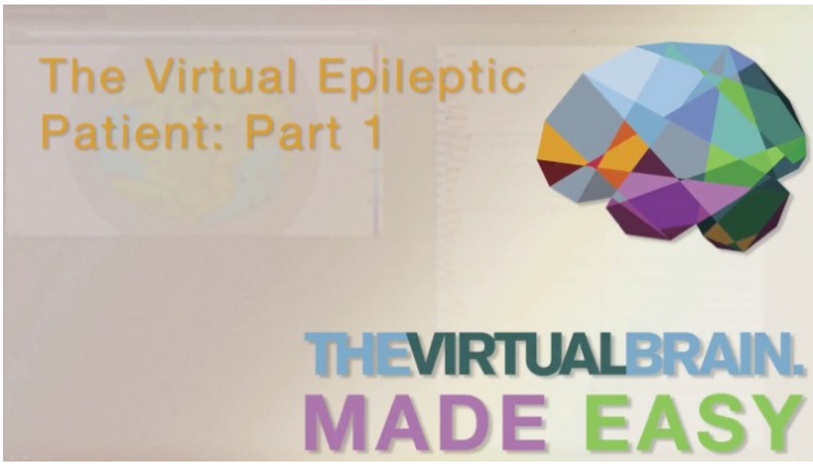
In **Spain** there is no recent data on the number of operating centers for epilepsy surgery. Notwithstanding, 14 were recognized nationally and five CSUR programs were created in 2010, as specialized units in hospitals of different provinces in the country (García de Sola, 2015) -currently 8 CSUR centers are recognized in refractory epilepsy-. In Italy, 2 centers specialized in surgery are located in Milan and Pozzilli, although LICE recognizes about 50 centers of diagnosis and treatment. According to the investigations it was possible to count also centers specialized in epilepsy: **France (13), Portugal (6), Switzerland (4), Denmark (1), Netherlands (1), Norway (2), Sweden (6), Finland (2), UK (23), Belgium (4)**.

Another aspect to consider within the strategic driver is the creation of innovation support structures in different regions, which provide physical, human and technological resources in EBRAINS, called **Facility Hubs**. With this they seek to encourage collaboration and international competitiveness, in specific physical points that promote the dynamics of networking in different regions of Europe. For the VEP, **would be an opportunity as a meeting point between researchers and technicians to improve the learning of the tool.**

In the present study it is recommended to establish in the Facility Hubs defined objectives related with each region and in line with the expectations of the HBP, considering local aspects of market introduction, different needs of end users and lead customers already defined above clear financial projections and expectations if applicable, and organizational aspects that can be measured to be improved in the long term, such as KPIs (understood as those variables that help us verify whether or not the objectives have been achieved, for example, number of users using the VEP, interactions within the software, technical assistance, etc). Another suggestion is to maintain and make more flexible the integration within the teams that are developed in the Hubs, understanding the multiple disciplines and enhancing the skills that can be developed for the benefit of the project.

On the other hand, educational driver will determine the diffusion of the tool in the market through courses and certifications, as well as **the exchange of new knowledge between medical platforms for the improvement of diagnostics**. The courses can be given from the health centers themselves or through the organization of the VEP and its specialists, to facilitate these international certifications.

Partnerships with other organizations in the field of epilepsy can facilitate participation in medical conferences and symposia on a regular basis, maintaining updates in the industry and in turn as a strategy for talent acquisition and an alternative income stream.



Video: VEP Tutorial. Source: INCF

VEP opportunity: Personal **branding for Physicians**, would make it possible to strengthen the range of services offered.

The collaborative environment driver has an important weight in the software and its long term positioning in the industry. On the part of hospitals and specialized centers, **allowing the tool to be adopted and the medical staff to perceive it as an opportunity to improve their diagnoses and strengthen their professional brand.** In addition, create spaces for exchange of opinions regarding the use of the VEP for specific cases of patients, whose dynamics can serve as an example for other specialists in the sector and generate more precise data, useful for improve the software.

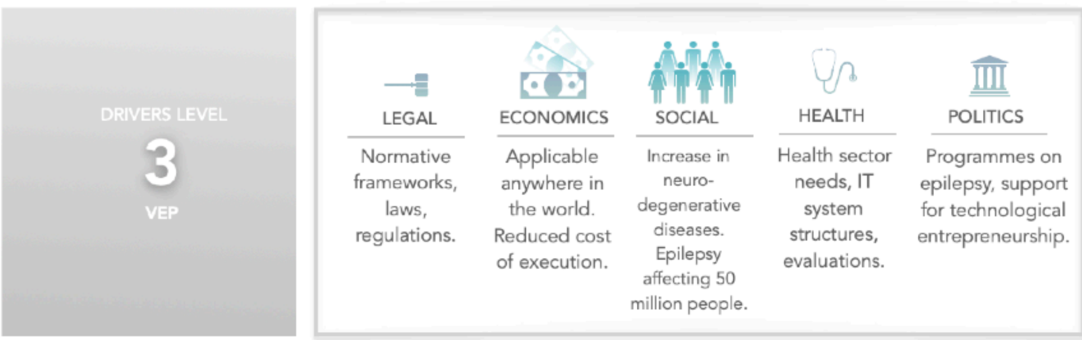
Equally, to encourage relationships with organizations which brings together professionals related to epilepsy worldwide, such as the well-known International League Against Epilepsy (ILAE), epilepsy associations, epilepsy and neurology societies, which concentrate their efforts on bringing together knowledge and specialists in the field, aimed at social programs and patient care, in addition to serving as a means of information on the disorder and procedures through conferences. They are organizations that are committed to new advances and show a warm welcome to initiatives that can help them fight the disease, evidently they have a network of contacts and an organizational structure that would allow them to position the VEP as a diagnostic tool in different regions on an international level.

A further reflection is that, if efforts and resources are organized in the LMICs to **develop specialized surgical centers with the help of international organizations, not only would more people with this disorder benefit from not moving to receive better health care and surgery, but it also increases the international of the VEP.** As regards the ethical driver, such as those referring to NeuroRights in the field of neurotechnologies (Yuste et al., 2017); most of the medical technological innovations -including the issuance of their respective diagnoses by specialists, evaluations, prescriptions, patient care, etc.- are inevitably related to the ethical aspect, without this constituting any novelty. In the very long term, given a scenario in which AI is further developed through deep learning in diagnostics and surgical interventions autonomously, in a fully autonomous manner for example, a dilemma arises as to who is responsible for the diagnosis when it is not favorable to the patient, constituting a "black box" as explained by specialists in the sector (de Souza, 2019).

Neurorights
Originated by Columbia University in 2019 and directed by Dr. Rafael Yuste, created to protect our minds and our society. This neurorights rest on 5 basic pillars. (Neurorights Initiative, 2019).

However, beyond addressing the philosophical perspective inherent in their root cause, ethical factors show the *raison d'être* of the VEP, those who encourage him to collaborate in the field of neurodegenerative diseases, concern of the human being throughout his existence. Undoubtedly, the development of medical technologies including the VEP or any other, naturally they must be aligned with social needs and concerns, including those related to the treatments of patients. Those related to the protection of sensitive data and exclusively for the improvement of diagnostics, as well as avoiding control over third parties in the doctor-patient relationship in trials, this last aspect is more susceptible on the pharmaceutical market than on the software market.

LEVEL III DRIVERS



In this section are considered social, legal, economics, health and political drivers about the VEP:

In relation to **legal** driver, implies mainly the scenario where the VEP will be developed, including laws and regulations of the countries or locations where it will be used. This study has been approached from a basic general framework to a more specific one: **The first follows a basic pattern, for example, concerning patients' rights in Europe**[30], that fundamentally respect the patients's right to privacy and access to their clinical records, confidentiality, as well as protection against any interference of interests by a third party in doctor-patient relationship for the development of studies.

In this sense, the VEP create a virtual simulation process from the clinical analyses previously performed by the clinic staff, as a non-invasive procedure and in absence of risk for the patient, without implying a conflict of interest. Also laws in relation to epilepsy, those that defend the rights of those affected, mitigating the stigma and limitation on certain activities, although not directly related to certain activities, although not directly related to the VEP, are definitely part of this basic legal framework and should not go unnoticed. In the clinical trials, for example, there is a legal frame to be considered, as it is performed in France[31].

EMA does not have the authority to allow the marketing of products and services in the health field, but the European Commission. However, its reports and ratings are considered by it. (EMA, 2020)

It may also be considered the European Medicines Agency (EMA) in conjuction with the **European Network for Health Technology Assessment (EUnethta)**, as entities aimed at the supervision of medicines, procedures and technologies developed within the healthcare field. At any stage of development of a project in the medical sector, guidance can be requested, given that there are two routes in its scope, centrally or nationally, the first involves a single request facilitating its introduction in one or more countries members of the EU. It is true that the EMA is mostly directed to pharmaceutical sector, however, works with the EUnethta to unify and make the process of evaluating medical technologies more accessible. They also provide a qualification opinion for diagnostic programs and models, validating the hypotheses and tests executed in these projects, issuing reports in which claims to agree with the models and the approaches reached.

30 Declaration on the Promotion of Patients Rights in Europe in 1994. WHO, 2011.

31 Regulation (EU) N° 536/2014 of the European Parliament and of the Council of April 2014. EMA, 2020.

Health Technology Assessment (HTA),
Is defined for the first time in 1976 by the Office of Technology Assessment (OTA) -when it existed in the United States- was the entity responsible for its application and recognition in the industry, especially in the health field, later the technique was transferred to Europe. (Banta, 2003).

In fact, there is an evaluation process in medical technologies known as **Health Technology Assessment (HTA)**, although it is not mandatory and does not follow a strictly standardized procedure, it is applied and adapted by organizations and entities responsible for introducing new techniques or drugs into the industry, because in words of European Commission (2020): "Measures the added value of a new health technology compared to existing ones. Examples of health technologies include medicinal products, medical equipment, diagnostic and treatment methods, rehabilitation, and prevention methods"[32].

Therefore, the EUnetha is an European organization responsible for guaranteeing -among other aspects- that the HTA process for new medical technologies guarantees objective, useful and fair information for patients, medical staff, as well as for the partners of the responsible organization[33]. In the case of establishing a Spin-Off independent of EBRAINS AISBL, probably this organization could be a path to evaluate the technology, at the same time adhering to the government and integrating a network of accredited institutions in different parts of the EU.

Also has been identified another organization known as European **Clinical Research Infrastructure Network (ECRIN)**[34], and it is confirmed that EPINOV has a certification in data storage issued by them[35]. This organization offers multiple services to this type of projects, ranging from accompaniment at the start of clinical trials with free advice, validation of procedures, to the management of patient data. In long term, in case of establishing a Spin-Off, considering that personal data are registered through the VEP, probably the management and storage process of these once the clinical trial is over, either by the IT system of hospitals or medical centers where the studies are carried out, and on the other hand, with respect to the software, it could be by ECRIN or FENIX, if maintained as a support structure for data storage -information to be confirmed-.

32 Health technology assessment. European Commission (2020).

33 EUnetHA (2020).

34 ECRIN, 2020.

35 Dassault Systèmes, 2020; ECRIN, 2020.

Health **I**nsurance **P**ortability and **A**ccountability **A**ct of 1996, requested at the United States Department of Health and Human Services. (HHS, 2013)

Another compliance factor as far as data is concerned is the current **General Data Protection Law (GDPR)**[36] in Europe, as an important regulatory tool to consider. In Spain, for example, public organizations and companies that manage sensitive data are obliged to designate a figure as Data Protection Officer, who is responsible for compliance with the specifications of Law[37]. **In the United States, for example, the equivalent is HIPAA** created precisely due to the rise of technologies in this sector in favor of the protection of people's information, in the case that if this tool is to be introduced in that country.

Within this legal framework there are also those related to patents, such as the **PCT**[38], the patent laws and utility models published in each country. Similarly, other regulatory instruments concerning the introduction of the technology in different geographical areas are added, for example, in the United States, some requirements may vary by state, as Certificates of Needs (CON)[39] that, although are not directly related to software, are related to possible barriers to the introduction and operation of neuroimaging technologies in their healthcare centers-such as MRI or CT scanners. For the introduction of the VEP, in a general sense, the regulations are mainly related to the U.S. Food and Drug Administration (**FDA**)[40], in addition to complying with strict regulations by other agencies such as the Federal Communication Commission (**FCC**), the Federal Trade Commission (**FTC**), the Health Insurance Portability and Accountability Act (**HIPAA**)[41]. In Europe, there is the rating report issued by the **EMA**, already explained, which is considered by the European Commission.

Software as a Medical Device for diagnostic purposes, without being part of a hardware medical device.

For example, based on the concern of whether the VEP software is or not a medical device for legal purposes in the United States (for being a software) and in order to understand in a basic form the regulations that regulate this technology and how it could be introduced, the definition offered by **International Medical Device Regulators Forum** (IMDRF, pp. 6): "Software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device".

[36] General Data Protection Regulation (GDPR). Official Journal of the European Union, 2016.

[37] Ley Orgánica de Protección de Datos de Carácter Personal, 2017.

[38] Patent Cooperation Treaty. OEPM, 2018.

[39] American Health Planning Association (AHPA), 2016.

[40] Recognized Consensus Standards. U.S Food & Drug Administration, 2020.

[41] U.S Department of Heatlh & Human Services. HHS, 2013.

Image: U.S Food & Drugs Administration.

In this sense, the **IMDRF** is an organization composed of regulatory institutions in different parts of the world, precisely because it tries to consolidate within a single framework regulatory aspects inherent to new medical technologies. Thus, the VEP could be related to the Software as a Medical Device (**SaMD**)[42], concept also considered on the **EU regulatory framework for medical devices**[43], thereby, the VEP would be introduced as a device, for being a computer program for the purpose of diagnosis, prevention, monitoring and prognosis of epilepsy -Annex VIII, Chapter III, Classification of Software in Regulation (EU) 2017/745-, also of class I[44]; so in the United States it would not be directly regulated by the FD&C Act., in accordance with the FDA (2020)[45].

As briefly described, this regulatory frame could have a discouraging effect on both the creators of new medical technologies and the end users, for one side, **delays entry into competitive markets either by the time it takes to comply with the proposed processes and standards**, in other cases, the lack of homogenization of international standards has led to organizations such as the IMDRF to propose certain regulations in a global and standardized form[46], while on the other side, is kept waiting for users who could obviously improve their diagnoses (at least for technologies that accomplish their goal); so it could lead to other concerns such as how long it would take to expand the benefits of new medical technologies to LMIC, what is the spillover effect of these medical device regulations between the LMIC and HIC, and which regulations need to be more flexible for a scientific and technological entrepreneurial environment that is constantly growing and changing.

ISO 13485
Is an international certification for companies involved with the installation, design, production and service of medical devices. ISO, 2020.

Finally, the third level of the legal aspect concerns certifications and standards related to the software, as the **ISO 13485** used in the devices of the medical industry, as well as certifications that accredit the handling of VEP. Regarding the certifications, it issues **ECRIN**, one of which the EPINOV already has, as explained above, is part of the

[42] U.S. FDA, 2020.

[43] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017.

[44] I. e., it implies a lower risk for the patient, according to the three risk classification groups. MDR, 2017.

[45] Additionally, they request a report called Premarket notification or 510(k). Carey, 2020.

[46] In March of this year, a document was issued that harmonizes aspects related to cybersecurity, recognizing it as a global concern. Among other aspects, they want to channel the different regulations of these devices into a common framework, protect patient data so they can have a more accurate diagnosis, objective, errors free and difficult to access by unauthorized persons. IMDRF, 2020.

129 current standards or requirements regarding data management and storage in Europe (Ohman et al., 2017). It could also start to be more relevant the certification ISO 14971:2019 in relation to cybersecurity in medical systems, addressed in more detail in the Principles and Practices for Medical Device Cybersecurity[47].

Regarding the **economic driver**, first of all, studies explain that (Wiebe et al., 1995; Malmgren et al., 1996 and Schiltz et al., 2016; mentioned by Watila et al., 2019) in assessing the costs of surgical interventions, they either involve a significant investment of money for the patient to afford, but **in terms of cost they may be more effective than pharmacological treatment over time** - given their cost/time ratio according to the study-. However, deciding whether or not to resort to surgery is naturally an element considered with prudence by the specialists.

Technology Readiness Level (TRL)
Is a measure created by NASA that evaluates the degree of maturity of a particular technology, between 1 and 9 levels. It has been applied since its origin in the 70's on several innovation projects. NASA (2012).

In second place, the VEP is developed in the countries of Europe initially, has costs associated with the experts involved in the creation of the project, which has been taken over by the European Union. Also, as a diagnostic tool requires specific knowledge and experience of neurosurgeon, neurologists, radiologists and engineers for its application. Therefore, the long-term marketing price must consider both the investment of the intangible asset that makes it possible to virtually reflect the dynamics of the seizures, and the fees of the professionals who will use the tool, the physical facilities, etc. So far, the price of the software has not been published, and according to the self-evaluation of the research team, the technology is in the stage **7 of TLR Assessment** or in the test phase before its launch to the market.

It is true that the creation of new technologies do -as far as possible- a democratization of accessibility in the long term, in other words, that its use is available to as many people as possible and its cost is decreased over time. The medical industry is no an exception, however, requires huge amounts of money for the initial development and testing phases, commonly involving other companies, foundations, and governments, as well as the team of scientists, physicians, and other experts, who will eventually analyze the imaging tests and praxis. Therefore, the economic driver related to the introduction of a medical technology in the market also moves

[47] IMDRF, 2020.

according to the investment willingness of institutions and governments, not only to bring it to the market, but to make it accessible in the LMIC.

This area is also influenced by the political driver, or the willingness of governments in all parts of the world to maintain active epilepsy programs, to promote education regarding the disease, to value and finance technological and entrepreneurial initiatives. In relation to ***social*** **and** ***political*** driver, the first alludes to the intrinsic mission of VEP as it has been explained throughout the research, it facilitates an advance in the diagnostics, also achieving the participation of doctors and scientists from different parts of the world. Another social aspect is to differentiate the continuous needs of the human being, which can lead to apply the methodology to segments that have not been explored or to be able to move to new applications. The *health* aspect has to do with the willingness of institutions to recognize this assessment tool and its usefulness, which in the end will enhance and personalize the services offered to patients.

VEP PROGRESS TIMELINE

1. SPATIOTEMPORAL FORWARD SOLUTION OF THE EEG AND MEG USING NETWORK MODELING (2002)
2. NOISE DURING REST ENABLES THE EXPLORATION OF THE BRAIN'S DYNAMIC REPERTOIRE (2008)
3. KEY ROLE OF COUPLING, DELAY, AND NOISE IN RESTING BRAIN FLUCTUATIONS (2009)
4. TOWARDS THE VIRTUAL BRAIN (2010)
5. EMERGING CONCEPTS FOR THE DYNAMICAL ORGANIZATION OF RESTING-STATE ACTIVITY IN THE BRAIN (2011)
6. THE VIRTUAL BRAIN: A SIMULATOR OF PRIMATE BRAIN NETWORK DYNAMICS (2013)
7. ABNORMAL BINDING AND DISRUPTION IN LARGE SCALE NETWORKS INVOLVED IN HUMAN PARTIAL SEIZURES (2013)
8. BOTTOM UP MODELING OF THE CONNECTOME: LINKING STRUCTURE AND FUNCTION IN THE RESTING BRAIN AND THEIR CHANGES IN AGING (2013)
9. SYSTEMATIC APPROXIMATIONS OF NEURAL FIELDS THROUGH NETWORKS OF NEURAL MASSES IN THE VIRTUAL BRAIN (2013)
10. IDENTIFICATION OF OPTIMAL STRUCTURAL CONNECTIVITY USING FUNCTIONAL CONNECTIVITY AND NEURAL MODELING (2014)
11. ON THE NATURE OF SEIZURE DYNAMICS (2014)
12. PERMITTIVITY COUPLING ACROSS BRAIN REGIONS DETERMINES SEIZURE RECRUITMENT IN PARTIAL EPILEPSY (2014)
13. FUNCTIONAL CONNECTIVITY DYNAMICS: MODELING THE SWITCHING BEHAVIOR OF THE RESTING STATE (2015)
14. AN AUTOMATED PIPELINE FOR CONSTRUCTING PERSONALIZED VIRTUAL BRAINS FROM MULTIMODAL NEUROIMAGING DATA (2015)
15. THE VIRTUAL BRAIN: MODELING BIOLOGICAL CORRELATES OF RECOVERY AFTER CHRONIC STROKE (2015)

16

MATHEMATICAL FRAMEWORK FOR LARGE-SCALE BRAIN NETWORK MODELING IN THE VIRTUAL BRAIN
(2015)

17

SEIZURES, REFRACTORY STATUS EPILEPTICUS, AND DEPOLARIZATION BLOCK AS ENDOGENOUS BRAIN ACTIVITIES
(2015)

18

WHOLE-BRAIN ANALYTIC MEASURES OF NETWORK COMMUNICATION REVEAL INCREASED STRUCTURE-FUNCTION CORRELATION IN RIGHT TEMPORAL LOBE EPILEPSY
(2016)

19

INDIVIDUAL STRUCTURAL CONNECTIVITY DEFINES PROPAGATION NETWORKS IN PARTIAL EPILEPSY
(2016)

20

THE VIRTUAL EPILEPTIC PATIENT: INDIVIDUALIZED WHOLE-BRAIN MODELS OF EPILEPSY SPREAD
(2017)

21

EPINOV
(2019)

22

CLINICAL TRIAL
(2019-2022)

23

THE BAYESIAN VIRTUAL EPILEPTIC PATIENT
(2020)

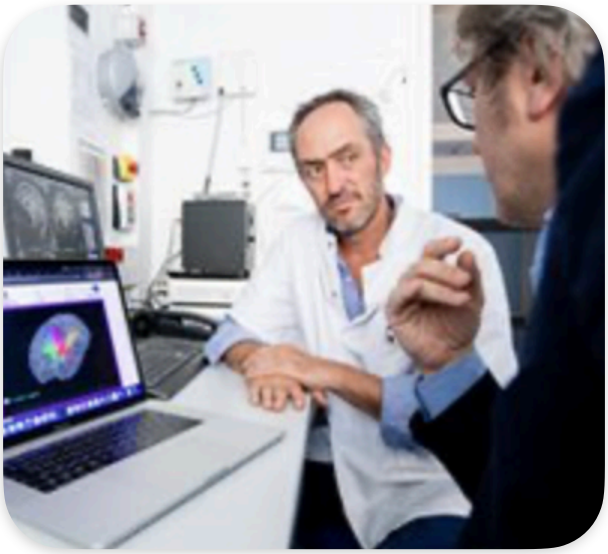


Image: Fabrice Bartolomei and Viktor Jirsa. Human Brain Project (2019)

As a complement to the driver evaluation, a **SWOT** analysis applied to the software VEP is presented, identifying the strengths of the tool and being able to fit them into possible market opportunities, with greater determination on possible weaknesses and points of improvement, coupled with present threats and possible factors that may arise to the detriment of the application and development of the tool.

For the software have been found so far **eight elements that starting from the demand of the health sector towards a personalized medicine**, addressing the needs of each patient coupled with the growing trend in the industry to offer digital solutions or intangible assets. The model allows the introduction of specific parameters as explained previously and provide the most precise diagnostics for each epilepsy patient. On the other hand, it is considered that it has the possibility of shortening the time in the surgical interventions, precisely by identifying with greater accuracy the EZ and PZ. Another opportunity that can be considered as part of the implementation, it is about the training methodology of the VEP and as another marketing strategy, through training courses, workshops, specialized forums, professional certifications, virtual discussions, webinars; all this with the idea of concentrating partners and professionals of the sector or related that, in a multidisciplinary space, can share opinions, knowledge and experiences, necessary scenarios to expand the benefits of the tool and its approach to potential customers.

Latest studies on Alzheimer's disease with machine learning show significant predictions in healthy individuals, the mean time to diagnosis was 7.59 years. (Eyigoz et al., 2020)

On the other hand, according to the VEP creator team, **is beginning to be tested on Alzheimer's patients**, developing that long-term possibility of extending to other neurodegenerative diseases and evidently to other market segments. Likewise, the model could contribute to the pharmacological industry in the long term to evidence reactions and changes at the neuronal level, constituting an opportunity towards an industry in constant growth. In reference to the fifth point in the opportunities matrix, regarding its possibility of serving as a support for other preoperative stereotactic evaluations, such as existing neurosurgical planning softwares, it can be stated that the VEP is is a model that contributes to decision making by expert personnel by identifying epileptogenic areas with a certain possibility of resection.

Image: Fabrice Bartolomei and Viktor Jirsa. Human Brain Project (2019)

Another aspect valued by physicians, according to opinions considered in the interviews, was precisely having this noble **possibility of inserting themselves in less privileged social sectors**. Being an open source model for now, extended to other countries where better assessments and personalized treatments are required, as mentioned in previous segments, 80% of epilepsy patients live in low- and middle-income countries, where access to treatment is extremely difficult. The VEP could also be inserted as a pre-surgical assessment in low resource countries, improving the quality of life of these people regardless of where they are.

Also, an important long-term assessment is that, as new data are entered into the model from hundreds of patients, there is a possibility that the VEP take those studies in the interest of simulating the EZ and PZ for new patients, without going through invasive pre-testing, because the model collects all the information from these evaluations, storing a record for the future to further develop and optimise the tool, both in the reconstruction of the virtual brain and in the parameters that allow the simulations. According to the Innovation UPM Team, **this would require much improvement in decision making procedures with Artificial Intelligence (AI).**

The rise of AI applied with precision to Neurodevelopmental disorders (NDDs) such as autism spectrum disorder, **epileptic** encephalopathy, *ADHD*, and rare genetic disorders. (Uddin et al., 2019)

Among the strengths, as shown in the next figure, it can be shown that with the support of The Virtual Brain a precise and personalized model of the brain is reconstructed, with cutting-edge software to detail the morphology. It is underlined the benefit of obtaining the final model of the software for a patient within 24 and 48 hours, as neuroscientist Viktor Jirsa argues, part of the creator team. Contrasting to the fact that, as Dr. Bryan Strange, Director of the Laboratory of Cognitive and Computational Neuroscience CTB-UPM, the decision to evaluate a surgical intervention can take years, however, **reconstructing the model takes a relatively short time and can contribute to making the best medical decisions**. Another strength of the software lies in its ability to project the evolution of the disease, which was another of the concerns that were raised as an

University Spin-Offs tend to explore different possibilities of application in the market given their short experience, through direct marketing or licensing; while **Corporative Spin-Offs**, generally founded by experienced managers focused on a potential market niche given a technology solution. (Clarysse et al, 2010).

attribution of the model, in other words, **disease progression means parameter progression**, as Jirsa points out.

Regarding the Threats, it is probably true that this type of simulation does not so far show a direct competitor in Europe, however, other countries also have the possibility of creating solutions that can be in line with the VEP, to offer software related to simulations. In addition, inconsistent strategic planning coupled with the difficulties of introducing new technology into the health field could undermine in the long term at least the intentions to make the model a cost-effective instrument, especially since data protection requirements and controls are emerging in this industry, certifications that support quality standards, for example, and naturally their procurement processes differ in different countries.

In this context, Hidalgo, León y Pavón (2013, pp. 472) point out: "New technology-based companies emerging from other pre-existing companies (corporative spin-offs) have a failure rate of around one third that of other types of new companies", in this sense, they claim that in Europe technology-based companies have presented challenges in their positioning over time, by maintaining a relatively minor experience curve compared to countries like the United States for example, whose technological industry has evidenced the development of important clusters, such as in Silicon Valley, which have helped to consolidate their technology-based companies. However, the authors emphasize the **activities in conjunction with scientific-technology parks**, to promote these new companies, which could be applied to the VEP.

In relation to the Weaknesses, naturally the model needs the introduction of parameters that are mostly obtained from previous medical evaluations and diagnosis of the patient, in other words, **it maintains some dependence on other diagnoses in order to achieve correct accuracy, tests that usually involve a high cost.** There is the long-term possibility as explained in the Opportunities quadrant, that it can simulate the EZ and PZ as more simulations are performed and data is entered into the model that serves as a reference for future testing and reduces the need for further testing. It is necessary, according to the creator team, for cases where MRIs do not show clear results due to lesions in the brain, the engineer must manually enter the parameters in the model, so if there are not enough exact metrics or the correct ones are not applied, it will evidently have a negative impact on the predictions, according to the creator team.

Images: Human Brain Project

STRENGTHS

1. Recreates an accurate and personalized brain model through its network connectivity.
2. Allows the establishment of precise hypotheses based on EZ y PZ, with the Epileptor as a mathematical model of the neural network.
3. Contributes to the precision of surgical interventions.
4. It allows to reflect certain lesions that are not detected in the MRI.
5. Non-invasive.
6. It is flexible in its application, allowing it to adapt to specific needs and parameters.
7. A macro level approach to the brain.
8. Support as an EU project.
9. It involves numerous talented scientists in a variety of disciplines.
10. According to the creator team, the progression of the disease means progression of parameters, being a long term benefit to reflect the evolution of the disease.
11. Registered patent application.
12. Fast response test (24/48 hours).

WEAKNESSES

1. Dependence on evaluations or alternative technologies (EEG, tractographies, etc.) as well as invasive neurological evaluations (SEEG) necessary to improve their predictions, increasing approach costs.
2. The definition of the parameters in the model are not sufficiently accurate, which affects their predictions (limited prediction of epileptogenic zones).
3. Its accuracy also depends on a specific level of preparation, experience and exchange of opinions among specialists while using the tool (doctors, engineers, radiologists).
4. The tool is still being applied to larger groups of patients (concrete results are expected in 2022).
5. Being open source, the VEP does not bring an associated economic return (for the moment), so their investment costs are translated into scientific and technological reach.
6. According to its creators, epileptic brains for the lesions do not show clear MRIs, requiring manual interventions by the VEP engineer.

OPPORTUNITIES

1. Improve the quality of medical diagnoses through personalized medicine.
2. Possibility of being inserted as a habitual use at clinical level, reducing times for surgical interventions.
3. Planning in the training of new skills, to facilitate their understanding and application in diagnosis.
4. It is being applied for other no less important diseases such as Alzheimer's.
5. Possibility to support other preoperative stereotactic evaluations by representing large scale neural networks.
6. Application in the pharmaceutical industry for testing new treatments and combinations on a virtual scale, as a long-term vision.
7. Being open source increases the possibility of creating new solutions and applications worldwide, being able to reach less developed countries.
8. By requiring the introduction of new and large-scale data to perfect the tool, there is a future possibility of simulating ZE and ZP without a patient requiring prior invasive evaluations.

THREATS

1. Emerging in the medium term in similar technologies in other international projects that inhibit their application to new markets.
2. Lack of strategic planning in the distribution and application of this technology.
3. Appearance of scenarios and external factors that eclipse the application and advancement of this technology.
4. If not applied correctly as a complement to diagnostics it shows weak predictions.
5. Do not plan a global training methodology for its application, undermining its relevance.
6. To stop making improvements to the tool in terms of parameters, interface and design.
7. Regulations for its introduction by the health industry of certain countries.

SWOT analysis of the VEP.

PART III.

ROADMAP, STUDIES AND TARGETS FOUND FOR THE VEP

1987
Year in which **Motorola** integrates crucial elements of its products into a strategic plan for the future, anticipating their business managers on new functionalities, market trends and ways to create and combine their products; through a **roadmap** (Willyard and McClees, 1987), philosophy that is ***preserved*** and ***appreciated*** today.

A technological roadmap allows to link information and processes under a scheme that supports business strategies and innovation planning. In this sense, a framework is created in which, through multiple layers, **the stages and evolution of key aspects related to the business are reflected, as well as the connection of these elements within a range of time**. Commonly, these elements are integrated by strategies, innovation and operations (SIO) with different time frames (short, medium and long term), whose processes are manifested in different layers, products modifications, service improvements or technology strategies reflected in the roadmap (Phaal et al, 2009). The roadmapping methodology can be applied at any level in the business arena, and enables the linking of business and technological objectives.

The roadmaps constitute a strategic planning tool in the technological field, integrating in a dynamic form the different levels in which an innovation is developed, identifying similar products and its weaknesses (Lichtenthaler, 2010). Until ten years ago, the process of acquiring licenses was ignored in the open innovation processes (Ibíd. pp. 430): "Technology exploitation in open innovation processes has received insufficient attention. Despite the major impact of research into open innovation, our understanding of technology exploitation in this context is limited"; in addition, **the large firms with active licenses have a greater advantage over the rest**, by including them as part of their exploitation strategy tighter with the fact that most of them are involved in the acquisition of external technologies.

For the creation of the roadmap for this technology, the different relationships between the developed software with its main features, its applications and the most influential drivers in a period of time of **10 years**, have been considered. In addition, for this planning method, the VEP approaches analyzed in this study, as well as those of the experts who created the model and the opinions of external experts are considered. Initially, it is reflected in the following table and taking as reference Velasco, Jing and Labra (2016) the macro-trends and others applicable to the industry in which the VEP will be introduced, as part of the international competitive scenario.

MACROTREND	TECHNOLOGICAL TRENDS AIMED TO NEURODEGENERATIVE DISEASES
VIRTUAL BRAIN MODELING	-Virtual simulators, three-dimensional representations or neural electrical networks. -Computational models/software to predict results of possible surgical interventions in patients.
RELATIVE INCREASE IN NEUROSURGICAL INTERVENTIONS	-Reduce effects after interventions. -Surgical planning software in epilepsy. -ROSA™ and the use of robotics assistant for interventions. -DBS (Deep Brain Stimulation). -Neural interfaces to mitigate damage from neuropsychiatric diseases and memory disorders.
BRAIN-MACHINE INTERFACE	-Inclusion of AI to the human body. -Neural plasticity and neurodegenerative diseases. -Light-sheet microscopy. -Neuromodulation of the organs of the human body. -Touch interfaces with the use of prosthetics. -Intracranial chips. -Synthetic communication.
NEUROIMAGING TESTS AND DIAGNOSTICS	-SEEG, EEG, M/EEG, neuropsychological evaluations. -Wireless electrical pulse recording devices with EEG technology. -Implanted electrodes and micro-stimulations. -Image processing algorithms. - Technological devices in graphene for early prediction of seizures (next introduced to the market at the international level).
DATA PROTECTION	-Storage of data on servers. -Interconnected medical collaborative platforms. -Certifications and regulations related to the industry.
OTHER RELATED TECHNOLOGIES	-Nanotechnologies and epilepsy. -Neural tissue engineering (NTE).
POSSIBLE APPLICATIONS AND FUTURE STUDIES OF VEP. *IDENTIFIED IN THIS STUDY (VEP).	- Highly personalized medicine. - Applications in the field of Alzheimer's and other neurodegenerative diseases. - More accurate identification of neural groups and electrics shocks responsible for certain human body functionalities affected by abnormalities*. - Region assessment for neural cell regeneration and for NTE*. - Evaluation of brain regions with neurological conditions after nanotechnologies treatments*. - Identifying areas for DBS system implantation*. - Derive its functionality to devices for crisis prediction and evaluation of EEG electrical impulses*. - Optogenetics*.

Segmentation for the VEP.

Although the **quality of a roadmap** and its relationship to metrics does not follow a standardized framework, these three rules can be evaluated to distinguish a good quality roadmap (Kostoff & Schaller, 2001):

- A **retrospective** component that considers the key technologies that shaped today's innovation.

- A complete and comprehensive **present** component that integrates the technologies related to current innovation.

- A **future** component that integrates areas related to the proposed objectives with the greatest possible scope.

Therefore, once the problem that the VEP software seeks to solve is understood, its nature, organized the macro-trends inherent to its market, evaluated its drivers, understanding its limitations, model functionalities, as well as considering the opinions about the needs of those who would possible use the tool and a market segmentation, this study identified and developed possible future applications, integrations and improvements; these can be considered in forthcoming studies in the area of technological exploitation and the medical sector.

The main factors that experts consider for any technological roadmap are essentially based on the project's vision and mission, objectives, deadlines and strategic areas. Secondly, the features and solutions it offers or the need it covers, the level of deployment, the market segmentation; in other words, the factors that have been evaluated throughout the research. With all this analysis we have identified the roadmap components and integrated the most relevant drivers and excluding those elements that have a lower degree of influence. To organize all the approaches of the present research in the technological roadmap, a table has been created showing the strategic areas of the VEP, along with other columns explaining its positioning, while the degree of influence is arranged in descending order:

THEMES RELATED	STRATEGIES	START DATES AND LENGTH	PROBLEM SOLVING	RESOURCES NEEDED & EXPERTS INVOLVED	STAGE OF DEVELOP MENT	LEVEL OF PRIORITY
1. VEP-INTERFACE & IMPROVEMENTS	1. a) Personalized large-scale brain network models.	2016-2023	- Deficient accuracy in EZ and PZ in epileptic brains.	- Massive and curation data from users. - Patients evaluations. - Medical expertise. - Feedback from companies related and clients. - HBP.	7/9	High
	1. b) VEP software licensing.	2016-2026	- Protecting technology. - Catch high N° of users. - Commercialize the VEP model.	- Expert in Property rights. - Engineers. - Programmers.	7/9	High
	1. c) Registration and data management.	2016-2026	- Integrate inputs that can improve the model accuracy. - Get new findings from multiple cases and validate the model. - Evaluate N° users and outputs generated. - Obtain internal feedback about performance. - Try to maintain the most accurate and real data possible, for ideal parameters. - Support in biobank systems improving new studies.	- Engineers, tools for analyze big data, cloud computing, massive storage, data analytics tools and machine learning algorithms.	8/9	High

THEMES RELATED	STRATEGIES	START DATES AND LENGTH	PROBLEM SOLVING	RESOURCES NEEDED & EXPERTS INVOLVED	STAGE OF DEVELOPMENT	LEVEL OF PRIORITY
	1.d) User interface (UI) improvements.	2024-2026	- Custom software. - Improve design. - Generate automatics informs.	- Lead/End customers feedback. - Engineers and designers' teams.	7/9	High
	1.e) Improvement seizures predictions and diagnostic accuracy.	2016-2024	- Development of biomarkers. - Validate the model. Trial end.	- Medical, scientific teams. - Hospital/Clinics equipment. - The EPINOV group.	7/9	High
	1.f) Apps: Epileptor, TVB. Operative systems: Windows, MacOS, Linux.	2013-2026	- Adapting software to all type of IT system. - Interconnect systems for different medical devices.	- Medical, scientific teams. - Engineers. - Technicians. - Programmers.	8/9	High
2. Virtual Brain Simulation	2.a) TVB and VirtualBrainCloud (TVB-Cloud).	2016-2026	- Large scale brain network modelling. - Cloud storage.	Same as previous.	8/9	High
	2.b) EBRAINS Services.	2019-2026	- Integrated computing resources and external storage infrastructure.	- Medical, scientific teams. - Engineers. - Technicians. - Programmers. - FENIX/ICEI.	8/9	High
	2.c) The Bayesian Virtual Epileptic Patient (BVEP).	2016-2020	- Estimate the epileptogenicity of the brain and improve surgery. - Novel framework applying Bayesian for model parameters. - Specific predictive algorithms and analytics.	- Medical, Scientific Teams. - Engineers. - Radiologists. - Hospital/Clinics equipment. - HBP. - The EPINOV group.	8/9	High
3. Brain Imaging Techniques	3.a) MRI, fMRI, SEEG, EEG, M/EEG. 3.b) Electrodes for brain stimulation and recording. 3.c) Algorithms for Medical-Image Processing. 3.d) Simulations in Virtual Reality (VR) and (AR).	Same as VEP and BVEP: 2016-2026	- Personalized diagnostics and simulations.	- Medical, Scientific Staff. - Engineers. - Radiologists. - Hospital/Clinics equipment.	7/9	High

THEMES RELATED	STRATEGIES	START DATES AND LENGTH	PROBLEM SOLVING	RESOURCES NEEDED & EXPERTS INVOLVED	STAGE OF DEVELOPMENT	LEVEL OF PRIORITY
4. Organizational & Strategic Planning	4.a) EPINOV.	2018-2022	- Clinical Trial (400 patients).	- HBP. - AMU. - CNRS. -Hospitals/Clinics (AP-HM).	8/9	High
	4.b) Spin-Off Creation.	To define in SGA3. 2023-2023	- Separate the final model from parent organization and commercialize it with a new organization.	- To define.	3/9	High
	4.c) Facility Hubs.	2020-2023	-Contributing with the local teams of researchers and Scientifics in different regions of Europe.	- National and local support. - Medical, Scientifics. - Engineers. - Radiologists. - EBRAINS community.	3/9	High
5. Educational-Formative	5.a) VEP professional staff recruitment.	2022-2026	- Implement and teach the methodology.	- Medical, Scientifics. - Engineers. - Radiologists. - EBRAINS community.	7/9	High
	5.b) VEP training courses.	2022-2026	- Specific certifications. - Learn about UI feedbacks. - Unified training platform.	Same as previous.	7/9	High
	5.c) Video tutorials.	2018-2026	- Support in digital tools. - Brand positioning. - Share knowledge among physicians, scientists and researchers involved.	Same as previous.	7/9	Medium
	5.d) Scientific and innovation articles.	2016-2026	- Publish new discoveries in epilepsy and VEP model. - Copyright. - Dissemination of relevant content.	Same as previous.	8/9	High
	5.e) Regular FAQS sessions with experts.	2022-2026	- Bring the scientific and medical community closer to regular case study sessions about VEP patients.	Same as previous.	7/9	Medium
6. Collaborative Resources	6.a) Medical Informatics Platform HIC/ MIP (internal).	2019-2026	- Optimize user experience UX. - Support clinical studies and scientists.	Same as previous.	8/9	High
	6.b) Virtual forums (TVB) (internal).	2013-2026	- Support service to solve doubts.	- Engineers. - Programmers. - Other Technical Support.	7/9	Medium
	6.c) Medical Informatics Platforms (external).	2024-2026	- Optimize user experience UX. - Support clinical studies and scientists.	- Hospitals, University Hospitals - Clinics - Epilepsy Research Centers	7/9	High
7. International Business & Market Strategic Actions	7.a) Market Segmentation: End User.	SGA3 2020-2023	- Necessity to improve preoperative evaluations. - Obtain specialized knowledge and abilities. - Improve diagnosis.	- International Business & Marketing support.	7/9	High

THEMES RELATED	STRATEGIES	START DATES AND LENGTH	PROBLEM SOLVING	RESOURCES NEEDED & EXPERTS INVOLVED	STAGE OF DEVELOPMENT	LEVEL OF PRIORITY
	7.b) Market Segmentation: Lead Customers.	SGA3 2020-2023	- Next-generation software and technical service. - Improve medical services in epilepsy. - Possibility to develop research studies.	- International Business & Marketing support.	7/9	High
	7.c) Market Targeting.	SGA3 2020-2026	- Evaluate which market segments evaluated in this study are most convenient in terms to offering a greater value to users and brand positioning.	- International Business & Marketing support.	7/9	High
	7.d) Software & Marketing KPIs, Analytic Trends.	2013-2026	- Software metrics related to progress, quality, effectiveness, performance, etc. - Social media, website maintenance, other digital communications.	- Code repository, software processes. - Engineers. - Programmers. - International Business & Marketing support.	7/9	High
	7.e) Horizon scanning.	2024-2026	- Identification and monitoring of new trends, anticipation of needs and possible diversification of technology.	- International Business & Marketing support. - Physicians. - Engineers.	7/9	High
	7.f) CRM.	2020-2026	- Management of potential clients.	- International Business & Marketing support. - Engineers.	7/9	High
	7.g) Customer Service.	2024-2026	- Online support.	- Customer service software. - Customer service representatives.	8/9	High
8. VEP Events	8.a) HBP FENS	2020-2020	- Share the basic VEP model operation. - Connect with scientists and physicians related to epilepsy.	- HBP Community. - Federation of Neuroscience Societies (FENS). - Society of Neuroscience (SN).	9/9	Medium
	8.b) VEP sessions: Short and regular	2021-2026	- Short and collaborative information sessions and exchange of medical cases between Teams of neurosurgeons.	- Medical, Scientifics. - Engineers. - Radiologists. - EBRAINS community.	7/9	High
9. Next Alliances & Closed Agreements (More countries and alliances to develop soon) (France)	9.a) Agreements with: - Research Centers. - Universities. - Hospitals, clinics. - Neuroimaging technology companies.	2018-2026	- Clinical trials. - Patient records. - Model validation.	- Epinov. - AMU. -13 French hospitals.	7/9	High
(Spain)	9.b) Same as previous.	2020-2026	- Patient records. - Model validation. - Introduction to Spanish market.	- UPM - CTB - Hospitals, clinics.	7/9	High
10. Legal Framework & Good Practices	Comply with procedures and legal requirements of healthcare technologies.	2016-2026	- Declaration on the Promotion of Patient's Rights in Europe. - Codes of ethics of the medical profession. - European Market: General Data Protection Regulation (EU GDPR). - Regulation (EU) N°536/2014 trials. - Opinion 05/2014 on Anonymisation Techniques. - EU electronic health records (EHR)- Article 29 - EMA (EU). - ISO 13485. - HIPAA data protection (USA) and FDA regulations.	- Legal advice, panel of experts.	7/9	High

THEMES RELATED	STRATEGIES	START DATES AND LENGTH	PROBLEM SOLVING	RESOURCES NEEDED & EXPERTS INVOLVED	STAGE OF DEVELOPMENT	LEVEL OF PRIORITY
11. Political & Government Support	11.a) Financial assistance programs.	2016-2023	- Financing and new resources.	- HBP Funding.	7/9	High
	11.b) Specialized programs related to neurological diseases.	2021- to define	- Advice about epilepsy programs. - Acquisition of data and information from official entities.	- ANR. - ILAE. - ESBACE. - IBE. - European Reference Networks (ERNs). - Etc.	7/9	Medium
	11.c) Programs to support new technology companies in the medical sector.	2023- to define	- Get support and advice to new technology companies of healthcare sector.	- EMA (EU) - EIT (Spain) - Fenin (Spain) - Etc.	7/9	Medium
12. External Related Events	Surveillance of neurotechnologies events related.	2020-2023	- Visibility, positioning and inclusion of new allies.	- International Business & Marketing support.	7/9	High
13. Possible Future VEP Fusions & Applications **Identified in this study*:**	Develop new studies and research in: 13.a) Smart wearable technology for seizure predictions*. 13.b) Smart wearable technology for tracking EEG brain waves*. 13.c) Identify brain areas to locate DBS System*. 13.d) Support studies in Neural tissue engineering (NTE)*. 13.e) Support studies in Optogenetics*. 13.f) Support studies in Migralepsy*. 13.g) Alzheimer disease and other neurodegenerative diseases.	2018- To define	- Perpetuate the use of the tool with new functionalities and value contributions to the neuroscientific community and society.	- HBP Funding and Community. - Medical, Scientifics. - Engineers. - Radiologists. - International Business & Marketing support.	3/9	High

Construction of technological roadmap variables for the VEP.

Did you know?
NASA's 15 technology roadmaps follow a 20-year timeframe, focusing on R&D activities. (NASA, 2020)

With the variables evaluated, we proceeded to organize and detail precisely the elements that compose the roadmap, finally reflected in the previous table. Considering the contributions of specialized authors in roadmapping as Phaal et al. (2009) and more recently Lombardo et al. (2017), it was possible to address some of the concerns raised at the time of creating the tool. The common drawbacks arise from the fact that the product does not get sufficient support either financially or in terms of marketing; secondly, the emergence of doubts regarding the product in terms of its characteristics and dates within the roadmap; and thirdly, cases where, for example, the ideas do not suggest alignment with the vision.

In the course of this research, the necessary depth of understanding of the problem has been reached, the VEP model, the market and future possible applications. However, this should be considered as **an assessment that will be subject to change both for the complexity of the model and for the diagnoses of the disease itself**. The table consolidates all the variables considered, also identifying the problem or necessity to be solved, the resources and human capital necessary to execute them, the degree of development or stage of the strategies and finally the level of priority.

The technology strategy aligned with its specific goals and key results -or measurable progress- OKRs. (Lombardo et al., 2017)

Aligned with this perspective, **setting priorities within each one of the activities** is another challenge that have been analysed, because as the authors suggests, numerous good ideas can be brought to light and executed, but the primary focus is to implement them with the level of urgency they deserve and in a timely manner so the marketing and commercial departments can follow through with plans without losing opportunities due to delays. Finally, identify for each of these elements, the reason that they have been considered as part of the roadmap, which need is expected to be covered and the level of priority defined so that different teams within the project can perform their duties in accordance with the future vision and the most important objective of the model. The programme online **SharpCloud** is used to reflect the evaluated elements in a dynamic way.

The main challenge within the VEP roadmap structure is to understand and be aware of what the needs are and how to adapt to the new diagnostics technologies (both Lead and End customers), and much of that effort has to be aligned with the **scientists and engineers working on improving the tool together with the marketing and commercial departments**, which are going to channel these needs

Questions associated with the components that integrate the **VEP roadmap** created, transferable to other models:

Themes Related
Which are the most influential factors or intrinsic elements associated with the technology?

Strategies
What actions need to be taken to achieve the general and specific objectives?

Start Dates and Length
What is the approximate duration of the elements that compose the framework of action?

into the markets, in other words, one of the roadmap's strategies is to achieve a technology that considers first of all the problem to be addressed and the needs of those who will make use of it, introducing the improvements in the software according to this continuous evaluation of perspectives, **contrary to users being the ones who may be adapting to the tool throughout its life cycle**.

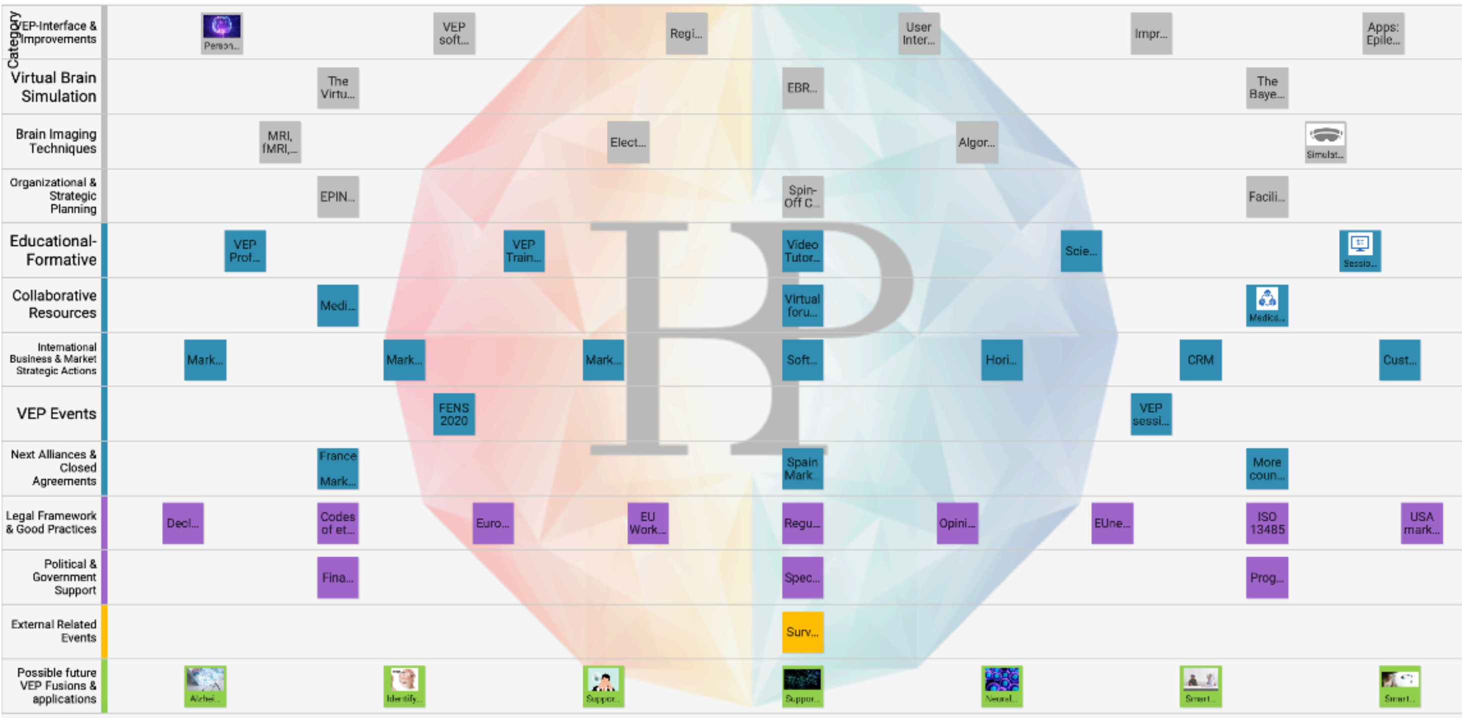
Another important output of this research is shown in the last row of the table, which reflects possible applications of VEP and fusions, some already explained in the study as they are: 1) *Smart wearable technology for seizure predictions, 2) *Smart wearable technology for tracking EEG brain waves, 3) *Identify brain areas to locate DBS System, 4) *Support advances in Optogenetics, 5) *Support advances in Neural tissue engineering (NTE), 6) in Migralepsy* and 7) in Alzheimer's disease*.

Problem Solving
What is the specific issue that we need to solve?

Stage of Development
What level of TRL is the Strategy at?

Level of Priority
What is the level of urgency?

Periodic Revaluation of the Elements:
Are the goals being achieved in the current state of the roadmap?



Preliminary version of the VEP roadmap using Sharpcloud

Roadmap as a communication tool between responsible departments, users and potential customers.

Therefore, an important aspect of the roadmap is that in addition to being a planning mechanism, it is also **considered a communication tool with the experts who will make use of the model**, because they are the ones who can bring valuable ideas and characteristics based on their own experience, considering their medical routine and their patients, even in the case of companies related to health sector technologies. The next challenge was identifying the exact dates and duration of all its elements, so they are displayed under the consideration that they represent times subject to change, although with the intention of being as approximate as possible.

Together with this perspective, the ideal in this planning mechanism is to avoid falling into the trap of promising objectives that are not fulfilled or low reliability, for this reason it has been evaluated at a deeper and more realistic level on the technology and the market, as well as validating it with experts in the area who can consider its future possibilities and technological improvements, for this reason a technological roadmap will be periodically updated. [48]

STUDIES AND TARGETS FOUND FOR THE VEP

OPTOGENETICS

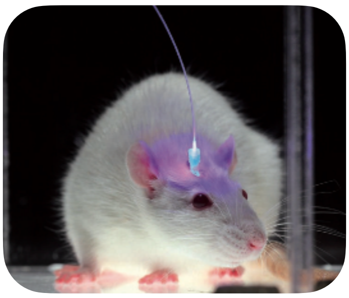


Image: Optogenetics.
(Nature, 2010)

Optogenetics is a technique that relies on the manipulation of specific neuronal groups through microbial light emission genes called opsins. To be more precise, (Deisseroth, 2011) define optogenetics as "the combination of genetic and optical methods to achieve gain or loss of function of well-defined events in specific cells or living tissue". In this regard, Choy et al. (2016) explain that, although optogenetics is a recent field of study, promising approaches have been developed **identifying the functionality of specific cells in the propagation and origin of epileptogenic seizures**.

As it is a recent area of study, it is still being tested on some mammals, before being definitively transferred to humans, precisely

[48] Roadmap Disclaimer: The information reflected in this roadmap integrates the activities and plans on which the project is working and the current results of this research. It is shared with an academic purpose and does not represent a binding commitment, so any element is subject to change as a result of technological advances, new features developed, events or circumstances that affect the software, etc.

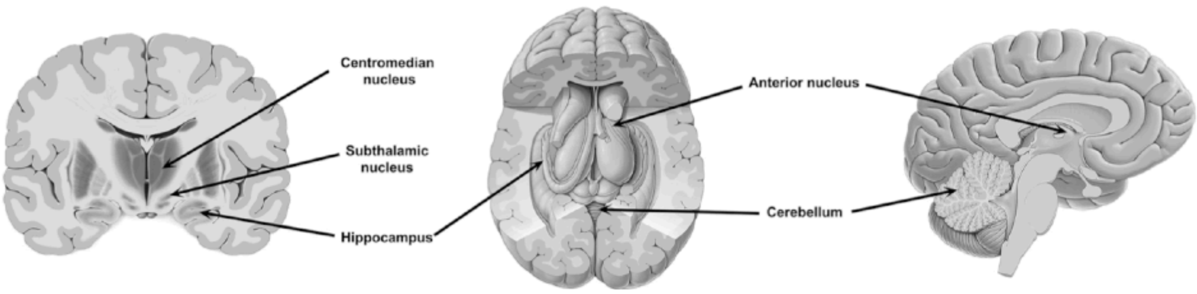
because it is a minimally invasive technique so far -compared to the known surgical interventions in epilepsy-. Therefore, the technique has the capacity to be permanent and not require other interventions or medicines, except for the light emissions themselves (Wykes et al. 2016). In this sense, certain opsins have the ability to excite or inhibit the activity of certain groups of cells, through a process of depolarization of the membrane (Nagel et al. 2003; Deisseroth, 2011) indicate that the opsin in charge of emitting positive ion charges is channelshodopsin 2 (ChR2), as well as other opsins -bacteriorhodopsin, halorhodopsin- which also have the ability to activate or deactivate neurons depending on their intensity and color.

In 2017, **scientists of the HBP** presented the dual RNA/protein to modify the activity of certain dendritic spines -a variant of SA-Channelrhodopsin- that could increase the number hippocampal synapses, named **SynActive**. (Gobbo et al, 2017)

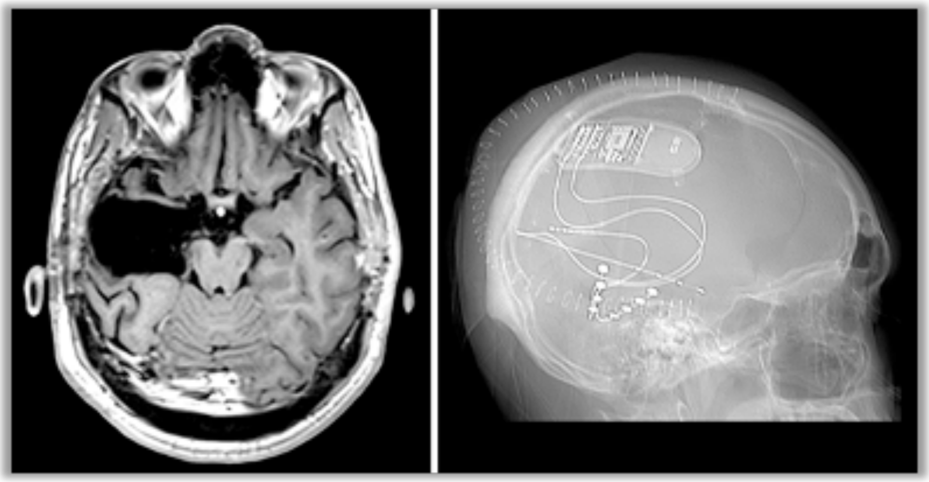
In this sense, other studies (Stroh et al., 2018), explain that the mechanism of light is supported fundamentally in implanting an optical fiber in the region to study, depending on the desired response is applied one of another opsin -the blue light activates the excitatory opsins, while the inhibitory respond to the yellow and green- to then have a greater definition of the group of neurons to be evaluated. In other words, given the recent rise of optogenetics in the field of neurology, **several studies indicate that it is crucial to precisely identify the group of neurons to be treated**, which will allow continuity in the techniques of modulation of cell groups: "After careful selection of light and opsin targeting strategies, proof of principle experiments need to be performed to test the viability, reliability, and selectivity of the opsin targeting strategy" (Gerlai, 2018, 550). These demands enhance the mechanism of VEP to support optogenetic specialists in the more precise identification of neural groups.

DEEP BRAIN STIMULATION OR DBS

In regard to **Deep Brain Stimulation or DBS** studies (Klinger and Mittal, 2018) explain that it is an intervention for those cases of refractory epilepsy in which a resection of the epileptogenic cortex is not desired. To this end, they point out that areas such as the nucleus, the hippocampus, the subthalamic nucleus and the cerebellum are stimulated with a specific device; with certain electrical stimulations that inhibit neuronal activity in these areas. These stimulations are mainly carried out towards the anterior nucleus of the thalamus (ANT), the centromedial nucleus of the thalamus (CMT), the hippocampus, the cerebellum, the subthalamic nucleus (STN), as shown in the image of their study:



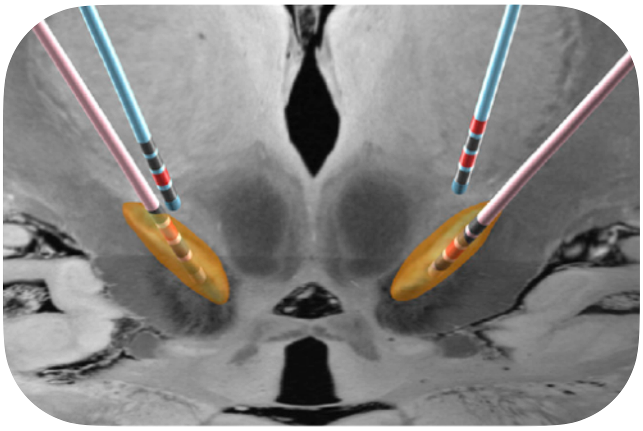
Common targets for DBS in the treatment of epilepsy. Picture courtesy of Klinger and Mittal (2018).



Patient with DBS intervention. Picture courtesy of Klinger and Mittal (2018).

In **1953** a case became known in neuroscience of M.H., a patient with drug-resistant epilepsy. A bilateral mesial temporal lobe resection was performed and, although the seizures diminished, he presented anterograde amnesia which did not allow him to keep new memories, so his experiences were novel every day. (Dossani et al., 2015)

The illustration shows a patient with disabling seizures with temporal lobe epilepsy, 80% of which originated on the right side. Right antero-medial temporal resection was performed (left image). However, after six months the seizures return, the RNS system is implanted for the stimulations, located under the scalp after a craniotomy and connected to two electrodes of intracranial depth. The procedure is not free of sequelae, it can produce long term pain in the area where the system is implanted, paresthesia, infection, dizziness, etc. The authors point out that new technologies such as infrared spectroscopy and intraoperative MRI can increase the precision of device placement. After the analysis, the application of the VEP model could be evaluated to identify the most effective areas of the brain and implement the DBS system, extending its scope of action.



Contact	**Best Responder**	**Poorest Responder**
K0	1.18	3.09
K1	0	**3.30**
K2	**0**	3.94
K3	0	5.02
K8	0	3.58
K9	**0**	**4.56**
K10	0	5.37
K11	1.58	**6.59**

Image: "Target report" showing the distance from contact centers to the subthalamic nucleus voxel centers, by Treu et al., 2020. For each contact, the optimal outcomes are shown in light red.

To further support the assessment, another recent and timely study published by Treu et al., 2020, explores new possibilities of DBS on no less important neurological disorders such as Parkinson's or depression, they point out: "In early clinical studies which led to FDA- and CE-approval for indications like Parkinson's Disease, Dystonia or Essential Tremor, the exact electrode placements were not investigated (Deuschl et al., 2006; Kupsch et al., 2006b; Schuepbach et al., 2013) (…) Still, a multitude of studies have shown that **DBS electrodes need to be accurately placed to maximize clinical improvements** (e.g. Dembek et al., 2019a; Horn, 2019; Horn et al., 2019a)". Among other interesting analyses, they emphasize that the process of locating the electrodes through software that allows the exchange of results between specialized centers is not new, however, they say that the dynamics could help predict results of behaviors that can be measured and comparable.

NEURAL TISSUE ENGINEERING OR NTE

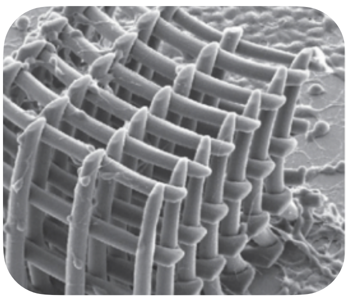


Image: Hydrogel systems in NTE. Madhusudanan et al., 2019

Interesting studies promote the formation of affected tissues in brain level, given the complex structure and the functioning of the central nervous system (CNS) that hampers the response of the traditional method of transplants (Papadimitriou et al., 2020). It is understood that the cellular regeneration of the CNS unlike the peripheral nervous system (PNS), tends to manifest a slower process of recovery after physical or chemical damage (Goh et al., 2009; Modo, 2019; Janowski et al., 2015), being tissue engineering **a promising alternative cellular scaffolds that are biocompatible and serve as temporary support for tissue regeneration**, since naturally the component is replaced by an extracellular matrix (Niri et al., 2019).

The usual methodology for the creation of materials related to neural tissue engineering starts from solvent casting for the manufacture of

There are **three ways for drug delivery with hydrogel**: implantable hydrogels, injectable hydrogels, and sprayable hydrogels. (Askari et al., 2020)

porous synthetic biodegradable polymers, phase separation to construct 3D scaffolds, self-assembly with nanofibers and their different applications, freeze-drying of porous scaffolds, gas foaming, hydrogels combined with bioprinting methods and designing bioinks for brain regeneration, as well as others methods related with molding and texturing (Papadimitriou et al., 2020).

Although the techniques are in the experimental phase, recent studies explain the rol of hydrogel systems with potential for cell regeneration, also applied in therapies such as the distribution of drugs, small molecules and extracellular proteins for neural regeneration (Madhusudanan et al., 2020). Its degradation can be manipulated through the density, weight and combination of the components described above for the manufacture of the fabric.

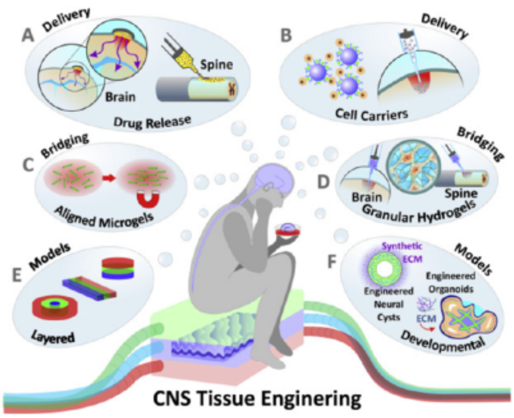


Image: Structured Hydrogels in CNS models and therapy (George et al., 2019).

Therefore, they explain that this component has been shown to have greater accessibility in the administration of drugs given the limitation of Blood-Brain Barrier (BBB) for the treatment in neurological disorders, functioning with highest effectivity in neurological disorders, working most effectively in nervous systems tumors, strokes, Parkinson's, Alzheimer's and seizures (Caicco et al., 2013; Adak et al., 2017 and Hsiao et al., 2012; mentioned by Madhusudanan et al., 2020, Niri et al., 2019).

In this sense, **the VEP model could support as a diagnostic test** -together with existing diagnostic imaging tests- the development of new experimental studies in NTE in the field of refractory epilepsy, confirming more precisely the areas where the affected tissue should be treated, either by the application of hydrogel drug therapies considering the BBB (Wang et al., 2016) and immune response, as well as in post-surgical therapies, in which this biodegradable system, combined with other specific chemical compounds, is being studied in diseases such as cancer, forming a gel in the wound and eradicating remaining tumor cells (Askari et al., 2020). Also the role of TVB as a virtual structure could be evaluated to reflect the evolution in the response with these NTE treatments.

PART IV. RECOMMENDATIONS AND SUGGESTED GUIDELINES FOR THE VEP EXPLOITATION

For the VEP Business Leaders

1. In terms of Business Management and Strategy:

As a result of the market evaluation, we consider it possible to distribute the software with higher priority in the countries of the South, Central and Eastern Europe, with less multidisciplinary epilepsy surgery programs per inhabitant. It would also reduce the number of displacements of affected people between EU regions to have access to better diagnostics and technologies.

Knowing that 80% of people with epilepsy reside in LMIC countries, in addition to having a standardized ratio of higher mortality in contrast to HIC, present greater vulnerability given the lack of medicines and advanced treatments, resulting in limited diagnosis and control in the evolution and long -term epileptic seizures, we would recommend distributing the software with a substantial discount for these countries- in case of choosing a freemium modality instead of open source- and in parallel establish partnerships with internationally recognized organizations in the field of epilepsy for the training of the software, present in these countries and with links to other medical specialists.

Within this segment, if more than a third of the specialized epilepsy and surgery centers are located in the capitals of the Latin America, we consider it is possible to begin to distribute in them and to train the technique. In the poorest countries, its usefulness lies in the fact that the introduction of the parameters in the VEP -can be adjusted only to the MRI -for those centers that do not have more advanced equipment as seen in the study-, at least in the first years of technological development.

In terms of pricing strategy, it could be applied the freemium modality for some additional VEP virtues. In case of choosing this modality, it could be considered to select an amount in exchange for validating the model, monthly cloud data storage, data access and more complex specific models, as well as the online consultation fully available with experts in the area in case of concerns to validate the results of the parameters of the patients in the model.

Define a clear framework of technological exploitation, as well as defined objectives and metrics which are desired to achieve -KPIs and OKRs-. Accompany it with a solid business plan in case of establishing a Spin-Off and appreciable marketing strategies that help distribute and maintain the model in continuous evolution to the speed of technological changes and the needs of the *Final* and *Lead Customers*.

In the field of technological exploitation, in addition to applications already found towards other neurodegenerative diseases such as Alzheimer's, we find possible a link to other surgical techniques, such as the location of Deep Brain Stimulation or DBS devices in the brain, already briefly explained in the study, as well as collaborating with other areas and companies not too far away in their proceeding, as Neural Tissue Engineering or NTE, optogenetics, migralepsy; all these studies with exciting advances in recent years.

With regard to the strategy on knowledge dissemination, organize continuous training courses and workshops under internationally valid certifications on the VEP addressed to neurologists, psychiatrists, radiologists, neurosurgeons, engineers and other staff who are motivated to specialize in the disorder of epilepsy, encouraging the importance of technologies for the treatment of these neurodegenerative diseases and a future highly personalized medicine.

Participate in seminars related to neurotechnologies and neurodegenerative diseases beyond the HBP organization, that encourage the sharing of knowledge, the updating of possible concerns of lead and final users, as well as the promotion of new discussion environments. Given the rise and rapid development of AI in neuroimaging techniques, technicians and professionals with this specialized knowledge are required to increase their competitiveness in the sector.

2. In terms of Technical Development:

It is considerable to improve the user interface of the tool in the long term, adding other useful functionalities such as reporting of VEP results for doctors and that it also has the possibility of receiving feedback from specialists who teach the model, as well as an even more attractive design and user interface. It could also include applications in virtual and augmented reality to teach the technique and make the simulations.

Likewise, move some VEP functionalities to brain-computer interface technologies, seizure prediction and tracking EEG brain wearables, that can generate new data as a consequence of the recording of the brain activity and make use of these for a greater personalization and precision of the neuronal electrical activity in a continuous and prolonged way in these patients.

Considering the valuable input received by the experts, is recommended try to transfer from now on the virtues to the pharmaceutical sector in order to virtually test the effectiveness of treatments at the brain level in the near future. In addition to recent advances in deep learning for NDDs, continue the development and validation of these approaches for the BVEP.

For the government & the public sector

Funding support programs for medical and specialist staff in the field of epilepsy in the EU for new studies that improve long-term diagnoses, generating a positive impact for the patient to avoid movement to other regions with greater availability and medical care, while increasing the possibilities of using the model and getting more accurate personalized data. As well as improve if possible, services or programs accessible to the most disadvantaged countries in the updating of neuroimaging evaluation equipment, allowing the training of new specialists.

Strengthen the support to these technology-based companies for the training of software, considering the importance of new technologies in the field of neuroimaging and motivate the specialists in the acquisition of these competitive advantages.

Make a special effort to further harmonize norms and laws in the field of new technologies for the health sector, promoting simplified processes and standards of assistance and management, considering the speed in which solutions are developed at an international level.

REFERENCES

Abellán, A. y Ayala, A. (2017). Un perfil de las personas mayores en España, 2017. Indicadores estadísticos básicos. CSIC. Madrid. http://envejecimiento.csic.es/documentos/documentos/enred-indicadoresbasicos17.pdf

Abhang, P., Gawali, B. y Mehrotra, S. (2016). Introduction to EEG- and Speech-Based Emotion Recognition. ScienceDirect. Elsevier.

Alceepilepsia (2020). Unidades de epilepsia de referencia del Sistema Nacional de Salud. https://www.alceepilepsia.org/unidades-de-epilepsia-de-referencia-del-sistema-nacional-de-salud

American Health Planning Association, AHPA (2016). Certificate of Need Matrix of Service Coverage. http://www.ahpanet.org/matrix_copn.html

Andersen, R., Musallam, S. and Pesaran, B. (2004). Selecting the signals for a brain-machine interface. Current Opinion in Neurobiology. Vol. 14, pp. 720-726. Elsevier. https://www.sciencedirect.com/science/article/pii/S0959438804001588

An Introduction to the Life and Work of John Hughlings Jackson: Introduction. (2007). Medical History. Supplement, (26), 3–34.

Arends, J., This, R., Gutter T., Ungureanu, C., Cluitmans, P., Dijk, J., Andel, J., Tan, F., Weerd A., Vledder, B., Hofstra W., Lazeren R., Thiel G., Roes K. Leijten F., and the Dutch Tele-Epilepsy Consortium (2018). Neurology. https://n.neurology.org/content/neurology/91/21/e2010.full.pdf

Askari, E., Seyfoori, A., Amereh, M., Samimi, S., Sadat, H., Sadat, Z., Khunjush, B., and Akbari, M. (2020). Stimuli-Responsive Hydrogels for Local Post-Surgical Drug Delivery. Gels, 6, 14. doi:10.3390/gels6020014

Baykan, B. (2016). Nonconvulsive Status Epilepticus: An Intriguing, Highly Heterogeneous Neuropsychiatric Condition with Blurring Clinical Margins, Sharpening EEG Criteria and Still Unsolved Background. US National Library of Medicine. National Institutes of Health. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5378208/

Baulac, M., De Boer H., Elger, C., Glynn, M., Kälviäinen, R., Little A., Mifsud J., Perucca E., Pitkänen, A., Ryvlin, P. (2015). Epilepsy priorities in Europe: A report of the ILAE-IBE Epilepsy Advocacy Europe Task Force. Wiley. 56(11): 1687–1695.

Beghi, E. (2020). The Epidemiology of Epilepsy. Neuroepidemiology. Karger. 54:185–191. https://www.karger.com/Article/Fulltext/503831

Bicheteau, N., Henry, O., Jourdan (1856). Diccionario de Medicina. Tomo I. Madrid Oficinas del Museo Científico.

Brigo, F., Trinka, E., Lattanzi, S., Bragazzi, N., Nardone R., y Martini, M. (2018). A brief history of typical absence seizures — Petit mal revisited. Epilepsy & Behavior. Vol. 80. P. 326-353. https://www.sciencedirect.com/science/article/abs/pii/S1525505017310168

Callixte, K. et al. (2013). Situation de l'épilepsie au Cameroon. African and Middle East Epilepsy Journal. Journal representative of Countries of Africa & Middle East. Vol. 2, No. 3. Neurology department, Ibn Tofail Hospital. Marruecos. https://www.uca.ma/public/files/publications/nameej/nameej_v2n3.pdf?/fr/public/files/publications/nameej/nameej_v2n3.pdf

Carey, C. (2020). United States food and drug administration. Academic Press. ScienceDirect Pages 764-773. https://www.sciencedirect.com/science/article/pii/B9780128134672001085

Castaño, D. (2014). Urgencias en epilepsia "código status" 5 (Estado epiléptico no convulsivo). Instituto Neurológico de Colombia https://www.youtube.com/watch?v=aFoy5QnAyVw

Choy, M., Duffy B., Hyung J. (2016). Optogenetic study of networks in epilepsy. Wiley Online Library. Journal of Neuroscience Research. https://onlinelibrary.wiley.com/doi/full/10.1002/jnr.23767@10.1002/(ISSN)1097-4547.IF6

Claassen, J. Mayer, S., Kowalski R., Emerson, L. y Hirsch, L. (2004). Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. https://n.neurology.org/content/62/10/1743.short

Clarysse, B., Wright, M. And Vandevelde, E. (2010). Entrepreneurial Origin, Technological Knowledge and the Growth of Spin-off Companies. Universiteit Gent. United Kingdom. https://wps-feb.ugent.be/Papers/wp_10_693.pdf

Clínica Universidad de Navarra (2020). Diccionario Médico. https://www.cun.es/diccionario-medico

Critical Care Services Ontario, CCSO (2016). Epilepsy Implementation Task Force. Canadá. https://www.ilae.org/files/dmfile/Epigraph-2016-2_Snead-7-RegionalSurgeryCentreGuidelines2016.pdf

Dassault Systèmes (2020). Living Brain for Targeted Epilepsy. What is Epilepsy?. https://www.3ds.com/stories/living-brain/

Defense Advanced Research Projects Agency, DARPA (2020). The Sputnik Surprise. https://www.darpa.mil/about-us/timeline/creation-of-darpa.

Defense Advanced Research Projects Agency, DARPA (2020). Next-Generation Nonsurgical Neurotechnology. Dr. Al Emondi. https://www.darpa.mil/program/next-generation-nonsurgical-neurotechnology.

Deisseroth, K. (2011). Optogenetics. Nature. Vol. 8., pp. 26-29. https://www.nature.com/articles/nmeth.f.324

De Souza, N., Neri, E., Brady, A., (2019). What the radiologist should know about artificial intelligence – an ESR white paper. Insights Imaging 10, 44 (2019). European Society of Radiology (ESR). https://doi.org/10.1186/s13244-019-0738-2

Dossani, R., Missios, S., and Nanda, A. (2015). The Legacy of Henry Molaison (1926–2008) and the Impact of His Bilateral Mesial Temporal Lobe Surgery on the Study of Human Memory. World Neurosurgery. Elsevier. October 2015, PP. 1127-1135. https://www.sciencedirect.com/science/article/pii/S1878875015004337

Elsevier (2017). Escala de Coma de Glasgow: tipos de respuesta motora y su puntuación. Generación Elsevier. https://www.elsevier.com/es-es/connect/medicina/escala-de-coma-de-glasgow

Engel, J., McDermott, M., Wiebe, S., Langfitt J., Stern J., Dewar S., Sperling M., Gardiner I., Erba G., Fried I., Jacobs M., Vinters H., Mintzer S., Kieburtz K., Randomized E. (2012). Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. National Library of Medicine (NIH). 307 (9): 922-30. https://pubmed.ncbi.nlm.nih.gov/22396514/

Epinov (2020). EPINOV launches the first clinical trial of virtual brain technology to assist brain surgery: EPINOV TRIAL, a world first. https://www.3ds.com/fileadmin/Stories/Epinov/Pdf/launch-epinov-clinical-trial-press-release-2020.pdf
Fenix (2020). ICEI/FENIX helps lead virtual epileptic patient model to clinical trial. https://fenix-ri.eu/news/iceifenix-helps-lead-virtual-epileptic-patient-model-clinical-trial

European Clinical Research Infrastructure Network, ECRIN (2020). DATA Centers & OTHER PARTNERS. https://ecrin.org/who-we-are/partners

European Commission (2020). Health technology assessment. https://ec.europa.eu/health/technology_assessment/overview_en

European Medicines Agency (2020). Partners & networks. European Union. https://www.ema.europa.eu/en/partners-networks/health-technology-assessment-bodies

European Medicines Agency (2020). Scientific advice and protocol assistance. Science Medicines Health. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance

Eunetha (2018). Getting Involved in a Eunethta Assessment Information for Patients. European Commission. https://eunethta.eu/wp-content/uploads/2020/01/Electronic-Flyer-Patients.pdf

Eyigoz, E., Mathur, S., Santamaria, M., Cecchi G., Naylor, M. (2020). Linguistic markers predict onset of Alzheimer's disease. ClinicalMedicine. The Lancet. https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30327-8/fulltext

Fisher, R., Arzimanoglou, A., Bogacz, A., Cross, J., Elger, J., Engel, J., Forsgren L. French, J., Glynn M., Hesdorffer D., Lee b., Mathern, G., Moshé, S., Perucca, E., Scheffer T., Tomson, T., Watanabe, S. Wiebe, S (2005). ILAE official report: a practical clinical definition of epilepsy. Epilepsia, 55 (4), pp. 475-482. https://www.sciencedirect.com/science/article/pii/S0920121117303819#bib0040

Fortis (2019). Neurology. India, https://www.fortishealthcare.com/india/clinical-speciality/neurology-288

Fortiss (2020). Human Brain Project. https://www.fortiss.org/en/research/projects/detail/human-brain-project

García de Sola, R. (2015). Epilepsy surgery in Europe: a historical review. Unidad de Neurocirugía RGS. https://neurorgs.net/investigacion/epilepsy-surgery-in-europe-a-historical-review/#The_development_of_epilepsy_surgery_in_Italy

George, J., Hsu, C., Nguyen, L., Ye, H., Cui, Z. (2019). Neural tissue engineering with structured hydrogels in CNS models and therapies. Biotechnology Advances. Volume 42, September–October 2020, 107370

Gerlai, R. (2018). Molecular-Genetic and Statistical Techniques for Behavioral and Neural Research. Academic Press. Elsevier. United Kingdom. https://books.google.es/books?id=p89YDwAAQBAJ&printsec=frontcover&source=gbs_ge_summary_r&cad=0#v=onepage&q&f=false

Gil-Nágel, A. (2017). Epilepsia Refractaria: Tratamiento quirúrgico. https://youtu.be/x-lK-IslCjM. Fundación Síndrome de West España.

Gobbo, F., Marchetti, L., Jacob, A., Pinto, B., Binini, N., Pecoraro, F., Alia, C., Luin S., Caleo, M., Fellin, T., Cancedda, L., Cattaneo, A. (2017). Activity-dependent expression of Channelrhodopsin at neuronal synapses. Nature. 8: 1629 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5696361/

Goh, E., Song, H., Ming, G. (2009). Tissue Engineering Applications in Neurology. Springer Berlin Heidelberg. Fundamentals of Tissue Engineering and Regenerative Medicine. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-540-77755-7_56

Gómez, A., Urrestarazu, E. y Viteri, C. (2012). Estado epiléptico no convulsivo en el siglo XXI: clínica, diagnóstico, tratamiento y pronóstico. Revista de Neurología. España: https://core.ac.uk/download/pdf/83572961.pdf

Goselink, R., Van Dillen, J., Aerts, M., Arends, J., Van Asch, C., Der Linden, I., Pasman, J., Saris C., Zwart M., Van Alfen (2019). The difficulty of diagnosing NCSE in clinical practice; external validation of the Salzburg criteria. Wiley Online Library. https://onlinelibrary.wiley.com/doi/full/10.1111/epi.16289

Gumnit, R., Labiner, D., Fountain N., Herman, S. (2012). Epilepsy Across the Spectrum: Promoting Health and Understanding. Washington. https://www.ncbi.nlm.nih.gov/books/NBK100603/

Hammond, N. (2016). Tonic-Clonic Seizures. Reference Module in Biomedical Sciences. Elsevier. https://www.sciencedirect.com/science/article/pii/B9780128012383995126

Hardy, M. Y Harvey, H. (2020). Artificial intelligence in diagnostic imaging: impact on the radiography profession. Br J Radiol 2020; 93: 20190840. The British Institute of Radiology. https://www.birpublications.org/doi/pdf/10.1259/bjr.20190840

Harrahill, M. (1996). Glascow coma scale: A quick review. Journal of Emergency Nursing. Vol 22, Issue I. pp. 81-83. https://www.sciencedirect.com/science/article/abs/pii/S0099176796800857

Hashemi M., Vattikonda A.N, Sip V., Guye M., Bartolomei F., Woodman M.M, Jirsa V.K. (2020). Vol. 217. NeuroImage. Elsevier. The Bayesian Virtual Epileptic Patient: A probabilistic framework designed to infer the spatial map of epileptogenicity in a personalized large-scale brain model of epilepsy spread. https://www.sciencedirect.com/science/article/pii/S1053811920303268

Health Information Privacy (2013). Summary of the HIPAA Security Rule. Estados Unidos. https://www.hhs.gov/hipaa/for-professionals/security/laws-regulations/index.html

Healthpoint (2019). Epilepsy Surgery. Nueva Zelanda. https://www.healthpoint.co.nz/private/neurosurgery/peter-heppner-neurosurgeon/epilepsy-surgery/

Hidalgo, A., León, G. y Pavón J. (2013). La gestión de la innovación y la tecnología en las organizaciones. Ediciones Pirámide. España.

Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation (2009). Accelerating the Development of Biomarkers for Drug Safety: Workshop Summary. Washington. https://www.ncbi.nlm.nih.gov/books/NBK32710/

ISO (2020). ISO 13485 Medical Devices. Popular Standards. https://www.iso.org/iso-13485-medical-devices.html

Janowski, M., Wagner, D. C., & Boltze, J. (2015). Stem Cell-Based Tissue Replacement After Stroke: Factual Necessity or Notorious Fiction?. Stroke, 46(8), 2354–2363. https://doi.org/10.1161/STROKEAHA.114.007803

Jedrzejczak, J., Marusic, P., Haldre, S., Majkowska, B., Bojinova, V., Mameniskiene, R., Mindruta, I., Ravnik, I., Szupera, Z., Sykora, P., Verzbickis, A., Daniluk, J. (2013). Current status of epilepsy health care for adult patients from Central and Eastern European Union Countries—A survey of members of the Central Europe Epilepsy Experts Working Group. Seizure. Vol 22. Elsevier. https://www.sciencedirect.com/science/article/pii/S1059131113000666

Jelonek, D. y Chluski, A. (2014). Technological context of healthcare entity intangible asset management. International Institute for Applied Knowledge Management. Volume 2, Issue 2. http://www.iiakm.org/ojakm/articles/2014/volume2_2/OJAKM_Volume2_2pp120-131.pdf

Jirsa, V., T. Proix, D. Perdikis, M.M.Woodman, H.Wang, J. Gonzalez-Martinez, C. Bernard, C.Bénar, M. Guye, P. Chauvel, F. Bartolomei. (2016). The Virtual Epileptic Patient: Individualized whole-brain models of epilepsy spread. Elsevier.

Johns Hopkins Medicine (2020). Computed Tomography (CT or CAT) Scan of the Brain. https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/computed-tomography-ct-or-cat-scan-of-the-brain

Kelsey, J. (2017). Observational Epidemiology. International Encyclopedia of Public Health. https://www.sciencedirect.com/science/article/pii/B9780128036785003106.

Khiari, H., Khemiri, E., Parain, D., Hattab, N., Proust F., Mrabet A. (2010). Epilepsy surgery program in Tunisia: An example of a Tunisian French collaboration. Seizure. Volume 19, Issue 2, Pages 74-48. https://www.sciencedirect.com/science/article/pii/S105913110900243X

Klinger, N. y Mittal S. (2018). Deep brain stimulation for seizure control in drug-resistant epilepsy. Journal of Neurosurgery, JNS. https://thejns.org/focus/view/journals/neurosurg-focus/45/2/article-pE4.xml?rskey=WzQQJQ

Kissani, N., Harkani A., Chahidi, A. (2013). Moroccan Association Against Epilepsy (MSAE): side by side with epileptic patients in Morocco Since 2005. Marruecos.

Kwon, C., Agarwal P., Subramaniam, V., Dhamoon, M, Yeshokumar, A., Panov, F., Jetté, N. (2019). Readmission after neurosurgical intervention in epilepsy: A nationwide cohort analysis. Vol. 61. Wiley. https://onlinelibrary.wiley.com/doi/abs/10.1111/epi.16401

Lamberink, H., Otte, W., Blumcke I., Braun K., the European Epilepsy Brain Bank and the European Reference Network EpiCARE, (2020). Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. The Lancet Neurology. Vol. 19. Pp. 748-757. https://www.sciencedirect.com/science/article/abs/pii/S1474442220302209

Laso, J. L. (2020). Introducción a la Medicina Clínica. 4ta edición. Elsevier Health Sciences. España. Pages 295-307. ScienceDirect. https://books.google.es/books?id=Cb3TDwAAQBAJ&printsec=frontcover&hl=es#v=onepage&q&f=false

Levira, F., Thurman D., Sander J., Hauser W., Hesdorffer, D., Masanja H., Odermatt P., Logorscino, G., Newton C. (2017). Premature Mortality of Epilepsy in Low- And Middle-Income Countries: A Systematic Review From the Mortality Task Force of the International League Against Epilepsy. 58(1):6-16. https://pubmed.ncbi.nlm.nih.gov/27988968/

Lichtenthaler, U. (2010). Technology exploitation in the context of open innovation: Finding the right 'job' for your technology. Págs. 429-435. Technovation. Elsevier. WHU-Otto Beosheim School of Management, Alemania.

Lombardo, C., McCarthy, B., Ryan, E. and Connors, M. (2017). Products Roadmap Relaunched. How to Set Direction while Embracing Uncertainty. Oreilly. United States of America.

Low, L. (2019). Epilepsy prediction device receives Microsoft grant. Universidad de Sídney. https://www.sydney.edu.au/news-opinion/news/2019/05/16/Epilepsy-prediction-device-receives-Microsoft-grant.html

Madhusudanan P, Raju G, Shankarappa S. (2020) Hydrogel systems and their role in neural tissue engineering. J. R. Soc. Interface 17: 20190505. http://dx.doi.org/10.1098/rsif.2019.0505

Maiga, Y. (2016). La médecine intégrative promue par l'OMS: un atout pour la prise en charge de l'épilepsie. African and Middle East Epilepsy Journal. Journal representative of Countries of Africa & Middle East. Vol. 5, No. 1. Neurology department, Ibn Tofail Hospital. Marruecos. https://revues.imist.ma/index.php/AMEEJ/

Markoula S, Liampas A, Rubboli G, Duncan J, Velis DN, Schulze-Bonhage A, Guekht A, Bartholomeyczik K, Tisi J, Gras A, Lossius MI, Villani F, Staack AM, Hospes A, Baaijen JC, van Straaten ECW, Ronner HE, Casciato S, D'Aniello A, Mascia A, Santos SF, Bentes C, Aledo-Serrano Á, Gil-Nagel A, Dimova P, Hećimović H, Özkara Ç, Malmgren K, Papacostas S, Kelemen A, Reuber M, Trinka E, Ryvlin P. A European questionnaire survey on epilepsy monitoring units' current practice for postoperative psychogenic nonepileptic seizures' detection. Epilepsy Behav. 2020 Nov;112:107355. doi: 10.1016/j.yebeh.2020.107355. Epub 2020 Jul 31. PMID: 32745960.

Maxime O. Baud, Thomas Perneger, Attila Rácz, Max C. Pensel, Christian Elger, Bertil Rydenhag, Kristina Malmgren, J. Helen Cross, Grainne McKenna, Martin Tisdall, Herm J. Lamberink, Sylvain Rheims, Philippe Ryvlin, Jean Isnard, François Mauguière, Alexis Arzimanoglou, Serdar Akkol, Kaancan Deniz, Cigdem Ozkara, Morten Lossius, Ivan Rektor, Reetta Kälviäinen, Lotta-Maria Vanhatalo, Petia Dimova, Krassimir Minkin, Anke Maren Staack, Bernhard J. Steinhoff, Adam Kalina, Pavel Krsek, Petr Marusic, Zsofia Jordan, Daniel Fabo, Evelien Carrette, Paul Boon, Saulius Rocka, Rūta Mameniškienė, Serge Vulliemoz, Francesca Pittau, Kees P.J. Braun, Margitta Seeck (2018). European trends in epilepsy surgery. Neurology. https://n.neurology.org/content/91/2/e96

Medical Device Regulation, MDR (2017). Reglamento (UE) 2017/745 del Parlamento Europeo y del Consejo de 5 de abril de 2017. https://www.medical-device-regulation.eu/wp-content/uploads/2019/05/CELEX_32017R0745_ES_TXT.pdf

Modo, M. (2019) Bioscaffold-Induced Brain Tissue Regeneration. Front. Neurosci.13:1156. doi: 10.3389/fnins.2019.01156

Musk, E. (2019). An integrated brain-machine interface platform with thousands of channels. BioRxiv. https://www.biorxiv.org/content/10.1101/703801v2.full.pdf

NASA (2012). Technology Readiness Level. Thuy Mai. https://www.nasa.gov/directorates/heo/scan/engineering/technology/txt_accordion1.html

National Conference of State Legislatures (2019). CON-Certificate of Need State Laws. Estados Unidos. https://www.ncsl.org/research/health/con-certificate-of-need-state-laws.aspx

National Institute of Mental Health, NIMH (2018). Improving EPilepsy Surgery Management and progNOsis Using Virtual Epileptic Patient Software (VEP) (EPINOV). Identification No. NCT03643016. Retrieved from https://clinicaltrials.gov/ct2/show/NCT03643016?term=NCT03643016&draw=2&rank=1

Neligan, A., Haliasos N., Pettorini B., Harkness W. y Solomon J. (2013). A survey of adult and pediatric epilepsy surgery in the United Kingdom. UK ILAE Chapter, UCL Institute of Neurology, Society of British Neurological Surgeons. United Kingdom. https://onlinelibrary.wiley.com/doi/pdf/10.1111/epi.12148

Niri, A., Zarchi, A., Harati, P. (2019). Tissue engineering scaffolds in the treatment of brain disorders in geriatric patients. Artificial Organs. Wiley. Volume 43, Issue10 October 2019, Pages 947-960

Ntsambi E. Mampunza M., Kulimba M., Mananga L. y Okito J. (2015). Potentiel D'indication Chirurgicale De L'epilepsie En Milieu Neuropsychiatrique A Kinshasa: Cas Du Centre De Santé Mentale Telema Etude Préliminaire. El Congo. https://ajns.paans.org/potentiel-dindication-chirurgicale-de-lepilepsie-en-milieu-neuropsychiatrique-a-kinshasa-cas-du-centre-de-sante-mentale-telema-etude-preliminaire/

OEPM (2016). La Protección Internacional de las Invenciones. Ministerio de Industria, Energía y Turismo. Oficina Española de Patentes y Marcas. http://www.oepm.es/cs/OEPMSite/contenidos/Folletos/07-proteccion-internacional-invenciones.html

Official Journal of the European Union (2016). Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016. https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679

Ohman, C., Canham, S., Ghene, G., Lauritsen J., Martins, H., Mendes, R., Nicolis, E, Svobodnik A. (2017). Raising standards in clinical research – The impact of the ECRIN data centre certification programme, 2011–2016. Contemporary Clinical Trials Communications. Volume 5, March 2017, Pages 153-159. https://www.sciencedirect.com/science/article/pii/S2451865416300825

Organización Mundial de la Propiedad Intelectual, OMPI (2020). Clasificación Internacional de Patentes. https://www.wipo.int/classifications/ipc/ipcpub/?notion=scheme&version=20200101&symbol=none&menulang=en&lang=en&viewmode=f&fipcpc=no&showdeleted=yes&indexes=no&headings=yes&notes=yes&direction=o2n&initial=A&cwid=none&tree=no&searchmode=smar

Organización Panamericana de la Salud, OPS (2018). El abordaje de la epilepsia desde el sector de la salud pública. Organización Mundial de la Salud, Oficina Regional para las Américas. https://iris.paho.org/bitstream/handle/10665.2/49509/epilepsia_español_OK.pdf?sequence=2&isAllowed=y

Page, R., Shankar, R., McLean B., Hanna, J., Newman C. (2018). Digital Care in Epilepsy: A Conceptual Framework for Technological Therapies. Frontiers in Neurology. Vol. 9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5841122/

Pan American Health Organization, PAHO (2013). Report on Epilepsy in Latin America and the Caribbean. Washington. https://www.paho.org/hq/dmdocuments/2014/epilepsy-ENG-final.pdf

Panteliadis, C., Vassilyadi, P., Fehlert, J., y Hagel C. (2017). Historical documents on epilepsy: From antiquity through the 20th century. Brain and Development. Vol 39, Issue 6. P-457-463. Elsevier. https://www.sciencedirect.com/science/article/abs/pii/S0387760417300293

Papadimitriou, L., Manganas, P., Ranella, A., Stratakis, E. (2020). Biofabrication for neural tissue engineering applications. Materials Today Bio Volume 6, March 2020, 100043. https://www.sciencedirect.com/science/article/pii/S259000642030003X#cebib0010

Prčkovska, V., Peeters, T., Dominguez, D., Rodrigues, P. (2017). BrainVis: A cloud-connected 3D exploration and visualization tool for multi-modal neuroimaging data. ResearchGate. https://www.researchgate.net/publication/323432129_BrainVis_A_cloud-connected_3D_exploration_and_visualization_tool_for_multi-modal_neuroimaging_data

Puch, Santi. (2018). Multimodal brain tumor segmentation in Magnetic Resonance Images with Deep Architectures. 10.13140/RG.2.2.35829.63208.

Rashkov, G., Bobe, A., Fastovets D., Komarova M. (2019). Natural image reconstruction from brain waves: a novel visual BCI system with native feedback. BioRxiv. Cold Spring Harbor Laboratory. https://www.biorxiv.org/content/10.1101/787101v2.full

Rathore, C. y Radhakrishnan, K. (2017). Epidemiology of epilepsy surgery in India. Neurology India. Volume 65, Issue 7, Page: 52-59. http://www.neurologyindia.com/article.asp?issn=0028-3886;year=2017;volume=65;issue=7;spage=52;epage=59;aulast=Rathore

Reif, P., Strzelczyk, A., y Rosenow F. (2016). The history of invasive EEG evaluation in epilepsy patients. Seizure. Elsevier Vol. 41. P. 191-195. https://www.sciencedirect.com/science/article/pii/S105913111630022X

Ryvlin, P. And Beniczky, S. (2020). Seizure detection and mobile health devices in epilepsy: Recent developments and future perspectives. Epilepsia. Wiley. https://onlinelibrary.wiley.com/doi/full/10.1111/epi.16702

Sanchez, J., and Miranda, R. (2019). Taking Neurotechnology into New Territory. Defense Media Network. Estados Unidos. https://www.defensemedianetwork.com/stories/taking-neurotechnology-new-territory/

Schijns, O., Hoogland, G., Kubben, P y Koehler, P. (2015). The start and development of epilepsy surgery in Europe: a historical review. Springer. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4469771/

Schiller, Y. and Najjar, Y. (2008). Quantifying the response to antiepileptic drugs: effect of past treatment history. Neurology. National Library of Medicine. https://pubmed.ncbi.nlm.nih.gov/18166707/

Schmidt, D. y Shorvon, S., (2016). The End of Epilepsy? A history of the modern era of epilepsy 1860-2010. Oxford University Press. United Kingdom

Shih, P., Nikpour A., Bleasel A., Herkes G., Mitchell R., Seah R., Mumford V., Braithwaite J., Vagholkar, S., Rapport, F. (2018). Leading up to saying "yes": A qualitative study on the experience of patients with refractory epilepsy regarding presurgical investigation for resective surgery. https://www.epilepsybehavior.com/article/S1525-5050(18)30034-9/pdf

Stroh, A. (2018). Optogenetics: A roadmap. Springer Protocols. Neuromethods. University Medical Center of the Johannes. Springer.

Serrano, A., Gil-Nagel A., Dimova, P., Hecimovic H., Ozkara C., Malmgren K., Papacostas S., Kelemen A., Reuber M., Trinka E., Ryvlin P. (2020) A European questionnaire survey on epilepsy monitoring units' current practice for postoperative psychogenic nonepileptic seizures' detection. Epilepsy & Behavior. Vol. 112, 107355. https://www.sciencedirect.com/science/article/pii/S1525505020305345

Sinha N., Dauwels, J., Kaiser M., Cash, S., Westover M., Wang, Y., Taylor P. (2017). Predicting neurosurgical outcomes in focal epilepsy patients using computational modelling. Brain a Journal of Neurology. Oxford Academic. https://academic.oup.com/brain/article/140/2/319/2736496

Sutter, R., Rüegg S. and Kaplan, P. (2012). Epidemiology, diagnosis, and management of nonconvulsive status epilepticus. Neurology. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5829470/

Thurman, D., Logroscino G., Beghi E., Hauser A., Hesdorffer, D., Newton C., Scorza F.A., Sander, J., Tomson T. (2016). The burden of premature mortality of epilepsy in high-income countries: A systematic review from the Mortality Task Force of the International League Against Epilepsy. Wiley Online Library. https://onlinelibrary.wiley.com/doi/full/10.1111/epi.13604

Treu, S., Strange, B., Oxenford, S., Neumann, W., Kuhn, A., Li, N., Horn, A. (2020). Deep brain stimulation: Imaging on a group level. NeuroImage, Vol 219. Elsevier. https://www.sciencedirect.com/science/article/pii/S1053811920305048#undfig1

Trinka, E., Kwan P., Lee, B. y Dash, A. (2018). Epilepsy in Asia: Disease burden, management barriers, and challenges. Wiley Online Library. Volume 60, Issue S1. https://onlinelibrary.wiley.com/doi/full/10.1111/epi.14458

Tubke, A. (2005). Success factors of corporate spin-offs. Springer. Estados Unidos.

Uddin, M., Wang, Y., and Woodbury, S. (2019). Artificial intelligence for precision medicine in neurodevelopmental disorders. Nature. https://www.nature.com/articles/s41746-019-0191-0#ref-CR86

University of Florida (2015). Controlling Drones With Your Mind. https://youtu.be/hLjxMjBlB9k
Wiebe, S., Blume W., Girvin J. y Eliasziw M. (2001). A Randomized, Controlled Trial of Surgery for Temporal-Lobe Epilepsy. https://www.nejm.org/doi/full/10.1056/NEJM200108023450501

U.S Department of Health & Human Services, HHS (2013). Summary of the HIPAA Security Rule. https://www.hhs.gov/hipaa/for-professionals/security/laws-regulations/index.html

U.S Food & Drug Administration (2020). Recognized Consensus Standards. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

U.S Food & Drug Administration (2020). Software as a Medical Device (SaMD). Digital Health. https://www.fda.gov/medical-devices/digital-health/software-medical-device-samd

Vakharia V., Duncan J., Witt J., Elger C., Staba R. y Engel J. (2018). Getting the best outcomes from epilepsy surgery. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5947666/#ana25205-bib-0002

Velasco, G., Jing X., y Labra, E. (2016). Horizontes científico-comerciales en La Araucanía. Desarrollo de Capital Social para impulsar la Ciencia, Tecnología e Innovación en el sector Agroalimentario en La Araucanía. Innovation Foresight Board Ltd.

Verrotti, A., Striano, P., Belcastro V., Matricardi, S., Pia Villa, M., Parisi, P. (2011). Migralepsy and related conditions: Advances in pathophysiology and classification. Elsevier. Seizure. Vol. 20, pp. 271-275. https://www.sciencedirect.com/science/article/pii/S1059131111000689

Wang, Y., Ying, X., Chen, L. et al. Electroresponsive Nanoparticles Improve Antiseizure Effect of Phenytoin in Generalized Tonic-Clonic Seizures. Neurotherapeutics 13, 603–613 (2016). https://doi.org/10.1007/s13311-016-0431-9

Watila M., Xiao F., Keezer, M., Miserocchi A., Winkler, A., McEvoy A., Sander J. (2019). Epilepsy surgery in low-and middle-income countries: A scoping review. Epilepsy & Behavior, Vol. 92, Pages 311-326 https://www.sciencedirect.com/science/article/pii/S1525505018309533?via%3Dihub#bb0955

Wiebe, S., Blume W., Girvin J. y Eliasziw M. (2001). A Randomized, Controlled Trial of Surgery for Temporal-Lobe Epilepsy. https://www.nejm.org/doi/full/10.1056/NEJM200108023450501

Williams R. (2020). Deep Brain Optogenetic Control Without Implants. The Scientist. https://www.the-scientist.com/news-opinion/deep-brain-optogenetic-control-without-implants-67498

Wirrell, E. (2020). Epilepsy due to specific causes. Epilepsy Foundation. https://www.epilepsy.com/learn/epilepsy-due-specific-causes

Willyard, C., and McClees (1987). Motorola's Technology Roadmap Process. Taylor & Francis Online. Vol. 30, Issue 5. https://www.tandfonline.com/doi/abs/10.1080/00345334.1987.11757057?journalCode=urtm19

World Health Organization, WHO (2011). Epilepsy in The WHO European Region: Fostering Epilepsy Care in Europe. Epilepsy out of the shadows. Países Bajos. https://www.who.int/mental_health/neurology/epilepsy/euro_report.pdf?ua=1

World Health Organization, WHO (2013). Epilepsy in the African Region: Bridging the Gap. Regional Office for Africa. Epilepsy. https://www.ilae.org/files/dmfile/Declaration-English-reduced.pdf

World Health Organization, WHO (2017). Atlas, country resources for neurological disorders. 2° edition. https://www.who.int/mental_health/neurology/atlas_second_edition/en/

World Health Organization, WHO (2019). Epilepsy. A public Health Imperative. https://www.who.int/mental_health/neurology/epilepsy/report_2019/en/

Wykes R., Kullmann D., Pavlov I., Magloire V. (2016). Optogenetic approaches to treat epilepsy. Journal of Neuroscience Methods. Vol. 260, pp. 215-220. https://www.sciencedirect.com/science/article/abs/pii/S0165027015002216?casa_token=wWyTYL1-YdcAAAAA:7F1x8iprJSApiUiUXKQAHFmsOjiuROLYHLNalcJWu8vXVIFZY_-lMT9voPPEgGCANdZkSdXi1w

Yuste, R., Goering, S., Aguera y Arcas, B., Bi, G., Carmena, J., Carter A., Fins, J., Friesen, P., Gallant, J., Huggings J., Illes, J., Kellmeyer P., Klein E., Marblestone A., Mitchell C., Parens, E., Pham, M., Rubel A., Sadato N., Specker L., Teicher M., Wasserman, D., Wexler A., Whittaker, M., Wolpaw, J. (2017). Four ethical priorities for neurotechnologies and AI. Nature. https://www.nature.com/news/four-ethical-priorities-for-neurotechnologies-and-ai-1.22960

Yuste, R. and Bargmann, C. (2017). Toward a Global BRAIN Initiative. ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0092867417302015

Zack, M. and Kobau R. (2017). National and State Estimates of the Numbers of Adults and Children with Active Epilepsy — United States, 2015. MMWR. 66 (31): 821-825. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5687788/

Zelano J., Klecki, J., Christensen J., Tomson T., Malmgren K. (2019). The provision of epilepsy care across Europe 2017: A 17-year follow-up survey. The ESBACE consortium Collaborators. Epilepsia Open/Vol. 4, Issue 1. https://onlinelibrary.wiley.com/doi/full/10.1002/epi4.12306

APPENDIX

COMPANY	TYPE	REASON FOR INCLUSION	MAIN PRODUCT OR SERVICE	COUNTRY
EPIMINDER	HEALTHCARE COMPANY	Ultra long-term EEG monitoring of seizure activity in patients with epilepsy.	Epilepsy implantable device	AUSTRALIA
SEER MEDICAL	HEALTHCARE COMPANY	Home-based diagnostic testing for epilepsy.	Medical technology for patient monitoring	AUSTRALIA
EUROPEAN SOCIETY OF RADIOLOGY	ASSOCIATION OF HEALTH PROFESSIONALS	An apolitical, non-profit organisation dedicated to strengthening and unifying European radiology, works closely with national radiological societies across Europe (would help disseminate the courses).	Educational resources, events, international alliances	AUSTRIA
SYNERGIA MEDICAL	HEALTHCARE COMPANY	Optoelectronics for neural stimulation therapies.	Neurostimulator	BELGIUM
SYNDESI THERAPEUTICS	HEALTHCARE COMPANY	Molecules which act through a novel mechanism to modulate synaptic transmission, for AD and pro-cognitive effects in epilepsy.	Anti-epileptic SV2A modulators	BELGIUM
IMAGILYS	ENTERPRISE IMAGING	Brain Simulation Software, Brain imaging techniques.	Imaging Services	BELGIUM
EPIHUNTER	HEALTHCARE COMPANY	Seizure monitoring.	Epilepsy Wireless Device	BELGIUM
BYTEFLIES	HEALTHCARE COMPANY	SENSSOR DOT, seizure monitoring.	Epilepsy Wireless Device	BELGIUM (+USA)
ICOMETRIX	HEALTHCARE COMPANY	Medical Imaging AI for NDDs including epilepsy, radiology Imaging with AI.	Imaging Services	BELGIUM (+USA)
7D SURGICAL	ENTERPRISE IMAGING	Computer Assisted Surgery.	Neurosurgery Technology	CANADA
CYPRUS INSTITUTE OF NEUROLOGY & GENETICS	RESEARCH INSTITUTE	Private research and academic center/ Specialized center for diagnosis and treatment of epileptic disorders.	Educational and research projects in epilepsy	CYPRUS
CENTER FOR APPLIED NEUROSCIENCE-UNIVERSITY OF CYPRUS	RESEARCH INSTITUTE	Researches in epilepsy, traumatic brain injury, healthy and pathological ageing exhibiting neuropsychological deficits.	Educational and research projects in epilepsy	CYPRUS
RONNA	RESEARCH INSTITUTE	Robotic Neuronavigation System	Neurosurgery Technology	CROATIA
EPIREC	EPILEPSY RESEARCH CENTRE	Works with international consortiums of leading epileptology workplaces, and also with the faculty of electrical engineering of CTU university.	Educational and research projects in epilepsy	CZECH REPUBLIC
EPIREC	EPILEPSY RESEARCH CENTRE	Works with international consortiums of leading epileptology workplaces, and also with the faculty of electrical engineering of CTU university.	Educational and research projects in epilepsy	CZECH REPUBLIC
ISARG	EPILEPSY RESEARCH CENTRE	Focused on EEG signal analysis of epileptic patients.	Educational and research projects in epilepsy	CZECH REPUBLIC
NATIONAL INSTITUTE OF MENTAL HEALTH, NIMH	PSYCHIATRIC RESEARCH CENTRE	Focused on EEG signal analysis of epileptic patients.	Educational and research projects in epilepsy	CZECH REPUBLIC

COMPANY	TYPE	REASON FOR INCLUSION	MAIN PRODUCT OR SERVICE	COUNTRY
STAPRO	HEALTHCARE COMPANY	Supplier of information systems and healthcare technologies.	Software and other services for hospitals	CZECH REPUBLIC
DEYMED	HEALTHCARE COMPANY	EEG systems	Software and other services for hospitals	CZECH REPUBLIC
UNEEG MEDICAL	HEALTHCARE COMPANY	Diabetes, Epilepsy, EAR-EEG.	Epilepsy implantable device	DENMARK
NEUROLABS	HEALTHCARE COMPANY	Nelli workflow and platform, AI and human expertise, without EEG.	Epilepsy Wireless Device	FINLAND
EUROBIOIMAGING	ENTERPRISE IMAGING	Offers open access to imaging technologies, training and data services in biological and biomedical imaging and AI.	Imaging Services	FINLAND
INCEPTO MEDICAL	ENTERPRISE IMAGING	Platform for radiologists to collaboratively establish diagnosis around imaging findings.	Educational resources, events, international alliances	FRANCE
DIGITAL MEDIA TECHNOLOGY IDMT	RESEARCH INSTITUTE	AI-based sensor system for the automatic detection of epileptic seizures in daily life.	Epilepsy Wireless Device	GERMANY
BRAINLAB	ENTERPRISE IMAGING	Computer Assisted Surgery and neosurgery products.	Neurosurgery Technology	GERMANY (+16)
COMPUMEDICS	ENTERPRISE IMAGING	Sleep diagnostics, neurology diagnostics (including epilepsy).	Medical technology for patient monitoring	GERMANY (+4)
INOMED	ENTERPRISE IMAGING	Computer Assisted Surgery and neosurgery equipment.	Neurosurgery Technology	GERMANY (+5)
NEUROLOGICAL INSTITUTE OF ATHENS	RESEARCH INSTITUTE	Researches in epilepsy, traumatic brain injury, healthy and pathological ageing exhibiting neuropsychological deficits.	Educational and research projects in epilepsy	GREECE
FORTH	RESEARCH INSTITUTE	Institute of computer science, experience in implementing national and European projects.	Educational and research projects, ICT technologies for medicine.	GREECE
TERRABLUE XT	HEALTHCARE COMPANY	ML/AI-based software for epilepsy.	Epilepsy Wireless Device	INDIA
ORTHOKEY	COMPUTER AIDED SURGERY	Computer Assisted Surgery.	Neurosurgery Technology	ITALY
WISE	HEALTHCARE COMPANY	Medical device for epilepsy surgeries.	Neurosurgery Technology	ITALY
MRSLAB- POLITECNICO MILANO	RESEARCH INSTITUTE	Intelligent planners for neurosurgical keyhole interventions, Pre-operative planning.	Neurosurgery Technology	ITALY
TEMA SINERGIE	ENTERPRISE IMAGING	Intelligent planners for neurosurgical keyhole interventions, Pre-operative planning.	Neurosurgery Technology	ITALY
EDEN2020 (ENHANCED DELIVERY ECOSYSTEM FOR NEUROSURGERY)	ENTERPRISE IMAGING	Delivering an integrated technology platform for minimally invasive neurosurgery.	Neurosurgery Technology	ITALY(+3)
NIGHTWATCH	HEALTHCARE COMPANY	Clinically proven system for detecting dangerous epileptic seizures during sleep	Epilepsy Wireless Device	NETHERLANDS
NORDIC NEURO LAB	HEALTHCARE COMPANY	fMRI Software, clinical and research post-processing, academy.	Imaging Services	NORWAY
SOCIEDADE PORTUGUESA DE NEUROPEDIATRÍA	ASSOCIATION OF HEALTH PROFESSIONALS	Directory of hospitals and epilepsy centers	Educational and research projects in epilepsy	PORTUGAL

COMPANY	TYPE	REASON FOR INCLUSION	MAIN PRODUCT OR SERVICE	COUNTRY
FIDMAG, RESEARCH FOUNDATION	RESEARCH INSTITUTE	Training and research in neuroimaging techniques.	Imaging Services	SPAIN
BARCELONA BETA BRAIN RESEARCH CENTER	RESEARCH INSTITUTE	Neuroimaging Platform.	Imaging Services	SPAIN
QUBIOTECH HEALTH INTELLIGENCE	ENTERPRISE IMAGING	Software for advanced processing and quantification of medical images.	Software and other services for hospitals	SPAIN
INTELIMED IBERICA	HEALTHCARE COMPANY	Software and hardware for EEG, BCI, functional neuroimaging distribuitors in Spain	Software and other services for hospitals	SPAIN
QMENTA	ENTERPRISE IMAGING	Tools for diagnostics, monitoring and decision support for clinicians in Alzheimer's, Multiple Sclerosis, Parkinson's, brain oncology, stroke, and neuropsychiatric diseases.	Imaging Services	SPAIN (+1)
MEDIMSIGHT	ENTERPRISE IMAGING	AI in neurology and marketplace.	Imaging Services	SPAIN
SECTRA	ENTERPRISE IMAGING	Find and synchronize points of interest in CT, MR and nuclear medicine images.	Imaging Services	SWEDEN (+15 COUNTRIES)
PROXIMIE	AR MEDICAL PLATFORM	Empowering clinicians to share their skills in real-time with AR (Could be applied for the VEP).	Surgery Technology	UK (+2)
APOLLO EEG	HEALTHCARE COMPANY	EEG for long term monitoring, epilepsy, wearable ambulatory EEG equipment solution.	Epilepsy Wireless Device	USA
ARTERYS	ENTERPRISE IMAGING	Marketplace for AI technologies.	Imaging Biometrics algorithms for brain tumors, cardio, lung, chest.	USA
CEFALY	HEALTHCARE COMPANY	Device for migraine.	Neurostimulator	USA
IMAGING BIOMETRICS/ IQ-AI LIMITED	HEALTHCARE COMPANY	Brain imaging software, tumor analysis	Imaging Services	USA
EMPATICA	HEALTHCARE COMPANY	Clinically proven system for detecting epileptic seizures.	Epilepsy Wireless Device	USA (+3 COUNTRIES)
MINDTECSTORE- NEORYTHM	HEALTHCARE COMPANY	Neurofeedback headband for controlling pain, stress, sleep quality and mental fitness.	Neurostimulator	USA (+3 COUNTRIES)
MONTERIS	COMPUTER AIDED SURGERY	Minimally Invasive Robotic Laser Thermotherapy, surgical tool and software used in brain surgery.	Neurosurgery Technology	USA (+1)
NEUROPACE	HEALTHCARE COMPANY	RNS system for epilepsy, diagnostic testing to identify the location of seizures	Epilepsy implantable device	USA
SOMNOMEDICS	HEALTHCARE COMPANY	24-hour long-term EEG 32 and epilepsy screening.	Medical technology for patient monitoring	USA
SOTERIXMEDICAL	ENTERPRISE IMAGING	Brain Simulation Software, brain targeting and individual subject customization.	Neurosurgery Technology	USA
VIREPA (VIRTUAL EPILEPSY ACADEMY) FROM ILAE	ASSOCIATION OF HEALTH PROFESSIONALS	Organisation for the dissemination of epilepsy knowledge, resources, specialists and online training (would help disseminate the courses).	Educational resources, events, international alliances	USA (+120)

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