Technology & market watch trends

NEUROSTIMULATION DEVICES AND THEIR ROLE IN THE INDUSTRIAL HEALTH SECTOR

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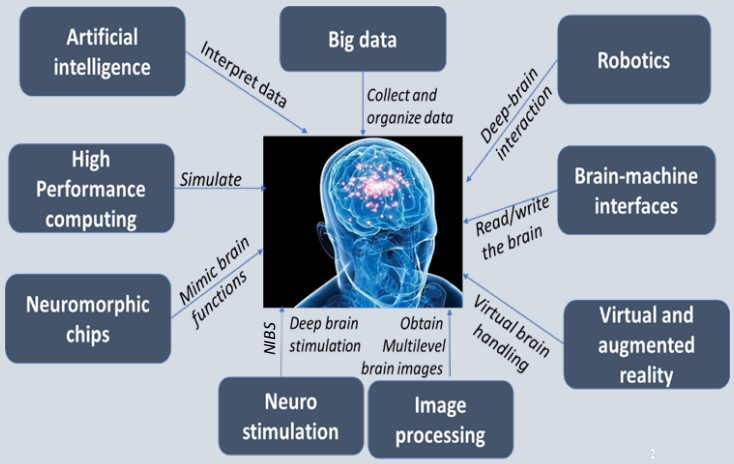
The report is available for all the HBP partners, and it is published in the HBP Innovation website.

Executive summary

PART 1: *Drivers of change*

Neurostimulation has evolved rapidly from a technological perspective. In the last decade this field has benefited from the ***convergence of multiple technologies*** as depicted in the next figure.



Today, several ***neurostimulation devices and techniques*** (implanted or not) have been approved by health regulatory bodies for clinical use, and others are still in the long approval process to reach the market in the next few years; many of them will be introduced by ***new technology-based start-ups*** closely related to research centres. However, the neurostimulation field is not yet mature, and many open research avenues will consolidate potential results only if the industrial and regulatory context evolves in the right direction balancing risks and innovation.

Despite some drawbacks and limitations, the expectations behind neurostimulation are growing very rapidly, making this field very relevant for developing a technology watch and market analysis report in the context of HBP and EBRAINS. From our point of view, there is a large set of opportunities to use EBRAINS services to speed-up the use of neurostimulation techniques and, vice versa, they will enhance brain data capture for feeding-up EBRAINS services working in the intersection of academic, industrial, and research markets.

Speaking in general terms, not only in the narrow domain of neurostimulation, the ***main drivers for sustaining the innovation role of the pharmaceutical industry today***, from our point of view, are as follows (from R&D and market perspective):

- Fast ***advances in fundamental life sciences***
- Convergence ***of several technologies***
- Advances in the ***development and use of sophisticated medical devices and equipment***.
- The ***digitization process***.

- The growing use of ***open innovation models***.
- The creation of very dynamic ***open innovation ecosystems***.

The case of ***neuroscience*** is especially relevant because it is at the crossroads of many convergent technologies where market opportunities for advanced products are exploding. Today, many companies (SMEs and large corporations) have started the development of ***disruptive medical devices*** able to apply artificial intelligence algorithms, manage large volume of data, create invasive or non-invasive brain-machine interfaces (BCI), supported when needed by specialised surgery robots, simulate brain regions with high-performance computing or neuromorphic processors (NP) for fast execution of deep neural networks, and present multilevel information to users through colourful images and videos by using virtual and augmented reality technologies.

The pharmaceutical industries are applying many of these enabling technologies to develop their own products and services for neural and mental disorders, independently or in combination with specific drugs, but ***they are not the only players in the field***. Today, many ICT companies (even the largest, FAGMA) have entered the health sector under the door of "***digital health***", and many others come from material science, robotics, sensors, etc. In the end, ***health is a huge vertical sector supported by horizontal enabling technologies where digitisation plays a key role***. One example of this trend is the growth of ***health wearables*** with multiple sensors to measure health conditions or new AI techniques where FAGMA companies and a myriad of start-ups are introducing new products partnering with research institutions due to the ***huge value of the health market***.

Pharmaceutical companies have invested enormous amounts of money in the last two decades in neurodegenerative diseases with no clear results. ***New drugs and clinical treatments for diseases such as Alzheimer's, Parkinson's, epilepsy, etc. did not fulfil the expectations created twenty years ago.*** This situation has stimulated the analysis and implementation of ***alternative innovative models driven by digital solutions and open innovation***. We see **five main general trends.**

1. The need to find more ***agile innovation models*** where big pharma companies are focusing their efforts on the clinical phases of drug development where the clinical experience is a must while opening the scope in pre-clinical phases to cooperate with other public and private actors.
2. The deep ***transformation of corporate research laboratories,*** which, in many cases, implied the size reduction and activity focus to concentrate in areas where positive results could be feasible and to compensate it with external alliances.
3. The increased number of ***targeted innovation partnerships*** established between pharmaceutical companies and ICT companies where both parties can access very specialised knowledge.

4. The interest in supporting the ***creation and funding of technology-based start-ups*** through specific programmes and merger and acquisition processes of some of them.
5. The search for **cost efficiency in the production, approval, distribution, and marketing of drugs** exerts a significant pressure on the industry and, in some developed countries, has become a greater expense for the final consumer.

It is perhaps too early to know how these ***market trends*** will be consolidated in this decade; however, our understanding is that health innovation will accelerate, and it requires faster strategic movements of actors and a better understanding of the impact of long-term trends.

PART 2: Neurostimulation techniques

Increased understanding of neurocircuitry and recent advances in neurotechnology and neuroimaging are factors contributing to the rapid increase in the use of ***neurostimulation therapies*** that involve the ***application of electrical or magnetic stimulation to drive neural function within a circuit to obtain a desired brain response***. The report reviewed the status of the neurostimulation techniques used today and future trends.

There are two main types: An **invasive** neurostimulation technique implies acting directly on one region of the brain, typically requires opening the skull and placing electrodes in specific regions (permanently or not); therefore, it involves neurosurgery. A **non-invasive** neurostimulation technique implies that stimulation is generated externally which for the most common techniques has fewer potential consequences on deep regions, but the technology should require more complexity to be efficient and the precision obtained is much lower compared to invasive techniques.

Invasive neurostimulation strategies use ***'neural implants'*** to obtain a controlled brain response and to deal with some specific neuro-disorders. Typically, they are made up of electrodes of some biocompatible materials inserted into the body. The electrodes contact the tissues that contain neurons and interact with neuronal populations in controlled ways through electric pulses. The established invasive neurostimulation strategies include **deep brain stimulation** (DBS), **motor cortex stimulation** (MCS), **responsive neurostimulation** (RNS), **spinal cord stimulation** (SCS), and **vagus nerve stimulation** (VNS).

There are many companies that have started the development of specific cortical implants (e.g., Neuralink, BlackRock Neurotech, Braingate). In some cases, they have got the designation of **a breakthrough device from the FDA** to start some trials with humans, while in other cases they are still waiting for approval, even the most sophisticated implanted devices are being tested on animals.

Current trends in implanted electrodes follow two complementary routes: 1) the possibility to connect the electrodes to many individual neurons and 2) the increase of the intelligence of the electrode to capture brain signals and stimulate tiny regions with higher precision.

The first route implies a ***deep miniaturisation of the electrodes and the increase of the number of active channels*** to connect from a few to thousands of neurons. This marks a transition from simple macroscale devices to complex, nanofabricated devices with more advanced capabilities. The second route to ***increase edge computing capabilities*** to complex electrodes will require integration with artificial intelligence or computational model-based programming and embedded wireless emitters and receivers to achieve optimal results.

In summary, invasive technologies offer the most precise approach for neurostimulation because electrodes are near neurons, and they could be implanted in deep regions of the brain. Risks associated with the use of these techniques have strongly conditioned their approval by health regulatory bodies and have also raised some ethical concerns. The risks of damage, inflammation, and infection due to direct contact with stimulation electrodes are infrequent but not completely overcome.

The problems derived from invasive techniques that require surgery to place implants in the brain have motivated the use of other ***minimally invasive techniques*** where risks are lower by placing the implant near the skin or by using heat instead of electric signals or by using brain vessels to place electrodes. The HIFU technique (High Intensity Focal Ultrasound) is a minimally invasive treatment in which thermal ablation is used to lesion abnormal tissue or tumours.

The approaches of the group of techniques known as ***non-invasive neurostimulation*** rely on electrical, magnetic, photonic, and acoustic or ultrasonic energy to influence nervous system activity, brain function, and behaviour from outside the human body. The main advantage of these methods relies on the reduction of risk (no surgery) and the possible use in non-clinical contexts which was offered the possibility to use neurostimulation to non-patients by opening the market to a huge number of consumers. The limitation comes from the difficulty of accessing deep brain regions with high precision and being able to stimulate specific (individual) neurons outside as implants can do.

Other non-invasive brain stimulation techniques with ***transcranial magnetic stimulation (TMS)*** or ***transcranial electrical stimulation (TES)*** have potential therapeutic applications in cognitive neuroscience, neurophysiology, psychiatry, and neurology.

TMS techniques are based on the application of a magnetic field that induces an electric field in the brain, via electromagnetic induction. In addition, ***Transcranial Static Magnetic Field Stimulation (tSMS)***, as a non-invasive modulation technique to reduce the excitability of the motor cortex.

Technologies such as stereotaxy and robotics in DBS systems, detection of abnormal electrocorticogram activity in responsive neurostimulation systems, and infrared navigation and special H coil in ***repetitive transcranial magnetic stimulation (rTMS)*** devices and protocols have been approved by the FDA for the treatment of medication-resistant depression, migraine, and obsessive-compulsive disorder.

For the first time, advanced tools for processing brain images are used to steer a specialised, high-dose magnetic pulse pattern of magnetic pulses to modulate neuronal activity. A specific type of TMS therapy called ***intermittent theta-burst stimulation (iTBS & cTBS)*** has been tested. It uses structural and functional magnetic resonance imaging information to inform a proprietary algorithm that identifies the optimal anatomic target for focused neurostimulation in people with MDD.

TES techniques include ***transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS),*** and ***transcranial random noise stimulation (tRNS).*** tDCS can be used to treat focal onset and generalised epilepsies in children and adult patients who are not surgical candidates.

Transcutaneous VNS (tVNS) is also a non-invasive technique intended to have effects like those of implanted VNS. It stimulates the auricular skin branch of the vagus nerve with much lower costs than the implanted VNS device. ***External trigeminal nerve stimulation (eTNS)*** is a non-invasive treatment for epilepsy like that of VNS, but the electrodes are placed non-invasively on both sides of the forehead.

The development of less invasive techniques is in a highly active phase with the creation of many start-ups moving disruptive research results to the market. Furthermore, some companies are combining two (or more) neurostimulation techniques that operate as stimulators independently or together on the same device.

All require the use of ***sophisticated machines to 'read the brain'*** (i.e., capture and measure brain activity) by measuring a variety of parameters of brain activity, from electrical activity to blood flow through a set of sensors located near the patient's head. The technological advances in sensors and integration that occurred in recent years were crucial in the development of a new generation of ***lightweight, non-invasive 'neurostimulation helmets'*** as portable devices.

The first generation of ***neurostimulation helmets*** (basically based on photobiomodulation, PBM) had low precision to stimulate a deep brain region. Today***, transcranial PBM (tPBM)*** and ***near-infrared (NIR) light*** are techniques applied to the forehead due to better penetration.

Some start-ups (e.g., *Kernel, gr8solutions*) have attracted the interest of investors, and it have obtained the approval from the FDA for conducting clinical trials for using its product for measuring anxiety and depression with a more sophisticated approach. Kernel is using time-domain near-infrared spectroscopy ***TD NIRS*** system (Time-Domain NIRS System) by using pulses of infrared light to track cortical

hemodynamics (lasers to track blood flow throughout the brain to measure changes in blood oxygenation levels).

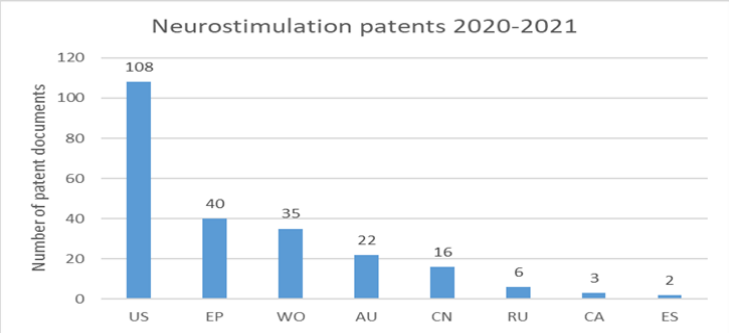
Another specific type of helmet-based device is the ***EEG neuro stimulation device***. State-of-the-art electroencephalogram (EEG) wearable technology relies on signal processing and machine learning tools to capture mainly temporal features that can be linked to a specific task. Relevant companies with advanced solutions in this field are BitBrain, Brainsway, BioElectronics, Cefaly Technologies, Galvani Bioelectronics, etc.

An advanced type to measure brain activity is the ***"Optically Pumped Magnetometer" (OPM).*** This system could be understood as an ***evolution of the magnetoencephalography (MEG)*** system as a device to expand the range of applications. The development and fabrication of OPMs exploit the quantum properties of alkali atoms to measure very small magnetic fields. The sensitivity of OPMs rivals that of superconducting devices used in conventional MEG systems, but OPMs do not require cryogenic cooling and can be placed on the scalp.

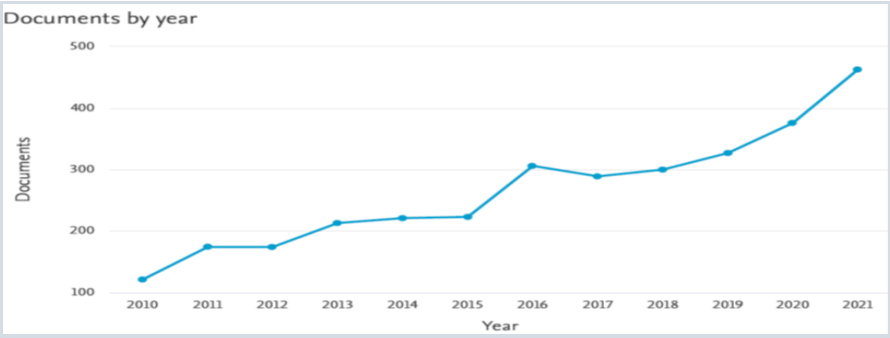
Disruptive ***breakthroughs for neurostimulation helmets*** will be driven by four complementary forces.

- Technical advances in sensors, lasers, imaging processes, etc. will offer better time and space resolution than the current generation of sensors can provide.
- Strong reduction in cost, space, weight, maintenance, etc. which will facilitate the adoption of these systems by a larger number of users.
- Time reduction in the approval of neurostimulation helmets as medical devices by regulatory bodies.
- Share of clinical practice and protocols in the application of these systems to a broader range of neurological diseases.

The technological review of this report does not address other fundamental research activities on neurostimulation that have not generated prototypes to be tested in clinical experiments (usually, with TRL above 5) through companies. However, progress during this decade will accelerate in some selected areas for neural sensors, where both patents and articles have grown very fast and strongly dominated by the US. The next figure shows the patents filed in the EPO in 2020-2021.



The search of articles on neurostimulation ins Scopus database shows the data of the next figure with an steady growth in the period 2010-2021.



The five areas where disruptions can occur during this decade are as follows:

Electroceuticals. There are many companies with very advanced cortical implants in several stages of development. To offer a general overview of these fields, this report has focused on three companies with very innovative systems close to commercialisation*: Neuralink, Blackrock Neurotech*, and *BrainGate*.

Minimally invasive implants. Researchers were looking for minimally invasive approaches to implant devices using the blood vessels by avoiding open brain surgery. *Synchron* has developed an endovascular brain computer interface that uses blood vessels. Its product***, Stentrode***, has received FDA approval as "breakthrough device designation'.

Micromagnetic stimulation (μMS). This is a promising alternative to the use of electrodes because stimulation with magnetic fields does not require an electrochemical interface and therefore can be scaled down in. Some micromagnetic devices / arrays, such as microcoils (μcoils) and spintronic nanodevices, may be able to stimulate with much larger amplitudes and tissue volumes than the same-sized electrodes.

Photobiomodulation. VieLight has developed a less invasive treatment modality for PBM, intranasal delivery of light delivery. Light can penetrate through the scalp, skull, and brain to depths of 4 cm or more. Furthermore, NIR light can also diffuse intranasally through the nasal channel. *Openwater Technology* is developing a non-invasive, low-cost, and portable technology allowing for broader applications. It uses highly coherent, near-infrared, laser light to measure blood flow inside the human body. Its technology enables to detect this laser light about one million times more efficiently than is possible with traditional approaches.

Brain biomarkers. Biomarkers in existing brain stimulation devices and systems are of two types: ***electrophysiological*** and ***neurochemical***. Although neurochemical biomarkers indicate the state of neurotransmitters, electrophysiological biomarkers (e.g., action potential (AP) as well as local field potential (LFP)) provide electrical activity of the brain. The use of ***neural oscillations*** (repetitive electrical activity generated spontaneously or in response to stimuli by neurons) has been proposed as a more promising brain biomarker. In 2021, two start-ups, *Ksana Health* and *Thymia,* in the field of ***digital biomarkers for mental health*** closed their first VC investment rounds. *Cumulus Neuroscience* and *Healios* are also in the field.

To finish this analysis, the constraints found with invasive techniques are the following:

- Infections and other dangers to brain integrity, derived from the necessary brain surgery (which could require sophisticated robotics equipment for precise placement).
- The formation of connective tissue in the brain that ends up disabling the connection and then, to reduce the operation time and the need for surgery repair.
- The possible decrease of some cognitive functions, if implants are in brain areas with effects not totally understood on other intensively interconnected brain regions.
- The difficulty in creating software that speeds up brain/machine communication, even more so when the execution of AI algorithms should be done in external systems.
- The possibility of arising (some patients with neuroprostheses have already complained about it), the feeling of hybrid or shared agency (not completely intentional),
- Personality changes due to stimulation of certain brain areas and
- The possibility of mental hacking.

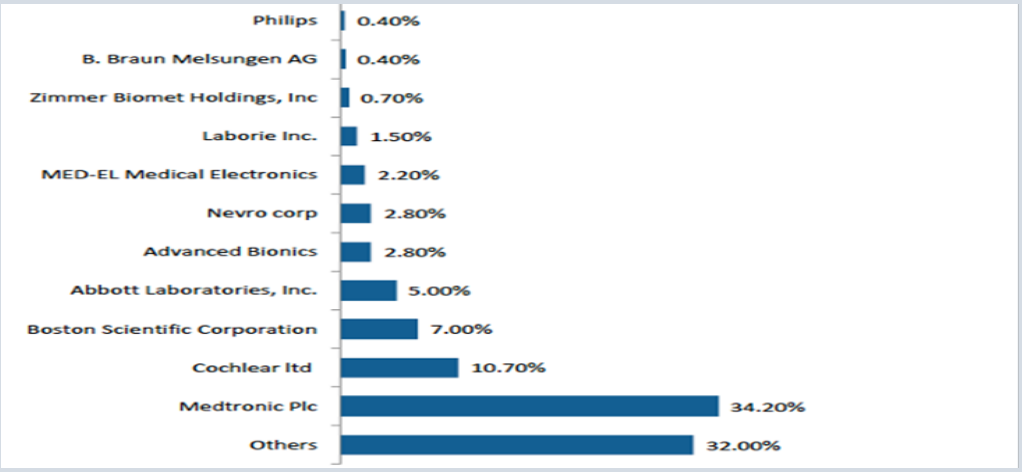
Due to all these constraints, it is obvious that regulatory agencies have adopted a very restrictive strategy in the approval of trials and the market introduction of these invasive brain devices.

PART 3: Market structure and regulation

The structure of the neurostimulation market can be defined from four complementary dimensions which globally provide the position of companies and countries. The dimensions are as follows:

- ***Product Type*** (Spinal Cord Stimulators, Deep Brain Stimulators, Sacral Nerve Stimulators, Vagus Nerve Stimulators, Gastric Electric Stimulators)
- ***Application Type*** (Pain Management, Epilepsy, Essential Tremor, Urinary and Fecal Incontinence, Depression, Dystonia, Gastroparesis, Parkinson's Disease, Others)
- ***Type*** (Implantable, External)
- ***End Use*** (Hospitals/Clinics, Cognitive Care Centres, Research Institutes, Others)

Aa a global figure, the world ***Neurostimulation Devices market*** was valued at USD 4.98 Billion in 2018 and is expected to reach USD 12.7 Billion by the year 2026, at a CAGR of 12.4 %. According to a recent report of Report Ocean Pvt. Ltd, the ***CR4*** (ratio of the four major players of the market) *is ~56.90%: Medtronic plc (34.20%); Cochlear ltd (10.70%); Boston Scientific Corporation (7.00%),* and *Abbott Laboratories, Inc. (5.00%).*

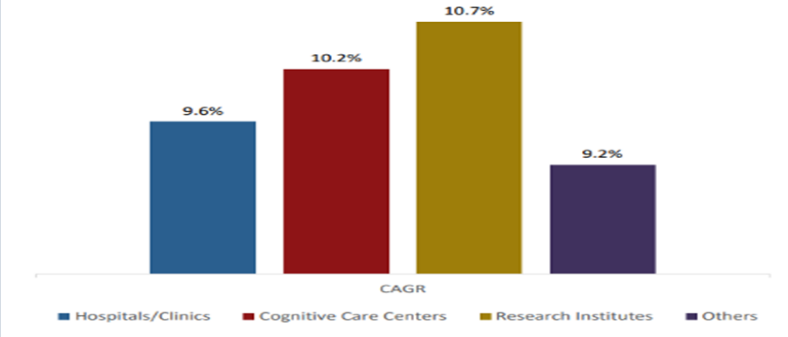


The large number of **neurostimulation-based start-ups** described in the report has not obtained a large market quota and, probably, some of them will be purchased by large players. Some promising high-growth start-ups identified in the report with products in the market are: Neuropace, ElectroCore, LivaNova, NeuroOne Medical Technologies, Neuvotion, Xanastim, Koninklijke Philips, Braun Melsungen and Zimmer Biomet Holdings, CERCA Magnetics, Nevro, Advanced Bionics, Med-El Medical Electronics. Annex 2 includes a list of all the identified companies.

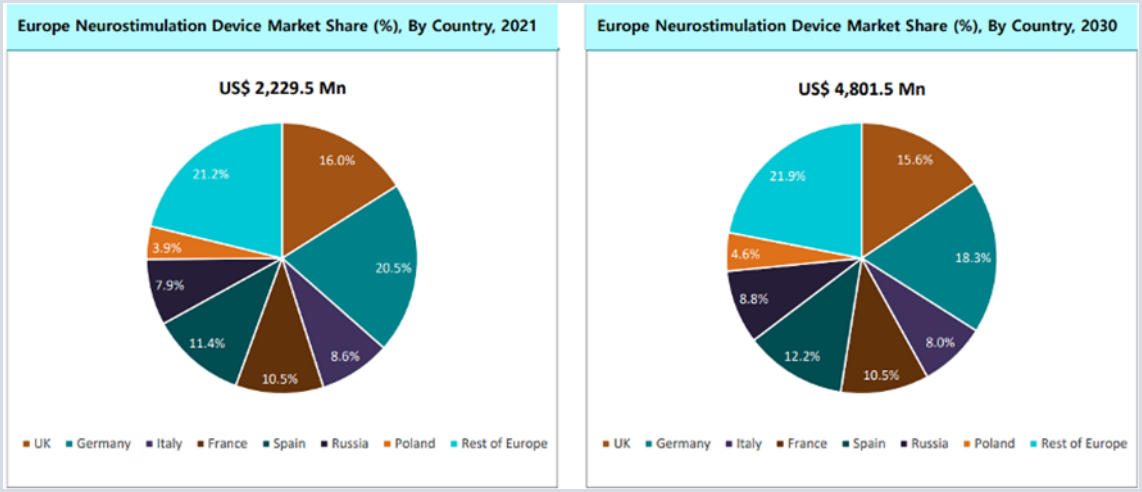
Key data extracted from the Ocean Market Report:

- Chronic pain application accounts for the market for highest revenue in the neurostimulation devices, with a predicted value of 6850.9 US dollars by 2030.
- The increasing number of spinal cord problems will boost the market for spinal cord stimulation devices in the coming years.
- The neurostimulation device market for Parkinson's disease segment is expected to grow from 885.3 US$ Mn in 2021 to 2063.3 US$ Mn in 2030 at a CAGR of 10% for the forecast period of 2017 to 2030.
- The neurostimulation devices market for the Epilepsy and Depression segments is also expected to grow from 546.1 US$ Mn in 2021 to 1299.3 US$ Mn in 2030 at a CAGR of 10.2% and from 295.9 US$ Mn in 2021 to 721.4 US$ Mn in 2030 at a CAGR of 10.5% for the forecast period of 2017 to 2030, respectively, by the increasing prevalence of the disease worldwide.

By end users, the expected growth evolution 2022-2030 (from Ocean Report) in the use of neurostimulation techniques is shown in the next figure. Notice that research institutes are growing more than 10%, which is an indicator that research will be very active.



The *European Neurostimulation market* was valued at approximately 2,045.8 US$ Mn in 2022 for Implantable Device and is expected to reach by 2030 (a CAGR of 9.3% from 2017 through 2030). In terms of countries the next figure shows the evolution of the European market where UK and Germany will keep a very strong position.



Some key data from the European market:

- Germany, France, the UK, and Spain have a large proportion of neurostimulation market revenue given that they are among the largest EU countries.
- The UK market is witnessing a CAGR of 7.3% during (2017 - 2030).
- From the 2017 to 2030 period, the Germany and Italy markets are anticipated to grow at a CAGR of 6.3% and 6,7%, respectively.
- Two countries leading the growth in the European neurostimulation market are France and Spain, which are expected to post CAGRs of 9.1% and 9.8% from 2017 to 2030, respectively.
- Poland's market of neurostimulation devices is projected to grow with the highest CAGR of 10.9%.

The authors have elaborated on a ***group of SWOTS on different neurostimulation techniques*** (deep brain stimulation, chronic subthreshold cortical stimulation, responsive neurostimulation system, spinal cord stimulation, and Vagus Nerve Stimulation) to understand the specificities of the market on neurostimulation and the way companies can take advantage of opportunities. The next figure shows the general SWOT which summarizes the situation found today from our point of view.

The ***detailed SWOT analysis*** should serve as a basis for defining governmental and institutional policies at the European level and, more specifically, in the context of EBRAINS, the possible evolution of its services to address neurostimulation requirements.

There are ***many factors that hinder the growth of the neuromodulation device market***. The major constraint for market growth is the ***high investment in capital needed***. The high investment in neuromodulation devices is creating a problem for the new key players, mainly technology-based start-ups, and it has become a major restraint for the market. In addition to that, the use of neuromodulation devices requires ***highly skilled professionals***, and the lack of trained professionals is a constraint for the market of neuromodulation devices. This is one of the areas where the ***creation of a targeted open innovation ecosystem can accelerate innovation***.

A singular aspect of health innovation (brain innovation has also inherited this challenge) that collides with the usual start-up methodology used in other domains like ICT is the ***impossibility of producing a Minimum Viable Product (MVP) in the short-term***, to test it in the market (with exploratory users), and then to refine it by adding additional features. The only area where the situation is like ICT is the development of ***non-invasive mental health products based on wearables*** if they are not considered as medical devices.

Efforts made in the United States with the ***OpenMind Consortium*** to build up a targeted ecosystem on neurotechnologies. This is not the case in Europe where ecosystems have a broader target (e.g., digital health) and are not only focused on neuroscience. These European ecosystems are distributed nature and use some of the EU programmes such as ***EIT Health*** or some ***Digital Innovation Hubs (DIH)*** focused on health.

Closely related to neurostimulation market evolution is the regulatory issue. Then the ***neurostimulation systems and devices described in this report require the approval of regulatory agencies as 'medical devices'.*** To get the approval of a new medical device is a lengthy process to ensure that it is safe for patients, and it produces clear cost-benefits with respect to pre-existent methods. There are two approaches to regulate medical technologies.

- ***Pre-market evaluations***, which cover safety and performance aspects. An additional demonstration of efficacy may be required depending on the authorization system and the risk of the device.
- ***Post-market evaluation*** systems that also aim to consider effectiveness in the usage context, cost effectiveness, and other domains potentially relevant for coverage decision making.

Unfortunately, the wide range of products under the general category of 'medical device' precludes the use of a single regulation to obtain the highest level of flexibility in launching trials. ***The risk-based level (from low risk to high risk) used in the EU directives should be applied differently considering the primary objective of the medical device: diagnostic or therapeutic use.*** Then, three types of medical device types are identified for each use. Note that according to this taxonomy, ***neurostimulator medical devices are considered as high-risk devices***.

Due to scientific and technological advances and the social perception of health risks, the regulations for medical devices cannot be static. The USA through the ***FDA*** (Food and Drug Administration) and the European Union through the ***EMA*** (European Medical Agency) have approved ***specific regulatory procedures to approve a new medical device for clinical use.*** Both the FDA and the EMA have recently started the modification of the procedures to cope with new requirements: speed-up procedures for breakthrough devices, better connections to other regulated areas like artificial intelligence, electromagnetic or nuclear radiation, etc.

One of the key issues in HBP and the services that EBRAINS is related to the capture of detailed information about the human brain. Specifically, many of the activities associated with capturing detailed information on human brain microstructure or brain activity are related to the use of microscopy and brain imaging (MRI, MEG, PET, etc.). These are techniques that cannot be considered neurostimulation techniques (unless combined with other techniques) because they do not act directly on brain activity but obtain brain data that could be useful in providing advances in neurostimulation devices.

An issue related to the ethical use of the neurostimulation technique is the ***potential dual use***. The launching in 2018 of the N3 (Next Generation Nonsurgical Neurotechnology) programme by DARPA (The Defense Research Agency of the USA) aims to develop a safe and portable neural interface system capable of reading from and writing to multiple points of the brain at once without the requirement for surgery. DARPA funded projects like ***BrainStorm*** and ***MOANA*** have achieved disruptive results.

Based on a ***PESTLE analysis*** on the impact of regulation, two ***simplified scenarios*** (named 'optimistic' and "pessimistic") on the evolution of neuro-rights seem feasible towards the 2030 horizon:

Scenario 1: Optimistic. Neuro-rights legislation and regulations are adopted in all advanced countries, institutions and companies, and citizens are aware of its need and consequences. The driving forces are.

- Growing awareness of the need to protect individual minds from abuses in a fully digitised society.
- The adoption of technological advances is well balanced with the precautionary principles adopted by society.
- Citizens are confident in the use of neurostimulation as medical devices.
- Companies (both large and SMEs) have a stable scenario to adopt their decisions.

Scenario 2: Pessimistic. Patched scenario with fragmented social views of consequences and lack of a shared vision on the need to adopt common regulatory frameworks. The driving forces are:

- No agreement on the consequences of the regulation of neuro-rights creates a very fragmented legislative framework with a national bias constrained by national interests.
- Reluctance to adopt neurostimulation devices in society due to a poor understanding of effects and effective control.
- Very limited adoption of neurorights in public institutions.

PART 4. Neurostimulation in HBP-EBRAINS context

Some HBP research can boost the use of neurostimulation by providing information to medical areas such as neurosurgery. Specifically, four research activities carried out in HBP have been identified for this purpose, and a European research infrastructure is under construction.

Neuromorphic computing.

The relevance of neuromorphic computing for neurostimulation comes from its ***potential use in the development of a new generation of smart micro brain implants with embedded processing capabilities***. The Neuromorphic Processor (NP) approach can be very useful when it is necessary to move intelligence 'to the edge" (in this case to the brain implant itself). This could be the case of smart medical devices with NP capabilities. ***The main advantages of neuromorphic chips are the low energy consumption and the efficient execution of deep learning algorithms.*** As implanted devices for closed-loop neurostimulation required more processing capabilities and less consumption of energy, the use of NPs is a natural approach.

The ***neuromorphic computing platform of the HBP*** allows users to simulate experiments on two different systems: ***BrainScaleS-2*** and ***SpiNNaker-2***. The two NP

systems developed in the HBP context (and specifically novel chip architectures could be used for developing very advanced smart brain devices. Miniaturization and energy harvesting from the human body is still a challenge to see these disruptive devices very soon on the market. Novel materials for improved performance are expected to emerge in the near future to enable higher computational capability within smaller sizes. Organic materials hold great promise to merge advanced computation with extreme miniaturization.

Perturbational Complexity Index (PCI).

Measures of brain complexity have recently begun to move from the realm of theoretical neuroscience into the field of experimental neurophysiology to study differences between global brain states, from wakefulness to sleep and anesthesia. Additionally, measures of brain complexity have been considered useful paraclinical indices for assessing consciousness at the bedside of brain-injured patients.

This approach is motivated by the general theoretical principle that a brain's capacity for conscious experience is based on its ability to integrate information. In this view, a key mechanism of consciousness is the ability of different neural elements to engage in ***complex patterns of causal interactions*** such that the whole system generates information beyond and above its parts. Then, the use of ***controlled 'perturbations' by using TMS of specific areas of the brain and the received processing of the EEG responses can be used as a method to assess the level of consciousness.***

The ***PCI is an index developed in HBP that measures the algorithmic complexity of electroencephalographic (EEG) responses to transcranial magnetic stimulation (TMS),*** a method that has been validated in conditions such as comma and other critical conditions related to the brain response after injury.

HBP researchers have built models of the brain networks associated with different states of consciousness, systematically connecting the microlevel of nerve cells, the intermediate scale of neuronal circuits, and the whole brain scale. The first two states that were modelled are wakefulness and slow-wave sleep. The theorists used high-quality data to build network models from the ground up. They were able to create an ***experimental set to test PCI with patients***.

Virtual Epileptic Patient (VEP).

An important proportion of epilepsy patients, pharmacological treatment is not effective, and surgical intervention is the only option. HBP scientists from France have developed personalised brain models to identify areas where seizures emerge in a patient's brain. The ***EBRAINS human brain atlas*** built by the HBP now serves to further enhance accuracy. The model uses structural data of individual patients (mainly from MRI, EEG, SEEG) and mathematical modelling of brain dynamics. The team behind this innovation is integrated by HBP medical doctors and engineers who have been working on it for the last decade, which is currently in a clinical trial in around 400 patients in France.

The relevance of VEP for the field of neurostimulation is not direct because it is not a technique developed for neurostimulation. VEP is used as a tool to have more precise epilepsy surgery by using a virtual brain model. However, we see its usefulness to deep brain stimulation to help in the insertion of brain implants in the right place to deal with any type of seizure.

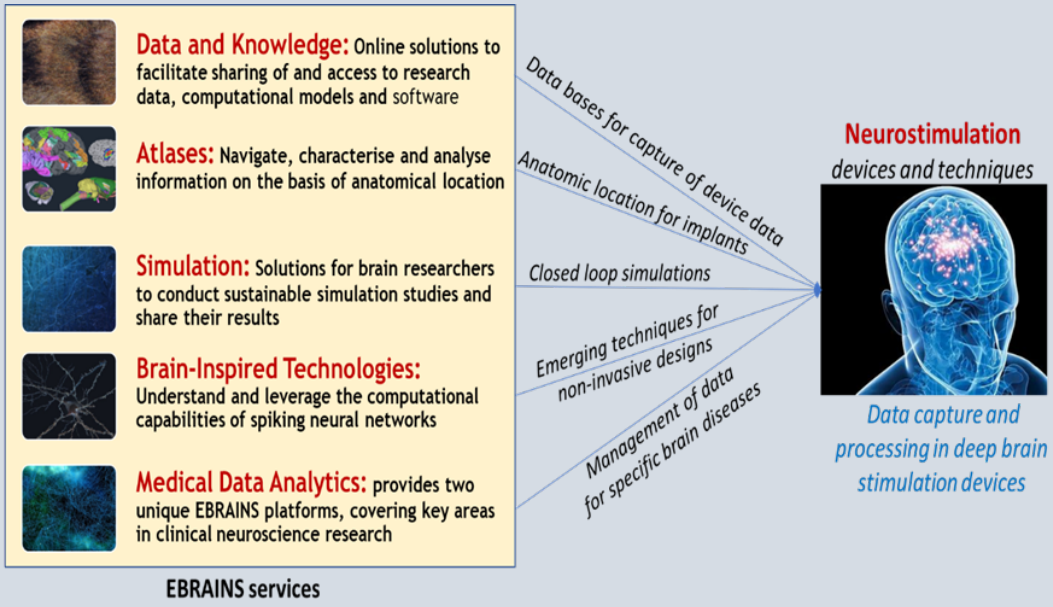
Photoneuromodulation (PNM).

A study led by researchers from IBEC and IDIBAPS achieved, for the first time, the ***control of brain state transitions using a molecule that is sensitive to light, named PAI.*** The results could lead to the development of photomodulated drugs for the treatment of brain lesions or diseases such as depression, bipolar disorders, or Parkinson's or Alzheimer's diseases. PAI is light responsive and allows for spatiotemporally controlled modulation of brain neurons, binding and controlling the activity of muscarinic cholinergic receptors, key receptors on neuronal interaction and communication.

Relevance for the field of neurostimulation. The drug could reach one area of the brain using other invasive or minimally invasive techniques (eg, through the brain vessels). Once placed in the right place in the brain is ready to be light activated externally.

EBRAINS

HBP was able to push the creation of a ***European Brain Research Infrastructure, EBRAINS***, included in 2020 in the European roadmap to be fully operational in 2023. It provides a set of ***services to advance brain research and innovation by offering them to academics, clinical and industrial communities***. Not all EBRAINS services have the same relevance with respect to neurostimulation.



The areas of ***relationship between neurostimulation and the types of EBRAINS services*** are described as follows:

1. ***Relationships with the data and knowledge services***. EBRAINS can provide support or manage databases of information captured by neurostimulation devices. Data from several devices can be curated and shared.
2. **Relationships with atlases and navigation services**. anatomical support for intelligent implant and multilevel navigation with implanted electrodes.
3. ***Relationships with Simulation Services:*** Closed-loop simulations platforms and application for neurostimulation/neuromodulation surgery planning.
4. ***Relationships with brain-inspired technologies***: emerging techniques for non-invasive designs and robotic platforms for the placement of neurostimulation devices.
5. ***Relationships with medical data analysis***. Management of data captured in deep brain stimulation and their integration in databases for specific diseases, interoperability platforms, and proposals for industry standards.

The report includes detailed tables to see the relationships of any neurostimulation technique with HBP and EBRAINS activities.

PART 5. Conclusions and future work

This report has presented a ***global view of the current and future evolution of neurostimulation technologies and the associated market*** with an eye on the possible interaction with the results of the HBP and EBRAINS services.

R&D will continue for many years because a better understanding of the therapeutic mechanisms of neurostimulation for various neurologic disorders is required, allowing the discovery of biomarker feedback signals that effectively inform the closed-loop system, to extend these approaches in clinical neurology services.

The development of neurostimulation techniques is based on and driven not only by theoretical and fundamental research but also by technological advances. Today, we are surfing a wave of ***technology convergence*** when the combination of techniques such as artificial intelligence, nanoelectronics, new biomaterials, low energy consumption for wireless communications, and smart sensors will offer additional neurostimulation functionalities that were unthinkable only a few years ago. An improved understanding of epileptogenesis, as well as patient and clinician demands, has resulted in the development of technology.

This document has also discussed the ***structure and evolution of the neurostimulation market***, where high CAGR are expected. The relative reduction of investments from large pharmaceutical companies in the last ten years (mainly due to lack of success of new drugs for neurodegenerative diseases) is being compensated by consolidated ICT companies (even the largest ones) and a numerous group of ***brain-technology start-ups with disruptive products*** which have attracted the interest of venture capital and pharmaceutical companies.

The neurostimulation field is very dynamic, and new scientific and technological breakthroughs, patents, products, start-ups, and clinical use will rapidly evolve. Then, ***it will be necessary to conduct regular updates of the present report.***

Even when start-ups face regulatory barriers to approve their medical devices***, we are confident that many of the start-ups presented in this report will consolidate in the future***. It will not be an easy and fast way and it will take some years to obtain commercial profits. Fortunately, VC is betting for them.

From the perspective of HBP and EBRAINS, we propose conducting ***three activities*** related to the field of neurostimulation:

- To launch a more ***comprehensive market analysis focused in Europe*** on the areas of neurostimulation and neuromodulation ***supported by a survey to previous companies in the field***. The emphasis on start-ups will continue and complete the work carried out in 2021.
- To make a ***specific patent analysis*** on several sub-areas that can condition the emergence of future breakthroughs.
- To ***analyse the current regulation on medical devices and clinical trials***, we propose some changes to accelerate the introduction in clinical practice.

PART 1

1. Context and objectives of the report

Within the innovation activities developed in the ***Human Brain Project (HBP)*** (https://www.humanbrainproject.eu/en/) and, specifically during its ***phase SGA3*** (2020-2023), the UPM Innovation team is developing a set of technical and market reports to analyse the evolution of critical areas for the HBP activities.

The underlying interest of this activity is to provide *'business intelligence'* support for decision making at a crucial moment when the project is approaching its end, to facilitate the exploitation of results and to increase their impact in society. This phase of SGA3 is happening in a moment where technology convergence driven by full digitisation is opening new alternatives for intelligent brain data capture and processing with huge potential for disruptive neuro products and services.

Furthermore, **EBRAINS** (https://ebrains.eu/) is emerging as a powerful ***European Brain Research Infrastructure*** where many of the tools, methods, and datasets generated in HBP since 2013 are being integrated to support the international scientific and technological community as a new research infrastructure incorporated into the ***ESFRI roadmap*** (https://www.esfri.eu/esfri-roadmap) since July 2021. Then the success of EBRAINS will depend on the way that potential users were able to accelerate their research using the EBRAINS services.

For the strategic evolution of EBRAINS, three main market segments were identified: ***academic markets*** populated by researchers where EBRAINS services can help them to accelerate research activities in the area of neuroscience, ***industrial markets*** where small and large industries could use EBRAINS services to develop their own products and services focused on neurotechnologies, and the ***clinical market*** where neurology services located in hospitals and health services can incorporate standalone EBRAINS services or integrated into commercial products to improve their clinical practice.

Other sectors also have the capacity to contribute to this development, such as non-profit organisations (foundations, biobanks), which have both networks of researchers in different neurological specialties, as well as medical equipment providers to promote and accelerate collaborative studies; with the vision of bringing these innovations closer to the health sector and its patients.

As a brief aside, there are multiple definitions of neurostimulation, understood as ***the application of electric current in different parameters, through electrodes to activate or inhibit the function of specific neuronal groups*** (Krames et al, 2018). It is mainly performed with devices that use batteries and electrodes to provide electrical or magnetic forces through the scalp to certain regions of the brain (Fitz

and Reiner, 2015), thus, it may involve both invasive and non-invasive technologies (Agrawal et al, 2020).

Neuromodulation is defined by the International Neuromodulation Society (INS) as: ***"The alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body"***. Authors suggest that neuromodulation can be used to refer to neurostimulation (Sakas et al, 2007, mentioned by Krames et al, 2018).

This report is focused on ***neurostimulation***[1], which is one of the fastest growing subsectors of the industrial market, which became very relevant for the pharmaceutical industry and, more specifically, for those pharmaceutical companies with marketed medical devices and services related to neurology.

Box 1.

"The high prevalence of road accidents resulting in harmful traumatic injury has significantly increased the cases of spinal cord injuries resulting in dysfunctioning of the nervous system. According to the Global Health Data Exchange, in 2017 the combined global incidence of neurological disorders and chronic pain was 3.97 billion, which includes several medical conditions such as Alzheimer's disease and other dementias, low back pain, stroke, traumatic brain injury, migraine, epilepsy, multiple sclerosis, spinal cord injury, and Parkinson's disease". ***Source: Businesswire (2019)***

The selection of neurostimulation for this study was supported by two main reasons: From the technology side, it is clearly a medical area (e.g. the use of deep brain stimulation for neurodiseases) where the use of emerging technologies can offer benefits for many neurodegenerative diseases, mainly those involving movement disorders and seizures such as Parkinson and epilepsy, and many very innovative solutions are leaving out from research labs; from the market perspective, it is one of the highest growth medical areas for this decade with a fast evolution of players in the sector.

This does not mean that funding for neural disorders has been very high until now (see Box 2). With a 7% of the total R&D funding in health, is much lower than oncology or respiratory diseases where in the last decade many therapeutic advances entered clinical practice. However, we envisage a fast change in these figures due to the readiness of technology convergence, as will be presented in this report.

Box 2.

"Brain diseases are the greatest contributor to the global burden of diseases, comparable to the impact of cardiovascular diseases. The World Health Organisation (WHO) estimates that 700 million cases of mental and neurological disorders (MNDs) are reported annually—accounting for 13 per cent of the global disease burden and expected to double by 2030. And yet it's one of the least funded therapy areas. A

[1] Although there is still a debate in the literature about the employability and scope of these terms, as well as a lack of standardisation in terms of classification (Kumar et al, 2015), we will refer in a practical way in this report as neurostimulation.

report from ABPI (Association of the British Pharmaceutical Industry) suggests that 38 per cent of global R&D is invested in oncology and immuno-oncology, whereas other areas, such as respiratory (9.3%) and nervous system (7%) attracted less funding." (Read more)

In Bell (2020), the venture funding, in billions, by therapeutic area is shown from 2009 to 2018. Even if oncology is the most relevant, the second is neurology with a clear increase in the last three years. Obviously, it is fuelling-up the creation and scale-up of many start-ups in the field, as described later in this report.

Neurostimulation has evolved rapidly from a technological perspective driven by the use of new generations of probe materials and dramatic improvements in brain signal processing. As Vebraité and Hanein (2021) recently expressed, *"the field of neurostimulation has evolved over the last few decades from a crude, low resolution approach to a highly sophisticated methodology that involves the use of state-of-the-art technologies".*

In the last decade this field has benefited from the ***convergence of multiple technologies*** such as microelectronics and nanoelectronics, new materials (e.g., biomaterials and bidimensional materials), high-speed wireless communication and energy transfer integrated in advanced invasive implants and non-invasive sensors.

Today, several ***neurostimulation devices*** (implanted or not) have been approved by health regulatory bodies for clinical use, and others are still on the long approval process to reach the market in the next few years; many of them will be introduced by new technology-based start-ups closely related to research centres to exploit disruptive scientific ideas.

Nevertheless, the neurostimulation field is not yet mature, and many open research avenues will consolidate results only if the industrial and regulatory context evolves in the right direction. For example, the ***lack of industry standards***, the continuous ***testing of new materials*** with better performance but also higher costs, and ***innovative packaging techniques for implanted devices*** constitute another challenge for market consolidation.

Then many research labs, start-ups, and large companies should work in a very dynamic neurostimulation market field with very high innovation rates; Europe is one of the most active ones, as described later in this report, but innovation in neurostimulation became a global issue.

Even when the number of available neurostimulation devices and techniques used in clinical practice is still limited, we postulated that they could benefit from innovative and complementary techniques developed in HBP and from their future integration into EBRAINS services. To realise these possibilities, a deeper interaction between neurostimulation companies and HBP researchers is needed.

Despite those drawbacks and limitations, the expectations behind neurostimulation are growing very rapidly, making this field very relevant for a technology watch and

market analysis report in the context of HBP and EBRAINS. From our point of view, there is a large set of opportunities to use EBRAINS services to speed-up the use of neurostimulation techniques and, vice versa, they will enhance brain data capture for feeding-up EBRAINS services working in the intersection of academic, industrial, and research markets.

The structure of the report is as follows.

- Section 2 will describe general trends in the evolution of the pharmaceutical industry as an answer to its main challenges.
- Section 3 will provide, starting with some definitions, a general view of the most relevant neurostimulation technologies and the way to integrate them with other emerging technologies.
- Section 4 will describe the current neurostimulation market and estimates of its potential evolution during this decade.
- Section 5 will address the relationship between neurostimulation technologies and the market, and the services provided by EBRAINS to understand the role that this European research infrastructure could play in the future in the field of neurostimulation.
- Section 6 will extract a set of conclusions and recommendations for future work.
- Finally, references used in writing the report are compiled in the last section.
- A glossary of terms is included in Appendix 1 and the list of identified technology-based start-ups on neurostimulation is in Appendix 2.

1.2 Evolution of the biomedical industry

1.2.1 Roots of the current situation

Mainly in advanced countries, consistent data have demonstrated that the evolution of demography and life expectancy is clearly related to health expenditure (see figure 1 with data from 1970 to 2015 for several countries).

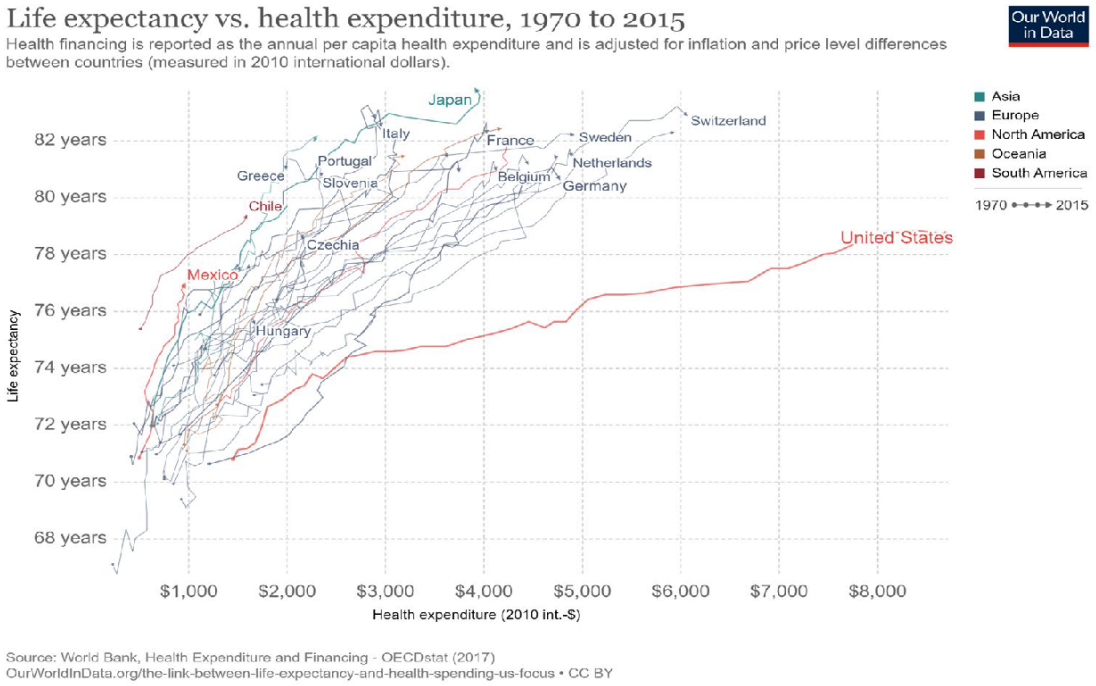


Figure 1. Life expectancy vs. health expenditure 1970-2015 (source: World Bank)

Even when other factors could also explain the increase in life expectancy like food safety, wider access to drinkable water and better housing which globally affects human health, the consolidation of health systems innovation is one of the most relevant ones.

Historically, the ***pharmaceutical industry*** has been one of the key actors in the health innovation process. Both large pharmaceutical companies and very innovative technology-based start-ups, in many cases working with incumbent big pharma companies, have introduced an increasing number of drugs, products, and services in many clinical areas. For many years, this sector has been instrumental in stimulating R&D in health.

This situation has provoked pressure on public administrations to increase efforts on health research with additional funding linked to powerful research and innovation programmes like Horizon Europe 2021-2027 in the EU and other large global initiatives.

Pharmaceutical companies make up a large part of global investment in health R&D. The largest 23 pharmaceutical companies (informally termed as "*Big Pharma*") invested about €100bn in R&D in 2017/18, of a total of €140bn invested by the top 400 pharma companies (see EU R&D Scoreboard). This might be estimated as, at

least, one third of global health R&D expenditure. Therefore, it can substantially shape health research priorities in all countries (CWTS, 2021).

Figure 2 lists the ranking of the 20 most relevant pharmaceutical companies in their R&D investments. We could imagine that this huge effort in one year will result in successful marketed products. Reality is much harder because market success depends on many other factors, as has happened in several clinical areas.

2020 PHARMA 50 RANK - R&D (% OF REVENUE)	COMPANY	R&D SPEND	R&D AS % OF REVENUE
1	**Incyte**	$2,215,942,000	83.10%
2	**Regeneron Pharmaceuticals**	$2,735,000,000	32.19%
3	**Biogen**	$3,990,900,000	29.68%
4	**Vertex Pharmaceuticals**	$1,830,000,000	29.49%
5	**UCB**	$1,767,718,200	29.00%
6	**Merck**	$13,558,000,000	28.25%
7	**Bristol Myers Squibb**	$11,143,000,000	26.21%
8	**H. Lundbeck**	$694,954,128	25.72%
9	**Eli Lilly**	$6,086,000,000	24.80%
10	**Roche Pharmaceuticals** (division of Roche Group)	$12,164,234,743	24.57%
11	**Daiichi Sankyo**	$2,129,172,130	23.62%
12	**AstraZeneca**	$5,991,000,000	22.51%
13	**Pfizer**	$9,405,000,000	22.44%
14	**Otsuka Holdings** (pharmaceutical business)	$1,927,327,215	21.55%
15	**Janssen** (Johnson & Johnson's pharmaceutical segment)	$9,563,000,000	20.98%
16	**Gilead Sciences**	$5,039,000,000	20.41%
17	**Eisai**	$1,312,193,295	20.14%
18	**Sumitomo Dainippon Pharma**	$867,269,152	19.18%
19	**Boehringer Ingelheim**	$3,245,614,035	18.91%
20	**Novartis**	$8,980,000,000	18.45%

Figure 2. The top 20 pharma industries in R&D expenditure (source: https://www.drugdiscoverytrends.com/pharmas-top-20-rd-spenders-in-2020/ accessed in Dec 2021)

In addition, they have also made disruptive process innovations in the way new drugs and medical devices are created and introduced into clinical practice by changing the conventional development life cycle. In this context, the combination of digital models of the human brain and access to continuously increased computation power (high performance computing by using conventional architectures or very innovative neuromorphic computing systems) allowed the introduction of simulation phases to better focus the target on later phases.

Speaking in general terms, not only in the narrow domain of neurostimulation, the ***main drivers for sustaining the innovation role of the pharmaceutical industry today***, from our point of view, are as follows (from R&D and market perspective):

From the research and development perspective:

- Fast ***advances in fundamental life sciences*** where a better understanding of molecular bases of living beings, the capacity to manipulate their genomics, proteomics, microstructure, and evolution, have made possible the modelling and simulation of cells, organs, and human behaviour with impressive results in

the last two decades. The case of the human brain is one of them where the detailed knowledge on the brain connectome (mainly in some brain regions) allows the design of new technological approaches to develop products and services.

- The ***convergence of several technologies*** in a very short period, where biomaterials, nanoelectronics, big data, artificial intelligence, robotics, image processing, virtual and augmented reality, high-bandwidth communication, and the Internet of Things have pushed the development of new generations of disruptive intelligent medical devices. Here is where neurostimulation has found its way.
- Advances in the ***development and use of sophisticated medical devices and equipment*** (e.g., dual beam and atomic force microscopy, AI-based image processing, surgery robots, wireless controlled implanted devices) fed-up for smart and miniaturised implants, sensors, etc. have also changed the diagnostics, treatment, and monitoring of patients in many medical areas.
- The ***digitization process,*** which has allowed the capture, sharing and processing of enormous amounts of clinical data, with all associated ethical constraints, the use of high-performance computing for modelling and simulation, the availability of smart systems to react, and above all, the growing use of artificial intelligence techniques.

From the general innovation context perspective, two trends are visible:

- The growing use of ***open innovation models*** where pharmaceutical companies in the sector are cooperating with research actors in the academic sector, and between companies from several sectors in many types of innovation partnerships looking for external knowledge not available in-house supported by corporate venture risk funds.
- The creation of very dynamic **open innovation ecosystems** where cooperation among actors, capital risk, business incubators, start-up creation and scale-up, and the availability of talented skilled people is a must promoted by regional, national, and international administrations. Europe has an opportunity to boost investments in this sector if we make the appropriate decisions stimulated by the recovery and resilience funds of Next Generation EU, structural (regional funds), Digital Health, and Horizon Europe based on long-term public-private partnerships focused on digital health.

These are not six fully independent drivers. They are mutually interdependent and taking them together could help create a very ***competitive context for the European high-tech pharmaceutical sector***. Even if this is a reality in all health areas, the case of ***neuroscience*** is especially relevant because it is at the crossroads of many convergent technologies where market opportunities for advanced products are exploding.

1.2.2 The opportunities offered by the technology convergence

The benefits of ***technology convergence*** in one domain of application such as health have been clearly demonstrated fuelled by intense digitisation. In addition, some prototypes tested today could be considered science-fiction only ten years ago, but, nowadays, are experimental approaches (many are with TRL 2-3) which can mature very soon if funding is available.

Figure 3 schematically describes how many emerging technologies merge to provide better knowledge on brain structure, its dynamics, and behaviour. Others, not represented in the figure, could join this convergence process in the coming years.

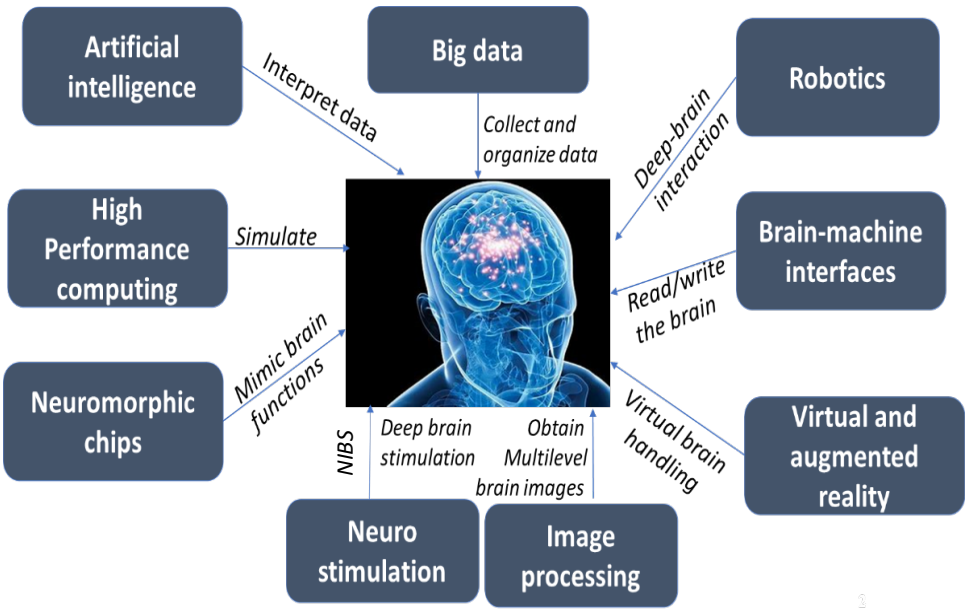


Figure 3. Technological convergence in the brain research field (source: own elaboration)

Today, many companies (SMEs and large corporations) have started the development of disruptive medical devices able to apply artificial intelligence algorithms, manage large volume of data, create invasive or non-invasive brain-machine interfaces (BCI), supported when needed by specialised surgery robots, simulate brain regions with high-performance computing or neuromorphic processors for fast execution of deep neural networks, and present multilevel information to users through incredible colourful images by using virtual and augmented reality technologies.

Technology convergence is also expanding with the use of nanotechnology in some medical areas (e.g., to transport drugs to specific targets in the human body or to develop nanorobots for internal body maintenance purposes), which will herald future breakthroughs.

Obviously, pharmaceutical industries are applying many of these enabling technologies to develop their own products and services for neural and mental disorders, independently or in combination with specific drugs, but ***they are not the only players in the field***. It is relevant to notice that companies involved in many

advanced developments on brain issues are not only coming from the conventional health sector, but from other sectors where they dominate enabling technologies and they are ready to apply them to the health sector; the case of ICT, large players and start-ups, is very well-known.

Today, many ICT companies (even the largest, FAGMA) have entered the health sector under the door of "*digital health*", and many others come from material science, robotics, etc. In the end, *health is a huge vertical sector supported by horizontal enabling technologies where digitisation plays a key role*.

One example of this trend is the growth of *health-wearables* with multiple sensors to measure health conditions or new AI techniques where FAGMA companies are introducing new products partnering with research institutions.

Marketed wearables today are far from having the ability for *monitoring brain activity (neuromonitoring)* related to the field of neurostimulation (see figure 4 for typical functionality of wearables in the cases of Google and Apple), but expected improvements in sensors' functionality (and associated cost reduction), with the fast evolution of edge computing with powerful processors able to execute deep learning algorithms in the wearables, low-energy consumption, and wireless connection to minimally invasive (subcutaneous) implants can dramatically change the wearable market for health in a few years.

Figure 4. State of the art smartwatch functionality (left Apple, right Google (Fitbit)

An example of the new generation of wearables with applications for neurology came from Apollo Neuroscience (see figure 5 and box 3).

Figure 5. Apollo Neuroscience wearable (source: Apollo https://apolloneuro.com/)

Box 3.
"Apollo Neuroscience is the first wearable that uses low-frequency inaudible sound waves (vibrations) to help reduce stress levels, speed up recovery, and positively influence your nervous system by changing your heart rate variability (HRV). Apollo was developed by neuroscientists at the University of Pittsburgh.
The Apollo device creates gentle waves of vibration that you can't hear but feel. The basic principle is that those inaudible sound waves can change how you feel by stimulating your sense of touch. More specifically, certain frequencies and vibrations can increase the parasympathetic tone, while others can increase your heart rate and activate other parameters of sympathetic activity."
Source: *https://michaelkummer.com/health/apollo-neuro-review/*

The huge value of the market makes it very relevant for all FAGMA companies to enter in the health area, if necessary, by partnering with other companies to get the required knowledge. In these cases, products and services were not explicitly designed for neurostimulation, but for monitoring the general brain status of consumers. The approach followed by these large ICT companies is to adapt, when necessary, their generic solutions to specific health areas by assuming that many of them will take advantage of similar approaches (e.g., data management, microelectronics).

As an example of these efforts by FAGMA (CBInsights, 2021):

- Apple
    - Apple has been a leader in its effort to make health data easier for consumers to access. It launched Health Record in 2018 so consumers can store their medical records in iOS. Apple recently announced that customers will be able to share those records with caregivers and other healthcare providers. Apple is generating its own health data through iOS and Watch sensors and algorithms.

- Google
    - 179 services are available within Azure's HIPAA-compliant, *HITRUSTcertified* platform. These include several purposes built for healthcare organisations:
        - *Azure API for FHIR*: a FHIR-native data ingestion and preparation service designed to help health systems prepare and normalise clinical data for data science projects.
        - *Azure IoT Connector for FHIR*: a service that leverages ML to assign FHIR resources to clinical facts extracted from streaming IoT data.
        - *Azure Health Bot*: a chatbot service trained to support healthcare consumer engagement
    - Google's healthcare research is heavily focused on building AI to support diagnostics, clinical surveillance, and treatment optimization.
    - Many activities of using AI and retinal image processing in the fields of ophthalmology (more than 50 eye diseases, including diabetic retinopathy and macular degeneration), cardiovascular (retinal scan models to prevent heart attacks and strokes), anaemia (based on retinal images to quantify haemoglobin levels), or cancer treatment.
- Microsoft
    - Microsoft is building an innovation platform for enterprise by combining Power Platform, Azure, and Teams to support AI, automation, and low-code app development efforts.
        - This tech stack is *HITRUSTcertified* and *FHIR-enabled* and comes with architecture plans to address common innovation use cases in healthcare.
    - Explainable AI. Doctors need more than a risk score; they need to consider the underlying factors that contributed to a model's prediction for their patient.
        - Model outputs produced by "black box" algorithms are notoriously difficult to explain. Microsoft is working to fix this with *InterpretML*, an open-source toolkit designed to bring clarity to model outputs.

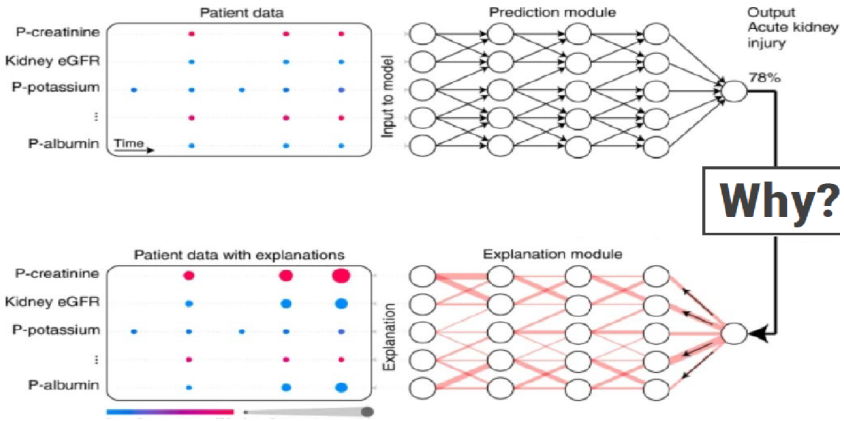


Figure 6. Explainable AI platforms for Microsoft (source: Microsoft)

- Amazon
  - Amazon has brought a portfolio of clinical-grade medical devices to market, a sensor-equipped smartwatch focused on capturing health data and a smart speaker with a HIPAAcompliant voice assistant.
  - There is also untapped opportunity for Amazon in diagnostic imaging services. A key cost driver in the US, diagnostic imaging services account for $100B in largely unnecessary annual spend – and a growing number of images can now be acquired by in-home technicians.
  - 120 services are available within AWS's HIPAA-compliant, HITRUST-certified platform, including:
    - *HealthLake*: a FHIR native data ingestion and preparation service designed to help health systems connect EHR data with AWS AI (SageMaker) and Analytics (QuickSight) tools
    - *Transcribe Medical*: a speech-to-text service built with a clinical vocabulary trained to support medical transcription use cases
    - *Comprehend Medical*: a service that leverages ML to extract and code key clinical facts from unstructured text
- Facebook.
  - Facebook AI Research (FAIR) lab developed machine learning models that can generate equally accurate and detailed MRIs using about a quarter of the raw data traditionally required for a full MRI. Since less data is required, MRI scans can run nearly 4x faster.
  - Facebook has partnered with a team of researchers at University of California, San Francisco (UCSF) to support research working to help patients with neurological damage speak again by detecting intended speech from brain activity in real-time.

- UCSF's results demonstrated an average error rate as low as 3% when tested with vocabularies of up to 300 words.

Because of this fast evolution, the number of articles mentioning *"breakthrough device designation"*[2] or *"breakthrough therapy designation"*[3] since 2016 to 2021, and the number of interventional clinical trials since 2010 to 2021 (see figure 7) shows a steady increase with a huge increase in 2021[4].

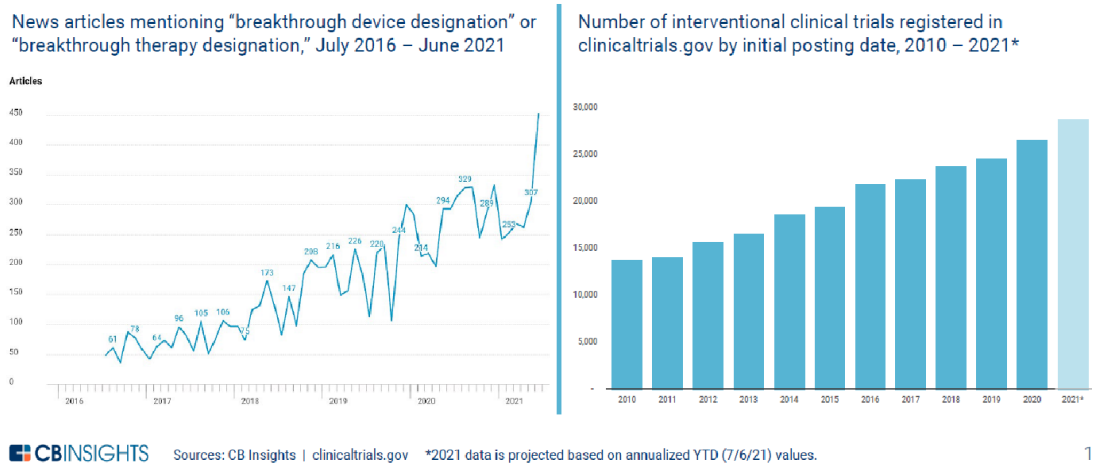


Figure 7. Evolution of breakthrough therapy designation and interventional clinical trials (Source CB Insights 2021)

Nevertheless, during the last decade, the above-mentioned main drivers were insufficient to support the breakthrough innovation rate expected in the health sector to find solutions to many of the illnesses related to humans and to offer clear returns to investments.

There are several reasons to explain that. First, ***technology maturation was not very fast*** (lower than expected due to problems in engineering promising prototypes (TRL 4-5) which did not become commercial products); in addition, there were also ***ethical and regulatory*** aspects to address, which should also be necessary to cope with and to find an international consensus to increase the innovation rate[5].

Focusing this general view about the way that ***capital risk investments on medical devices*** is evolving, recent data from CB Insights (see figure 8) depicts a situation

[2] FDA Breakthrough Device designation is granted to novel medical devices that have the potential to provide more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. This includes devices subject to premarket approval applications (PMAs), premarket notification (510(k)), or requests for De Novo designation. https://solvdhealth.com/what-is-an-fda-breakthrough-device-designation/

[3] Breakthrough Therapy Designation (BTD) is a rather new drug designation category that was signed into law with the approval of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012. Drugs which are designated as a breakthrough therapy showcase significant improvement upon current therapies and its planned outcome. https://www.biopharmaglobal.com/breakthrough-therapy-designation/

[4] Maybe the situation is explained by the strong increase in governmental funding in R&D health fed-up by citizens' pressure to public administrations in the last two years motivated by a pandemic situation.

[5] The experience with COVID-19 in the last two years has demonstrated that translational research can be accelerated without putting the precautionary principle at bay.

where the number of deals are quite stable since 2018, but the funding is growing (then, capital investment per deal is also growing). Even if results are not available yet in the clinical practice, these data could be the prelude of a coming disruption from start-ups getting the approval from regulatory agencies.

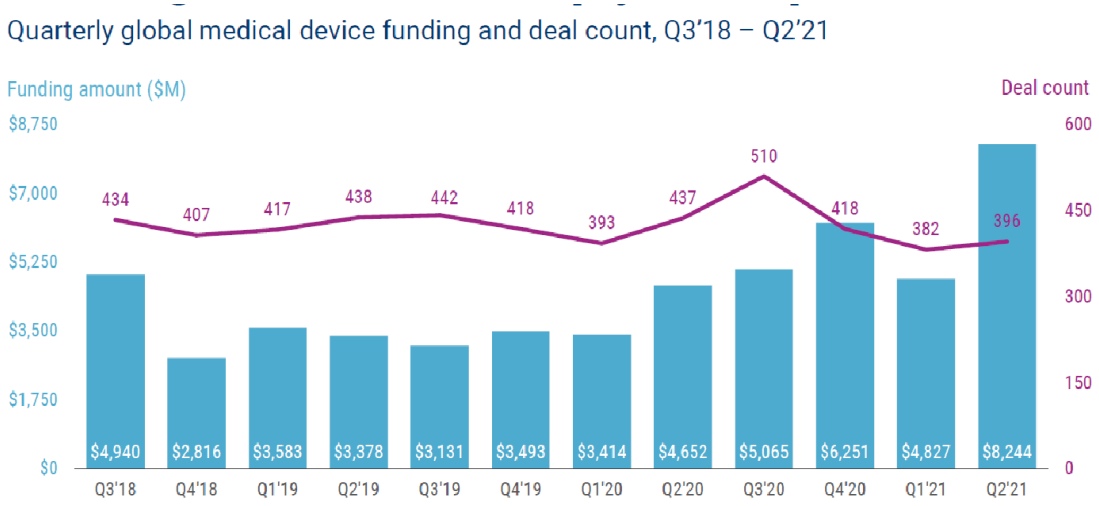


Figure 8. Evolution on the number of deals and funding for medical devices (Source: CB Insights 2021).

The current situation focused on the subsector of the pharmaceutical industry is less optimistic with mixed results in successful innovations during the last decade despite their internal R&D efforts. These drawbacks in the innovation process are found in many clinical domains, but they are very relevant in the case of ***neurodegenerative diseases***.

Pharmaceutical companies have invested huge amounts of money in the last two decades in neurodegenerative diseases without clear results, despite relevant, but partial, advances in the understanding of the molecular bases of many of the above-mentioned diseases. ***New drugs and clinical treatments for diseases such as Alzheimer's, Parkinson's, epilepsy, etc. did not fulfil the expectations created twenty years ago.***

Then, they felt the need to extend the capability of screening of molecules with potential therapeutic effects but, simultaneously, it was necessary to reduce the high costs involved. This situation has stimulated the analysis and implementation of ***alternative innovative models boosted by digital solutions and open innovation by partnering with other stakeholders***[6].

The total number of publications by the largest 23 companies has slightly declined from more than 12,500 publications in 1995 to around 11,500 since 2001. This decline is surprising given that in this period, the total number of publications on

[6] Today, the research and innovation cooperation between big pharma companies for neurodiseases is very limited (except in cases where public funding requires it). Then, cooperation is mainly based on agreements with technology-based start-ups and the academic research sector, or with large companies from other sectors like in the ICT where complementary knowledge is a must. Probably, a mentality change is needed to overcome management and strategic barriers.

health research increased 125% for all the world and increased 70% in selected large industrial countries.

The decline is at odds with the increase of R&D Big Pharma expenditure in the last 20 years. The trend is possibly due to closure of R&D laboratories by Big Pharma, often following mergers and acquisitions, as well as to externalisation of R&D to universities and small companies.

Box 4.
"The difficulties in obtaining successful market results in the field of neurosciences have motivated deep changes in the research labs priorities of many big-pharma industries. As an example, Bristol-Myers Squibb (BMS), GlaxoSmithKline (GSK), Pfizer and AstraZeneca have dramatically reduced their internal research activities, and more recently Amgen announced the closure of its research centre in the UK Likewise, BMS exited but continues to support some CNS research through its subsidiary, Celgene. Developing drugs to treat CNS disorders on average took 20% longer than other drugs that won marketing approval and took 38% longer to win that approval, according to a completed analysis by the Tufts Center for Drug Development." **Source:** *Siddiqui, 2021*

This does not mean that medical innovation for neurological and mental health disorders is less relevant to large pharmaceutical companies, but the way to get faster results has changed. The deep reduction in investments observed in the period 2010-2016 has changed since 2017 onwards when new research approaches were widely adopted.

We see **five main general trends**, which also have consequences in the (re)structure of the industrial health sector with peculiarities in specific geographies linked to industrial tissue. These are as follows.

1. The need to find more ***agile innovation models*** where big pharma companies are focusing their efforts on the clinical phases of drug development where the clinical experience is a must while opening the scope in pre-clinical phases to be able to cooperate with other actors.
   This trend has also been very relevant in supporting the development of open digital innovation platforms to help in drug discovery processes through platform-based tools, where external potential partners can use them to address specific challenges and to use some of the corporate tools under specific conditions.
2. The deep ***transformation of corporate research labs,*** which, in many cases, implied the size reduction and activity focus to concentrate in areas where positive results could be feasible and to compensate it with external alliances. This trend has also motivated the location of research facilities in health innovation ecosystems where access to external talent and cooperation is easier and less expensive. Then some innovation hotspots around the world became more and more relevant in terms of patents, the attraction of start-ups, capital risks, and public support.

3. The increased number of ***targeted innovation partnerships*** established between pharmaceutical companies and ICT companies where both parties can access very specialised knowledge. This situation explains the multiple agreements found today between large ICT players and big pharma (in many cases with the introduction of artificial intelligence approaches).
   Furthermore, we also see a growing interest in ICT companies to enter the sector with solutions offered by themselves without the participation of the pharma industry. It reveals, as is also happening in other industrial sectors (e.g., automotive, retail), how the irruption to entrants like FAGMA (Facebook, Amazon, Google, Microsoft, Apple) companies have modified the sector as understood by incumbents.
4. The interest in supporting the ***creation and funding of technology-based start-ups*** through specific programmes for business incubation, risk capital (seed and first rounds), and merger and acquisition processes of some of them instead of using more conventional organic growth models.
   Practically, all pharma companies have created their ***corporate risk venture funds***, in some cases with other companies, and they invest and co-invest in selected start-ups within their priority areas.

5. The search for **cost efficiency in the production, approval, distribution, and marketing of drugs** exerts a significant pressure on the industry and, in some developed countries has become a greater expense for the final consumer. Although mergers and acquisitions have increased in the pharmaceutical industry, the differences between countries are becoming more visible, for example, in terms of optimization in the supply chain, the number of participants until their final consumption, management and effectiveness in terms of intellectual property protection, approval by regulatory bodies, etc.

   Not only does delaying the introduction of drugs to the market cause cost but also makes it expensive to access specific treatments, including those prescribed for neurological diseases. For this and other reasons, more cost-effective technologies and application in preventive medicine are demanded, including neurostimulation, which contribute to the reduction of the cost in the current services and treatments.

It is perhaps too early to know how these ***market trends*** will be consolidated in this decade; however, our understanding is that health innovation will accelerate, and it requires faster strategic movements of actors and a better understanding of the impact of long-term trends in the health sector.

The next section will address the ***technological aspects of the field of neurostimulation*** to analyse the situation today and forecast future technological breakthroughs.

PART 2

2. Neurostimulation / Neuromodulation technologies

2.1 Definitions, types and clinical applications

Increased understanding of neurocircuitry and recent advances in neurotechnology and neuroimaging are factors contributing to the rapid increase in the use of ***neurostimulation therapies*** to treat an increasingly wide range of neurologic and psychiatric disorders.

The basis is that under the appropriate conditions (i.e., amplitude, polarity, duration, frequency), neurons react to electric fields in their vicinity by firing action potentials in a manner closely resembling their response to natural neuronal signaling. The information that is then received by the brain can be controlled and guided to mimic natural processes (Vebraité and Hanein, 2021). This process can be used to address some brain disorders.

Neural stimulation was applied to various applications including upper/lower limb prostheses, vagus nerve stimulation, deep brain stimulation (DBS) for Parkinson's disease, epilepsy and depression, cochlear implants, and visual prostheses (37–39). Except for visual implants, these medical devices are built on low-resolution technology (4–22 electrodes). The two domains where high-resolution stimulation appears to be of highest value are cochlear implants and visual prostheses.

Box 5 reproduces the definitions of two related terms: ***neurostimulation*** and ***neuromodulation***. In practice, both terms are used to describe the same type of approaches and medical devices.

Box 5.

"Neurostimulation is the delivery of low voltage electricity to a specific nerve or target in the spinal cord or brain in an attempt to affect neuronal transmission. It can be used to treat neuropathic pain or to modulate motor function (e.g., in the treatment of gastroparesis).Source:

Source: https://medical-dictionary.thefreedictionary.com/neurostimulation

The International Neuromodulation Society defines therapeutic Neuromodulation as the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body. **Source**: https://www.neuromodulation.com/neuromodulation-defined

Neurostimulation therapies include invasive and non-invasive approaches that involve the application of electrical or magnetic stimulation to drive neural function within a circuit to obtain a desired brain response.

An **invasive neurostimulation technique** implies acting directly to one region of the brain, which requires opening the skull and placing electrodes in specific regions (permanently or not); therefore, it involves surgery. A variation of this technique, termed the **minimally invasive neurostimulation technique**, only requires the

placement of *subcutaneous implants,* which only require small surgery, or by using other techniques to use the brain vessels to introduce specific devices.

Finally, a **non-invasive neurostimulation technique** implies that stimulation is generated externally which has fewer potential consequences, but the technology should require more complexity to be efficient (e.g., sophisticated helmets) and today, the precision obtained is much lower compared to invasive techniques.

These techniques require the use of specific medical devices known as ***"electroceuticals"***. These are devices that use electrical impulses or currents in the body to treat conditions and diseases with a growing world market.

Brain Computer Interfaces (BCIs) based on electroceutical have started to offer impressive results for people with specific disabilities. As an example, today it is possible to decode imagined handwriting movements from neural activity in the motor cortex and translate it to text in real-time, using a novel recurrent neural network decoding approach (Willett et al., 2020).

2.2 Invasive neurostimulation strategies

Invasive neurostimulation strategies use ***"neural implants"*** (devices placed inside the body that interact with neurons) to obtain a controlled brain response and to deal with some specific neuro disorders like "tremors". Typically, they are composed of electrodes of some materials inserted into the body. The electrodes contact tissues that contain neurons and interact with those neurons in controlled ways through electric pulses.

The following established invasive neurostimulation strategies include **deep brain stimulation** (DBS), **motor cortex stimulation** (MCS), **responsive neurostimulation** (RNS), **spinal cord stimulation** (SCS) and **vagus nerve stimulation** (VNS). All of them are used clinically to modulate disordered circuitry to restore functionality.

- *Deep brain stimulation therapy* (DBS) is FDA approved for medically refractory PD, essential tremor, dystonia; In addition, other disorders under investigation include Tourette syndrome, treatment-resistant depression, chronic pain, alcohol and drug addiction, cluster headache, schizophrenia and Alzheimer's disease (Lyons, 2011).

  DBS with anterior nucleus of the thalamus (ANT) target has been approved in Europe for the treatment of focal epilepsy in adult patients aged 18 to 65 years and is waiting for approval in the United States by the FDA (Fisher et al, 2010). Hippocampus DBS is a valuable option for patients with drug-resistant mesial temporal lobe epilepsy in whom surgery is contraindicated (Tellez-Zenteno et al, 2006; Velasco et al, 2007; McLachlan et al, 2010). A favourable safety profile and demonstration of efficacy in several randomized controlled trials has led to increased interest in the potential application of DBS to psychiatric disorders. (Lozano et al., 2019). Following a positive randomized controlled trial published

in 2008, DBS for obsessive–compulsive disorder (OCD) was granted CE approval and an FDA Humanitarian Device Exemption (Mallet L, et al, 2008).

In recent years, the possibility of regulating DBS over time according to one or more feedback signals has attracted considerable attention. The name of this approach is the term 'adaptive DBS' (aDBS). During implantation, aDBS strategies use LFPs to help target brain regions more accurately. Moreover, aDBS may also be used to reduce side effects and extend the longevity of DBS devices (Lozano et. al., 2018).

- *Cortical stimulation* is an emerging treatment option for a variety of neurological disorders, in contrast to deep brain stimulation, where electrodes are implanted deep in the brain, cortical stimulation uses electrodes that are placed on the surface of the brain (Neuromodulation, 2022). Unlike DBS, cortical stimulation requires a craniotomy to implant electrode-like grids or paddle electrodes.

  Motor Cortex Stimulation (MCS) has been reported to be effective not only on pain, but also in improving movement disorders such as Parkinson's disease, tremor, dystonia, post-stroke movement disorders, and hemiparesis.

- *The Responsive Neurostimulation System* (RNS) of Neuropace (https://www.neuropace.com/) is a combination of a brain stimulation implant and electrical sensors that detect and prevent the occurrence of seizures in patients with focal epilepsy (which is 1/3 of all epilepsies). They have received FDA Breakthrough Device Designation, and is going through clinical trials with promising results[7]. The RNS System is a programmable and responsive device that consists of leads, a pulse generator, and an external programmer. An algorithm detects specific patterns of epileptogenic activity and triggers focal stimulation to interrupt a seizure (Caio et al, 2019).

  The FDA approval in the USA of RNS for the adjunctive treatment of DRE heralded a paradigm shift in neuromodulation for epilepsy (Heck et al, 2014). Approval of the implanted RNS device for MRI in early 2020 is an important step in allowing the device to be used in cases in which frequent MRI scans are required.

  Indications for spinal cord stimulation (SCS) include a myriad of refractory chronic pain conditions, including failed back surgery syndrome, complex regional pain syndrome, angina pectoris, ischemic limb pain, and abdominal pain (Rokyta, 2012; Haddadan and Krames, 2007; Taylor et al, 2009). SCS technology has shown promise for regaining volitional movement for people with spinal cord injuries.

[7] The company has received in March 2021 the Breakthrough Device Designation status from the U.S. Food and Drug Administration (FDA) for the potential use of its RNS® System to treat idiopathic generalized epilepsy (IGE), which constitutes as many as one third of all epilepsies and is understood to have a strong underlying genetic basis (https://www.neuropace.com/fda-breakthrough-device-designation-for-rns-system/)

- *Vagus nerve stimulation* (VNS) is the first neurostimulation technique approved in clinical practice and it has been used worldwide as an efficient treatment for drug-resistant epilepsy. In this regard, it provides treatment for focal and generalised seizures, both for children and adults, and for mood problems in adults with epilepsy, depression (Rush et al, 2000; Sackeim et al, 2001; Marangell et al 2002; Revesz et al, 2016). The VNS is limited to the management of more severe, intervention-resistant cases as a second or third-line treatment option due to the perioperative risks involved with device implantation.

Both VNS and DBS are ***open-loop stimulation systems*** (see figure 9) that control seizures by continuously modulating the activity of certain hubs of the epilepsy network. On the contrary, the ***RNS system is the first closed-loop stimulation system*** that works by delivering electrical pulses when a seizure is detected.

Compared to open-loop stimulation, RNS has a longer battery life due to the lower stimulation dose. Furthermore, stimulation is restricted to one or two foci of seizures and does not disrupt normal brain function, thus resulting in fewer adverse events (Skarpaas et al, 2019).

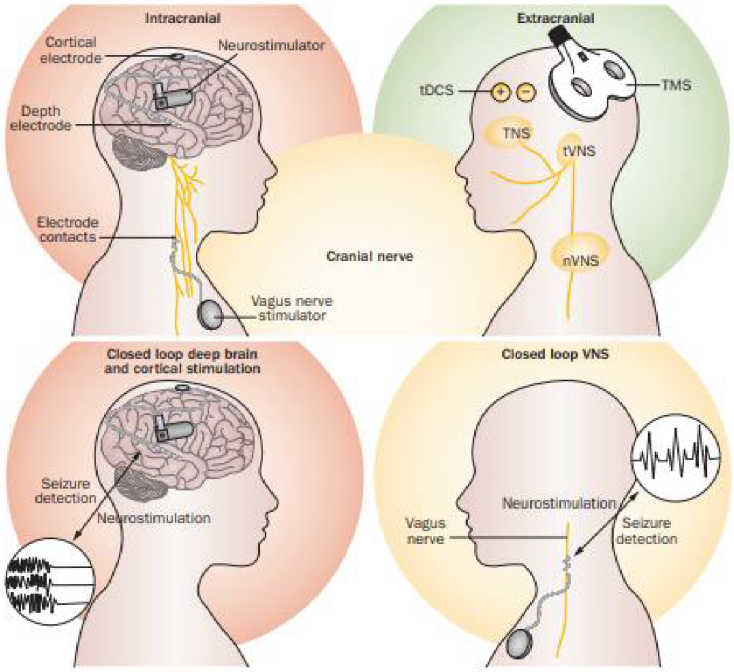


Figure 9. Overview of intracranial and extracranial neurostimulation techniques for patients with epilepsy. Combined invasive and non-invasive approaches, combined open and closed-loop approaches, as well as individualised strategies may be required (Vonck and Boon, 2015)

Brain-responsive stimulation represents a safe and effective treatment option for patients with medically intractable epilepsy, including patients with unilateral or bilateral MTLE who are not candidates for temporal lobectomy or who have failed a previous MTL resection (Geller et al, 2017).

Today, from the market perspective, many companies are building microelectric arrays and DBS devices. Their primary differentiations are in the technology of implantation and in the populations of their target patients. It is surprising that even

though there are many types of neuroimaging technologies, ***the most common approach being explored for implantation is the measuring electrical signals***[8]. Other approaches are less common.

One example of this type of neurostimulation device sending electrical signals is the *Percent PC DBS* system marketed by Medtronics after the FDA approval (Box 6).

Box 6.

"Ireland-based medical technology company Medtronic has received the US Food and Drug Administration (FDA) approval for its Percept PC Deep Brain Stimulation (DBS) system (see figure 10).

Figure 10. Percept PC Deep Brain Stimulation (DBS) system

The neurostimulation system uses BrainSense technology to chronically capture and record brain signals while delivering therapy to patients with neurologic disorders related to Parkinson's disease, essential tremor, dystonia, epilepsy or obsessive-compulsive disorder (OCD). It enables physicians to track patient brain signals and correlate them with patient-recorded actions or experiences, including symptoms, side effects, or medication intake, offering a personalised, data-driven neurostimulation treatment. DBS is an individualised therapy delivered from a small pacemaker-like device, which can be placed under the skin of the chest or abdomen. It is designed to send electrical signals through very thin wires to a targeted area in the brain related to the symptoms of a neurological disorder.

In addition to BrainSense technology, the Percept PC DBS system uses several other features, Enhanced Patient Programmer, and low-pulse width, which enables expanded stimulation options".

***Source**: https://www.medicaldevice-network.com/news/medtronic-fda-approval-dbs-neurostimulation-system/*

There are many companies which have started the development of specific cortical implants: Neuralink, BlackRock Neurotech, Braingate. In some cases, they have got

[8] https://neurogenesis.substack.com/p/invasive-neurotech-companies?s=r

the designation of *Breakthrough device* from the FDA to start some trials with humans, while in other cases they are still waiting for approval even the most sophisticated implanted devices are being tested on animals.

In other cases, the impact on patients of brain implants is so relevant (for instance, to provide vision for blinded people, see box 7) could compensate for risks based on enough data collection. The case of the start-up "phosphoenix" founded in The Netherlands in 2019 is a good example.

Box 7.

"The quest of restoring vision in blind patients through a brain prosthesis is on the verge of becoming reality. Our goal is to provide profoundly blind people with artificial vision via an implant in the visual cortex, allowing people to recognise objects, navigate more independently, and enjoy enhanced quality of life. We are creating the world's first large-scale, chronically implanted, wireless device that imparts visual percepts directly to the visual cortex, through the translation of fundamental neuroscience insights into clinical applications. We create breakthrough technology by combining expertise across the fields of brain-machine interfaces, neuroscience, materials science, microchip fabrication, artificial intelligence, and wireless power and communications. Our neuroprosthesis will enable blind people to regain functional vision, even after extensive damage to the eye or optic nerve. Phosphoenix is a neurotechnology company, spun off in 2019 from the NESTOR programme (supported by the Netherlands Organisation for Scientific Research)." ***Source****: Phosphoenix, 2022*

This leaves many domains unexplored, including infrared and optogenetics, now used in humans with blindness (Sahel et al, 2021). It may be that these applications are currently not possible in humans but given the scope of what experimentation on mice looks like, one would expect more diversity in the core technologies of sensors.

The problems derived from invasive techniques which require surgery to place implants in the brain have motivated the use of other minimally invasive techniques where risks are lower by placing the implant near the skin or by using heat instead of electric signals.

As an example of current developments, Figure 11 depicts the scheme of a minimally invasive technique under development from ***Merck*** in cooperation with ***Neuroloop GmbH*** – a B. Braun subsidiary and early-stage start-up company[9]. This is an example of the ***trend of research cooperation between a large pharma company and one start-up***[10] mentioned above to accelerate the development of medical neuro devices from research outputs.

[9] Neuroloop GmbH is an early-stage healthcare spin-off company from the Freiburg University and the Freiburg University Hospital with investment of Aesculap AG, a division of the B. Braun Melsungen AG. https://neuroloop.de/

[10] Neuroloops neurostimulation system consists of a unique, patented and very thin multi-channel cuff electrode that is wrapped around the vagus nerve. The electrode is connected to an implanted pulse generator in the chest area, which is wirelessly charged and programmed. The platform allows for selective

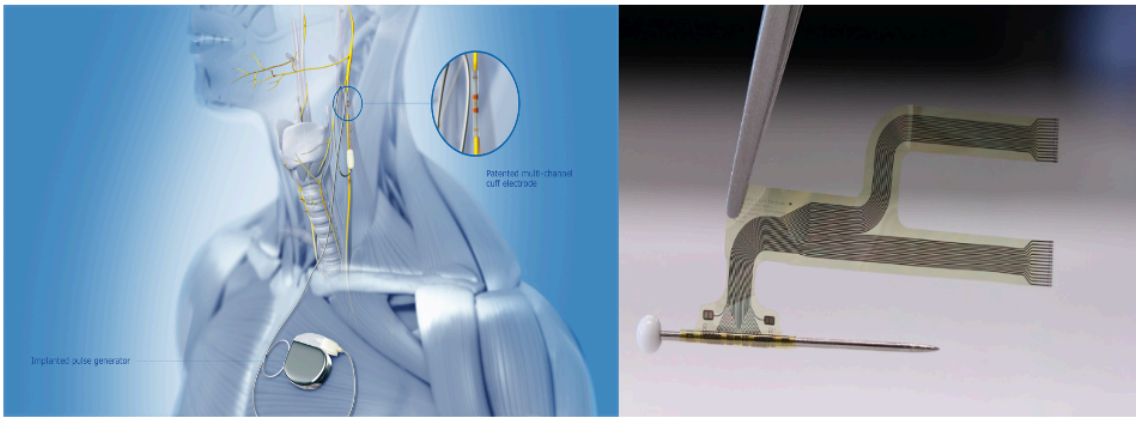


Figure 11. Neuroloop system and electrode (right) (Source: https://www.merckgroup.com/en/news/bioelectronics-bbraun-neuroloop-29-06-2021.html and https://neuroloop.de/wp-content/uploads/2015/01/IMG_1988_Elektrode-01-900x506.png)

One available technology is the ***use of ultrasounds*** to reduce tremors in illnesses like Parkinson (see figure 11). The technique is named: HIFU (High Intensity Focal Ultrasound) . The "HIFU" technique is a minimally invasive treatment in which thermal ablation, that is, localised intense heat, is used to destroy abnormal tissue or tumours. Temperatures between 55°C and 80°C are applied for a few seconds at focused points to cause cell death. Monitoring temperature changes provides three-dimensional images in the target tissue that minimise the risk of damaging adjacent tissues, and thus the possibility of adverse effects or potential complications.

Stimulating Peripheral Activity to Relieve Conditions (SPARC) is an NIH Common Fund program that focuses on understanding peripheral nerves — nerves that connect the brain and spinal cord to the rest of the body — and how their electrical signals control internal organ function. Modulation of these control signals is a potentially powerful way to treat common conditions and diseases such as rheumatoid arthritis and heart failure. Methods and medical devices that modulate peripheral nerve activity are becoming available, but more research is needed to fully understand how these therapies act on a target organ's cells. Such understanding could help both explain why a particular therapy may be effective in one individual but not in another as well as resolve the issue, thereby making these therapies more effective.

2.2.1 Neuro implants for invasive techniques

The use of invasive deep brain stimulation techniques relies on the development of ***neuro implants***. A neural implant is a device—typically an electrode of some kind—that's inserted into the body, meets tissues that contain neurons, and interacts with those neurons in some way.

stimulation of the vagus nerve and sets new standards for treating chronic diseases associated with autonomous vital functions.

Figure 12 shows an X-ray of a Parkinson's disease ***patient with implanted electrodes for deep brain stimulation***. These kinds of invasive techniques require sophisticated clinical environments (operating theatre) and continuous monitoring of the status of the implants.

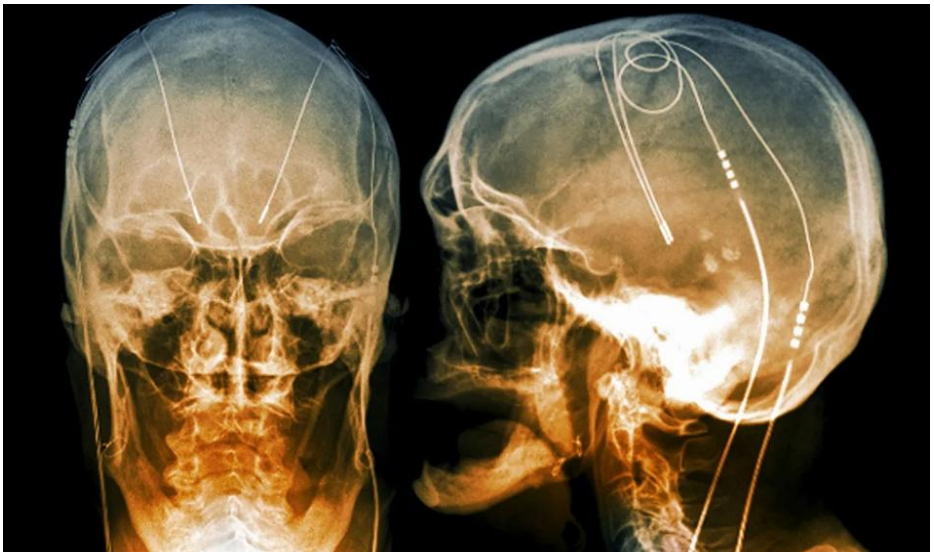


Figure 12. X-rays of a patient with Parkinson's disease show the electrodes of a deep brain stimulator implanted in the brain. This "brain pacemaker" emits electrical impulses to treat the disease's motor symptoms. (IMAGE: ZEPHYR/SCIENCE, IEEE Spectrum https://sp

The development of successful neuro implants for clinical applications implies two key factors: the ***design of shapes*** to minimise the tissue damage, and the use of ***biomaterials*** to avoid rejects.

The crucial characteristics of an electrode include biocompatibility, inertness, durability, stability over time, surgical feasibility, good conductivity, electrical properties, tractability, appropriate current delivery, and spatial configuration. Additional considerations include MRI compatibility and the potential for sensing (Angelov et al., 2016), (Koenen et al., 2017). Figure 13 shows several types of electrodes available today.

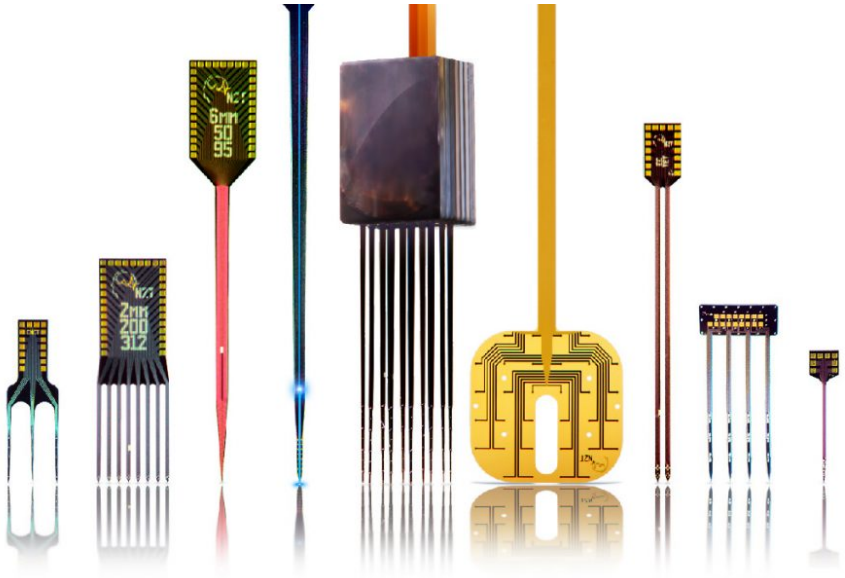


Figure 13. Electrodes (source: NeuroNexus neural probes NeuroNexus)

There are many types of neural electrodes. Electrodes that climb nerves like a vine, electrodes made from flexible materials such as a nanoelectronic thread, stent-like electrodes, or "stentrodes," that can get to the brain via blood vessels and record electrical activity, injectable electronic mesh made from silicon nanowires, electrodes that can be injected into the body as a liquid and then harden into a stretchy taffy-like substance, and more (Waltz, 2020).

Research on neurostimulation electrodes, which actively deliver charge, have yet to reliably demonstrate continuous functionality for ten years or more in vivo, the accepted metric for clinical viability. This has not yet been clinically achieved. The key to achieving long-term stability is an increased understanding of electrode interactions with the surrounding tissue and subsequent systematic analysis of their failure modes (Oldroyd and Malliaras, 2022), (Iwasa et al., 2020).

Current trends on designing implanted electrodes are following two complementary routes: 1) the possibility to connect the electrodes to many individual neurons, and 2) the increase of the intelligence of the electrode to capture brain signals and stimulate tiny regions with higher precision.

The first route implies a ***deep miniaturisation of the electrodes and to increase the number of active channels*** to connect from a few to thousands of neurons. Significant advances have been made recently in the miniaturization of and increasing the density of recording electrodes—such as the flexible "thread" electrodes of the Neuralink device and the high density Neuropixels probe[11] This marks a transition from simple macroscale devices to complex, nanofabricated devices with more advanced capabilities.

[11] Each probe features 384 dual-band, low-noise recording channels that can individually be configured to simultaneously record AP (action potential) and LFP (local field potential) signals from 960 selectable, low-impedance TiN electrodes densely tiled along a 10-mm long, 70 x 24 µm cross-section straight shank. Voltage signals are filtered, amplified, multiplexed and digitized on-chip, allowing the direct streaming of digital data from the probe. https://www.neuropixels.org/probe

Figure 14 depicts the probe from Neuropixel, a fully-integrated silicon CMOS digital neural probe with on-chip circuitry for signal conditioning and digitization combined with a dedicated control system.

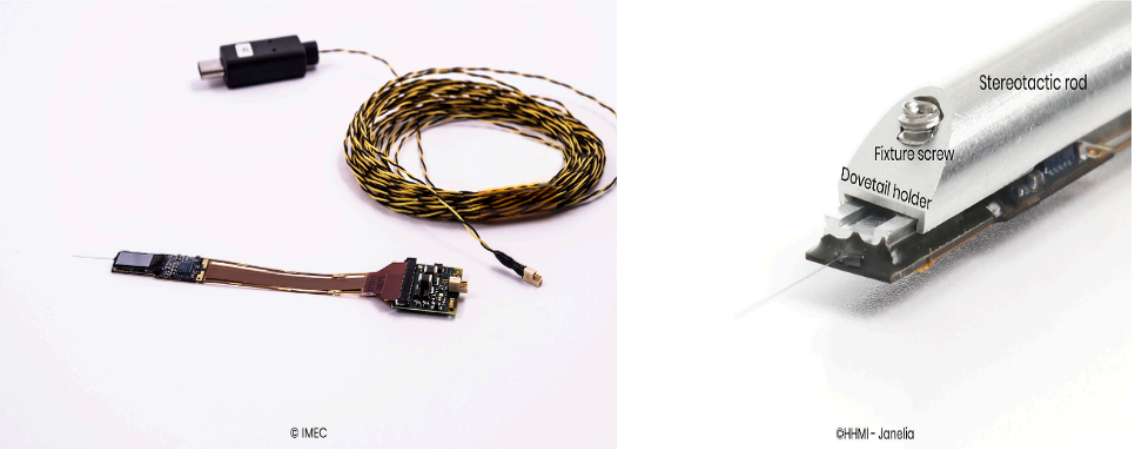


Figure 14. Neuropixel probe integrated silicon CMOS digital neural probe with on-chip circuitry for signal conditioning and digitization (source: https://www.neuropixels.org/probe)

To be effective from the clinical perspective, this evolution requires a deep knowledge of the microanatomy of the human brain to decide where the target neurons are located (e.g., by using a precise brain Atlas to navigate), and a deep knowledge of the brain microcircuit functionality.

The placement of this kind of electrodes with multiple connections to individual neurons requires a highly precise robotic neurosurgery tool. Neuralink microelectrode is one of the well-known examples of this approach[12]. Figure 15 and 16 shows some of the microelectrodes used by Neuralink.

[12]The initial models had 96 electrode threads, which are just 0.007mm thick. The robot is installing six electrode threads per minute, such that the most invasive part of the procedure is over in less than twenty minutes according to Neuralink. New models of the neuro implant have 1.024 electrodes and they have announced the intention to go to ten times this number.

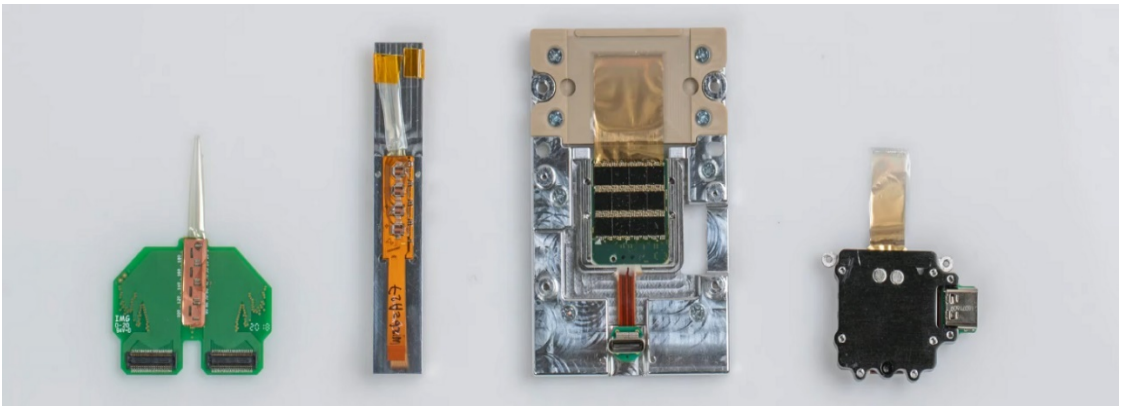


Figure 15. Neuralink microelectrodes. The microelectrode on the left side held 64 electrodes. (source: Neuralink,)

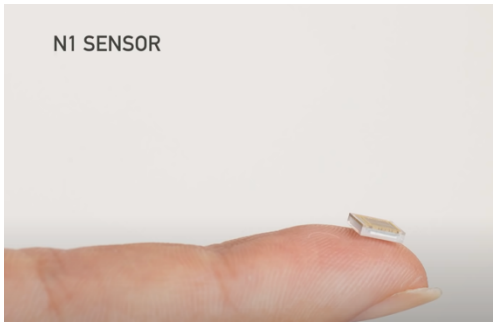


Figure 16. N1 chip created in 2019 is 8mm in diameter, replaced by the current "Link" (still under development) with 1024 electrodes to capture information from the brain. (source: Neuralink)

To address the second route, increasingly complex implanted electrode systems will require the integration with artificial intelligence or computational model-based programming and embedded wireless emitters and receivers to achieve optimal results. Then, the intention is to increase edge computing capabilities to complex electrodes.

For example, a commercially available system from Boston Scientific allows clinicians to designate a desired volume of tissue activated after which the programming software will determine the scheme for contact activation. In this context to increase the processing capability of implants through low-energy systems (e.g., neuromorphic chips for edge computing) could offer disruptive solutions in the future.

The development of less invasive techniques is a highly active phase with the creation of many start-ups moving to the market research results. Box 8 provides details on ***ni20***, one of the latest examples created from Oxford University research and its Kinetic Intelligent Wireless Implant (KIWI).

Box 8.

"Ni2o was founded by a global team of experienced entrepreneurs, technologists and neuroscientists, research started at Oxford and then continued at MIT's Mind Machine Project: Developing a revolutionary brain-computer interface that addresses the most pressing and costly medical needs of a rapidly ageing global population, the treatment of neurodegenerative brain diseases and disorders. The Kinetic Intelligent Wireless Implant (KIWI) is a small, self-contained, wirelessly connected, wirelessly charged, AI-

*driven replacement for current deep brain stimulation (DBS) solutions. KIWI will record brain activity and deliver electrical and optical signals to target areas, with algorithms that will determine the therapeutic response and be continually improved by machine learning. It is implanted using an internally-developed, minimally-invasive surgical procedure. A cloud-based software platform will then securely collect and interpret information in real-time. No larger than a grain of rice, KIWI is embedded via a minimally-invasive operation into areas of the brain where clinical treatment is required. Neurons readily grow around the device's carbon nanotube connectors, which deliver the small electrical pulses that are the basis of the effectiveness of DBS.". **Source:** KIWI -ni2o*

Current technologies used for electrodes are limited in their ability to obtain with precision, high fidelity, and spatial resolution ultra-slow or low-frequency brain signals which is very relevant in some brain diseases like epilepsy (see Box 9).

Box 9.
"Epileptic signals cover a wide range of frequencies, much wider than the band monitored by the conventional electroencephalogram. Biomarkers of a crisis onset zone include very rapid oscillations, as well as ultra-slow activity and continuous potential variations. The latter can provide very relevant information associated with the onset of crises but are rarely used due to the poor performance of the available electrodes."
Source: El Español, 2021

The ability to record simultaneously DC-shifts, low frequency oscillations (<0.1 Hz), typical local field potentials (0.1–80 Hz) and higher frequencies (80–600 Hz) using the same recording site would particularly benefit preclinical epilepsy research and could provide clinical biomarkers for improved seizure onset zone delineation (Calia et al, 2021).

Unfortunately, commonly used metal microelectrode technology suffers from *instabilities* that hamper the high fidelity of DC-coupled recordings, which are needed to access signals of very low frequency. More research on appropriate materials to improve the performance of neural probes is necessary to test other materials with better properties.

In this context, the use of bidimensional materials like graphene could provide the solution soon as it is represented in Figure 17.

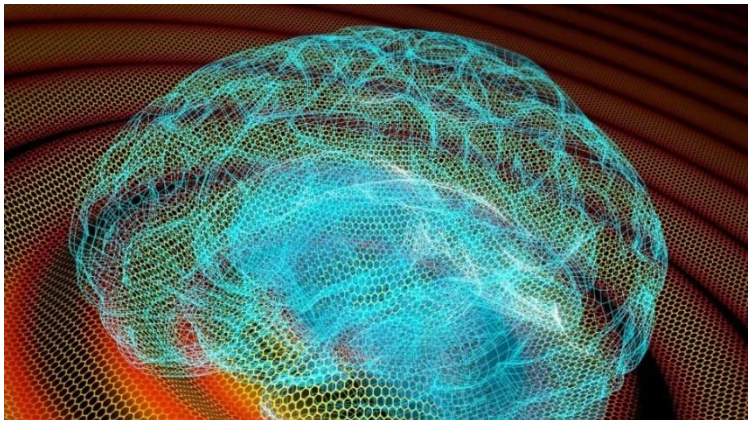


Figure 17. Graphene probes for epilepsy (source: CSIC)

Recent research (Bonaccini et al., 2021) has demonstrated the use of flexible graphene depth neural probes (gDNPs) manufactured with graphene-based Field-Effect Transistor (FET), which are able to record the full spectrum of brain signals, included low frequency.

The gDNP probe consist of a linear array of graphene micro transistors, to concurrently record DC-shifts and high-frequency neuronal activity in awake rodents. They show that gDNPs can reliably record and map with high spatial resolution seizures (Calia et al, 2021), pre-ictal DC-shifts and seizure-associated spreading depolarizations together with higher frequencies through the cortical laminae to the hippocampus in a mouse model of chemically induced seizures.

Moreover, researchers have demonstrated the functionality of chronically implanted devices over 10 weeks by recording with high fidelity spontaneous spike-wave discharges and associated infra-slow oscillations in a rat model of absence epilepsy. The suitability of this technology for *in vivo* electrophysiology research, and in particular epilepsy research, by allowing stable and chronic DC-coupled recordings will be a potential breakthrough.

Another company using graphene is **InBrain Neuroelectronics** (https://inbrain-neuroelectronics.com/), a spin-off of the Catalan Institute of Nanoscience and the Nanotechnology and ICREA programme, was established in 2019 with the mission of developing graphene-based brain implants for application in patients with epilepsy, Parkinson's, and other neuronal diseases.

Inbrain solves a problem that current neuroelectric companies don't tackle: ***implant rejection***. Most metallic brain interfaces eventually result in rejection or scar tissue around the implant, reducing quality of signal. Inbrain uses graphene electrodes to record signal with high consistent fidelity and relies on nanoscale carbon fabrication to build much smaller electrodes than currently exist.

The future clinical translation of this technology offers the possibility of identifying and delimiting with greater precision the areas of the brain responsible for the appearance of seizures before surgical intervention. This would allow for less extensive resections and better results. By extension, this technology can also be

applied to improve understanding of other neurological diseases associated with slow, low-frequency brain signals, such as traumatic brain injuries, strokes, and migraine.

As a summary, invasive technologies offer the best approach for neurostimulation because electrodes are near the neurons, and they could be implanted in deep brain regions. Risks associated to the use of the technique have strongly conditioned their approval by health regulatory bodies and has also raised some ethical concerns[13]. The problem of damage, inflammation and infection due to direct contact with stimulation electrodes is not totally overcome.

A totally different approach is the use of ***non-invasive neurostimulation*** strategies which do not need to implant any electrode in the human body. The current situation and technological breakthroughs are presented in the next section.

2.3 Non-invasive neurostimulation strategies

The approaches of the group of techniques known as non-invasive neurostimulation rely on electrical, magnetic, photonic, and acoustic or ultrasonic energy to influence nervous system activity, brain function, and behaviour from outside the human body.

The physics underlying the ability of various non-invasive methods to modulate nervous system activity can be quite different from each other depending on the energy modality used.

Main advantages of these methods are the reduction of risk (no surgery) and the possible use in non-clinical contexts which was offered the possibility to use neurostimulation to non-patients by opening the market to a huge number of consumers. The limitation comes from the difficulty to access deep brain regions with high precision and to be able to stimulate specific (individual) or local population neurons from outside as some implants can do.

Non-invasive brain stimulation with ***transcranial magnetic stimulation (TMS)*** or ***transcranial electrical stimulation (TES)*** is valuable in research and has potential therapeutic applications in cognitive neuroscience, neurophysiology, psychiatry, and neurology.

TMS is based on the application of a magnetic field that induces an electric field in the brain, via electromagnetic induction. Transcranial Static Magnetic Field Stimulation (tSMS), is another non-invasive modulation technique to reduce the excitability of the motor cortex (Oliviero et al, 2011). The technological evolution of this technique has allowed implementing small sensors to be integrated in portable devices.

[13] In the case of Neuralink, the use of monkeys was criticised due to some deadly consequences in recent experiments.

Technologies such as stereotaxy and robotics in DBS systems, detection of abnormal electrocorticogram activity in responsive neurostimulation systems, and infrared navigation and special H coil in repetitive transcranial magnetic stimulation (rTMS) systems are making their way forward since the beginning of the century (Hallet, 2007).

Clinically, several rTMS devices and protocols have been approved by the FDA for the treatment of medication-resistant depression, migraine, and obsessive-compulsive disorder (Lefaucheur et al, 2014; Voelker, 2018). The available data support that rTMS is effective in reducing epileptiform discharges, but evidence for seizure reduction is still insufficient (Pang et al, 2013; Thordstein, 2012).

Scientists first used imaging technology to find out what part of each brain they should target. They then used a specific type of TMS therapy called ***intermittent theta-burst stimulation*** (iTBS & cTBS). One of the company in using this approach for major depression is **Magnus Medical** (https://www.magnusmed.com/) (see Box 10).

Box 10.
"The investigational double-blinded randomised controlled trial (RCT), which assessed SAINT technology, showed that it holds the potential to deliver rapid and better treatment for severe, refractory depression in a broader clinical setting. As part of the trials, 14 study participants secured active treatment and another 15 received sham (placebo) treatment. The clinical study results demonstrated that 79% of people in the active treatment arm entered remission compared to only 13% of people entering into emission in the sham treatment arm. In an earlier pilot study assessing SAINT, 19 of 21 study participants (90%) entered remission, stated the company".
Source: *https://www.nsmedicaldevices.com/news/magnus-medical-neurostimulation-technology-mdd/*

The company's breakthrough innovations combine advanced imaging technologies with individualised targeting and novel stimulation patterns, to yield a new approach to personalised neurostimulation for people with treatment-resistant depression (TRD). This new approach is designed to be delivered on an accelerated timeline and is precisely tailored to each person's brain connectivity. Figure 18 shows the resolution of the neurostimulation in a human brain.

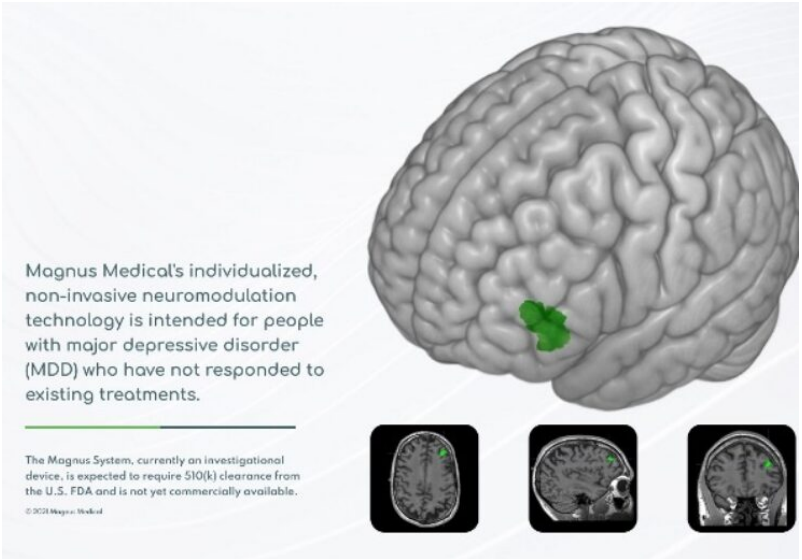


Figure 18. https://www.nsmedicaldevices.com/news/magnus-medical-neurostimulation-technology-mdd/

The system uses structural and functional MRI information to inform a proprietary algorithm that identifies the optimal anatomic target for focused neurostimulation in people with MDD. SAINT (Stanford accelerated intelligent neuromodulation therapy) was developed at Stanford and licensed to Magnus Medical in October 2021 for commercialization (see figure 18).

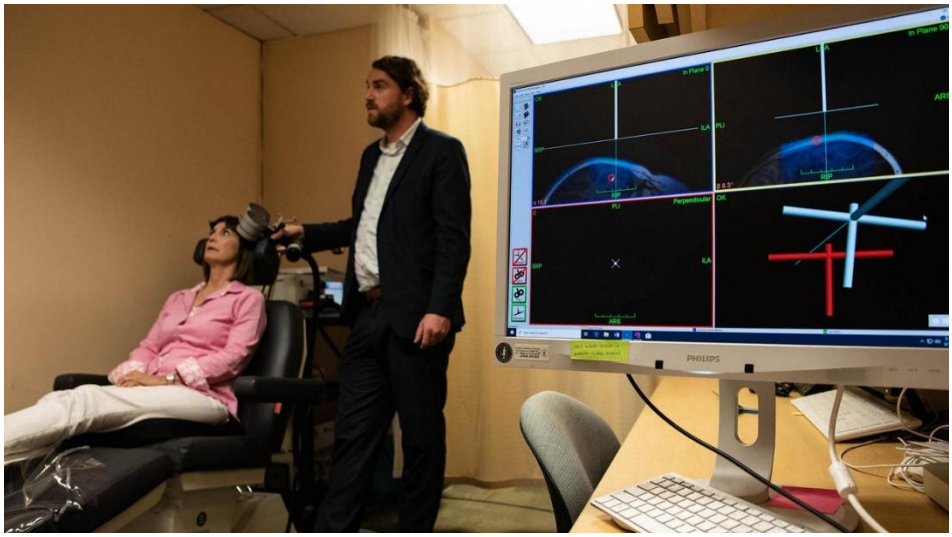


Figure 19. Applying the SAINT (Stanford Accelerated Intelligent Neuromodulation Therapy) treatment. (Source: https://www.cbsnews.com/news/saint-treatment-for-depression/)

For the first time, advanced tools for processing MRI-based images of the brain are used to steer a specialised, high-dose pattern of magnetic pulses to induce neurons to fire. This stimulation modifies activity in brain networks related to depression, changing the brain's circuitry to more effectively treat MDD. With this precise, personalised approach, Magnus Medical's proprietary technology for dosing and targeting may offer a new, rapid-acting treatment for intractable depression.

It is also possible to combine two (or more) neurostimulation techniques modalities that operate as stimulators independently or together on the same device. Figure 20 (Walton et al., 2021) schematically depicts some possibilities used today.

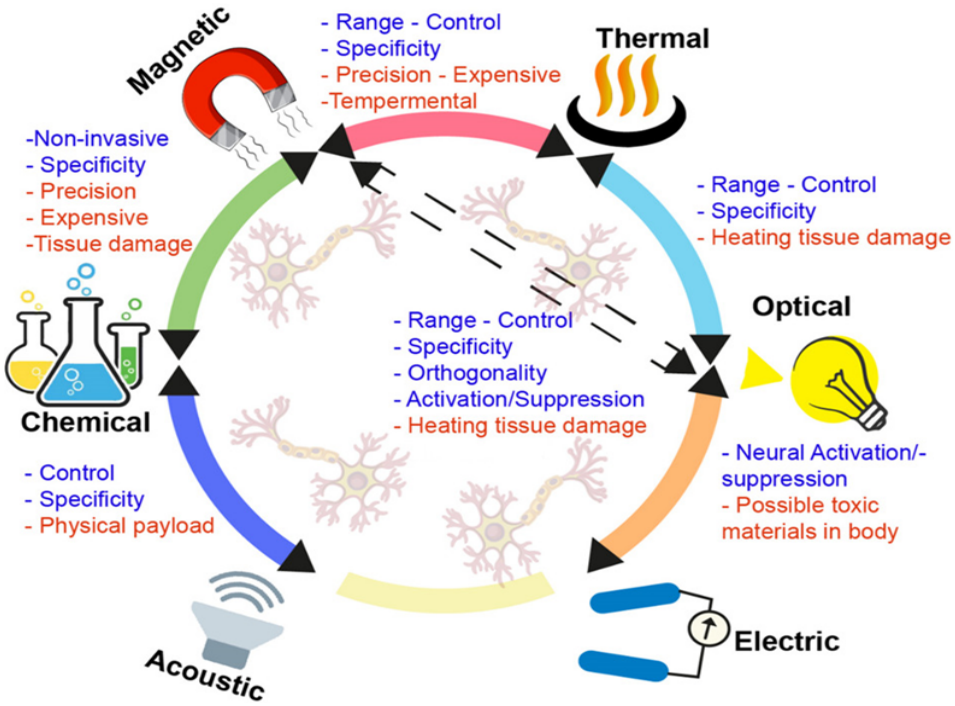


Figure 20. Main neurostimulation modalities, with coloured arrows depicting how they have been combined multimodally. (Source: Walton et al., 2021)

On the other hand, ***TES techniques*** include transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). Transcranial direct current stimulation (tDCS) consisting of the application of constant weak current (1–2 mA) to the brain via electrodes applied on the skin of the scalp, in correspondence with the specific cortical region (Boggio et al, 2015; Paulus, 2003).

tDCS can be used to treat focal onset and generalised epilepsies in children and adult patients who are not surgical candidates. Especially for young children who cannot tolerate the discomfort of magnetic stimulation or who move frequently during treatment, tDCS may be a more acceptable option (Auvichayapat et al, 2013; Auvichayapat et al, 2016; Tekturk et al, 2016).

Transcutaneous VNS (tVNS) is also a non-invasive technique intended to have effects similar to those of implanted VNS. It stimulates the auricular skin branch of the vagus nerve (Aihua et al, 2014; Rong et al, 2014). The tVNS device costs much less than the implanted VNS device and may provide bilateral stimulation that patients tolerate well, but the efficacy needs further investigation in epilepsy.

Finally, ***external trigeminal nerve stimulation (eTNS)*** is a non-invasive treatment for epilepsy that has been used in Europe, Canada, and Australia. The mechanism of eTNS treatment is like that of VNS, but the electrodes are placed non-invasively on both sides of the forehead (Soss et al, 2015). Based on published studies, eTNS is

not as effective as VNS. However, this method has several advantages: it is non-invasive and relatively inexpensive.

2.3.1 Portable non-invasive neurostimulation devices:

There is a wide range of methods and associated instruments to analyse brain activity in a non-invasive way: ***fMRI*** (functional magnetic resonance imaging), ***fNIRS*** (functional near-infrared spectroscopy), ***EEG*** (electroencephalography), ***MEG*** (magnetoencephalography), ***PET*** (positron emission tomography), etc.

All of them require the use of sophisticated machines to 'read ***the brain'*** (i.e., capture and measure brain activity) by measuring a variety of parameters of brain activity, from electrical activity to blood flow ***through a set of sensors located near the patient's head***.

The practical implementation of these methods required the development of ***expensive and very large machines*** that are not easy to integrate in a 'helmet-shaped' device due to the need to shield the patient's head from electrical or magnetic interference. Shielding allows sensors to avoid interference signals from the environment and capture only what is happening in the brain. Furthermore, these machines require the patient to sit still for the duration of the sampling to capture brain signals in a steady state, which prevents its use for children or persons in normal activity.

The technological advances in sensors and integration that occurred in recent years were crucial in developing a new generation of lighter ***non-invasive 'neurostimulation helmets' to deal*** with mental disorders with simpler and cheaper multisensory devices to stimulate the focused regions of the brain. Its commercial availability after approval from regulatory bodies has driven a huge world market with many potential users looking for treatment for depression, stress, etc., that involves no medication or for enhancing some abilities (e.g., sports).

To 'write ***the brain',*** it is also necessary to precisely generate 'signals' from specialised machines (helmet-based or not) to 'penetrate *the human skull',* if necessary, to reach internal regions ('deep *brain stimulation')* where specific brain neurons must be 'stimulated' to generate the intended functional neural responses. However, human brains (and the same happens in many other animals) have evolved over millions of years to prevent penetration to protect brain tissues. It is a fundamental well-known problem for effective non-invasive approaches.

Photobiomodulation (PBM)

The ***first generation of neurostimulation helmets based on Photobiomodulation*** (PBM) had many limitations and no clear therapeutic advantages for severe mental disorders. The precision to stimulate a deep brain region was not very high. Typically, transcranial PBM (tPBM) application and near-infrared (NIR) light is applied

to the forehead due to better penetration (no hair, longer wavelength) (Hamblin, 2016)

Box 11.

"Red/NIR light is able to stimulate complex IV of the mitochondrial respiratory chain (cytochrome c oxidase) and increase ATP synthesis. Moreover, light absorption by ion channels results in release of Ca2+ and leads to activation of transcription factors and gene expression. Brain PBM therapy enhances the metabolic capacity of neurons and stimulates anti-inflammatory, anti-apoptotic, and antioxidant responses, as well as neurogenesis and synaptogenesis.

*PBM therapy was developed more than 50 years ago; however, there is still no common agreement on the parameters and protocols for its clinical application. Some research teams have recommended the use of a power density of less than 100 mW/cm2 and an energy density of 4 to 10 J/cm2. Other research groups recommend as much as 50 J/cm2 at the tissue surface. Parameters like wavelength, energy, fluency, power, irradiance, pulse mode, treatment duration, and repetition rate can be applied in a wide range.". **Source:** Saleh et al., 2018*

The resolution level for allowing deep brain stimulation in a very specific brain region, which is injured or damaged resulting in a malfunctioning, is very poor; then, other types of more precise brain helmets are needed. Fortunately, advances in sensors have allowed the development of a second generation of helmets with more therapeutic advantages.

In collaboration with the team of Alim-Louis Benabid in Grenoble, France, several authors (Moro, C., Reinhart, F.) have been involved in testing the safety and efficacy of ***an implantable device for emitting light within the brain*** (i.e., intracranial PBM) (figure 21). The inspiration for designing such a device was to allow effective delivery of PBM to vulnerable midbrain neurons involved in Parkinson's disease.

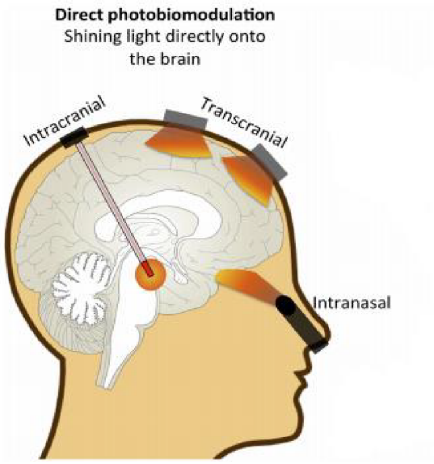


Figure 21. Examples of direct photobiomodulation. The image depicts different approaches for direct photobiomodulation of brain tissue, including transcranial, intracranial, and intranasal delivery. (Source: Gordon et al, 2019)

PBM is an innovative therapeutic approach that utilizes light in the red (with wavelengths usually in the range of 600 to 700 nm) or near-infrared region (780 to 1100 nm), at a relatively low power density to minimise tissue damage (Yang et al,

2020). Substantial focus has been placed on the PBM of the brain and nervous system, with a range of preclinical studies and some clinical trials producing promising results.

The team of Uri Oron has generated substantial evidence that 804-808 nm laser PBM of the bone marrow, achieved through irradiation of the exposed tibia, produces improved outcomes in several disease models (Blatt et al., 2016; Oron et al., 2014; Gordon, 2019), including a model of Alzheimer's disease.

Near-infrared (NIR)

It is a type of neurostimulation developed over ten years ago, which applies technology or laser light on tissue and temperature differentials (Wells et al, 2010). It has therapeutic properties and can be used as a navigating tool in surgical procedures or as a diagnostic tool in such interventions (ibid, 2010). The technique continues to be studied in brain diseases such as AD, Parkinson's, major depression, or ocular diseases.

Box 12.
The current and widely accepted proposal is that low level visible red to near infrared light (NIR) energy is absorbed by mitochondria and converted into ATP for cellular use. In addition, the process creates mild oxidants (ROS), which leads to gene transcription and then to cellular repair and healing. The process also unclogs the chain that has been clogged by nitric oxide (NO). The nitric oxide is then released back into the system. Nitric oxide is a molecule that our body produces to help its 50 trillion cells communicate with each other. This communication happens by transmission of signals throughout the entire body. Additionally, nitric oxide helps to dilate the blood vessels and improve blood circulation." ***Source:*** *https://pro.vielight.com/the-science/*

One example of this kind is the system marketed by ***gr8solutions*** (see Figure 22). It uses red or near-infrared light using a light-emitting diode (LED) to stimulate, heal, regenerate, and protect tissue that has either been injured or degenerating. The portable system depicted in the figure 22 consists of several components with a controller to adjust the intensity of the signal.

Figure 22. Advanced Helmet Multi Frequency 0 - 20,000 Hz with Touchscreen Controller (https://gr8solutions.com/summer-body-photobiomodulation-helmet-advanced/)

Some results on medical trials indicate actual improvements in patients' conditions after several cycles of neurostimulation. However, this technique requires additional clinical studies to check the effect of the temperature (increased significantly), and the optimal stimulation doses.

Figure 23 (on the left side) schematically depicts how NIR light penetrates, and the thermal images (on the right side) shows the effect in increasing the temperature with respect to the initial state (a) when no NIR light is generated[14].

[14] For a more technical description see: Shang-Ru Tsai and Michael R Hamblin Biological effects and medical applications of infrared radiation (2017). J Photochem Photobiol B. 2017 May; 170: 197–207. Published online 2017 Apr 13. doi: 10.1016/j.jphotobiol.2017.04.014 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5505738/

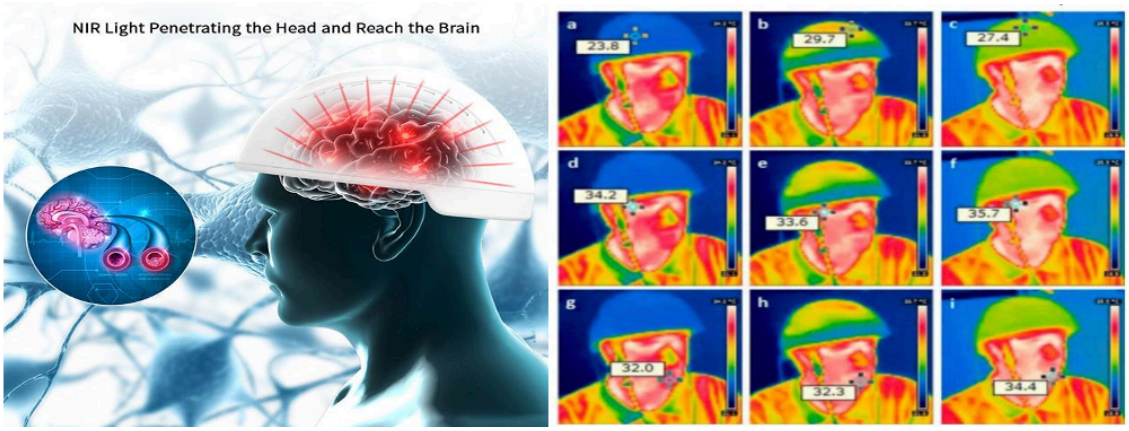


Figure 23. The effect of near infrared lit penetrating (left) and the thermal imaging (right) before, during and after treatment (Source: https://gr8solutions.com/summer-body-photobiomodulation-helmet-advanced/)

One company named ***Kernel*** (https://www.kernel.com/products), founded in 2016 (see box 13), has attracted the interest of investors and it has obtained the approval from the FDA for conducting clinical trials for using its product for measuring anxiety and depression with a more sophisticated approach.

Box 13.

"The U.S. Food and Drug Administration has approved a clinical trial using a neuroimaging helmet made by Los Angeles-based Kernel to track what happens in the brain when a human takes a psychedelic dose of ketamine. Cybin, a Toronto-based psychedelic therapeutics startup, is sponsoring the study. The study will begin before the end of the year with 15 patients at a ketamine-assisted therapy clinic in Marina Del Rey, California.

***Source**: https://www.forbes.com/sites/willyakowicz/2021/10/31/kernels-brain-imaging-helmet-approved-for-clinical-trial-on-patients-using-ketamine/?sh=4500cd4a6c15*

The product, ***Kernel Flow Helmet***, is a sophisticated and light (2.2kg for all 52 modules and the headset) multisensory helmet that measures NIRS (see Figure 24). Kernel has striven to close the gap by shrinking its sensors and finding smart ways to block electromagnetic interference (that were able to see and record more brain activity than any previous technology. The kernel device, which is about the size of a bicycle helmet, can be worn while the patient moves naturally.

Figure 24.Kernel Flow helmet (left) (source: https://www.bloomberg.com/news/features/2021-06-16/braintree-founder-s-helmet-size-hospital-aims-to-mine-mind-data) and the impact on the brain (right) (source: https://techohealth.com/how-kernel-neurotech-helmet-works

The basic technique of the kernel flow headset is a ***time-domain near-infrared spectroscopy TD NIRS system (Time-Domain NIRS System)***. *"As the name suggests, NIRS uses infrared light to measure brain activity. Specifically, a laser pressed against the head shines light into the body (...) the light travels through the various layers of skin, bone-brain, etc., bouncing around like so many pinballs"* (D'Anna, 2020). Some portion of the light is absorbed by the body, while some of it makes it back out after lots of bouncing around and can be measured. Figure 25 shows the way sensors are integrated into the Kernel Flow helmet.

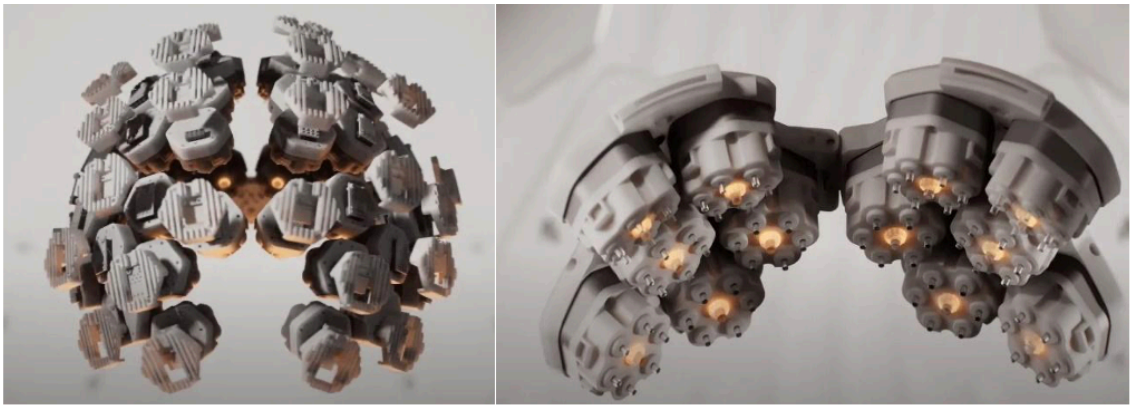


Figure 25. Sensors of Kernel Flow (source: https://techohealth.com/how-kernel-neurotech-helmet-works/)

Kernel flow uses pulses of infrared light to track cortical hemodynamic, or, in layman's terms, it uses ***lasers to track blood flow throughout the brain***. The helmet measures changes in blood oxygenation levels. As parts of the brain activate and neurons fire, blood rushes in to provide oxygen[15]. Flow takes advantage of this phenomenon by firing laser pulses into the brain and measuring the reflected photons to identify where a change in blood oxygenation has occurred. Different regions of the brain, under the influence of psychedelics, interact with other regions. The Kernel Flow helmet can measure interactions in real time.

[15] Blood also carries proteins in the form of haemoglobin, which absorbs infrared light differently when transporting oxygen. This is why the veins are blue, but we bleed red.

Another specific type of helmet-based is the ***EEG neuro stimulation device.*** State-of-the-art electroencephalogram (EEG) wearable technology relies on signal processing and machine learning tools to capture mainly temporal features that can be linked to a specific task.

Researchers are providing new models capable of capturing spatio-temporal dependencies, to be later used to determine which regions need to be sensed and which data contain more 'information'. Then, designers can leverage these insights to rethink wearable technology, by possibly minimising the number of sensors prescribed to monitor brain dynamics, which implies a smaller energy requirement and, hence, more autonomy. Figure 26 shows the bases of these systems, where electrical stimulus can be directed to a relatively large number of small areas.

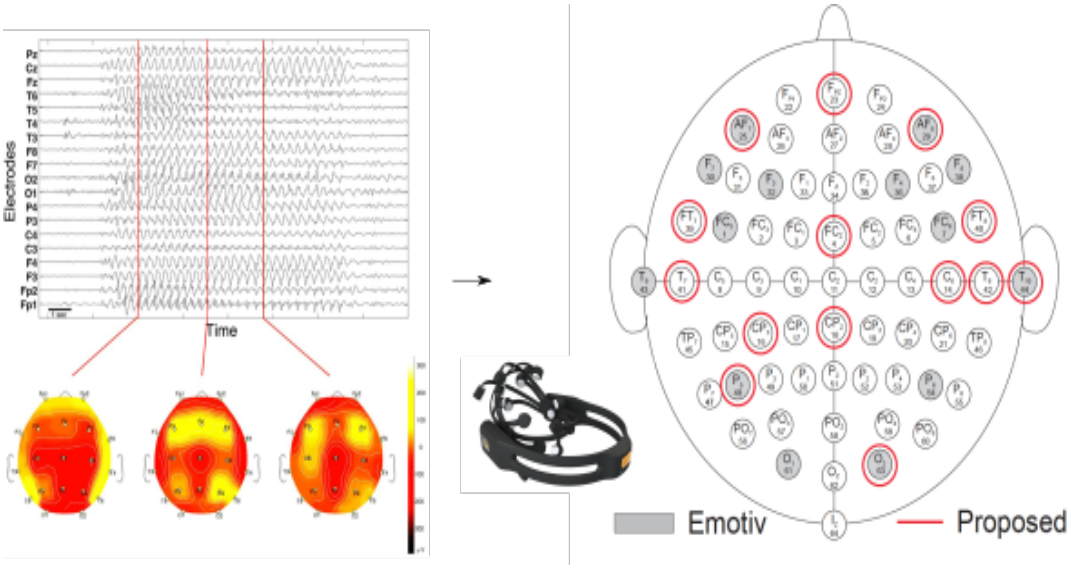


Figure 26. Bases of EEG neurostimulation devices (source: spequito, 2022)

Several start-up are entering the market with advanced solutions in the last five years. An example of a company with this type of product is **BitBrain** (https://www.bitbrain.com/). They do not need to adopt a full helmet structure as depicted in Figure 27, but simply a structural support to keep the sensors. The product is a portable and wireless *"semi-dry EEG cap"* with 8, 16, 32 and 64 channels for real-world research, providing freedom of movement to the user.

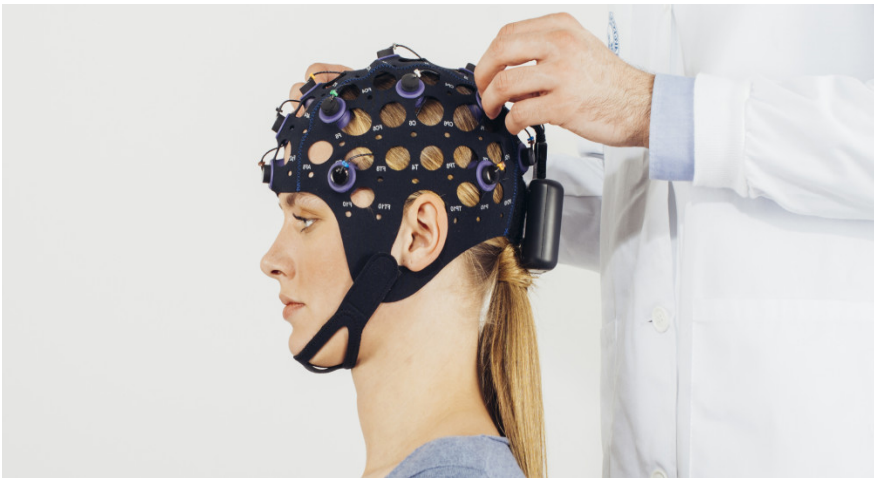


Figure 27. High-quality EEG that records with a resolution of 24 bits at 256Hz for 6+ hours thanks to active shielding with stable sensor contacts. (source: https://www.bitbrain.com/neurotechnology-products/semi-dry-eeg/versatile-eeg)

Its ***water-based EEG electrodes*** can be placed in any position or the predefined layout within the 10/20 and 10/10 international system and have been developed with highly stable contacts and active shields that allow for reliable and precise monitoring even in ambulatory conditions or in the presence of electromagnetic noise.

Another device of the same company is a ***"dry EEG" device***. It is a high-quality EEG that records with a resolution of 24 bits at 256Hz for 3+ hours thanks to active shielding with stable sensor contacts (see Figure 28). Ultralight design with flexible arcs and adjustments to ensure great comfort. Bluetooth streaming and SD storage on board.

Figure 28. Hero device from BitBrain.(Source: https://www.bitbrain.com/neurotechnology-products/dry-eeg/hero)

Developed with nine dry electrodes on specific areas of the brain (fronto-central, central, and centro-parietal areas), it ***is optimised for the estimation of cognitive and sensorimotor states***. Its high-performance active shielding and stable mechanical design provide outstanding robustness and signal quality, even with movement or during long recording periods. The company is applying it to improve sleep quality in a R&D project 'Wearable Neurotechnology for Improvement of Sleep Quality' funded by the EU within the EU H2020 program.

On the other hand, using magnetism rather than electrical stimulation offers several advantages. First, the shape of the coil leads to anisotropic shaping of the electric field that accompanies the magnetic field—this brings forward the possibility of selectivity stimulating neurons of a particular orientation, increasing precision. Second, magnetic stimulation does not require contact with the targeted neurons; magnetic fields pass readily through biological tissues, enabling greater range, as well as reducing the damage to the electrode/coil and tissue due to high amounts of charge (Walton et al., 2021).

A promising alternative is **micromagnetic stimulation (μMS)** due to the high permeability of magnetic field through biological tissues. The induced electric field from the time-varying magnetic field generated by magnetic neurostimulators is used to remotely stimulate neighbouring neurons. Due to the spatial asymmetry of the induced electric field, high spatial selectivity of neurostimulation has been realized. Furthermore, magnetic nanoparticles (MNPs), as another invaluable neurostimulation material, has emerged in recent years.

One interesting company in this field is the medical device maker ***Brainsway***[16]. It has entered the market for to treat a host of brain disorders such as obsessive compulsion and depression (OCD), as well as smoking addiction. The system is represented in Figure 29 with two types of coils for major depression (left) and for obsessive compulsion OCD (right).

Figure 29. Brainsway helmet system. (source: https://magneticsmag.com/brainsway-poised-to-grow-neurostimulation-market/)

The treatment utilises a magnetic field emitted by BrainsWay's patented H7 coil to directly reach broader and deeper brain regions than its predecessors, regulating the neural activity of brain structures associated with OCD and depressions. (Neurogenesisclinics, n.d.)

[16] Founded in 2003, Brainsway operates from offices in Cresskill, NJ and Jerusalem, Israel.

Box 14.
"The BrainsWay technology received FDA clearance for the treatment of major depressive disorder in 2013 and for the treatment of OCD in 2018. More recently, it was FDA-cleared as an aid for short-term smoking cessation. In April, Brainsway was granted FDA clearance for its Theta Burst three-minute protocol utilising its Deep TMS system for the treatment of major depressive disorder. In June 2021 the company received another authorization for insurance coverage of OCD treatment using its Deep TMS transcranial magnetic stimulation system, the latest one coming from Health Care Service Corporation". **Source**: https://magneticsmag.com/brainsway-poised-to-grow-neurostimulation-market/

Advances in the materials used for sensors, better alignment techniques, and laser generation, could provide more precise helmets both for brain reading and writing functions for a wider range of brain diseases.

Box 15.
"It's a classic European success story, having started life as a research project funded by the EU's Graphene Flagship Project, a €1bn effort to find commercial applications for the material. Barcelona-founded brain science startup Neuroelectrics has raised $17.5m to fund a Phase 3 clinical trial that could transform the lives of millions of people suffering with epilepsy. A recent pilot study of 20 participants showed that Neuroelectrics' neurostimulating electrical headcap, Starstim, can significantly reduce seizures in patients with treatment-resistant epilepsy, non-invasively.". **Source**: *Neuroelectrics raises $17.5m to transform epilepsy treatment | Sifted*

An interesting medical area is to provide neurostimulation solutions to relieve chronic pain. As an example of the product available within this area, three companies are selected:

- **BioElectronics Corporation** (http://www.bielcorp.com/) is an award-winning developer and manufacturer of innovative consumer medical devices that are designed to treat both acute and chronic pain. These medical devices are a *pioneering advance in pulsed short-wave therapy*. Advances in microelectronics have allowed the delivery of clinically proven superior extended-duration therapy in a small, convenient, and economical medical device. The company boasts four FDA 510 (k) clearances for its PSWT devices, backed by safety and effectiveness data from five randomized, controlled clinical trials and numerous other registry trials.
- **CEFALY Technology** (https://www.cefaly.com) is a Belgian company that specialises in electronic devices for medical applications. Although the causes of migraine are not fully understood, current research shows that the largest and most complex cranial nerve, the trigeminal nerve, is heavily involved in the sensation of migraine headache pain. CEFALY DUAL has been specifically engineered to *modify the pain sensation in the trigeminal nerve through its ophthalmic branch, which runs under the skin of the forehead*.

- **Galvani Bioelectronics** (https://galvani.bio/)[17]. Galvani Bioelectronics is a pioneering medical research company dedicated to the development of bioelectronic medicines to treat chronic diseases. Galvani has developed a *neuromodulation platform with components that are suitable for modulating multiple nerve targets*. The implantable components are designed to be inserted via a minimally invasive laparoscopic procedure with the intent to reduce patient discomfort and recovery times.
  The company has announced in January 22 that the first patient with Rheumatoid Arthritis (RA) has been treated through stimulation other splenic nerve using its novel bioelectronics platform. The investigational treatment is the first in the clinic of a new class often referred to as 'bioelectronic medicines' that stimulate nerves specific and near to individual visceral organs central in disease. The Galvani System is an investigational device and is not available for sale.

2.4 Future of Neurostimulation Helmets and Related Wearables for Health and Wellbeing

Today, the helmet-based systems presented above were developed for medical or research purposes with a limited number of end-users. But this situation is rapidly changing. Obviously, commercial companies are very interested in applying some of the neurostimulation techniques to other non-medical uses to expand their potential customer basis. If neurostimulation demonstrates its usefulness to enhance some functions in non-patients (e.g., for improving sport performance or enhancing memory capabilities for aged people or students), the potential number of users could dramatically grow in the future.

These uses are driven by a better understanding of brain functions and the accumulated evidence of the effect that electrical stimulation can generate in some regions. This evolutionary scenario, maybe within the 2030 horizon (beyond that period, other disruptive breakthroughs could appear which will push other scenarios), will be driven by four complementary forces[18]:

- **Technical advances in sensors, lasers, imaging processes, etc. will offer better time and space resolution than the current generation of sensors can provide.**

  The consequence is the possibility to read brain activity by detecting weaker signals and to provide more precise stimulation in smaller brain regions (in the range of mm.). Furthermore, the rest of the system as controllers and software

[17] Formed through a partnership between two global healthcare companies, GlaxoSmithKline (GSK) and Verily Life Sciences (formerly Google Life Sciences), a subsidiary of Alphabet Inc., Galvani Bioelectronics combines GSK's life science knowledge with Verily's expertise in software and electronics for clinical applications.

[18] The future of neurostimulation: Smart neuromodulation (neuronewsinternational.com) https://www.sciencetimes.com/articles/33317/20210908/ai-powered-neurostimulation-mapping-treat-chronic-pain-developed-google-research.htm

packages will evolve too with less energy consumption (more autonomy), and more intelligence in signal processing. Based on that, the range of users and applications will expand.

- **Strong reduction in cost, space, weight, maintenance, etc. which will facilitate the adoption of these systems by a larger number of users.**

  Usually, the learning curve of manufacturers and the number of customers have been key factors in reducing the costs of final products. In addition, miniaturisation in electronics, lasers, sensors, etc. will make these helmets cheaper, lighter, and easier to maintain. Then, it is very possible to see faster adoption rates as mass media gadgets for average citizens in the same way that smartphones and other wearables have shown in the past.

- **Time reduction in the approval of neurostimulation helmets as medical devices by regulatory bodies.**

  The marketing of neurostimulation helmets as medical devices for clinical use in patients with some neuro diseases (e.g., epilepsy, dementia, Parkinson, depression) is conditioned by its approval by regulatory agencies. If on-going modifications in the regulation of medical devices were finally adopted, the time required to enter the market and launch clinical trials could be dramatically reduced. This process could facilitate the creation and scale-up of technology-based start-ups in the field of neurostimulation helmets.

- **Share of clinical practises and protocols in the application of these systems to a broader range of neurological diseases.**

  The development of multicentric clinical trials, the sharing of data collected during those trials, and the use of digital platforms where curated data could be retrieved will provide the bases for a consolidation of clinical protocols on the use of medical devices in many hospitals. Then, the clinical (professional) market will grow, where neurostimulation helmets could become part of the usual equipment not only in neurology, but also in psychiatry, and in pain relief units.

Let us finish this section with a view on the future evolution of mobile communications (see figure). Telecom operators are deploying 5G which implies a huge leap forward in bandwidth, low latency, and density to connect all devices (mobile internet of things), but it is still a conventional approach.

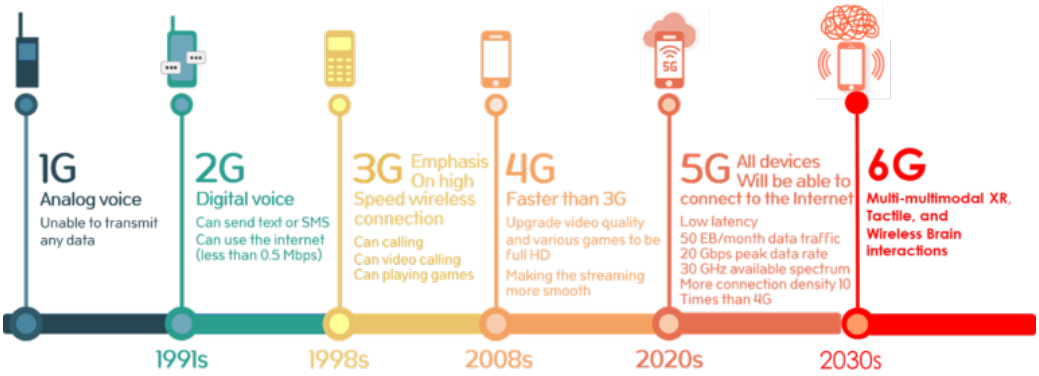


Figure 30. Evolution of mobile communications. (source: Gashemian et al., 2022)

During this decade, 6G will be on the road which will imply the availability of not only multimodal and multisensorial (haptic) communications[19], but it is also the way to move to ***"wireless brain interactions"***. For that vision, technology should provide a new generation of wearables linked to brain interfaces, and latency should be less than 1 ms which is necessary for haptic scenarios.

Box 16.
In addition to shaping technology capabilities, the standards are defining the service requirements as well, with many of the key performance indicators (KPIs) for this technology coming directly from neuroscientists. From telesurgery to gaming to simply alerting pedestrians on the street, KPIs like one-millisecond latency are coming directly from neuroscientists, biologists, and other individuals who understand what the minimum perceived delay in a tactile or haptic scenario needs to be. While the standards targeting one millisecond latency are geared towards interactions involving humans, applications involving robotics can perceive much lower latencies –as low as 125 microseconds – at levels that humans cannot perceive. Those specifications will also need to be written into the standards as well, based on information from the appropriate robotics experts. **Source**: Gashemian et al., 2022

2.4.1 Optically pumped magnetometer (OPM)

In this section, we have included a brief analysis of the potential of a new approach to measuring brain activity using helmets known as the ***"Optically Pumped Magnetometer" (OPM)***. Formally, it is not a brain stimulation technique because it only reads the brain activity and, if not complemented with another technique, it cannot provide signals to stimulate one specific brain region and to close the loop.

Traditionally, the only way to detect the extremely small magnetic fields generated by the brain (a billion times smaller than the Earth's magnetic field) was to exploit ***superconducting sensors known as SQUIDs***. The SQUIDs must be kept at cryogenic temperatures (-269 ° C), which means that the sensors in a conventional MEG system

[19]Multimodal communication involves the exchange of haptic data (including position, velocity, and interaction forces) and other user modalities (like audio, visual, gestures, head movements and posture, eye contact, facial expressions, and user's emotion).

must be immersed in liquid helium. This, in turn, makes scanners heavy and very expensive. This has proven to be a significant barrier to widespread uptake of MEG.

OPMs rely on the manipulation of a quantum property known as spin (a property that underlies a particle's magnetic moment and therefore its response to a magnetic field). With OPMs, optical pumping is used to manipulate the atomic (i.e., both nuclear and electron) spin. Although the physics fundamentals were set up in the fifties of the XX century, its medical use was only possible some years ago when its use for brain imaging was set and clinical applications appeared. The development and fabrication of OPMs exploit the quantum properties of alkali atoms to measure very small magnetic fields. The sensitivity of OPMs rivals that of superconducting devices, used in conventional MEG systems, but OPMs do not require cryogenic cooling and reduce the size (Cercamagnetics, 2022).

Optically pumped magnetometers are incredibly sensitive, picking up subtle magnetic fields on the quantum scale of femtoteslas, about a billion times smaller than the Earth's magnetic field. The optically pumped magnetometer sensors work by passing a laser beam through a glass cell filled with vapour. Magnetic fields generated by the brain shift the vapour's atomic energy levels in the cell, either enhancing or fading the light current. The cell sensor detects changes in the laser beam and produces an electric current proportional to the amount of light passing through it, converting a magnetic signal into an electric one.

The field is continuously advancing. Wang et al., (2021) have recently published improvements with magnetic field compensation (Figure 31). In (a) an internal schematic of a general OPM is described. A Laser light is shone through a glass cell containing a vapour under high pressure. The amount of light detected at the photodiode is a function of the ambient magnetic fields perpendicular to the axis of the laser beam (Bz and By). In (b) a Gen-2 Quspin OPM can be seen with the directions of the measured magnetic fields, laser and position of vapour cell. In (c) an OPM array of 17 sensors inserted into a wearable scanner-cast is displayed.

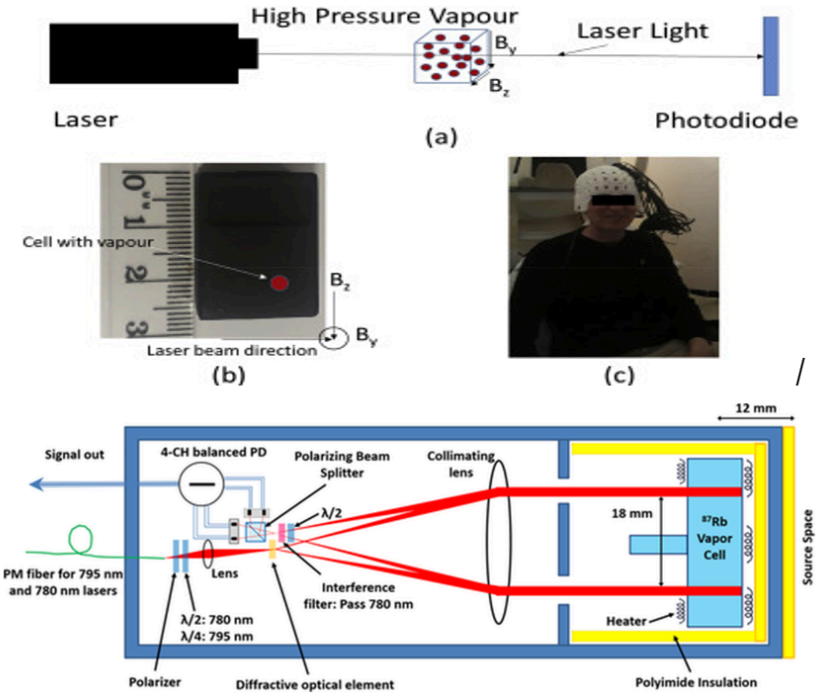


Figure 31. The OPM sensor's schematic. depicts the scheme of an OPM sensor. PBS: polarising beam splitter; PM: polarisation maintaining, PD: photodiode, λ/2: half wave plate, λ/4: quarter wave plate. (Source: https://doi.org/10.1371/journal.pone.0227684.g002

Other researchers at the *Fralin Biomedical Research Institute* at Virginia Tech have also received funding from the NIH to measure the subtle magnetic signals of the brain in two research volunteers simultaneously during face-to-face social interactions, capturing the rich complexity of brain signalling in real time. Figure 32 presents the system developed by Virginia Tech (USA).

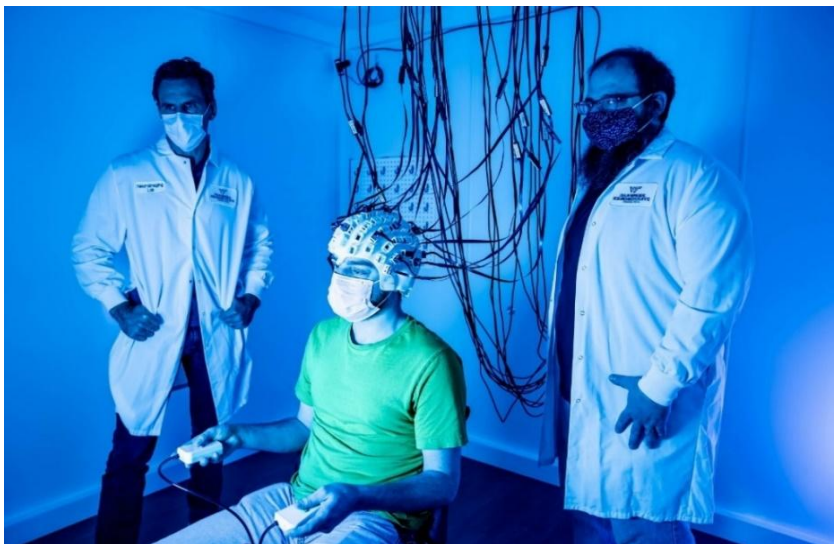


Figure 32. Virginia Tech system. (source: https://vtx.vt.edu/articles/2021/05/virginia-tech-launches--next-generation--human-brain-imaging-lab.html)

Compared to conventional MEG systems, OPM-MEG (see table 1) presents many distinctive useful features for brain imaging:

Feature	SQUID-MEG	OPM-MEG
Environment	Shielded environment 30nT[20]	Shielded environment
Footprint	4 m x 3 m shielded room	From 1.3 m x 1.3 m shielded room
Sensor	Cryogenic (liquid helium-cooled) SQUID	Non-cryogenic OPM
Scanner weight	>500 kg	
Age of patient	Optimised for adults	Suitable for all ages
Movement	Patients must remain still	Patients can move during scan
Range of use	Brain only	Brain, heart, spine, muscles, gut, foetal monitoring
Sensitivity	Limited due to distance from head	Closer proximity - higher sensitivity
Spatial resolution	Limited due to distance from head	Closer proximity - higher spatial frequencies
Cost (approx.)	EUR 2.5 million	EUR 1.3 million
Diffusion (2021)	Less than 100	Less than 10

Table 1. Comparison between conventional MEG and OPM-MEG (source: own elaboration adapted from CERCA)

The analysis of the Table 1 shows some striking differences between a conventional MEG and one OPM-MEG (see Figure 33). Unfortunately, shielding is still a problem, even when OPM-MEG requires a substantially smaller room[21]. The use of helium is also another problem which makes more expensive the use of MEG technology. Maybe, in the future other types of helmets with embedded electromagnetic noise reduction could be developed to reduce the external shielding requirements.

[20] Conventional MEG systems are housed inside a magnetically-shielded room (MSR) which comprises multiple layers of high permeability material known as MuMetal®, as well as a single layer of highly conductive material such as copper. This acts to reduce magnetic interference (i.e., magnetic fields that vary over time), however in conventionally designed rooms, the presence of the metal means that there is a residual static magnetic field.

[21] Typically, the cost of the shield-room for a conventional MEG is about EUR 0.5 million.

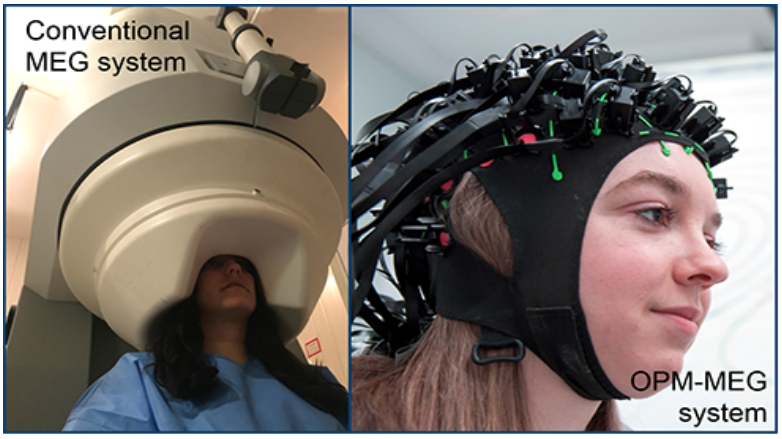


Figure 33. Comparison between conventional MEG and OPM-MEG system (source: https://www.birmingham.ac.uk/university/colleges/eps/news/2021/an-interview-with-cerca-developers-of-the-world's-most-accurate-brain-scanner.aspx

2.4.2 Dual application of neurostimulation

For the European Union *"Dual use goods are products and technologies normally used for civilian purposes, but which may have military applications"*. Neurostimulation is one of these cases.

The launching in 2018 of the N3 (Next-Generation Nonsurgical Neurotechnology) programme by DARPA (The Defence Research Agency of the USA) continued the Targeted Neuroplasticity Training (TNT) program started on 2016[22]. The N3 program aims to develop a safe, portable neural interface system capable of reading from and writing to multiple points of the brain at once. Whereas the most advanced existing neurotechnology requires surgical implantation of electrodes, N3 is pursuing high-resolution technology that works without the requirement for surgery so that it can be used by able-bodied people (see figure 34).

[22] The TNT program aims to explore various safe neurostimulation methods for activating synaptic plasticity, which is the brain's ability to alter the connecting points between neurons — a requirement for learning. DARPA hopes that building up that ability by subjecting the nervous system to a kind of workout regimen will enable the brain to learn more quickly.

Figure 34. https://medium.com/hummtech/darpa-and-the-brain-initiative-5fa45e9557a#:~:text=DARPA%2C%20as%20an%20organization%2C%20has%20a%20history%20of,interfaces%20and%20neurostimulation%2C%20with%20medical%20and%20technological%20applications

The N3 teams are pursuing a range of approaches that use optics, acoustics and electromagnetics to record neural activity and send signals back to the brain at high speed and resolution. The research is split between two tracks. Teams are pursuing either ***completely noninvasive interfaces*** that are entirely external to the body or ***minutely invasive interface systems*** that include nanotransducers that can be temporarily and non-surgically delivered to the brain to improve signal resolution.

DARPA was looking for multidisciplinary research by combining research results in neuroscience, cognitive psychology and physiology for the improvement of personnel in the Army. The programme was open to academics and private entities[23]. Two examples of the funded projects are BrainSTORMS led by Batelle and MOANA led by Rice University.

The ***BrainSTORMS (Brain System to Transmit or Receive Magnetoelectric Signals)*** project by Battelle for EM transducers aims to develop a minutely invasive interface system that pairs an external transceiver with electromagnetic nano transducers that are non-surgically delivered to neurons of interest. The nanotransducers would convert electrical signals from the neurons into magnetic signals that can be recorded and processed by the external transceiver, and vice versa, to enable bidirectional communication. See these nanotransducers in figure 35.

[23] Battelle Memorial Institute, Carnegie Mellon University, Johns Hopkins University Applied Physics Laboratory, Palo Alto Research Center (PARC), Rice University, and Teledyne Scientific were funded to lead multidisciplinary teams in the first phase of N3. https://www.technocracy.news/darpa-funding-wearable-brain-machine-interfaces/

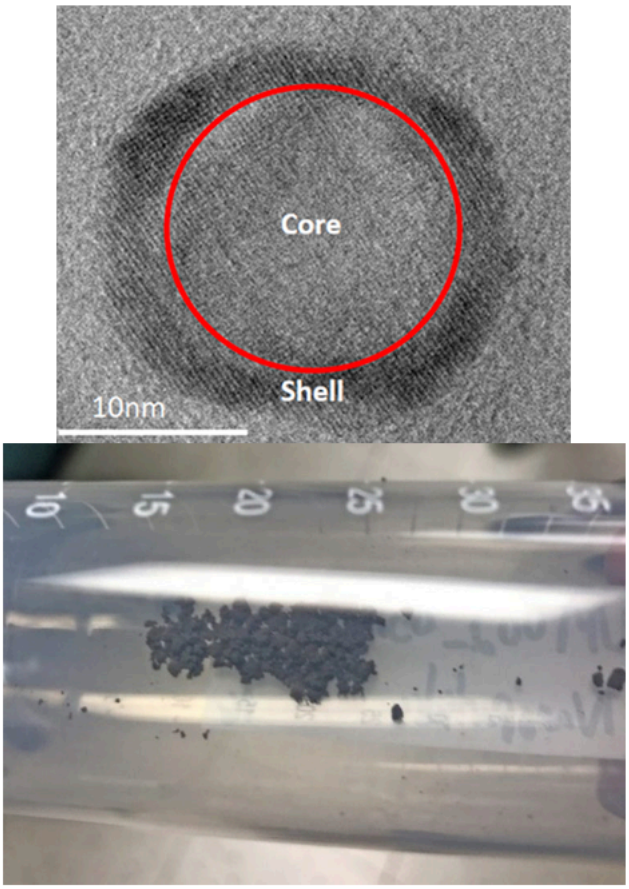


Figure 35.Single nanotransducer MEnT (left) and multiple MEnTs (right) (Source: https://magneticsmag.com/magnetism-plays-key-roles-in-darpa-research-to-develop-brain-machine-interface-without-surgery/)

The BrainSTORMS programme will continue in the second phase of N3 to develop a high-performance, bi-directional brain-computer interface (BCI) for clinical applications or for use by able-bodied members of the military. As DARPA explicitly mentions (see figure 36) *"neuronal connection are tuned to improve cognitive skills"* (for patients or not) [24].

[24] The debate on this ethical aspect of the TMS application for the possible induction of supernormal capacities of brain activity brings to the debate of the Transhumanist current in philosophy which is beyond the scope of this report. This philosophical current can be defined as *"Philosophies of life that seek the continuation and acceleration of the evolution of intelligent life beyond its currently human form and human limitations by means of science and technology, guided by life-promoting principles and values "* (More, M., 1990

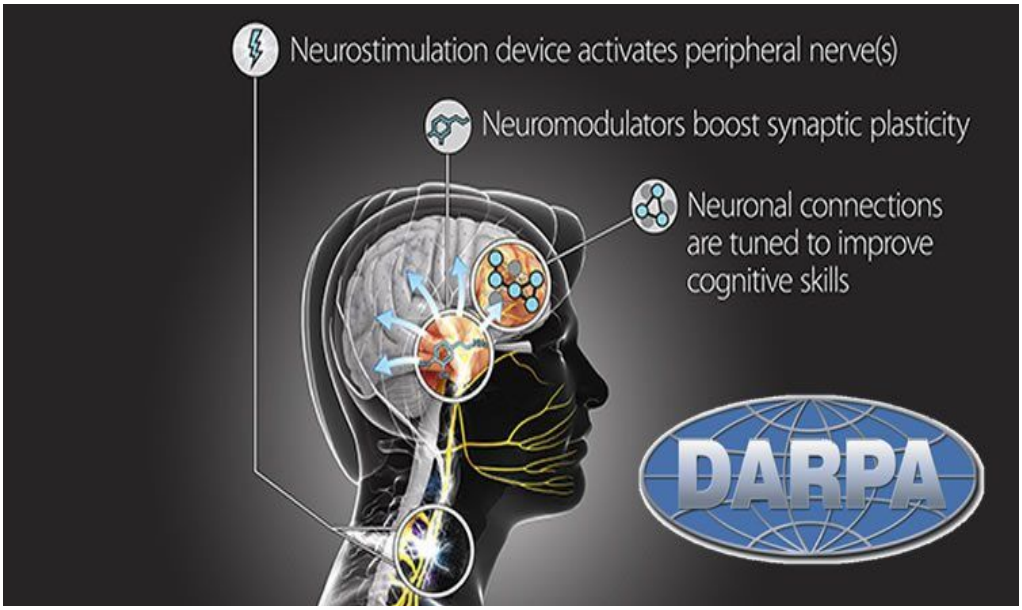


Figure 36.DARPA TNT and N3 programmes. https://www.technocracy.news/darpa-hacking-human-brain-upload-skills-directly/

The *MOANA (Magnetic, Optical and Acoustic Neural Access)* project, led by Rice University aims to develop a minutely invasive, bidirectional system for recording from and writing to the brain. For the recording function, the interface will use diffuse optical tomography to infer neural activity by measuring light scattering in neural tissue. To enable the write function, the team will use a magneto-genetic approach to make neurons sensitive to magnetic fields (see figure 37).

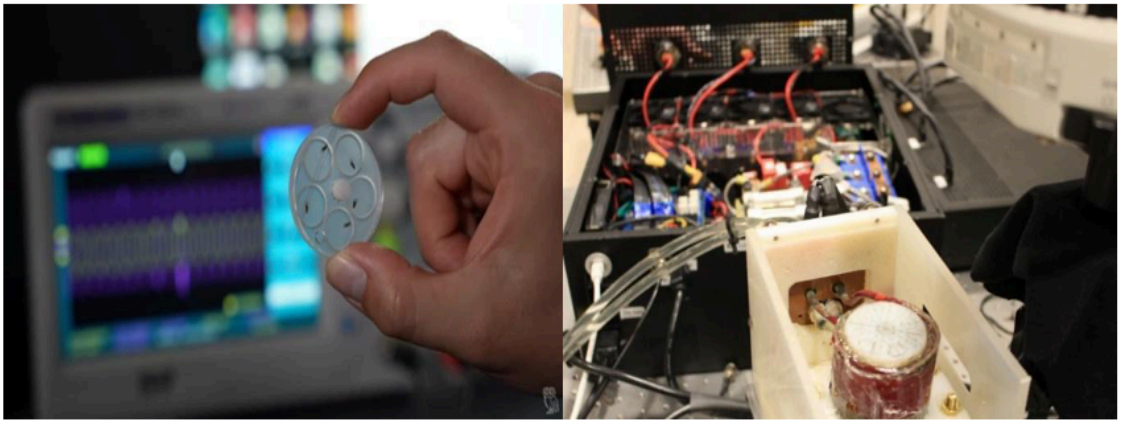


Figure 37.MOANA results. (Source DARPA)

Box 17.
MOANA technical details.
The objective is to design to provide a high-bandwidth brain-computer-interface without the need for a surgically implanted device. The device will consist of an array of flexible complementary metal–oxide–semiconductor (CMOS) chiplets that can conform to the surface of the scalp and implement our optical readout technology based on Time-of-Flight Functional Diffuse Optical Tomography (ToFF-DOT).
In addition, a magnetic stimulation array will be fitted into a head cap to activate genetically engineered magnetic sensitive ion channels. This stimulation and readout

technology will communicate wirelessly with a base station and will fold into a volume of < 125 cm3. The modular system is planned to be configurable to cover any portion of the head to interface with multiple cortical regions.
***Source**: https://magneticsmag.com/magnetism-plays-key-roles-in-darpa-research-to-develop-brain-machine-interface-without-surgery/*
MOANA uses viruses to deliver two extra genes into the brain. One encodes a protein that sits on top of neurons and emits infrared light when the cell activates. Red and infrared light can penetrate through the skull. This lets a skull cap, embedded with light emitters and detectors, pick up these signals for subsequent decoding. Ultra-fast and ultrasensitive photodetectors will further allow the cap to ignore scattered light and tease out relevant signals emanating from targeted portions of the brain, the team explained.
***Source**: https://www.killerrobots.org/2021/09/03/darpa-developed-nonsurgical-brain-interfaces-to-control-drones-using-thoughts/*

Regardless of the final scientific and technological results obtained in the N3 programme, DARPA was looking for dual use technologies. The expected results in the six funded projects could have civil applications (for instance, MOANA could help blinded people[25]), but also military applications (MOANA could be used to control multiple drones using thoughts).

DARPA was aware of the ethical, legal, and regulatory consequences derived from the development of the N3 programme. For that reason, it invited regulatory agencies to participate in the writing support and evaluation of proposals to match with the requirements from Investigational Device Exemptions and Investigational New Drugs. Furthermore, independent legal and ethical experts advised the agency as the N3 program was being formed and will continue to help DARPA think through new scenarios that arise as N3 technologies take shape.

Worries about the bad use of technology are not new. It has also appeared for many disruptive technologies (e.g., AI) and it could also happen for neurotechnology (box 18).

Box 18.
"The problem of dual use in neurotechnology is exacerbated by the fact that national security and military applications are not the only way to repurpose civilian neurotechnologies. Misuse by malevolent individuals or groups is likely to become a concrete risk in the near future. Proliferation of both civilian and military neurotechnology is increasing the chances that neuro-devices could land in the wrong hands.
Malevolent uses of neurotechnology could be potentially performed not only by individual actors, but also in the context of organized criminality, terrorist organizations, and other State and non-State actors, hence raising global security concerns." **Source**: Lenca, Jotterand and Elger, 2017

[25] In the second round of DARPA funding the team coordinated by Rice University will demonstrate that the system can work in a real brain, beginning with rodents. If the demonstrations are successful, they could begin working with human patients within two years.

One of the key issues is to understand the bases for a regulation on neurostimulation, to agree on a set of principles, and to develop a consensus on the regulation. This is still an open issue.

2.5 Emerging technological breakthroughs

2.5.1 Patent analysis

One of the most relevant sources for understanding future breakthroughs is access to ***patents documents***. They are open documents where protection of the idea for 20 years is provided based on making public detailed technical information and, hopefully, to speed-up the innovation rate. The analysis of these documents in one specific field can also provide statistical information not only on the number of patent documents and its evolution over time, but also, countries, inventors, and language.

The access to the patents database of the European Patents Office (EPO) named ESPACENET delivers 454 documents under the term ***"neurostimulation"*** in the period 2010-2021. The list is strongly dominated by the US with 882 patents. If the query in ESPACENET is on the term ***"neuromodulation"***, it delivers 569 patents in the period 2010-2021 and 233 in the period 2020-2021, slightly higher than for "neurostimulation". For the purposes of this document, we will continue the analysis on the term neurostimulation.

It is possible to make more detailed queries. For instance, the query on ***"neurostimulation helmet"*** delivers a total of 30 results (10 in the period 2020-2021). The search on the term "***Optically pumped magnetometer***" delivers 144 results in 2010-2021, when the results in the period 2020-2021 is 87. These data are useful to understand the evolution of the scientific interest in one specific technology of the searching terms are well selected.

Coming back to the search on neurostimulation, ESPACENET can show the evolution of patents in a given period (see figure 38 for the period 2010-2021, and figure 39 for the period 2020-2021. Globally, they reflect the interest in neurostimulation and pave the way towards new generation of products.

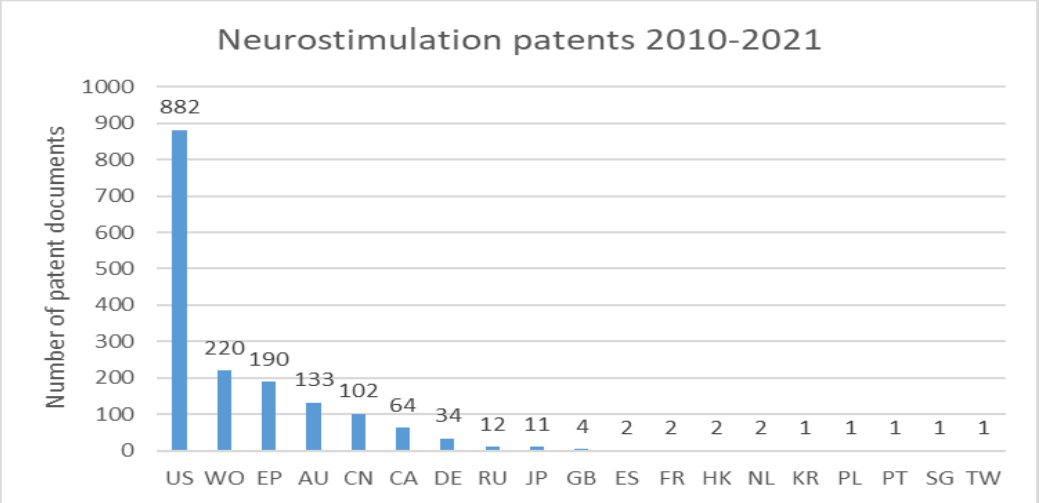


Figure 38. Neurostimulation patents 2010-2021 (Source: ESPACENET)

Focusing the analysis on the last two years, the US is still the most relevant country with 108 patents, but the EU (European patents, EP) is the second one with 40.

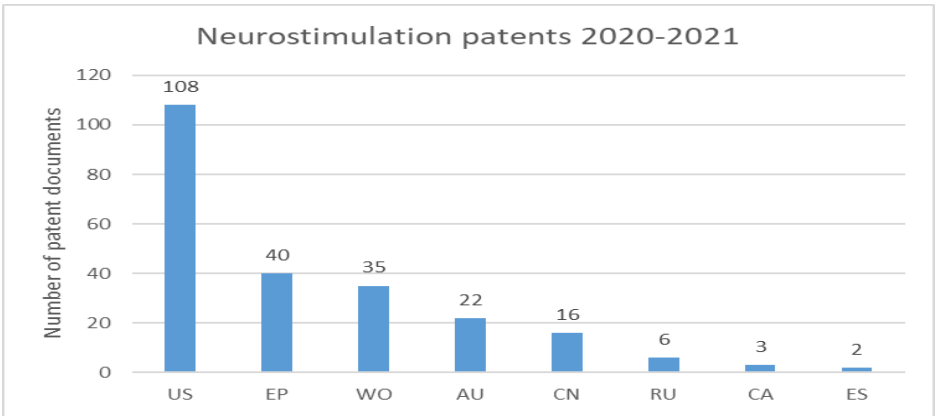


Figure 39. Neurostimulation patents 2020-2021 (source: ESPACENET)

A ***triadic patent family*** is defined as a set of patents registered in various countries (i.e. patent offices) to protect the same invention. Triadic patent families are a set of patents filed at three of these major patent offices: the European Patent Office (EPO), the Japan Patent Office (JPO) and the United States Patent and Trademark Office (USPTO). Triadic patent family counts are attributed to the country of residence of the inventor and to the date when the patent was first registered. This indicator is measured as a number.

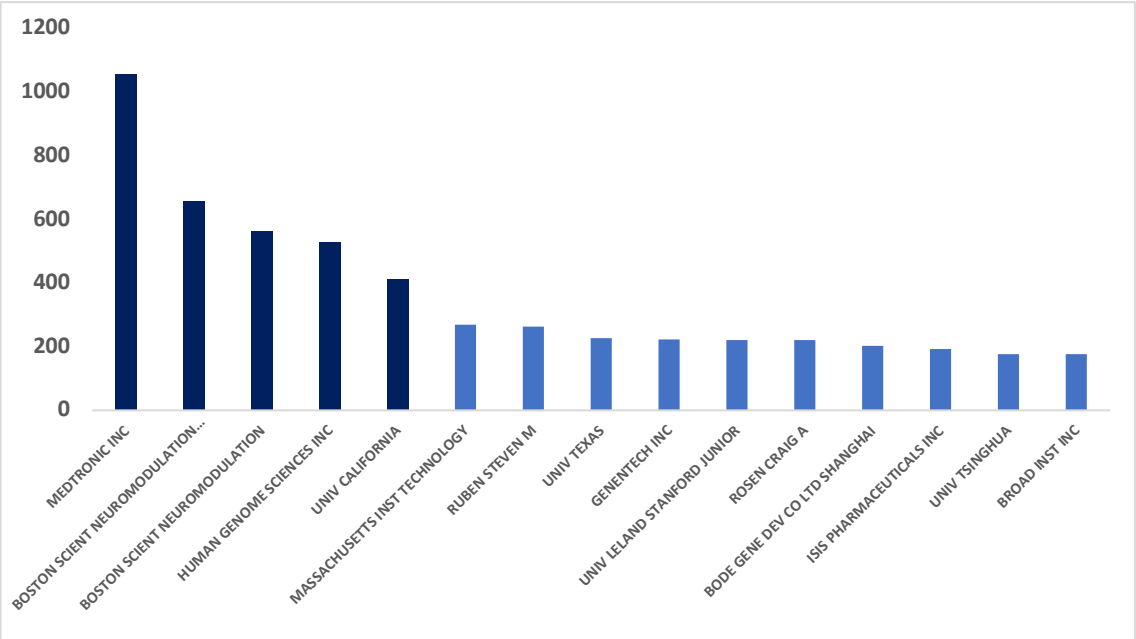


Figure 40. Neurostimulation patents (Deep brain stimulation) by the medical device company. (Source: ESPACENET)

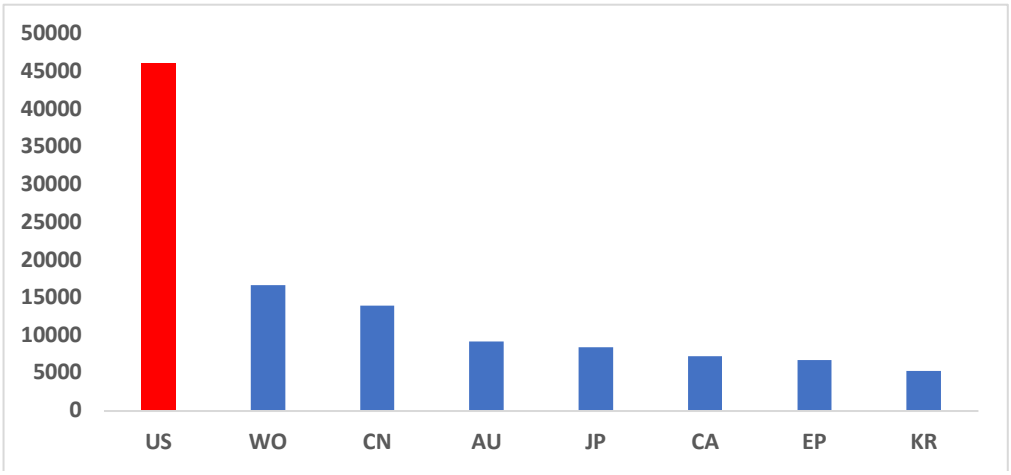


Figure 41. Neurostimulation patents (Deep brain stimulsation) by countries. (Source: ESPACENET)

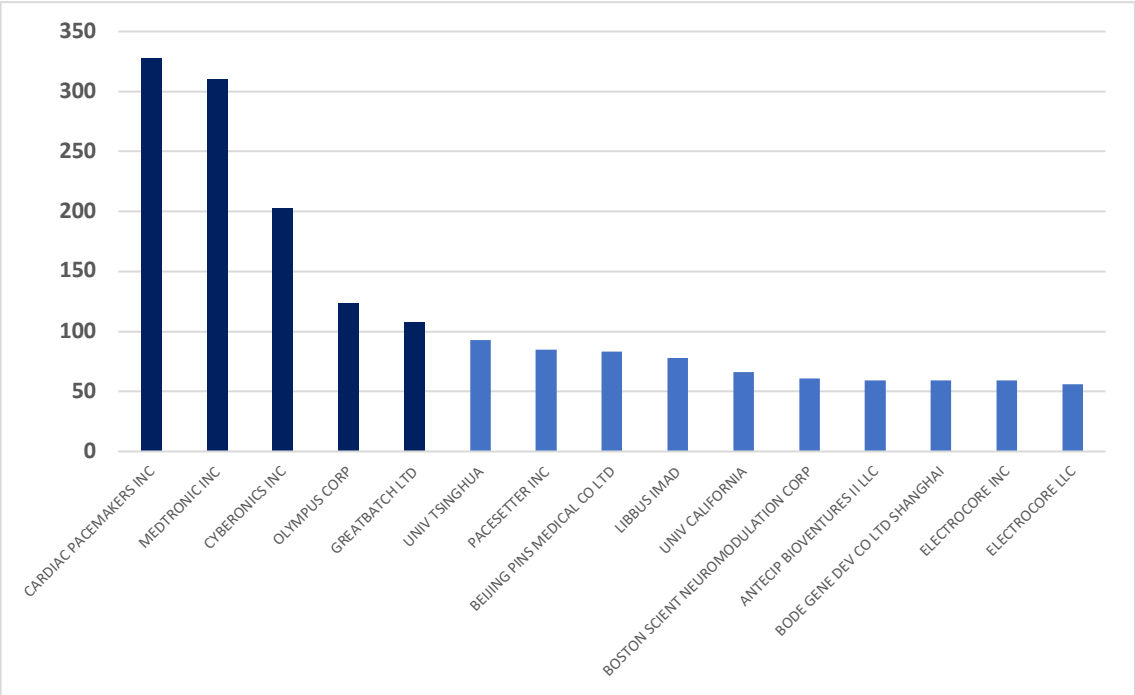


Figure 42. Neurostimulation patents (Vagus Nerve stimulation) by the medical device company. (Source: ESPACENET)

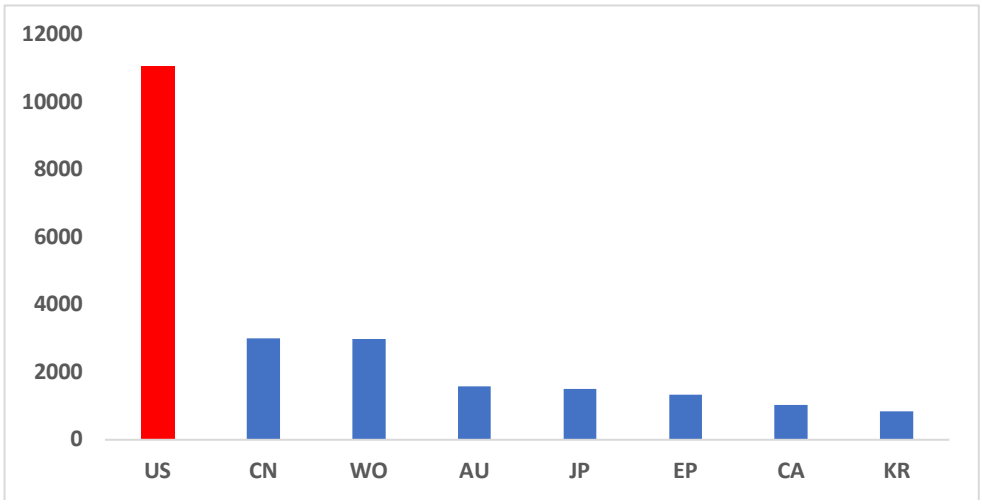


Figure 43. Neurostimulation patents (Vagus Nerve stimulsation) by countries. (Source: ESPACENET)

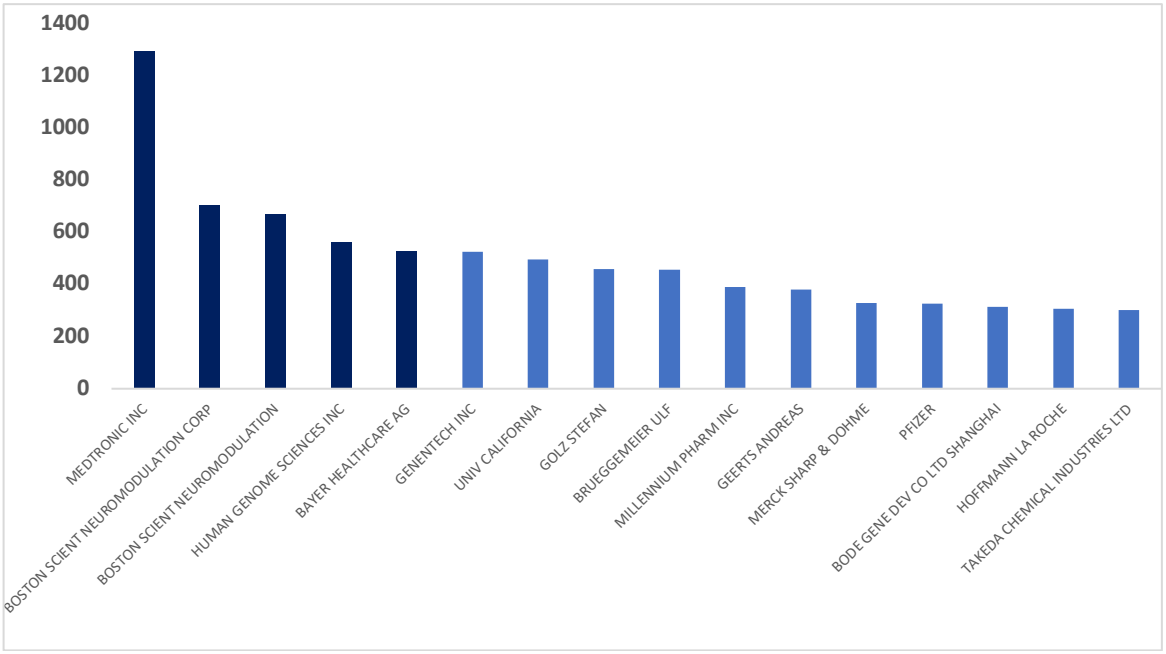


Figure 44. Neurostimulation patents (Spinal Cord stimulation) by company. (Source: ESPACENET)

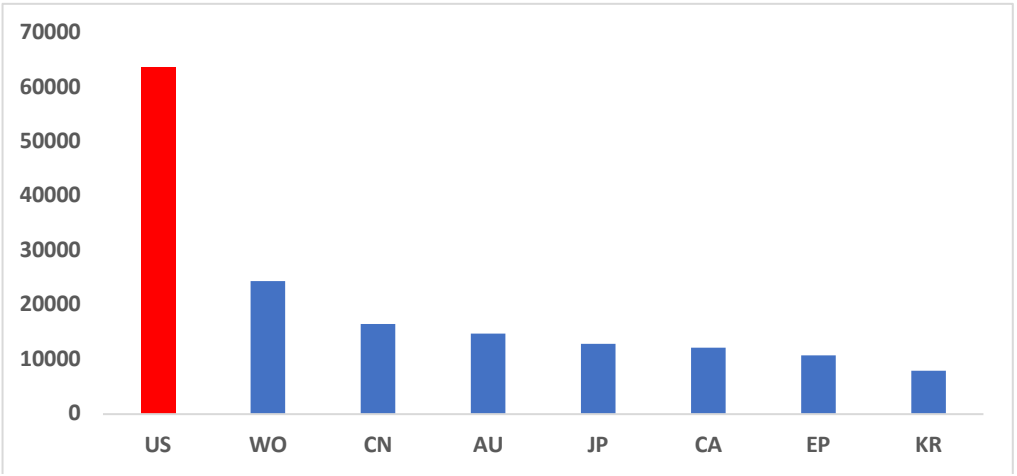


Figure 45. Neurostimulation patents (Spinal Cord stimulsation) by countries. (Source: ESPACENET)

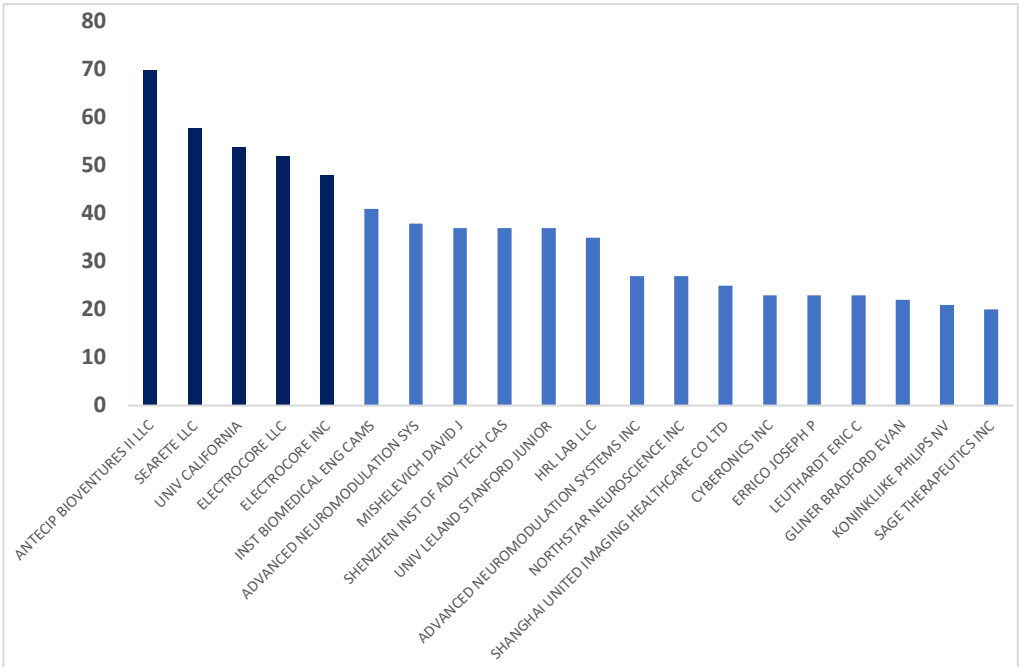


Figure 46. Neurostimulation patents (Transcranial magnetic stimulation) by company. (Source: ESPACENET)

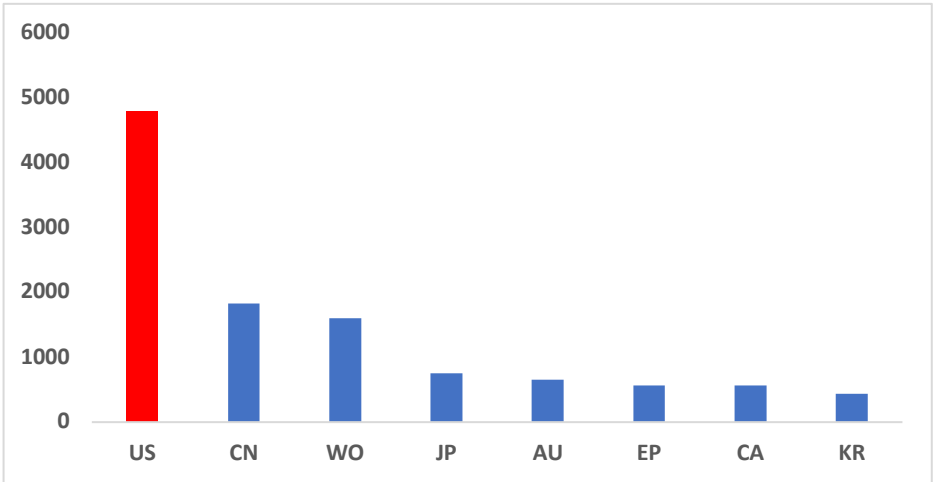


Figure 47. Neurostimulation patents (Transcranial magnetic stimulation) by countries. (Source: ESPACENET)

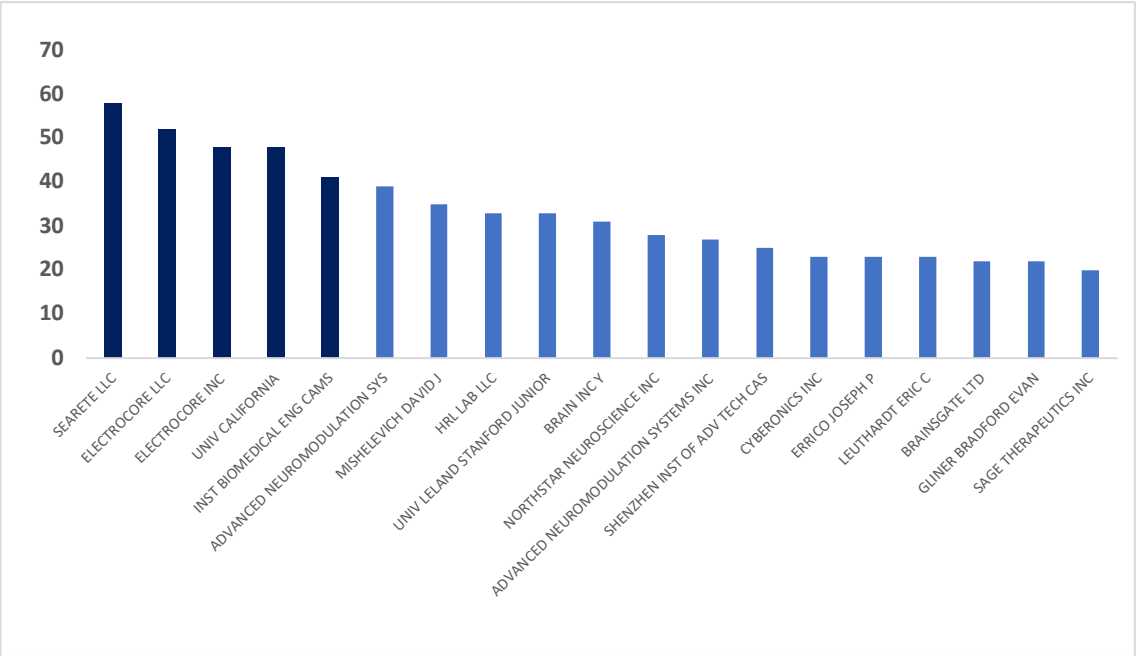


Figure 48. Neurostimulation patents (Transcranial electrical stimulation) by company. (Source: ESPACENET).

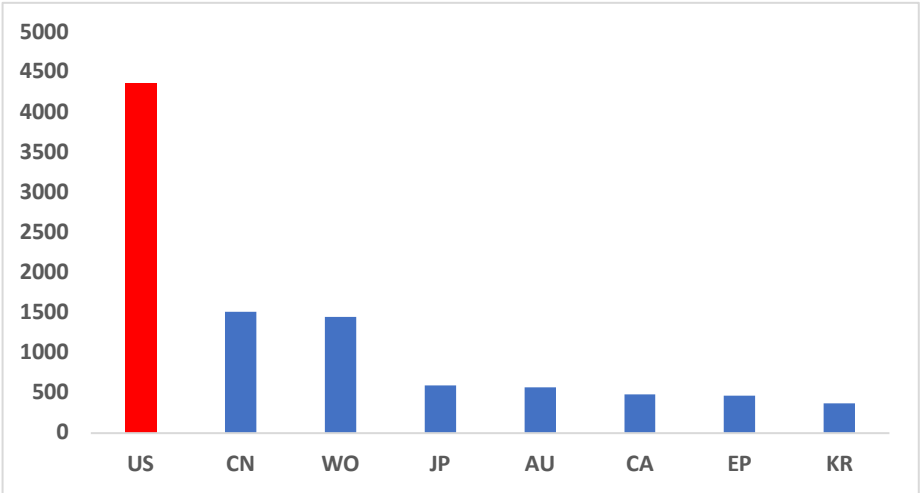


Figure 49. Neurostimulation patents (Transcranial electrical stimulation) by countries. (Source: ESPACENET)

We can obtain similar graphs for one specific item like Optically Pumped Magnetometer (OPM). In this case, ESPACENET delivers consistent results per country in the selected periods 2010-2021 (figure 50 left) and 2020-2021 (figure 50 right). In both periods, the position of the USA is clearly dominant.

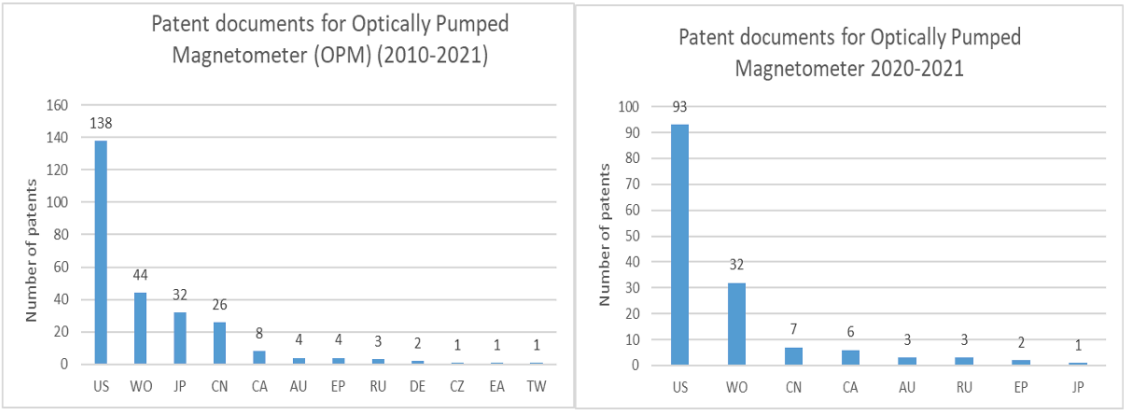


Figure 50.Patent documents for OPM filed in 2010-2021 (left) and 2020-2021 (right). "WO" stands for WIPO patents publications. Source: ESPACENET

It does not mean that world markets will follow the evolution of the patents. Many of the patents are not commercialised (or licensed) for many reasons. Specifically, in this field we can mention the difficulties to obtain good therapeutic results, the cost for engineering the proposed techniques, and regulatory barriers to be used in humans in clinical contexts.

2.5.2 Evolution of scientific articles

The interest of mental health in the academic field could be measured in the number of new published articles.

Figure 51 shows the ***distribution of neurology documents*** per country in the period 1996-2020 from the Web of Science database with some impact indicators like citation and H index (https://www.scimagojr.com/countryrank.php?category=2808). Notice that the USA with more than 115.000 documents is the lead country followed by Germany and UK.

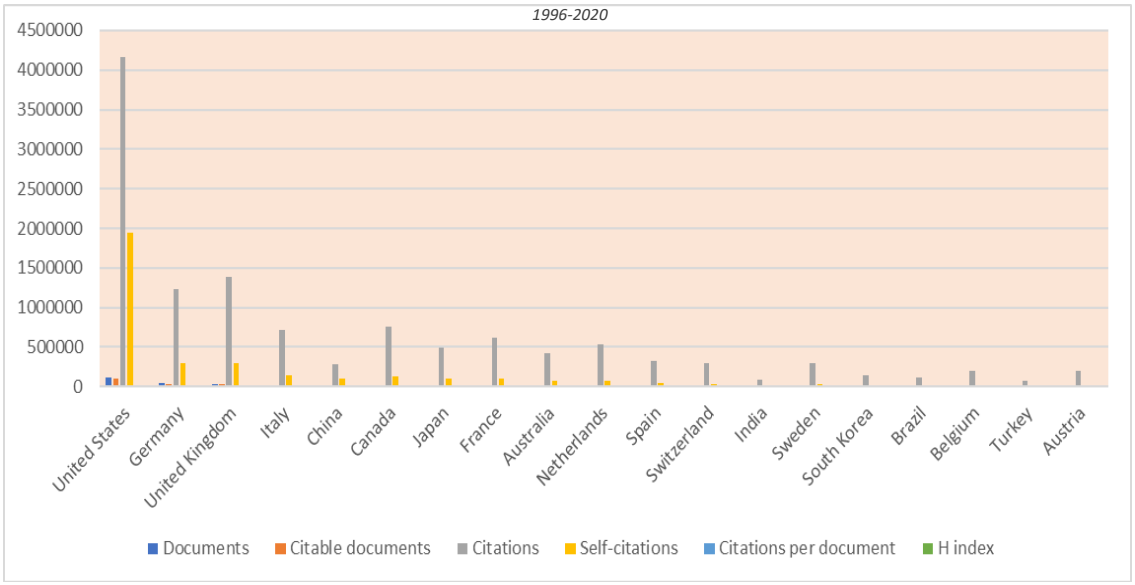


Figure 51. Documents on neurology (1996-2020). (source: Web of science)

Progress of China can be noticed because if in the whole period occupies the fifth position, in 2020 it had a dramatic leap forward. ***In 2020 USA is still the lead country (with 8,063 documents) but it is followed by China (with 3,732).*** The third position is for UK with 2,463) and then Germany (with 2,457). Unfortunately, it is not possible to obtain detailed rankings for neurostimulation (a subset of neurology), but probably the trend is similar.

From a wider perspective of mental health, and according to CBInsights (period July 2016- June 2021), there is a peak in the interest (see figure 52).

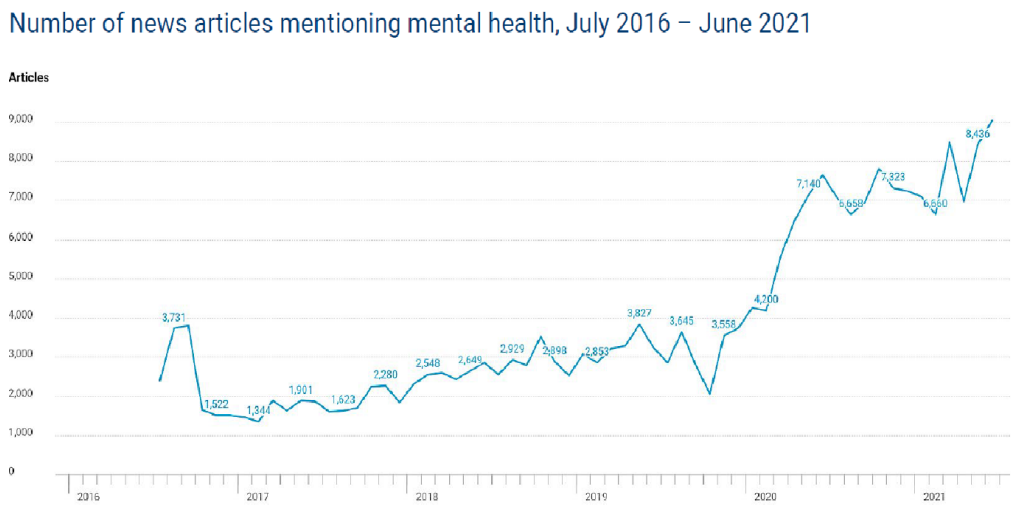


Figure 52.Number of new articles mentioning mental health (source: CBInsights, 2021)

A more specific search in the ***Scopus data base of articles on neurostimulation***[26] generates the results depicted in figure 53. Data show a very strong growth in the number of articles (from 121 in 2010 to 463 in 2021).

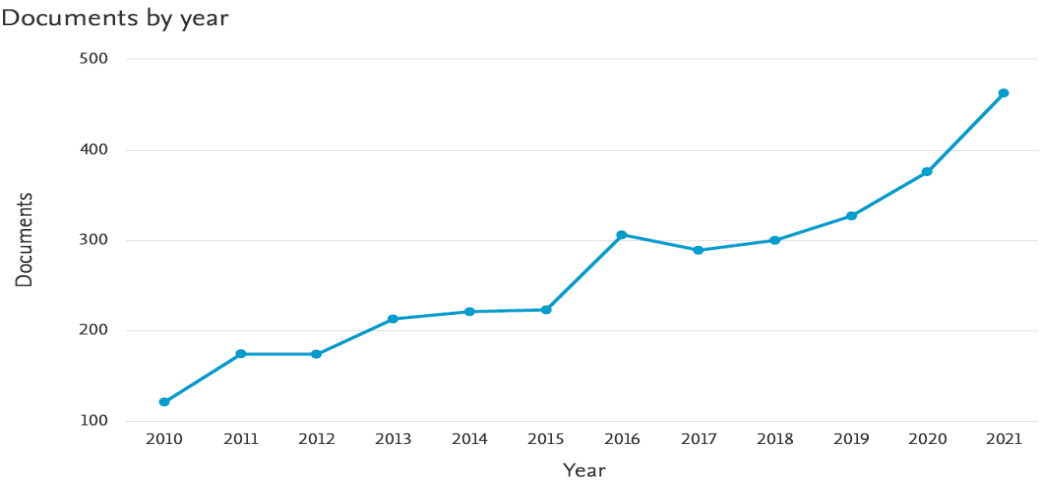


Figure 53. Articles on the Scopus Data Base on "neurostimulation" (Source: Scopus)

[26]https://www.scopus.com/term/analyzer.uri?sid=bf412f9377dd45880925d7964e20d268&origin=resultslist&src=s&s=TITLE-ABS-KEY%28Neurostimulation%29&sort=plf-f&sdt=b&sot=b&sl=31&count=4422&analyzeResults=Analyze+results&txGid=e52643e418ae412e83ae69f38c2be6df

As a conclusion, when combined with the growth in patents presented above in this report, ***neurostimulation is a very active field in knowledge generation***, and it will pave the way towards the generation of disruptive innovations in the next years. Furthermore, it will benefit from the convergence with other technologies like artificial intelligence or edge computing which could support the generation of smarter medical devices in this field.

The next section will pay attention to some specific emerging neurostimulation areas where disruptive products are expected to reach the market very soon.

2.5.3 Emerging neurostimulation technologies going to the market

This section will describe ***five areas of emerging neurostimulation technologies*** that have not yet been commercialised, which could disrupt the market during this decade.

This section does not address other fundamental research activities on neurostimulation that have not generated prototypes at least to be tested in clinical experiments (usually, with TRL above 5) through commercial companies. The selected areas are:

- Electroceuticals
- Photobiomodulation
- Biomarkers
- Neurovascular minimally invasive implants
- Bidimensional materials for neural sensors
- Digital Twins

These areas are representative of translational research activities in the field. Practically, in all cases, the research efforts were protected through patents. This is typically the area where many start-ups (and spin-offs) have been created and some of them have attracted substantial amounts of capital risk, even when products were not commercialised.

2.5.4 Electroceuticals

There are many companies with very advanced ***cortical implants*** at several stages of development. To offer a general overview this report will focus on three companies with very innovative systems close to commercialisation: *Neuralink*, *Blackrock Neurotech*, and *BrainGate*.

Neuralink (https://neuralink.com/)

Neuralink is a well-known company in the media due to one of its major investors (Elon Musk). At the end of 2021, the company had not received yet the FDA approval for starting the testing of its system in humans (expected by Neuralink in

2022) and its invasive system was only tested in animals until now. Figure 54 depicts the ***implanted device (Link)*** with a very advanced multi-channel brain interface.

Figure 54.Source: Neuralink (https://neuralink.com/)

Box 17.

"The Link is a starting point for a new kind of brain interface. As our technology develops, we will be able to increase the channels of communication with the brain, accessing more brain areas and new kinds of neural information. This technology has the potential to treat a wide range of neurological disorders, to restore sensory and movement function, and eventually to expand how we interact with each other, with the world, and with ourselves. Micron-scale threads are inserted into areas of the brain that control movement. Each thread contains many electrodes and connects them to an implant, the Link. We are designing the Link with the goal that a user would be able to get an MRI in a scanner with at least 1.5T magnet or smaller, which includes most clinical facilities." Source: https://neuralink.com/applications/

The Neuralink approach requires a ***complex robotic surgery*** (see figure 55) to implant the system. The threads on the ***Link*** are so fine and flexible that they can't be inserted by the human hand. To solve the problem, Neuralink has developed a robotic system that the neurosurgeon can use to insert these threads exactly reliably and efficiently where they need to be.

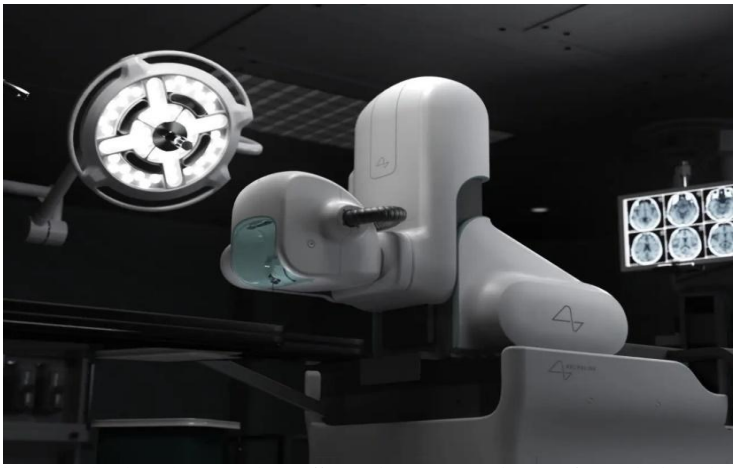


Figure 55. Neuralink surgical robot. (Source: https://www.businessinsider.com/neuralink-and-woke-studios-ai-chip-implantation-robot-2020-9)

Blackrock Neurotech (https://blackrockneurotech.com/)

It is a company renamed in 2021 as **Blackrock Neurotech** (former Blackrock Microsystems founded in 2008) with a consolidated BCI product, the ***NeuroPort Array***, which has received the approval of the FDA (2021 Breakthrough Designation "MoveAgain Brain Computer Interface (BCI) System).

It is a miniaturised, wired system with proven efficacy – more than 7 years chronically implanted in humans and nearly 10 years in non-human primates. Figure 56 shows the integrated circuitry (ASIC) and the implanted device.

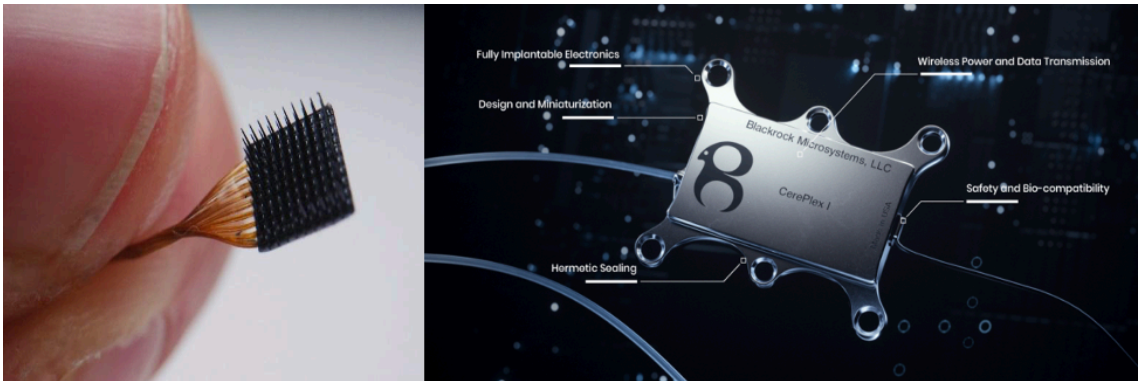


Figure 56. NeuroPort Array from Blackrock NeuroTech and the implantable device (source: https://blackrockneurotech.com/brain-computer-interfaces/)

The company has announced plans to commercialise a BCI platform in 2022, with the aim of restoring communication function in patients impaired by disabilities caused by ALS, paralysis and other spinal cord injuries.

Box 18.

"The Blackrock BCI platform, along with the decoder algorithms licensed from Stanford University, has been shown to enable much faster rates of thought-to-text typing and with higher accuracy than previously demonstrated by other BCI applications to date. The decoders enable typing speeds of up to 90 characters per minute, with 94% thought-to-text live accuracy and up to 99% accuracy with post-processing auto-correction work" ***Source:*** *https://www.prnewswire.com/news-releases/paralyzed-individuals-will-soon-type-with-only-their-thoughts---new-bci-platform-to-be-released-by-blackrock-neurotech-301433635.html?tc=eml_cleartime*

Braingate (https://www.braingate.org/)

The transfer of high bandwidth signals to external (even distant) electronics normally requires premature data reduction. Percutaneous, and thus suboptimal, connector components are required. Braingate has developed new approaches to overcome these limitations via entirely implantable, wirelessly powered and communicating, integrated neural recording microsystems (see figure 57).

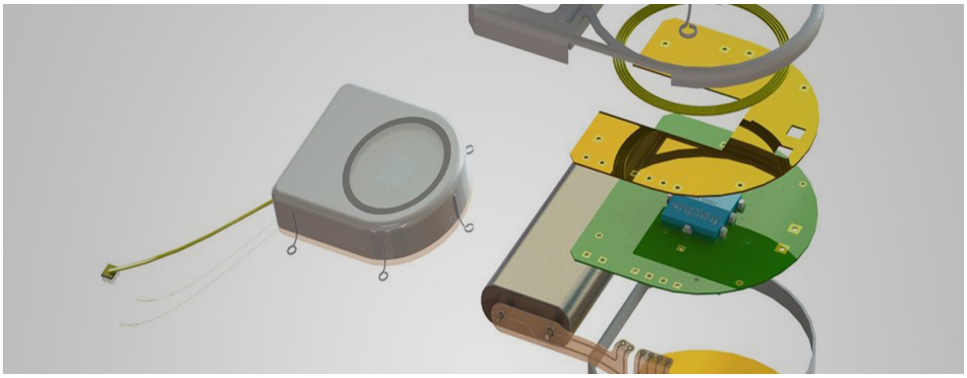


Figure 57. Braingate implant (source: Brraingate)

One practical limitation of current iBCIs is their reliance on recording cables that link an implanted array's head-mounted titanium connector ("pedestal") to the signal processing and decoding computers enabling iBCIs for long-term recording and independent mobile use at home without technical supervision will require wireless acquisition of intracortical signals to eliminate tethering cables to the head.

The company and its partners have demonstrated the **first human use of a wireless broadband iBCI in a pilot clinical trial of the BrainGate Neural Interface System** (FDA, Investigational Device Exemption #G090003). Based on a prototype system previously used in pre-clinical research, the new approach has replaced the external cables of a 192-electrode iBCI with wireless transmitters and achieved high-resolution recording and decoding of broadband field potentials and spiking activity from people with paralysis.

The purpose of the pilot clinical study of the BrainGate2 Neural Interface System is to obtain preliminary device safety information and to demonstrate the feasibility of people with tetraplegia using the investigational BrainGate system to control a computer cursor and other assistive devices with their thoughts (Simeral et al., 2021).

Box 19.

*"A goal of the study is to determine the participants' ability to operate communication software, such as e-mail, simply by imagining the movement of their own hand. The study is invasive and requires surgery. Individuals with limited or no ability to use both hands due to cervical spinal cord injury, brainstem stroke, muscular dystrophy, or amyotrophic lateral sclerosis (ALS) or other motor neuron diseases are being recruited into a clinical study at Massachusetts General Hospital (MGH), VA Providence Healthcare System, and Stanford University Medical Center. Clinical trial participants must live within a three-hour drive of Boston, MA, Palo Alto, CA or Providence, RI. Clinical trial sites at other locations may be opened in the future. The study requires a commitment of 13 months.". **Source:** https://www.braingate.org/clinical-trials/*

Figure 58 shows the system used in the pilot. (a) BWD transmitter (52 mm x 44 mm) showing battery compartment. Turn-screw disc is used to attach the device onto a percutaneous pedestal. (b) The BWD connected to T10's posterior pedestal (here, the anterior pedestal is covered by a protective cap). (c) A two-frequency wireless receiver system in a four-antenna configuration as deployed for T10. The output optical fibers (orange) connect to downstream NSPs. (d) T5 in his home with two

transmitters. The antenna in the background was one of four mounted around the room.

Figure 58.components of the wireless system (source: Simeral et al., 2021)

One relevant subarea of electroceutical is the use of ***"neurovascular minimally invasive implants"*** addressed in the next subsection. This is a special type which solves some of the problems found in penetrating the human skull.

2.5.5 Neurovascular minimally invasive implants

Researchers were looking for minimally invasive approaches to implant devices by using the blood vessels by avoiding open brain surgery. One company in the "neurovascular" subfield named Synchron (https://synchron.com/) has obtained remarkable success with this approach. Synchron has developed an endovascular brain computer interface that can access "every corner of the brain using its natural highways, the blood vessels".

The company claims that its breakthrough platform launches a new field of medicine: ***Neurointerventional Electrophysiology (Neuro EP***). The technology could transform three medical verticals: Neuroprosthetics, Neuromodulation, and Neurodiagnostics.

The product, ***Stentrode*** (see Figure 59), is a fully implantable medical device, which can translate brain activity or stimulate the nervous system from the inside of a blood vessel. The Stentrode captures brain activity associated with intended movement and sends these signals through a wire to a small device implanted just under the skin on the chest, which can be connected to a computer wirelessly. The device transmits signals from the brain's motor cortex and can help people with upper limb paralysis control a digital device without using their hands, a study shows.

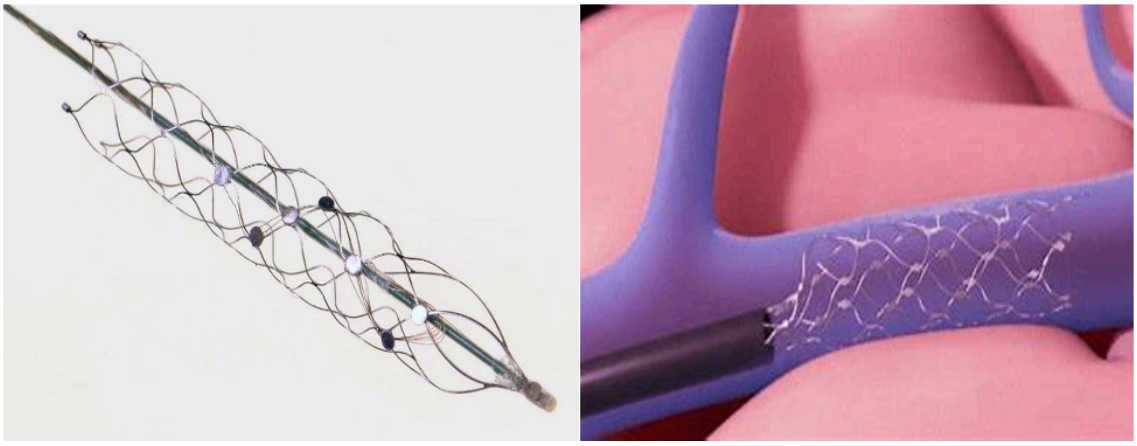


Figure 59. Stentrode (source: Synchron)

Compared to the Neuralink approach which requires a complex robotic surgery, the Stentrode could be implanted by using more conventional vascular surgery.

This device has obtained the FDA approval as *"breakthrough device designation"* from the US Food and Drug Administration (FDA) to test it in humans. In a first-in-human experience, the device has been implanted successfully into two people with amyotrophic lateral sclerosis (ALS) who could not move their upper limbs. A couple of months after implantation, patients could control a computer and complete daily tasks such as online banking, shopping, and texting.

Recently, based on the good results in Mount Sinai Hospital, Synchron has obtained (July 2021) green light from FDA to begin breakthrough trial of implantable brain computer interface in US. This device has obtained substantial funding for clinical trial from the NIH (see box 20).

Box 20.

A $10-million grant from the National Institutes of Health (NIH) will help fund the first U.S.-based clinical trial of Synchron's Stentrode, a wireless brain device, implanted without open brain surgery, that transmits signals from the brain directly to a computer. The COMMAND trial will evaluate whether the device can help people with severe paralysis — including those with amyotrophic lateral sclerosis (ALS) — regain functional independence and the ability to communicate digitally.

The grant will be managed by Carnegie Mellon University, in Pittsburgh, while recruitment and study procedures will be conducted at the University of Pittsburgh Medical Center and Mount Sinai Health System. Approved by the U.S. Food and Drug Administration (FDA) in July, the study will enroll six patients and is expected to start later this year.

The commercial product ***brain.io™*** (https://synchron.com/technology/brain-io) is a motor neuroprosthesis – designed to bypass damaged neural pathways in patients with severe paralysis, allowing them to control digital devices and restore functional independence. Figure 60 schematically depicts the operation of ***brain.io*** with *Stentrode* implanted in brain vessels of the patient.

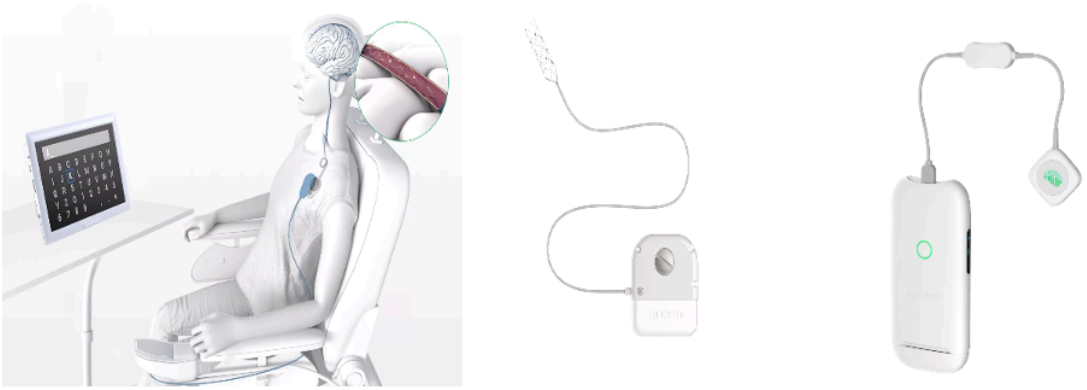


Figure 60. Operation of brain.io. Left: patient. Centre: Stentrode and the internal receiver-transmitter unit that is placed in the chest under the skin. Right: axon. (source: Synchron)

The system operates in three phases:

1. The Stentrode™ is placed on top of the motor cortex which generates any signal related to movement.
2. A device in the chest sends the neural signals through a transmitter to a decoder.
3. A machine learning algorithm translates those signals into specific digital commands.

Stentrode is a nice example of the possibilities offered by technology convergence in the field of neurostimulation. In this case, the combination of new materials, wireless protocols, artificial intelligence, and minimally invasive surgery was able to generate a breakthrough medical device for clinical use.

2.5.6 Magnetic and spintronic neurostimulation

A promising approach for neurostimulation is the ***micromagnetic stimulation technique (μMs)*** (Saha et al., 2022). Figure 61 schematically shows that micromagnetic stimulation should be considered as a new group of techniques.

The technique takes advantage of the high permeability of magnetic field through biological tissues. The induced electric field from the time-varying magnetic field generated by magnetic neurostimulators is used to remotely stimulate neighbouring neurons, The advantage of this approach is the high spatial selectivity of neurostimulation due to the spatial asymmetry of the induced electric field.

Micromagnetic stimulation (μMS) becomes a promising alternative to the use of electrodes because the stimulation with magnetic fields does not require an electrochemical interface and therefore can be scaled down. Some micromagnetic devices/arrays such as microcoils (μcoils) and spintronic nanodevices (may be able to stimulate with much larger amplitudes and tissue volumes than the same sized electrodes.

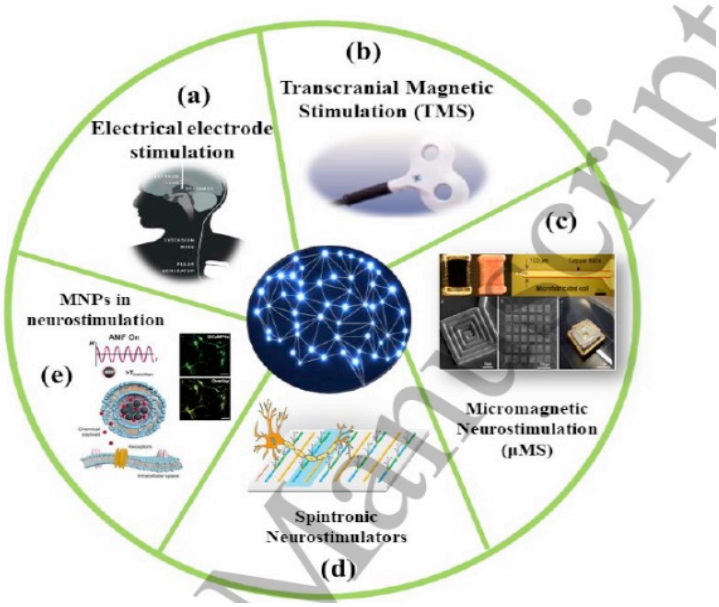


Figure 61. Grouping of neurostimulation techniques (source: Saha et al., 2022)

Implantable micromagnetic stimulation (μMS) of neurons using ***spintronic nanodevices*** is a nascent concept, with theoretical studies reported so far and no experimental demonstration. The spintronic nanodevice is one type of nanomaterial that utilizes the intrinsic spin of the electron and its associated magnetic moment[27].

There are various promising devices based on microcoils (μcoils) (see figure 62). Many of them are prototypes reaching the market.

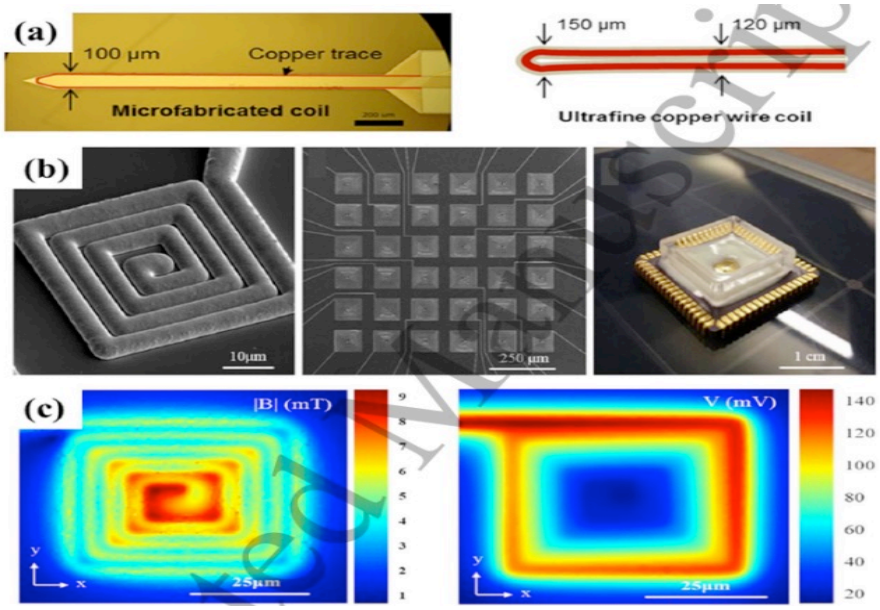


Figure 62. μcoils used in micromagnetic neurostimulation (source: Saha et al., 2022)

[27] The interplay of electron spins with their motion inside a potential (in the form of electric and/or magnetic) can be fine-tuned to generate a time-varying magnetic fields. Which, as a result, generates a localized, time-varying electric field.

2.5.7 Evolution of Photobiomodulation

The use of photobiomodulation (PBM) is not new and the main ideas were presented in a previous section. In this field, new advances towards ***less invasive techniques*** are being explored.

Box 21.

Photobiomodulation (PBM) is a non-invasive technique that utilizes light energy with wavelengths in the visible (400–700 nm) and/or near-infrared (750–1100 nm) range to activate cellular activity. When PBM is applied to the head, it is called photoneuromodulation (PNM) and can be used to improve brain function. ***Source****: https://www.nature.com/articles/s41598-021-93228-2*

The principal effect of photomodulation is that the photoreceptors or chromophores (cytochrome c oxidase and heat-gated ion channels) inside neuronal cells absorb photons that penetrate into the brain and activated different signaling pathways and transcription factors that lead to the eventual effects of PBM in the brain (L.F. De Freitas et al, 2016). These processes can be divided into short-term stimulation (ATP, blood flow, lymphatic flow, cerebral oxygenation, less edema). Another group of processes center around neuroprotection (upregulation of anti-apoptotic proteins, less excitotoxity, more antioxidants, less inflammation). Finally, a group of processes that can help the brain in process of reparation could include neurogenesis and synaptogenesis. Results of small animal model studies as well as human studies show that PBM can also act to reduce swelling, increase antioxidants, decrease inflammation, protect against apoptosis, and modulate the microglial activation state (Lane N, 2006; Waypa G.B., 2016; Anders J.J et al, 2015).

Low-level light therapy (or photobiomodulation therapy) is a rapidly growing approach to treating a wide range of diseases and disorders that afflict humanity. PBM has now been shown to be effective against neurodegenerative diseases (Alzheimer's and Parkinson's) and psychiatric disorders (depression, anxiety and opioid addiction). Cognitive enhancement in normal individuals is another application.

Transcranial Photobiomodulation (tPBM) provides a safe and noninvasive brain stimulation to intervene with brain functions. Its therapeutic benefits have been reported in several studies. For, example tPBM significantly improved outcomes in human stroke patients, when applied at 18 h post-stroke (Lampl Y., 2007). In another study, investigators from Clarke Brain Institute Charities Inc., demonstrated that the tNIR (transcranial near-infrared) light treatments were very safe and positive to improve cognition in patients with dementia (Nizamutdinov D, et al, 2021). Very interesting results was published in Word J. Neuroscience and described the use of **intravascular PBM** to treat patients with AD who received PBM or standard treatment with memantine and rivastigmine. The PBM consisted of threading a fiber-optic through a cathéter in the fémoral artery and advancing it to the distal site of the anterior and middle cerebral arteries and delivering 20 mW of red laser for 20–40

min. The PBM group had improvement in cerebral microcirculation leading to permanent (from 1 to 7 years) reduction in dementia and cognitive recovery (Maksimovich I.V., 2015).

There are some companies with very advanced technology and used for cover of different therapeutic areas.

We are focus on four companies with technology that used in clinical practice and for treatments of different pathologies (pain, dermatology, inflammation).

Thor Photomedicine (NovoTHOR®)- With over 5,000 customers using THOR lasers in 70 countries including Harvard Medical School, NASA researchers, US Navy, RAF, British Army, Royal Navy, NHS, BUPA, THOR can rightly claim to be the number one supplier in the world of PBM technology and training. Significant reduction of inflammation equal to or better than NSAIDs within 2 hours, analgesic effects that last for 48 hours, healing time of chronic tendinopathies reduced by 70%.

The **Visium Light** is a patent pending polychromatic variable pulsed hand-held light therapy devices. By applying more than one color of light at a time during treatment, additional healing benefits may be experienced.

NeoMedLight is French based startup and develops innovative medical devices. The company benefits from a novel, a unique and proprietary technology allowing the emission of light through woven optic fibers. In March of 2020 the company has launched CareMin 650 for severe cancer treatment complications (Figure 63).

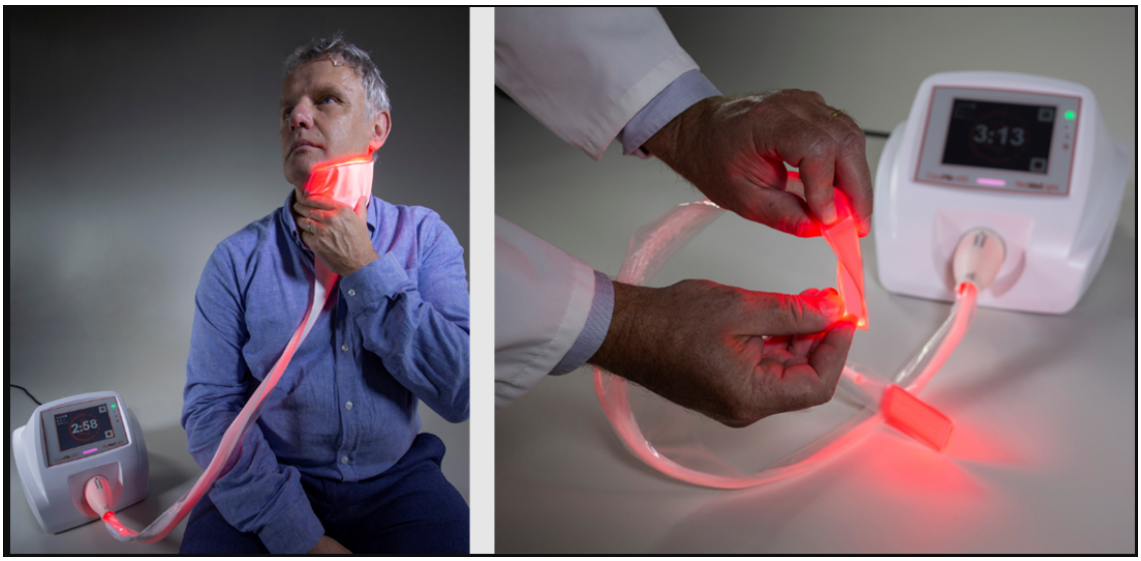


Figure 63. Device in use for Dermatitis (left side) and CareMin650 Oral Pad (right side) (Source: https://cordis.europa.eu/project/id/858849/reporting).

LumiThera is medical device company commercializing a multiwavelength Photomodulation devices for treatment of dry age-related macular degeneration (AMD).

Box 22.

In the United States, there is no explicit acknowledgement of PBM by the FDA, there is a Centers for Medicare & Medicaid Services (CMS) treatment code (LLLT for 15 mins),

*BUT it is declared as "not necessary" and is "not payable by Medicare". The American Medical Association rejected a proposal for permanent code last year, and no government (CMS) or private medical insurance reimbursement. In the United Kingdom, the National Health Services have no treatment/procedural or payment codes for PBM, and it seems the rest of the world has also not yet "seen the light"- **Source**: https://www.pbm2021.com/wp-content/uploads/2021/10/eBook-of-Abstracts-for-Podium-Presentations_PBM2021-Oct-1-3.pdf.*

A less invasive treatment modality currently being developed by ***VieLight, Inc.*** (https://www.vielight.com/) is the *intranasal delivery of light*. Clinical studies have shown that NIR light of sufficient power density is capable of diffusing transcranially. Thus, the light can penetrate through the scalp, skull, and brain to depths of 4 cm or more. Furthermore, the NIR light can also diffuse intranasally, through the ***nasal channel***. Figure 64 schematically depicts the use of this technique.

Figure 64. Source: https://pro.vielight.com/neuro-pro/#why

The company claims that its products have advantages with respect to other photobiomodulation approaches based on:

- Microchip-boosted cold LED diodes generate substantial power without releasing heat, enabling direct contact with the scalp's surface to maximize energy transmission and penetration.
- Patented intranasal photobiomodulation technology uniquely stimulates the underside (ventral area) of the frontal lobe, which contains important areas otherwise unreachable transcranially.

It delivers an 810 nm near infrared (NIR) energy via four transcranial LED modules and a nasal applicator. The headset's transcranial LED modules target the hubs of the brain's default mode network (DMN), which often represent the overall health of the brain.

Box 23.

"A recent pilot study of five patients with mild to moderate cognitive impairment investigated the efficacy of daily PBM (810 nm pulsed LED light at 10 Hz), delivered by

a combination of transcranial and intranasal modalities, over a 12-week period. Interestingly, the participants showed a significant improvement in measures of cognitive function at the end of the 12-week treatment period and a decline in cognitive performance after discontinuation of treatment. These quantitative results were mirrored by positive qualitative feedback from patients or their caregivers. ***Source****: Saltmarche et al., 2017*

It will be interesting to see whether these exciting findings are confirmed in a large randomised controlled trial and whether, in addition to dementia, intranasal PBM holds promise for neurological conditions that affect deep brain structures.

Another company is Openwater technology, "uses highly coherent, near-infrared, laser light to measure blood flow inside the human body. Its unique technology enables to detect this laser light about one million times more efficiently than is possible with traditional approaches (see Figure 65). The technology is non-invasive, low-cost, and portable allowing for broader applications including initial point-of-care".

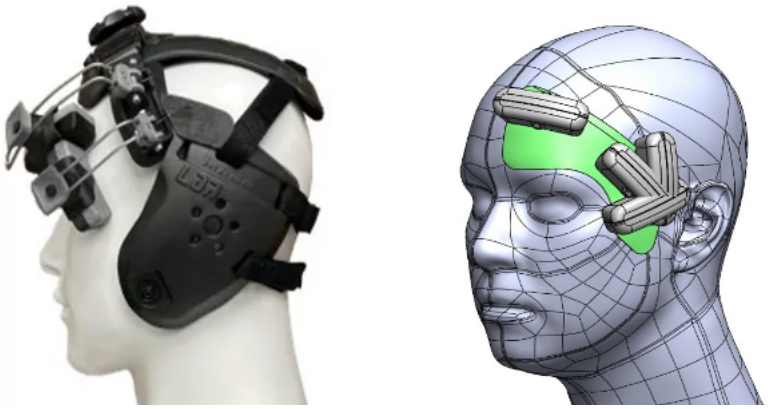


Figure 65.Headset of Openwater. Source: https://www.openwater.cc/products

2.5.8 Use of non-invasive brain stimulation techniques as biomarkers

The concept of biomarkers in medicine exceeds the conventional understanding of chemical changes that accompany the disease process. Nowadays, radiological biomarkers, genetic biomarkers, and even microbial biomarkers (microbiomarkers) are used. In the field of neurological diseases, specific biomarkers should be used to evaluate the status of the patient's brain, and to understand the progress or reaction for specific treatments.

In many cases, physical biomarkers based on observable and objective conditions of the person are not sufficient (e.g., speech clarity or eye movement) or even impossible to obtain. For instance, an objective understanding of the level of pain or the evolution of obsessive dementia, requires obtaining comparable brain data against a pre-defined scale. To date, in clinical studies ***pain intensity*** is determined by the subjective ratings that participants give using numerical rating or visual analogue scales. Other techniques are needed.

The use of some ***neurostimulation techniques*** described in this report as a potential approach to obtain better information could be possible if some ***brain biomarkers*** could be linked to the characteristic brain activity of specific neurological diseases.

For instance, developing a ***non-invasive tool that can objectively measure pain*** is of the utmost importance, not only as it can be used in clinical research to be able to assess and diagnose presence of pain in subjects that are not able to communicate. Currently there is no robust EEG biomarker of pain perception; however, EEG has potential and future research should be attempted[28].

Biomarkers in the existing brain stimulation devices and systems are of two types: ***electrophysiological*** and ***neurochemical***. While neurochemical biomarkers indicate the state of neurotransmitters, electrophysiological biomarkers (e.g., action potential (AP) as well as local field potential (LFP)) provide electrical activity of the brain. The action potential or high frequency neural spike is the fundamental method of communication between neurons, and hence is considered an important signal for understanding the underlying neurological conditions. (Kumari and Kouzani, 2021).

Over the recent years EEG has become an important non-invasive clinical tool that has helped increase our understanding of brain network complexities and for the identification of areas of dysfunction. Although no robust EEG biomarkers of pain perception have been identified yet, EEG has potential and future research should be attempted. Designing strong research protocols, controlling for potential risk of biases, as well as investigating brain networks rather than isolated cortical changes will be crucial in this attempt (Zis et al., 2021).

The use of ***neural oscillations*** has been proposed as a more promising brain biomarker. Neural oscillations are the repetitive electrical activity generated spontaneously or in response to stimuli by neurons[29]. There is extensive evidence to suggest that these neural oscillations and the synchronization between these neural oscillations in various cortical regions help in establishing different cognitive phenomenon and memory functions. Phase selective stimulation is an added attribute to the deep brain stimulation paradigm for increasing its efficacy in altering the neural oscillations in specific frequency bands (Biondi et al., 2022).

To apply neurostimulation as a basis for neuro biomarker, it is necessary to use a ***closed-loop approach*** in which the stimulation parameters can be adjusted in real-time depending on a feedback signal from the subject, thus making it possible for changing the stimulation based on the fluctuating symptoms and further paving the way for patient-tailored treatment for neurological disorders. Establishing accurate

[28] Beta-endorphins were also used as a pain biomarker in chronic pain patients treated with non-invasive brain stimulation techniques (Bonifacio de Assis et al., 2021).

[29] Oscillatory activity of the neural assemblies can be categorized as delta (0.5–3.5 Hz), theta (3.5–7 Hz), alpha (8–13 Hz), beta (18–25 Hz), gamma (30–100 Hz), and high-frequency oscillations, HFO (100–200 Hz).

biomarkers for disease states is crucial for increasing the efficacy of the closed loop brain stimulation systems[30] (see Figure 66).

Closed loop deep brain stimulation paradigms with neural oscillations as biomarkers could be used as a mechanism to understand the function of these oscillations. For making use of the neural oscillations as biomarkers to manipulate the frequency band of the oscillation, phase of the oscillation, and stimulation signal are of importance.

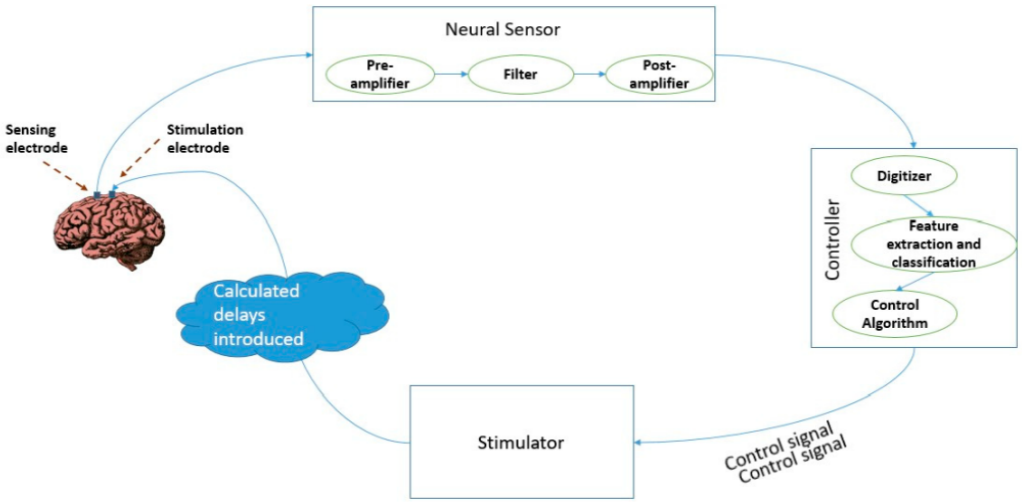


Figure 66. Closed loop neurostimulation system (source: Kumari and Kouzani, 2021)

The ***blood oxygenation level-dependent (BOLD) signal*** provides an indirect measure of neuronal firing and reflects slow-evolving hemodynamic activity that fails to capture the faster timescale of normal physiological function. The combined use of fMRI-guided transcranial magnetic stimulation (TMS) and simultaneous electroencephalography (EEG) to characterize individual brain dynamics within discrete brain networks at high temporal resolution has been useful. Findings illustrate the potential of TMS-EEG perturbation-based biomarkers to characterize network-level individual brain dynamics at high temporal resolution, and potentially provide further insight on their behavioural significance. (Ozdemir et al., 2019).

The use of biomarkers for non-invasive brain stimulation (NIBS) techniques may be useful to identify groups of patients more likely to respond to rTMS compared to another intervention or placebo (Brunoni et al, 2019). high inter-individual variability of clinical response and ineffective outcomes in a significant number of patients underscored the need to identify factors associated with the clinical response to rTMS. To date, most of the studies investigating biomarkers have been of low methodological quality (Saltmarche et al, 2017). However, two studies indicated possible predictors of response. One study indicated that a subtype of depressive patients, identified on the basis of syndromic and neuroimaging characteristics, may

[30] A closed loop stimulation is realized by sensing an individual's brain signals and using it as the feedback signal to the stimulation circuit. Finally, this feedback signal could help in accurately adjusting the stimulation parameters for better control of disease symptom with lesser side effects

respond better to rTMS. The authors suggested that there is a 'neural signature' associated with the clinical response to rTMS.

Experimental NiBS applications that might help improve the efficacy of future NiBS uses in Alzheimer's Disease (AD), including perturbation-based biomarkers for early diagnosis and disease tracking (Menardi et al., 2022).

Box 24.

"For the first time, researchers have recorded electrical signals from the brains of patients undergoing deep brain stimulation for obsessive compulsive disorder over a prolonged period of time, allowing them to capture the brain activity of patients with daily OCD symptom fluctuations. In a study recently published in Nature medicine, researchers used this data to identify potential neurological markers for OCD symptoms — a breakthrough in the development of more effective OCD treatments. But in order to develop a device that adapts to symptom fluctuations, scientists must first identify a biomarker, or a biological indicator, of OCD symptoms in the brain that the device can respond to.

The researchers used new Medtronic recording technology to measure the brain activity of five OCD patients over a prolonged period of time as they went about their daily lives. Over 1,000 hours of brain recordings of patients during daily behavioral tasks and teletherapy sessions were collected. By comparing these recordings with self-reported OCD symptom intensity, researchers were able to identify brain signaling patterns that correlated to high symptom intensity. They also recorded participant facial expressions, and used computer-vision machine learning techniques to compare changes in emotional states to brain recordings.

After comparing patient behavioral reports to recorded brain activity, the researchers found that less brain activity at a specific delta frequency of electrical impulse emitted from the DBS corresponded to higher levels of OCD symptoms. They identified this specific delta frequency as a potential biomarker for OCD symptoms.

***Source**: https://www.browndailyherald.com/article/2022/01/u-researchers-identify-ocd-biomarkers*

In 2021 two start-ups, **Ksana Health** (https://ksanahealth.com/) and **Thymia** (https://thymia.ai/) in the field of ***digital biomarkers for mental health*** (see figure 67) closed their first VC investment rounds (CBInsights, 2021). Even if the investments were modest, they mark a change of attitude of venture capital funds towards a potentially huge market if results from pilot studies were consolidated.

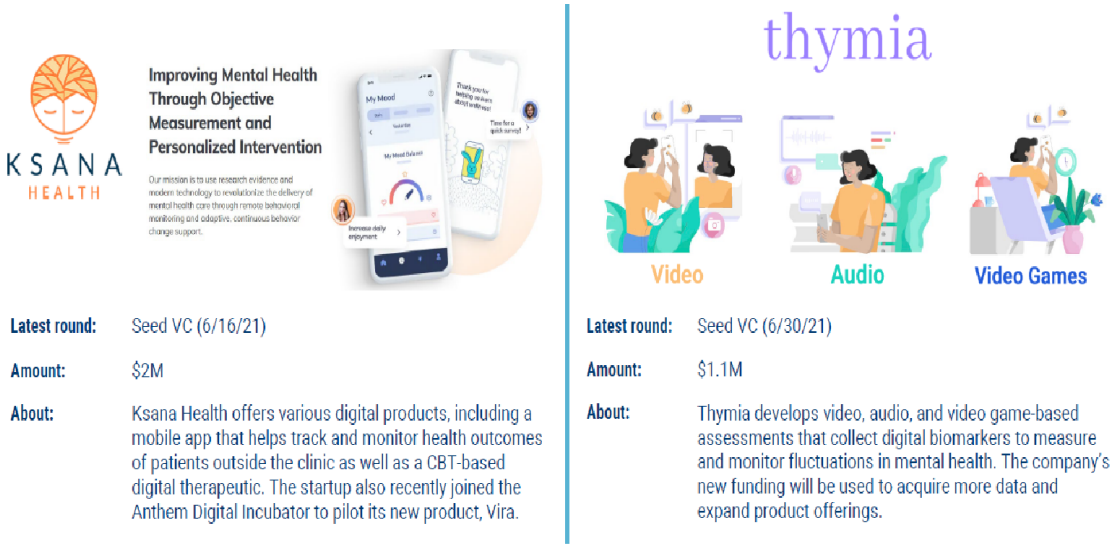


Figure 67.Starts-ups in the field of mental biomarkers (source: Bidimensional materials for neural sensors)

Ksana Health (USA) uses smartphones and wearables to validly measure mental behaviour as depression and anxiety (Adelavood et al., ,2019). They have obtained evidence that the passive and active social media use and depressive symptoms are related, and associations between passive and active forms of screen time as biomarkers of adolescent mood and anxiety disorders.

Thymia (UK) uses video games based on Neuropsychology alongside analyses of video and speech to make mental health assessments smart, starting with depression. The online platform allows clinicians to make faster and more accurate clinical decisions by making mental illness as objectively measurable as visible physical conditions.

Cumulus Neuroscience (UK) has created a next generation integrated physiological and digital biomarker platform. Cumulus Neuroscience's integrated solution is a state-of-the-art platform capable of capturing frequent, longitudinal measurements of brain activity synchronously with a comprehensive range of functional and symptomatic domains outside of the clinic, and providing unparalleled insights, powered by AI techniques, to support clinical trial decision making and execution.

Healios (Switzerland) is a Medical Device Software Manufacturer that is dedicated to finding solutions in clinical research and patient monitoring through innovative digital technologies. Digital Biomarkers focused on the following domains: Movement, Balance, Dexterity and Vision. From 2015 this start-up actively collaborated with big pharmaceutical companies (Roche, Johnson & Johnson) and research institutions for the discovery and validation of digital biomarkers for different neurological disorders.

2.5.9 Global comparison between invasive and non-invasive neurostimulation techniques.

Despite the innovative approaches for invasive neurostimulation based on a new generation of neuro implants presented above, they should solve some technological challenges to be widely accepted by the market due to the inherent derived problems with implants. The use of cortical implants as the brain interface is an invasive procedure that requires surgery to patients and any neuro implant still faces significant technical problems. Some of the most noted in the literature are the following (Diéguez, 2021):

- Infections and other dangers to brain integrity, derived from the necessary brain surgery.
- The formation of connective tissue in the brain that ends up disabling the connection, and then, to reduce the operation time and the need of surgery repair.
- The possible decrease of some cognitive functions, if implants are in brain areas with effects not totally understood on other intensively interconnected brain regions.

To these difficulties, there are others ***common to the intracranial and extracranial electrodes*** related to the way that brain information is processed:

- The difficulty in creating software that speeds up brain/machine communication, even more when the execution of AI algorithms should be done in external systems.
- The possibility of some patients with neuroprostheses have already complained about the feeling of hybrid or shared agency (not completely intentional),
- Personality changes due to stimulation of certain brain areas, and
- The possibility of mental hacking or external unauthorized access to device.

Due to all these constraints, it is obvious that ***regulatory agencies have adopted a very restrictive strategy in the approval of trials and the market introduction of these invasive brain devices.***

Meanwhile, the ***non-invasive techniques are also improving their capacities to read and write on deep brain regions*** (today they have less spatial precision compared to the invasive ones), and during this decade, some clinical applications only possible today using brain implants can be addressed with external neurostimulation technologies with close similar results.

It is too early to see if the disruptive products described above will hit the market with relevant quota and will be massively adopted in health systems. Anyway, they

also open the door to other types of applications (e.g., dual use) not directly related to neuro diseases, where stricter ethical concerns will need to be carefully considered.

2.5.10 Will digital twins be the next generation in personalised medicine for neurostimulation?

In a nutshell, the digital twins (DT) constitute a digital representation of a physical model and, although they were originally conceived in the industrial field, their usefulness has been transferred to other domains of expertise, such as the healthcare field. Since it is a technology with the capability to replicate and simulate a physical model without altering the original condition, continues to open new avenues to analyse therapeutics pathways, analyse consequences of interventions, or prevent possible impairments, to mention some benefits. In the industrial field, it has helped to implement changes in the design and development of assets, combining innovative technological areas such as Internet of Things (IoT), simulation and AI (Croatti et al, 2020).

Arguably, the initiative closest to the digital twin concept, which has sought to simulate the human brain virtually, has been the Human Brain Project, through The Virtual Brain. As previously mentioned, the technology reflects data from imaging evaluations and other diagnostic tests (also the VEP), in order to evolve towards a personalization of neural network dynamics. It is a technology that will continue to grow and refine its predictions, among other reasons, due to the evaluation data from evaluations that are entered into the model. However, it is not fully considered a DT, as it is not yet synchronized with real-time data on patient's brain dynamics. In this sense, authors such as (Evers and Salles, 2021), explain that three requirements must be met to overcome the physical-virtual bridge: seamless connection -or what it is understood as the difference between the real object and the digital-, unique key establishing bijective connection and continuous real-time data exchange.

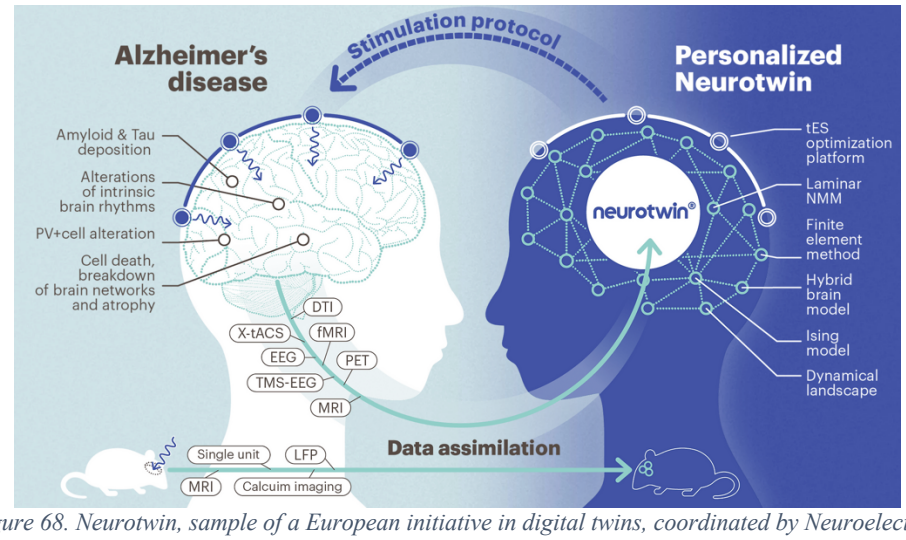


Figure 68. Neurotwin, sample of a European initiative in digital twins, coordinated by Neuroelectrics

Certainly, other companies in the neuromodulation sector and research institutes have taken the initiative to develop the so-called DT, taking advantage of the usefulness of the data at their disposal, towards a next forthcoming approach to personalised medicine. Other European projects such as **Neurotwin** (figure 63), aim to build personalised models of the human brain to investigate neuromodulation methods and help patients with Alzheimer's disease, using data from medical image evaluations. Recently, the company **Dassault Systèmes**, which had already presented its Living Heart DT, showed its most recent breakthrough, the Living Brain, however, its goal is to create a digital model of the entire human body. Also in Europe, research groups such as **ProModell** in Germany, have announced their intention to develop DT models to improve their neurostimulation strategies and surgical planning. In the United States, some of these interesting projects in DT are Unlearn AI, advancing in DG models towards clinical trials, training historical data from previous trials. Their outputs are based on predictions of CNS and I&I disease progression for each patient.

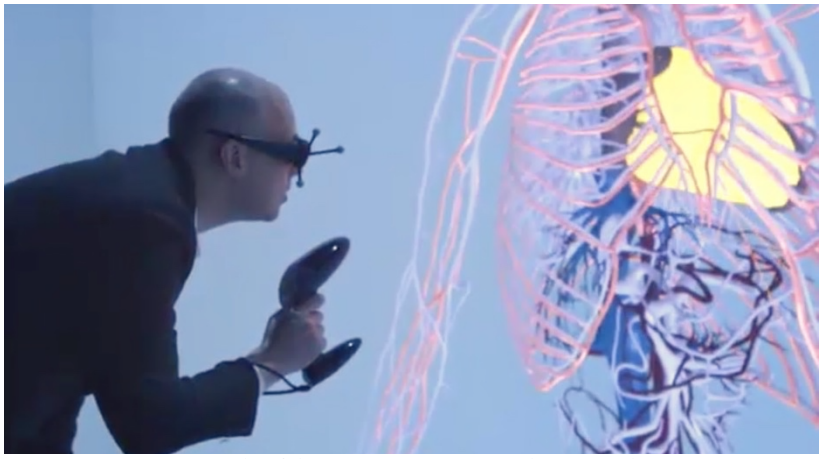


Figure 69.Sample of the Living Heart project by Dassault Systèmes.

2.6 Final discussion

It is understood that ***current treatments are not sufficient to address the broad spectrum of neurological diseases.*** Fortunately, in a large part of the specialised studies there is a significant evolution of these in terms of the level of surgical complexity and the positive therapeutic effects that have managed to extend to other diseases and comorbidities. For example, the benefits of applying techniques such as VNS in improving other functions and organs of the human body may continue to encourage its application, however, it is not as highly effective in movement disorders such as DBS.

In this sense, each invasive technique has started from specific neurological conditions, and progressively new developments have been incorporated to expand their applications to other diseases (see more examples in SWOT analysis section III)

Other relevant factors identified in most of the studies, is the ***complementarity of these techniques with alternative pharmacotherapy and/or non-invasive***

neurostimulation methods, thus, should not be perceived as stand-alone systems. In addition, flexibility in instrumentation and demand for better designs (e.g. use of smaller, thinner, flexible electrodes) are evident. We also believe that in the near future, neurostimulation systems could be developed to integrate the usual pre-surgical assessments into a single device.

Of the five invasive methods described in these SWOT (see annex), Deep Brain Stimulation (DBS), Spinal Cord Stimulation (SCS) and Vagus Nerve Stimulation (VNS) have managed to approximate multiple neurological diseases, and in some cases improve cognitive functions. While Subcortical Cortical Stimulation (SCS) and Responsive Neurostimulation (RNS) have been developed with a specific approach to epilepsy, thus, there is currently little evidence in the literature on its benefits in other diseases. Numerous opportunities have been identified in each technique to initiate new studies, however, various factors emerge as threats, such as the length of clinical trials and future approvals from official bodies, increasing the competitiveness in industry. Although there are few leading distributors in these sectors, they undoubtedly maintain a relevant market share, intellectual property protections, and enjoy international recognition, making it more difficult for new products from existing leaders and start-ups to enter the market.

Another aspect to be highlighted is the ***cost of the procedures and devices***, not only are studies useful to analyse the cost-effectiveness of each technique, but also develop devices affordable for more patients. Furthermore, the battery of these systems -temporary all- or possible failures are also causes that drive the patient to undergo surgery again, and stop treatment if the case, resulting in medium-term costs.

PART 3.

3. Market structure

3.1. Global Neurostimulation Devices Market

Once discussed in previous sections the neurostimulation techniques used today, and to present a large set of examples of products and systems available or under development by large companies or start-ups, it is necessary to describe the ***current structure of the neurostimulation market and its possible evolution***.

The structure of the neurostimulation market can be defined from ***four complementary dimensions*** which globally provide the position of companies and countries. The dimensions are as follows:

- Product Type (Spinal Cord Stimulators, Deep Brain Stimulators, Sacral Nerve Stimulators, Vagus Nerve Stimulators, Gastric Electric Stimulators)
- Application Type (Pain Management, Epilepsy, Essential Tremor, Urinary and Fecal Incontinence, Depression, Dystonia, Gastroparesis, Parkinson's Disease, Others)
- Type (Implantable, External)
- End Use (Hospitals/Clinics, Cognitive Care Centres, Research Institutes, Others)

Aa a global figure, the world ***Neurostimulation Devices market*** was valued at USD 4.98 Billion in 2018 and is expected to reach USD 12.7 Billion by the year 2026, at a CAGR of 12.4 %[31]. Those data show a robust growth which reflects the population needs and the availability of new technologies in the market.

Differences between regions also reflect the structure of industrial tissue and the technological level of health systems in those regions. As an example, the Neurostimulation Devices market is growing at a CAGR of 13.6% in the Asia Pacific, followed by North America and Europe, with 12.3 % and 12.1% CAGR, respectively.

Some estimations on specific product types are: ***Spinal Cord Stimulators*** is the dominating Neurostimulation Devices in 2018, which holds 35.5% of the global market. The segment of ***Sacral Nerve Stimulators*** is expected to be the fastest-growing market segment during the forecast period 2019-2026, with a CAGR of 13.2%.

From the same reference and in relation to application type, the application segment of ***Pain Management*** was valued at USD 2.03 billion in 2018 and is expected to reach USD 5.3 billion by 2026.

[31] https://www.coneckey.com/read-blog/1060_neurostimulation-devices-market-size-revenue-share-major-players-growth-analysis.html

In terms of funding, ***risk capital is mainly focused on companies providing products with non-invasive techniques***. There are only a few invasive neurotechnology companies and that most of them have less than $100M in funding, with the exceptions of Neuralink and Neuropace (Shen and Nixon, 2021).

Despite the dramatic potential implications of the adoption of invasive technologies to provide treatments to patients which are not possible to obtain with non-invasive techniques, one would hope that there would be higher funding, but the numbers do seem in line with the amounts that medical device companies typically raise. Venture capital companies consider that cost-benefits are not clear and longer approval processes, which could make much riskier to invest.

3.2. Major Players in the neurostimulation market

3.2.1. Market structure

Neurostimulation represents a major part of the neurotechnology market whose key players are the giant medical device companies Medtronic, Boston Scientific or Abbott (formerly Saint-Jude Medical) taking most of the market shares (see figure 70), but also several smaller companies as Aleva Neurotherapeutics, Newronika, and Beijing PINS Medical are getting more market quota.

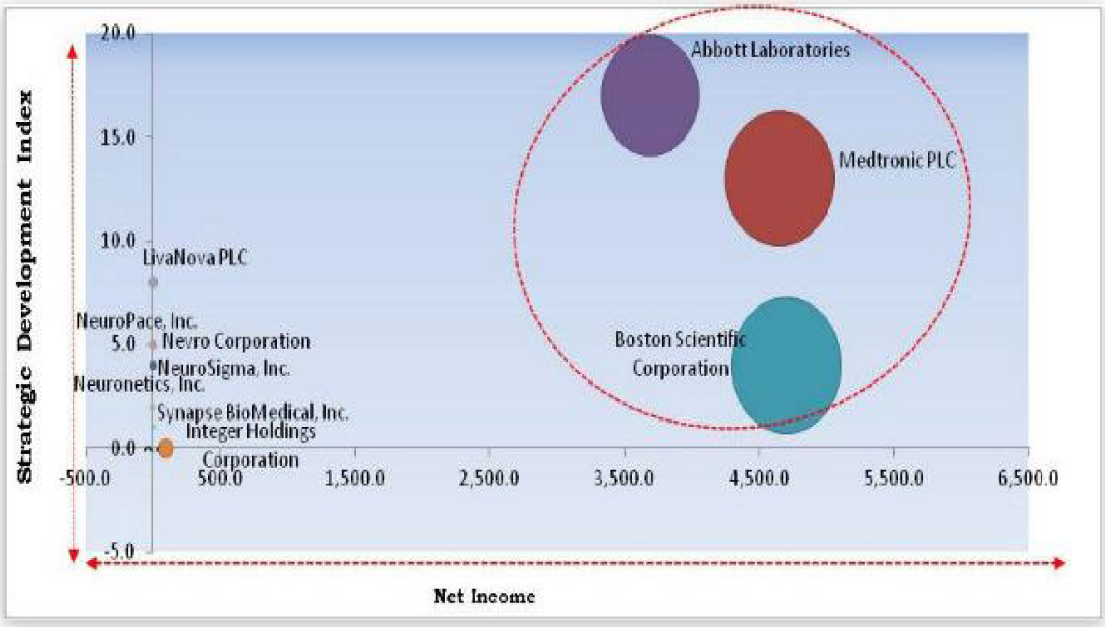


Figure 70. Market (source: https://www.kbvresearch.com)

According to a recent report of Report Ocean Pvt. Ltd, the ***CR4*** (ratio of the four major players of the market) ***is ~56.90%:*** Medtronic plc (34.20%); Cochlear ltd (10.70%); Boston Scientific Corporation (7.00%), and Abbott Laboratories, Inc. (5.00%).

The leading market players are undertaking numerous inorganic and organic growth strategies to gain a larger market share. Through extensive research, it is found that

big players have adopted various competitive strategies such as mergers and acquisitions in order to have a grip of emerging market. Large companies are also very active in getting control or purchasing other technology-based start-ups with disruptive solutions.

Medtronic is the primary manufacturer of clinical and investigative deep brain stimulation (DBS) systems, although ***Boston Scientific*** and ***Abbott*** (St. Jude Medical) are releasing similar devices and they directly compete. Medtronic stimulating electrodes are commonly used to deliver long-term DBS for clinical and investigative purposes.

In September 2019, ***Abbott*** received FDA approval for the ***Proclaim XR recharge-free neurostimulation device*** (Abbott, 2019). This approval helped the company expand its neurostimulation devices product portfolio and secured a larger market share for the company. In January 2020, Abbott Laboratories received approval from the US Food and Drug Administration (FDA) for its ***Infinity Deep Brain Stimulation (DBS)*** system. This system would be used in the treatment of Parkinson's disease. The system would allow targeting a specific area of the brain known as the internal globus pallidus (GPi) to improve the symptoms of Parkinson's disease not controlled by medication.

In January 2020, Medtronic secured a CE Mark for its ***Percept PC neurostimulator***. It is the only DBS system launched in the EU with ***BrainSense technology***, which senses and records brain signals while providing DBS therapy to people with neurological disorders such as Parkinson's disease. At the same time, Medtronic took over ***Stimgenics***, a startup company that has developed a novel spinal cord stimulation waveform. This acquisition enabled the company to expand its business in the SCS market.

In September 2020, ***Boston Scientific*** launched the ***Vercise Genus*** system in Europe. Vercise Genus is indicated for use in bilateral stimulation of the subthalamic nucleus as an adjunctive therapy to reduce the symptoms of moderate to advanced Parkinson's responsive to levodopa that are not adequately controlled with medication.

However, during the last 7 years, market shares are slightly moving due to technology improvement in neurostimulation with smaller players bringing new technologies like ***Neuropace*** and its closed loop neurostimulator or ***ElectroCore*** for the treatment of headache using non-invasive vagus nerve stimulation. But implanted neurostimulators such as spinal cord stimulators for the treatment of pain or deep brain stimulators for the treatment of Parkinson's disease and epilepsy still represent a large part of the product sold.

Other relevant companies in this field are:

- *LivaNova* (*https://www.livanova.com*)
  It is focused the activity on the stimulation of the vagus nerve to treat diseases like epilepsy and depression. In 2019, the Centers for Medicare & Medicaid

Services agreed to cover FDA-approved vagus nerve stimulation devices through Coverage with Evidence Development for treatment-resistant depression. It can safely lead to fewer and shorter seizures and better recovery after seizures.

- *NeuroOne Medical Technologies Corporation. (https://n1mtc.com/)*
  Medical device company focused on the development and commercialization of thin-film electrode technology for patients suffering from epilepsy, Parkinson's disease, and back pain. It has received FDA approval in 2019 to market its thin-film cortical electrode technology for temporary recording, monitoring, and stimulation (less than 30 days) on the surface of the brain.
- *Neuvotion (https://www.neuvotion-inc.com/)*
  Neuvotion is developing breakthrough solutions for facilitating and restoring movement. Our approach combines targeted neurostimulation and AI (artificial intelligence) to deliver unparalleled therapeutic value for patients with a movement disorder or impairment from stroke or injury. Neuvotion products allow doctors and therapists to leverage state-of-the-art technology, while monitoring patient progress in-person or remotely.
- *Xanastim (https://xanastim.com/)*
  It is a Swiss Neuro Technology company that creates non-invasive neurostimulation smart solutions to improve current therapies and neurostimulation approaches. Wireless earbuds anatomically customised to each user includes miniaturised electronics to manage two electrodes and one biosensor. They are easily controlled by the native App that is connected to intelligent cloud systems ready to gather and organise all the data needed to customise each treatment (see figure 71).

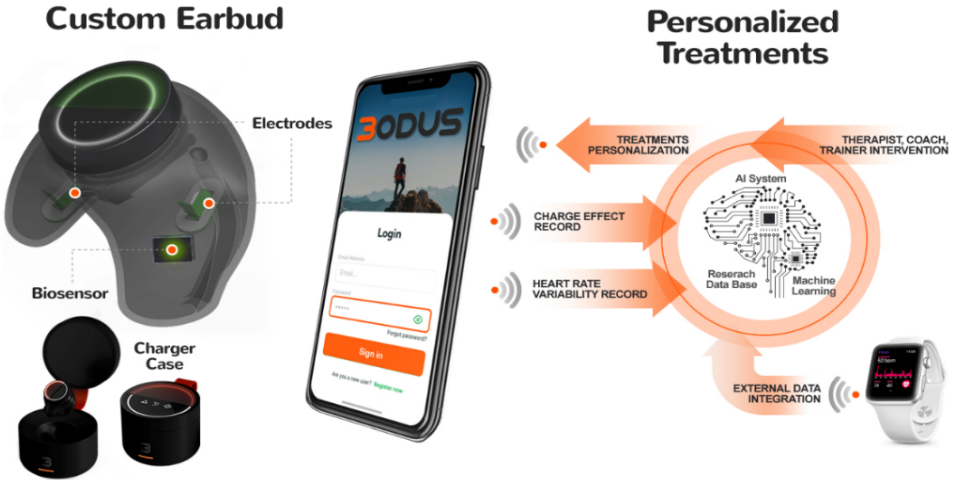


Figure 71. General view of the 3ODUS product (source https://xanastim.com/)

- *Koninklijke Philips (https://www.philips.com/global).*
  Renowned German multinational company founded in 1891, leader in innovation of medical devices and software in the field of neurostimulation. They market complete kits that include electrophysiological recording techniques and their components. In neuromodulation, they stand out for

their integrated systems of high electrical definition, up to 256 electrodes in tDCS, tACS, tPCS, tRNS and EEG.

- *Braun Melsungen (https://www.wlw.de/en/company/b-braun-melsungen-ag-291516).* German company founded in 2839 with headquarters in more than 64 countries. Collaborates with other industry giants through its subsidiaries in the development of new devices in neurostimulation and as a complement to drug therapies, such as Neuroloop GmbH and Merck[32]. In addition, in the field of neurosurgery it offers state-of-the-art platforms such as digital surgical microscopes, electric power systems, treatment of hydrocephalus and more.
- Zimmer Biomet Holdings (https://www.zimmerbiomet.com/en). American medical device company specialised in orthopaedic surgery and equipment to restore mobility and pain relief. It has created robotic solutions to support surgical procedures especially known among neurosurgeons, such as the Rosa Robotics line, as a multi-application platform.

Different companies every time more and more promote innovation and new advantages, entered the DBS market with technical innovations such as segmented leads, directional stimulation, longer battery duration, more flexibility in deciding stimulation parameters and remote internet-based programming. Annex 2 includes a set of tables with the identified companies.

3.2.2. Hints for the potential market evolution

There are many studies of the market evolution of neurostimulation devices, but they are not specific to helmets.

Box 25.
The global neurostimulation devices market size was US$4.7 billion in 2019. The global neurostimulation devices market is forecast to reach the value of US$14.5 billion by 2030 by registering a compound annual growth rate (CAGR) of 11.5% during the forecast period from 2021-2030.
The COVID-19 pandemic negatively impacted the global neurostimulation devices market. The healthcare sector shifted its priority to treating the CXOVID-19 affected patients. Moreover, patients with neurological disorders stopped visiting the hospitals to prevent themselves from the virus. As a result, the market witnessed a slight decline in revenue generation. However, the growing cases pertaining to neurological disorders are forecast to surge the demand for neurostimulation devices in the coming years.
Source:
https://www.taiwannews.com.tw/en/news/4366834#:~:text=The%20global%20neurostimulation%20devices%20market%20size%20was%20US%244.7,of%2011.5%25%20during%20the%20forecast%20period%20from%202021-2030.

[32] Pharmabiz (2019)

From a qualitative perspective, the consideration of ***non-clinical neurostimulation helmets as "brain wearables"*** could attach their evolution to other top model wearables. For that, the costs should be in the range of 1,000-2,000 euros, like a top smartphone. Maybe too expensive for many users, but even in these cases, many institutions with professional people like fitness centres, schools, residences for aged people, etc. could purchase them in the future.

TDCS (https://tdcsdevices.com/) has published an analysis of the best tDCS (Transcranial Direct Current Stimulation) devices available in the market in 2022. They work by applying a positive or negative current through electrodes to one area to help with the depolarization or hyperpolarization of neurons, in other words, increasing or lowering neurons' threshold to send electrical pulses. Relevant devices are:

- LIFTiD Neurostimulation
- The Brain Driver – tDCS Device v2.1
- Muse 2 Headband
- NeoRhythm by OmniPEMF
- Flow tDCS Headset (CE certified)
- Caputron Activadose II tCDS Starter Kit (FDA approved)
- EMOTIV Insight 5 Channel Mobile EEG
- MindWave Mobile 2 EEG headset

Box 26.
According to research published in the Journal of the American Medical Association in March 2018, Japan had 52 MRI scanners and 107 scanners per 1 million people, respectively. The U.S. had the second highest number of MRI scanners (38), and the third highest number of CT scanners (41). Furthermore, the U.S. performed 118 MRIs per 1,000 people compared to other 11 countries of 82 MRI's per 1,000 population.
North America holds a dominant position in the global magnetoencephalography market owing to presence of key players in the U.S. such as Advanced Brain Monitoring Inc., Cadwell Laboratories Inc., CAS Medical Systems, DePuy Synthes Companies, Electrical Geodesics, Inc., and HeadSense Medical, Inc. Among region, Europe accounts for the second largest market share owing to technological advancements in MEG. ***Source****: https://www.openpr.com/news/2215889/magnetoencephalography-devices-market-latest-innovations*

The structure of the MEG and OPM markets is very dynamic with mergers and acquisitions, partnerships, and creation of new companies (see figure 72). Then, innovative products are launched but they do not have a large customer basis.

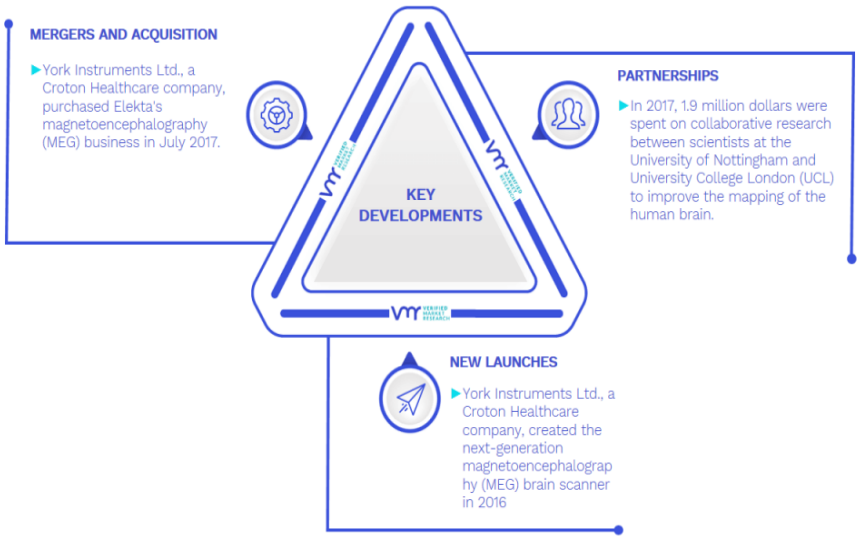


Figure 72. MEG market. Source: https://www.verifiedmarketresearch.com/product/magnetoencephalography-market/

An incipient market on OPM-MEG started in 2020 with the creation of ***CERCA Magnetics*** Ltd. (https://www.cercamagnetics.com/), one Spin-off company from Nottingham, UK[33]. First systems were delivered to several hospitals in 2021. The UPM in Spain will install one system in June 2022.

Leti (https://www.leti-cea.fr/cea-tech/leti), a France-based technology research institute (one of the units of CEA, Commissariat d'Energie Atomique), has developed a next-generation MEG scanning device, wearable brain scanner, or MEG helmet, in November 2017 for enhanced epilepsy and brain tumour diagnostics. The maintenance-free Leti device operates at room temperature, eliminating the need for cryogenic cooling and reducing the size and weight of the device's magnetic shield from 5,000 to 150 kg. For this advanced application, Leti refined its space quantum sensor (see figure 73), a device used in European Space Agency missions, to achieve performance superior to current MEG systems at a cost five times lower.

[33] The Nobel-Prize-winning Sir Peter Mansfield Imaging Centre, in conjunction with industrial partners Magnetic Shields Limited and QuSpin, has developed and brought to market the world's first commercial, fully-integrated brain imaging device based on OPMs. Cerca Magnetics was named best start-up medtech company at the annual OBN awards.

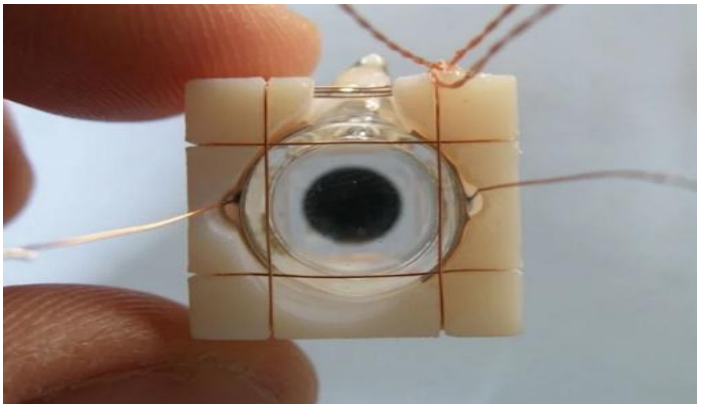


Figure 73. Quantum sensor for OPM-MEG from LETI (source: https://www.medicaldesignbriefs.com/component/content/article/mdb/tech-briefs/28353)

The charity Young Epilepsy worked in partnership with Cerca Magnetics Ltd, Magnetic Shields Ltd, the University of Nottingham, University College London (UCL) Institute of Neurology and the UCL Wellcome Centre for Human Neuroimaging to develop one helmet and associated system for children with epilepsy (see figure 74).

Figure 74.OPM-MEG for children (source: https://ca.news.yahoo.com/helmet-style-brain-scanner-offers-230100910.html)

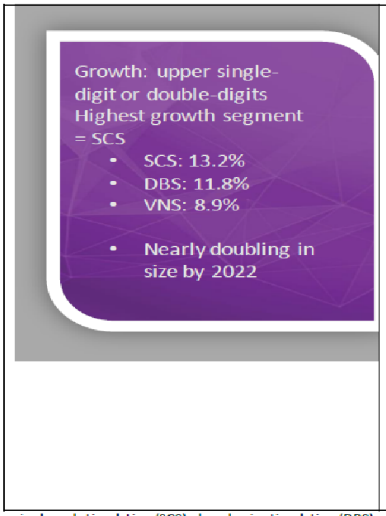
The introduction in the market of OPM-MEG systems could disrupt the future evolution of the MEG market. With half the cost and space required by MEG systems and the broader range of applications, it will be easier to purchase and install for clinical use. The potential problem is the lack of a large base of users which will require time to obtain more data of patients to consolidate clinical practice and to compare results with conventional MEG systems.

3.2.3. Estimations on the evolution and growth of the neurostimulation market

The estimations of evolution over time of the neurostimulation market produced by several consultancy companies differ both on total growth rate and the submarkets within the field of neurostimulation (e.g., for neurostimulation helmets). Many of those studies also provide data for geographical regions (with clear emphasis on the US) for 5 to 10 years.

From our point of view, technical advances derived from scientific breakthroughs, or deep regulatory changes can modify these estimations mainly based on extrapolation of current trends for the next years.

Figure 75 presents the evolution of the neuromodulation segment from one consultancy company *Meddevicetracker* (https://www.meddevicetracker.com/) with an average CAGR of 12.5%. Anyway, this is not a huge figure, showing that some barriers exist today to widely diffuse these techniques.



Neuromodulation Segment	Estimated Revenues/ Expected Growth (%)
SCS	$2,534m (2017) $4,713m (2022) CAGR: 13.2%
DBS	$620m (2017) $1,081m (2022) CAGR: 11.8%
VNS	$450m (2017) $688m (2022) CAGR: 8.9%
Total	**$3.6bn (2017) $6.5bn (2022) CAGR: 12.5%**

spinal cord stimulation (SCS); deep brain stimulation (DBS); vagus nerve stimulation (VNS).
Source: Meddevicetracker; company financials

Figure 75.Evolution of the neuromodulation segment (source: Meddevicetracker)

Spinal cord stimulation (SCS) is the dominant neurostimulation device, which holds 35.5% of the global market and an estimated CAGR of 13.2% (2017-2022) compared to DBS or VNS. The European regional market is the main revenue-generating source for this product segment. Sacral nerve stimulation is expected to be the fastest growing market segment during the forecast period 2019-2026, with a CAGR of 13.2%.

The Asia Pacific region is expected to account for 19.4% of the global market for neurostimulation devices. The China market dominated the Asia Pacific Hearing Loss Market by Country in 2019. The India market is expected to grow at a CAGR of 14.2% during (2020 - 2026). Additionally, the Japan market would show a CAGR of 14.3% during (2020 - 2026).

Figure 76 from Report Ocean (2020) presents the market position of the main companies. The report identifies the cumulative market share of large companies close to 68%, whose strategies include mergers and acquisitions to reach and dominate new geographical points.

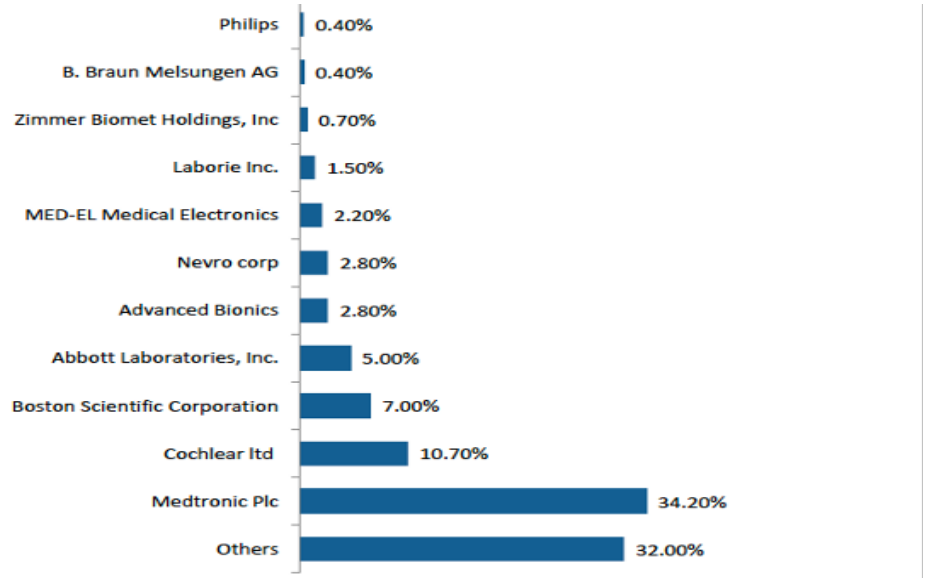


Figure 76. Market Share Analysis, by Company, based on revenue (Source: Report Ocean 2020).

According to Report Ocean Pvt. Ltd (2022), the global Neurostimulation market was valued at approximately 7119.8 US$ Mn in 2022 for Implantable Device and is expected to reach by 2030 (a CAGR of around 10% from 2017 through 2030). In the case of DBS and SNS the market was valued at 1476.1 US$ Mn and 1010.3 US$ Mn in 2022, respectively. Result of this report also demonstrated that the CAGR for external devices (TMS and TENS) will be expected to grow at a CAGR of 7.7% to 2097.3 US$ Mn in 2030.

The global neurostimulation devices market is expected to be driven by the high prevalence of chronic pain, Parkinson's disease, urinary incontinence, and overactive bladder (see figure 77). Chronic pain can be caused due to reasons such as neck pain, headache, low back pain, neuropathic pain, peripheral nerve injuries, failed back surgery syndrome, and complex regional pain syndrome.

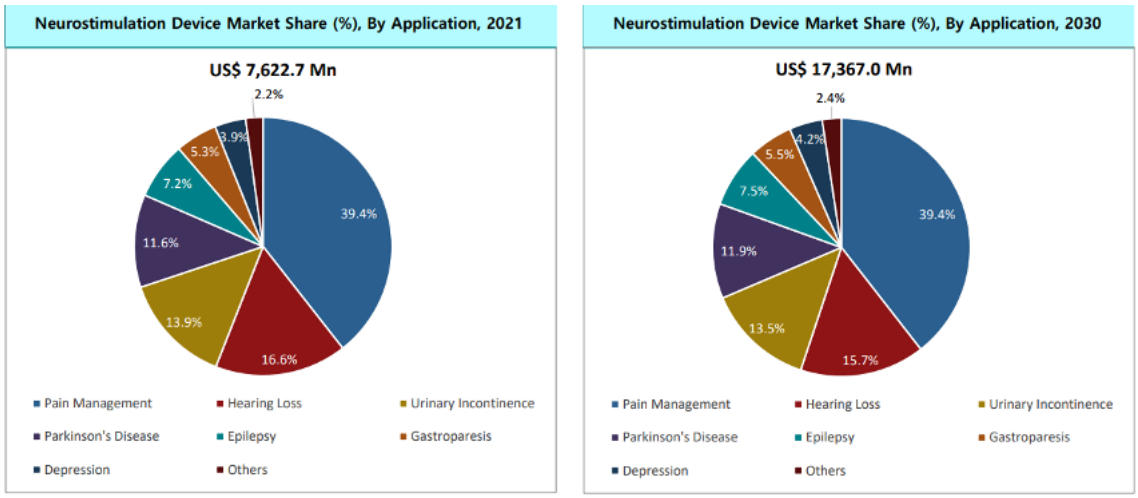


Figure 77.Neurostimulation Device Market Size and Forecast, By Application. (Source: 2022 Report Ocean Pvt. Ltd.)

Neurostimulation devices are largely intended for pain relief in those patients who do not respond adequately to neuropathic pain medications, physical therapies,

nerve blocker, among others, with a market share of 39.4% (Report Ocean, 2020). Factors such as the global increase in patients with this condition, opioid use, stress, spinal cord surgeries, will influence a greater demand for these therapies.

Key data extracted from the market report:

- The ***chronic pain application*** accounts for the highest revenue in the neurostimulation devices market, with a predicted value of 6850.9 US$ Mn by 2030.
- Increasing number of ***spinal cord problems*** will boost the spinal cord stimulation devices market in the coming years.
- The ***neurostimulation devices market for Parkinson's disease*** segment is expected to grow from 885.3 US$ Mn in 2021 to 2063.3 US$ Mn in 2030 at a CAGR of 10% for the forecast period of 2017 to 2030.
- The ***neurostimulation devices market for Epilepsy and Depression*** segments is also expected to grow from 546.1 US$ Mn in 2021 to 1299.3 US$ Mn in 2030 at a CAGR of 10.2% and from 295.9 US$ Mn in 2021 to 721.4 US$ Mn in 2030 at a CAGR of 10.5% for the forecast period of 2017 to 2030 respectively, by the increasing prevalence of the disease worldwide.
- With the growing aging population and increasing prevalence of ***chronic diseases like Parkinson's, Alzheimer's*** etc. are expected to increase in the coming years which will ultimately increase the number of patients requiring treatments for the above diseases.

In this scene, the market share of hospitals/clinics is expected to reach 84.3% in 2030 and the share of research institutes will increase by 0.9% from 2021 to 2030. The research institutes segment is expected to grow with the highest CAGR of 10.7%, while hospitals/clinics hold the highest market share of 84.9%.

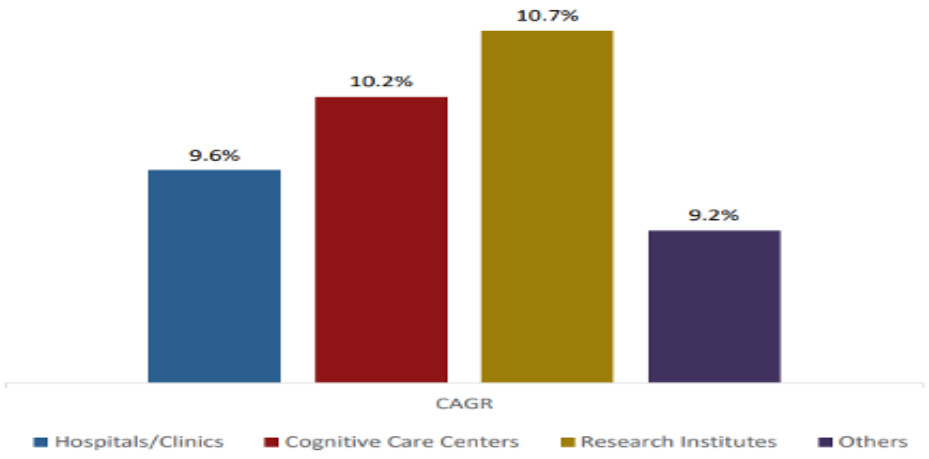


Figure 78.Neurostimulation Device Market Analysis, By End User, CAGR (%), 2022-2030. (Source: 2022 Report Ocean Pvt. Ltd.)

Among regional markets, the North American neurostimulation devices market was the most dominant in terms of the largest revenue, holding a share of 38.3% in 2021 and 41.9% in 2030. The North American neurostimulation market is the largest

segment, making up 41% of the market in 2022, followed by Europe (29%), Asia Pacific (22%).

The *neurostimulation devices market in Europe* (see Figure 79) is expected to grow at an impressive rate during the forecast period owing to the growing preference for advanced technologies and innovations.

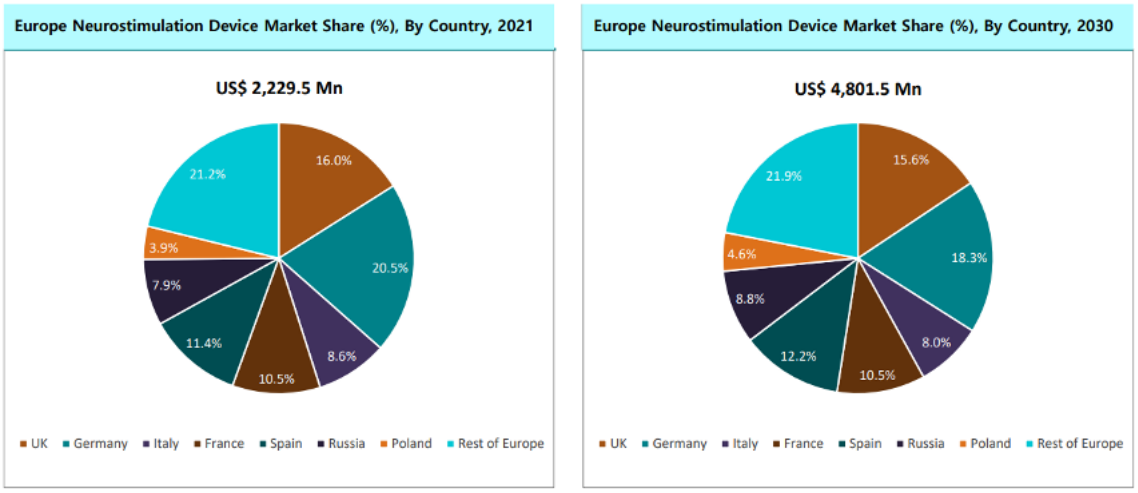


Figure 79. Neurostimulation Device Market Size and Forecast, By Country (Europe). (Source: 2022 Report Ocean.)

The *European Neurostimulation market* was valued at approximately 2,045.8 US$ Mn in 2022 for Implantable Device and is expected to reach by 2030 (a CAGR of 9.3% from 2017 through 2030). In the case of DBS and SNS the market was valued at 438.6 US$ Mn and 299.5 US$ Mn in 2022, respectively. For external devices (TMS and TENS) market also will be expected to grow at a CAGR of 7.2% to 623.7 US$ Mn in 2030.

- Germany, France, the UK, and Spain have a large proportion of neurostimulation market revenue given that they are among the largest EU countries.
- The UK market is witnessing a CAGR of 7.3% during (2017 - 2030).
- From the 2017 to 2030 period, the Germany and Italy markets are anticipated to grow at a CAGR of 6.3% and 6,7%, respectively.
- Two countries leading the growth in the European neurostimulation market are France and Spain, which are expected to post CAGRs of 9.1% and 9.8% from 2017 to 2030, respectively.
- It is also interesting to note that Poland's market of neurostimulation devices is projected to grow with the highest CAGR of 10.9%.

The U.S. Outpatient Rehabilitation/Physical Therapy market is more than $30 billion today and projected to grow at more than 5% per year (U.S. Physical Therapy, Inc.).

Outside Europe and USA, the *Asia-Pacific market* offers lucrative opportunities to the players in the neurostimulation market, as it is anticipated to be the fastest growing market. With the growing geriatric population in the Asia Pacific region and rising cases of depression and dementia in countries like Japan, South Korea, and China. Some hints:

- The Asia Pacific region is expected to grow the highest CAGR (12%) from 2017 to 2030 in comparison with North America (8,6%) and Europe (9%) for the same period.
- The ***China market*** dominated the Asia Pacific Neurostimulation Market by Country in 2022.
- The ***Indian market*** is poised to grow at a CAGR of 13.5% during (2017 - 2030).
- The ***Japanese market*** would showcase a CAGR of 10.5% during (2017 - 2030). The medical device agency in Japan has approved many neuromodulation devices for pain management, and the increase in the approval rate by the medical device agency in various countries will generate more opportunities for the market for neuromodulation devices.

Growth figures differ in specific markets of brain medical devices. In the case of MEG, Verified Market Research, a market analysis company, in its report of November 2021, indicates that the ***Global Magnetoencephalography Market*** size was valued at USD 199.81 Million in 2020 and is projected to reach USD 300.52 Million by 2028, growing at a CAGR of 5.32% from 2021 to 2028. This is a limited market with only a few providers[34] and small number of users (mainly for clinical applications (see Figure 80).

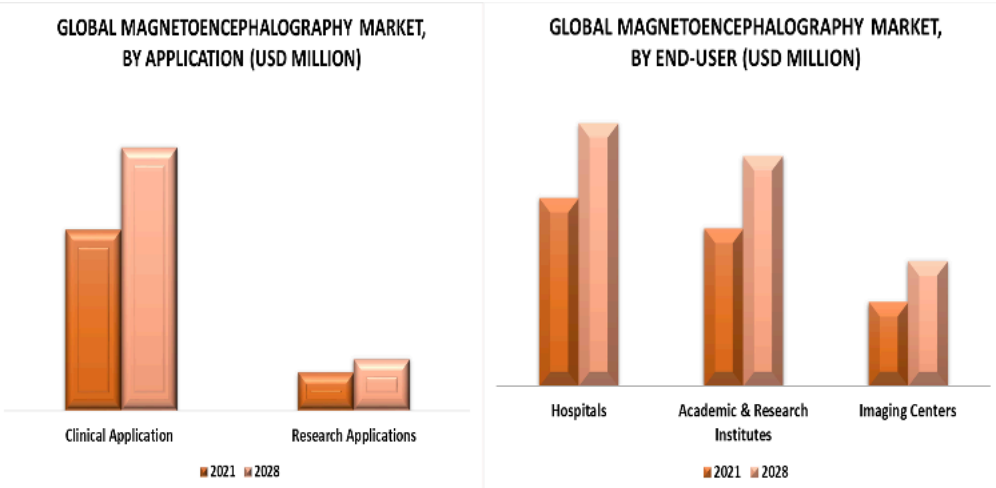


Figure 80. Global MEG market by application (left) and by end-users (right). (source: https://www.verifiedmarketresearch.com/product/magnetoencephalography-market/)

Based on the data presented above, some general conclusions of the market trends can be extracted:

- The adoption of advanced technology in the treatment of various diseases and rising diseases will also bring ***more opportunities to the neuromodulation device industry***. Relevant technologies include silicon microfabrication, hermetic packaging, wireless energy transfer, application-specific integrated circuit technology, flexible electronics, and many more.

[34] The major players in the market are Croton healthcare, Ricoh Company, Ltd., Compumedics Limited, CTF MEG International Services LP.

- ***Research and development of neuromodulation devices*** will create new opportunities for the market for internal neuromodulation devices in the forecast period.
- Recent advancements in ***implanted neural interfaces*** have significantly improved the designs and capabilities of existing miniature systems, allowing for the real-time delivery of user-programmed visual, chemical, and electrical stimuli.
- ***Increased incidences of pain*** caused by different diseases (cancer, diabetes) are forcing healthcare experts and manufacturers to collaborate on the development of improved neurostimulation devices.
- There are many factors that are hampering the growth of the Neuromodulation devices market.
    - One of them is the ***high cost of these devices*** may lead to disproportionate application in geographical regions with different levels of financial resources.
    - The higher cost of a rechargeable neurostimulation device leads to equivalent costs between the strategies being reached with a smaller number of patients failing the SCS screening trial.

3.3 SWOT analysis

With the information presented in the previous sections, it is possible to perform a ***SWOT analysis of the current situation*** (strengths and weaknesses) and ***possible evolution*** (opportunities and threats) on neurostimulation technologies and market evolution.

The analysis should serve as a basis for defining governmental and institutional policies at the European level and more specifically in the context of EBRAINS the possible evolution of its services to address neurostimulation requirements.

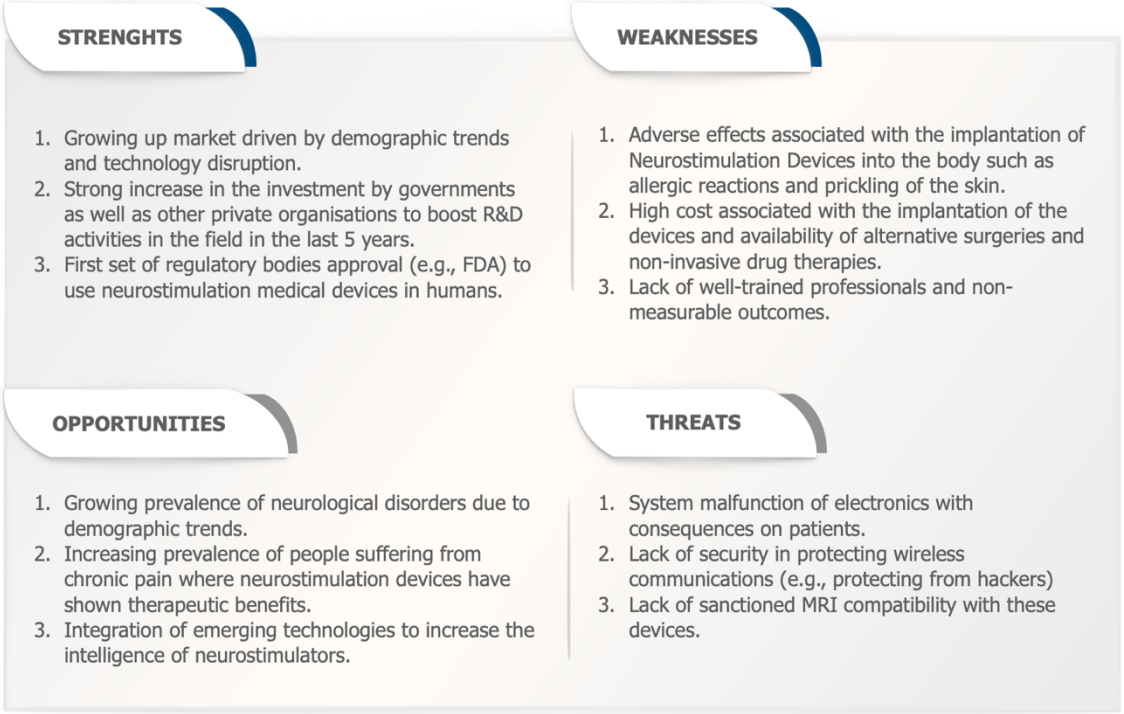


Figure 81. Generic SWOT analysis of neurostimulation (source: own elaboration)

This preliminary SWOT analysis shows the typical situation in the case of immature technologies where regulatory approval processes will require additional time to introduce massively innovative neurostimulators in the market and its diffusion in clinical practice. End users should need to increase the level of trustability of this type of technique. Based on the generic SWOT presented in Figure 81, detailed SWOTs will be presented for each neurostimulation technique described above.

STRENGHTS DBS

1. Proven effectiveness in the most severe symptoms for a broad spectrum of neurological diseases, especially those related to movement disorders: Parkinson disease (PD), essential tremor (ET), dystonia or Tourette syndrome (TS), Alzheimer's disease (AD), conscious states, pain, refractory epilepsy. Also, for psychiatric disorders such as major depressive disorder (MDD), obsessive-compulsive disorder (OCD), bipolar II disorder (BD), addiction, Traumatic Brain Injury (TBI) (Perlmutter, 2006; Fox et al, 2014).
2. Patients who choose the fixed-life battery, do not have to be aware to recharge the device weekly, in case of forgetting or when they must travel, as suggested by patients in some studies (Khaleeq et al, 2018).
3. It is not ablative surgery, despite being invasive, the damage is less.
4. Approved by the FDA.
5. Technology oriented to a personalised therapy, supported by medical evaluations and software for brain mapping, before and during the procedure, mainly.
6. Compatible with multiple software and equipment, open source or paid (Lead DBS, DBS Proc, GUIDE, among others).
7. Can be closed-loop devices and open-loop, but the latter is more used in this mechanism.
8. According to our experts, local anaesthesia is used to perform the intervention, therefore less risky than a general anaesthetic.

WEAKNESSES DBS

1. Invasive.
2. Lack of understanding or solid knowledge about the reasons that explain the effectiveness or ineffectiveness of the technique in the different neural networks of the brain.
3. Frequency parameters differ between publications and/or neurological conditions, with the highest usually being applied for this procedure. There are parameters ranging from 130 or 150 Hz, 185 Hz -considered highest-, and 60 or 80 Hz -for the lowest-, being the standard 130 Hz (Su et al, 2018; Ramasubbu et al, 2018). In this aspect, it is understood that the effectiveness depends in large part by the adjustment of this factor.
4. For patients who choose fixed-life batteries in their devices, they will need to undergo a new surgery between 3 and 5 years on average, given the lifespan of this type of battery (Medtronic, 2022).
5. Electromagnetic interference in patients with DBS can cause severe damage to them as well as in their device (Ibid, 2022).
6. It is highly effective to mitigate severe symptoms of the above-mentioned neurological diseases, but it does not eliminate them in their entirety. This may influence the patient's satisfaction and recovery after the surgery, whether expectations are met or not.
7. Compliance with preoperative protocols and/or presurgical evaluations to be followed by the patient.
8. Use of presurgical and complementary evaluations to place with high accuracy the electrodes (such as other invasive methods), making it more expensive the procedure (MRI, PET, etc.)

OPPORTUNITIES DBS

1. The heterogeneity of the results in the simulations for the different areas of the brain -achieves very positive effects for certain symptoms, while for others it does not necessarily have the same effect-, opens possibilities in exploring new hypotheses and testing theories that can explain brain functions, their relationships and the changes that occur in cognitive impairments, complex to manage in the clinical practice.
2. We consider that the effectiveness of ineffectiveness of DBS in relation to the multimorbidity of some neurological diseases is still uncertain or inconclusive in the literature. This opens new possibilities to explore this mechanism in those patients with multiple conditions.
3. Certain psychiatric disorders are showing improvements in recent years after DBS. For example, OCD, depression, anorexia nervosa (Mocking et al, 2021)
4. Development of increasingly smaller and more effective devices (such as "SenSight", from Medtronic, 2022).
5. Some devices offer long battery life, about 15 years (Medtronic, 2022), unlike those with a fixed duration.
6. Emerging innovations in DBS: Creation of new algorithms with the ability to detect brain activity and adjust the level of stimulation (Brown University, 2022).
7. Compatible with HBP/EBRAINS services such as: VEP, EEG datasets, HIP.

THREATS DBS

1. There are no precise guides to help determine the correct parameters when performing the technique for all conditions. In addition to compromising the degree of effectiveness associated with the method, intervention can be dispensed with, and alternatives with standardised and less invasive procedures can be sought.
2. Most of the companies that market DBS systems have a long history, experience, and greater confidence in the medical community. This increases the barriers to entry for new companies in this market, which introduce better innovations and a better cost-effectiveness solution.
3. Exclusion criteria: Patients with a psychiatric history of significant depression or anxiety, who must access treatment before undergoing the intervention (Baltuch, 2007). A specific time for which DBS takes effect is unknown, it will depend on multiple variables and the results differ between publications.
4. Possible severe side effects (Intracranial haemorrhage, bradykinesia, infections, chronic morbidity, among many others) (Saleh, 2015; Medtronic, 2022)

Figure 82.SWOT analysis for Deep Brain Stimulation (DBS) technique (source: own elaboration)

Deep Brain Stimulation (DBS)

In general, manufacturing of DBS devices is concentrated in a limited number of medical technology companies in North America, Europe and Asia. On the one hand, it is noteworthy the volume of patents registered in the last ten years related to DBS -*North America with 44%, Europe 14% and Asia 23%*- by companies such as Boston Scientific, Medtronic, Beijing Pins Medical, Brainsway, Sapiens Steering Brain Stimulation, The Cleveland Clinic Foundation, Intelect Medical Inc, Brainlab AG and Deep Brain Innovations (Patentscope, 2022). A strong barrier for new brands wishing to venture into the market, who will have to introduce DBS devices with a much more significant value proposition, comply with clinical trials and defined regulatory frameworks.

In the strength's matrix, DBS has shown effectiveness in a variety of neurological diseases, supported by a handful of clinical studies. In conversations with expert neurologist, the technique is performed with local anesthesia, eliminating the risk associated with general anesthesia. It also facilitates that during the intervention the patient performs certain cognitive tasks to evaluate the response in specific areas if necessary. Among other strengths worthy of note, the surgery is not ablative, and the devices have different battery options, including long-lasting -up to 15 years-.

For the specialists, a variety of free and paid software is available (Lead DBS, DBS Proc, GUIDE, etc.), allowing collaboration between other specialists and adapting to the needs of the medial team in surgical planning.

As for the weaknesses, the procedure is still invasive, and the battery has limited lifespan, which means that in subsequent years the patient will have to undergo surgery again. According to studies, the effectiveness of the therapy depends largely on the adjustments of the parameters of frequency employed, with high frequencies being the most used. Another disadvantage is the high cost of the intervention, in addition of the time and effort in performing preoperative evaluations (see other details in the matrix).

On the opportunities, our first reflection starts from the heterogenicity of the results after the stimulation in the different areas of the brain, opening possibilities to test hypotheses and theories that would help a better understanding of brain functions and neuronal networks involved in other diseases. Likewise, the effectiveness of the technique to significantly reduce symptoms in diseases such as depression or anorexia nervosa is also noteworthy. Applications with AI are being incorporated in certain devices to automatically graduate the levels of stimulations, in other cases the reduction of the size of the devices is proposed, scenarios that appear useful innovations and growth in the sector.

Chronic Subthreshold Cortical Stimulation (CSCS)

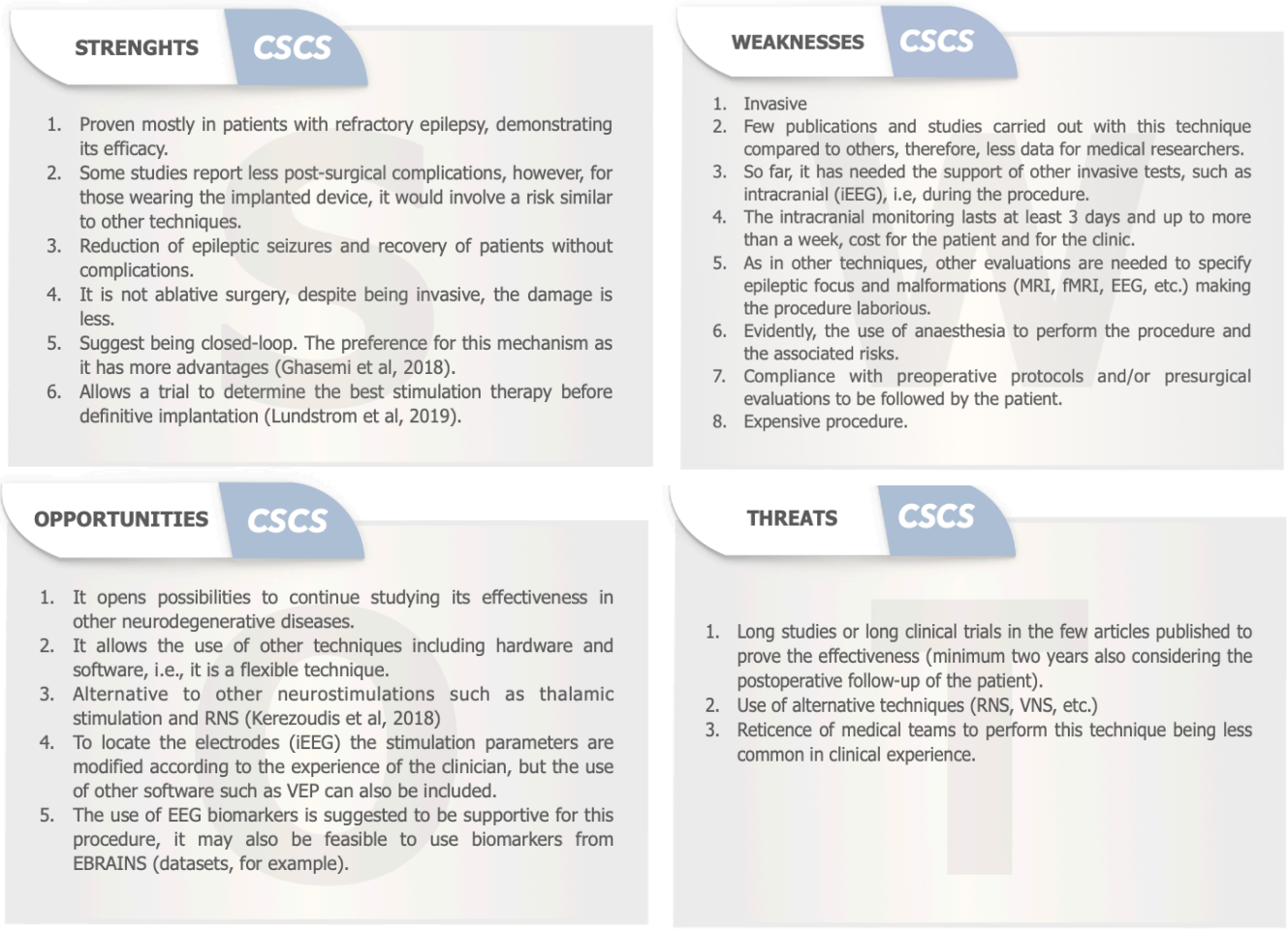


Figure 83.SWOT analysis for Subthreshold Cortical Stimulation neurostimulation technique (source: own elaboration)

The technique began to be tested in patients with epilepsy by implanting the chronic cortical stimulating system just over nine years ago. Among its strengths include its effectiveness in reducing seizures in those patients who for some reason cannot undergo surgery, and in some publications, it suggests fewer post-surgical complications. It does not involve ablative surgery and allows a previous trial in the patient to determine if it is convenient to start with therapy. Considering the benefits achieved in epilepsy, funding agreements have been reached between the clinical sector and neuromodulation companies to initiate new clinical trials and obtain FDA approval[35]. In addition to investment opportunities, it could be applied as an alternative to techniques such as RNS, being able to adapt to other software and hardware at the request of the medical team. On the other hand, although the technique was created several years ago, it has had a slow growth in the sector compared to other methods, being limited studies and clinical trials published, being applied so far in the United States. The application of other invasive and non-invasive diagnostic test makes the procedure costly.

[35] Cadence Neuroscience commercializes neuromodulation therapy created by Mayo Clinic to treat patients with drug-resistant epilepsy, securing $15MM in Series A financing. (PRNewswire, 2019)

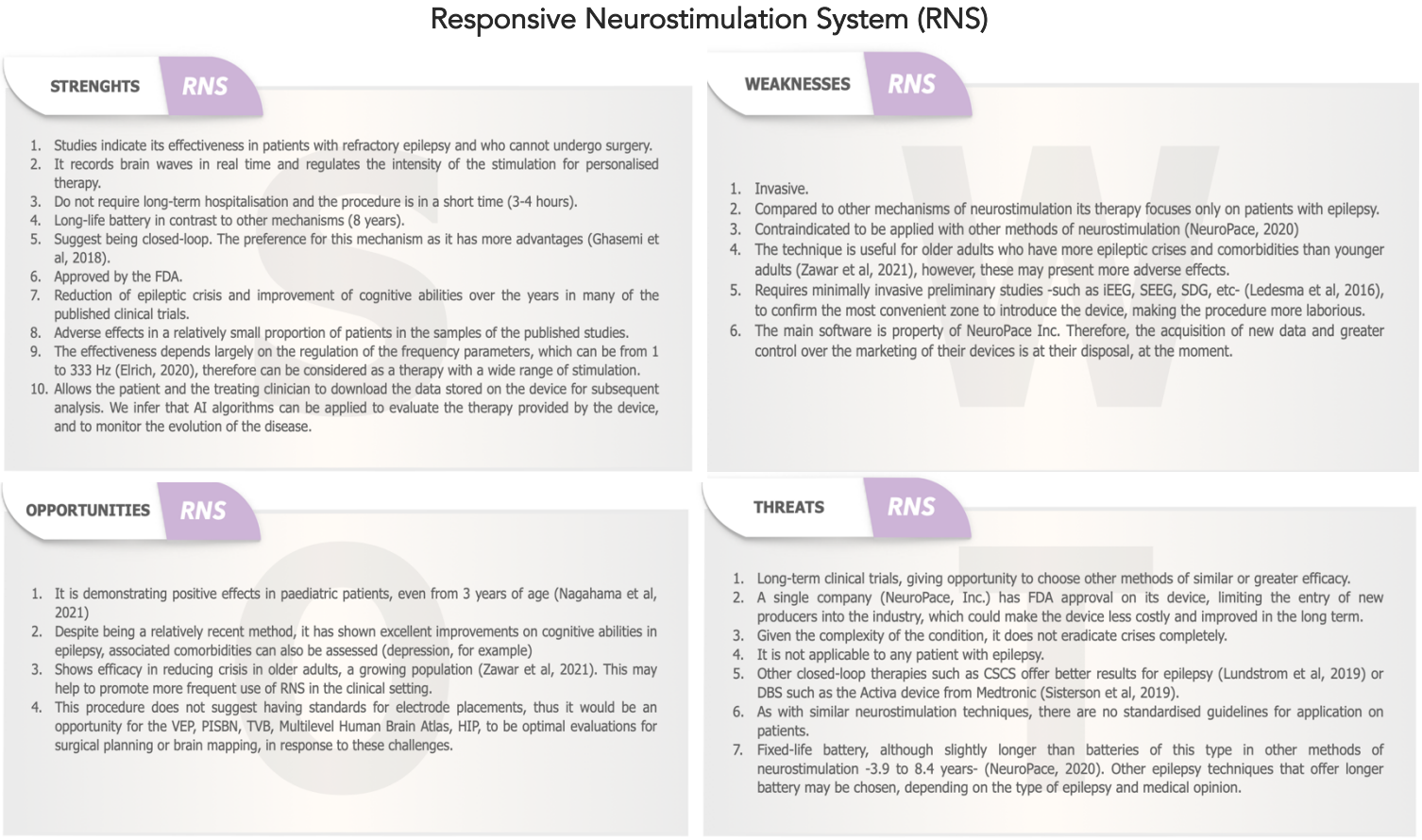


Figure 84.SWOT analysis for RNS neurostimulation technique (source: own elaboration)

Among its strengths, its effectiveness in patients with refractory epilepsy stands out together with an improvement in cognitive abilities in the long term. It is a short-term procedure, which has registered a low percentage of patients with adverse effects and shows good results in pediatric patients. Its devices -marketed mostly by NeuroPace- record brain waves continuously, allowing patients and clinicians to download data resulting from brain activity for further analysis, facilitating better seizure control. Until now, most of the devices in the industry did not allow the continuous recording of data as an EEG, whose company also offers the software to collect and storage this data, derived in form of reports (NeuroPace, 2022). Among the opportunities, both the positive effects in pediatric patients and in older adults make this technique useful for relieving epileptic seizures, in addition to other conditions such as depression. Among other aspects, it leaves open the possibility of using software to locate the position of the electrodes, also useful from the EBRAINS/HBP perspective.

In terms of weaknesses, it is still an invasive procedure, it is also not compatible with another method of neurostimulation and in terms of data storage and management, it is mostly available to the aforementioned company. The threats in the market for these devices start mainly from the time of clinical trials to be validated in other diseases, leaving it to the discretion of the specialist to choose alternative methods

to help their patients. Likewise, it is not applicable to any patient with epilepsy and in terms of technical specifications, other technologies such as CSCS or DBS are competitive. In addition, the battery is time-limited and slightly shorter than other neurostimulation techniques.

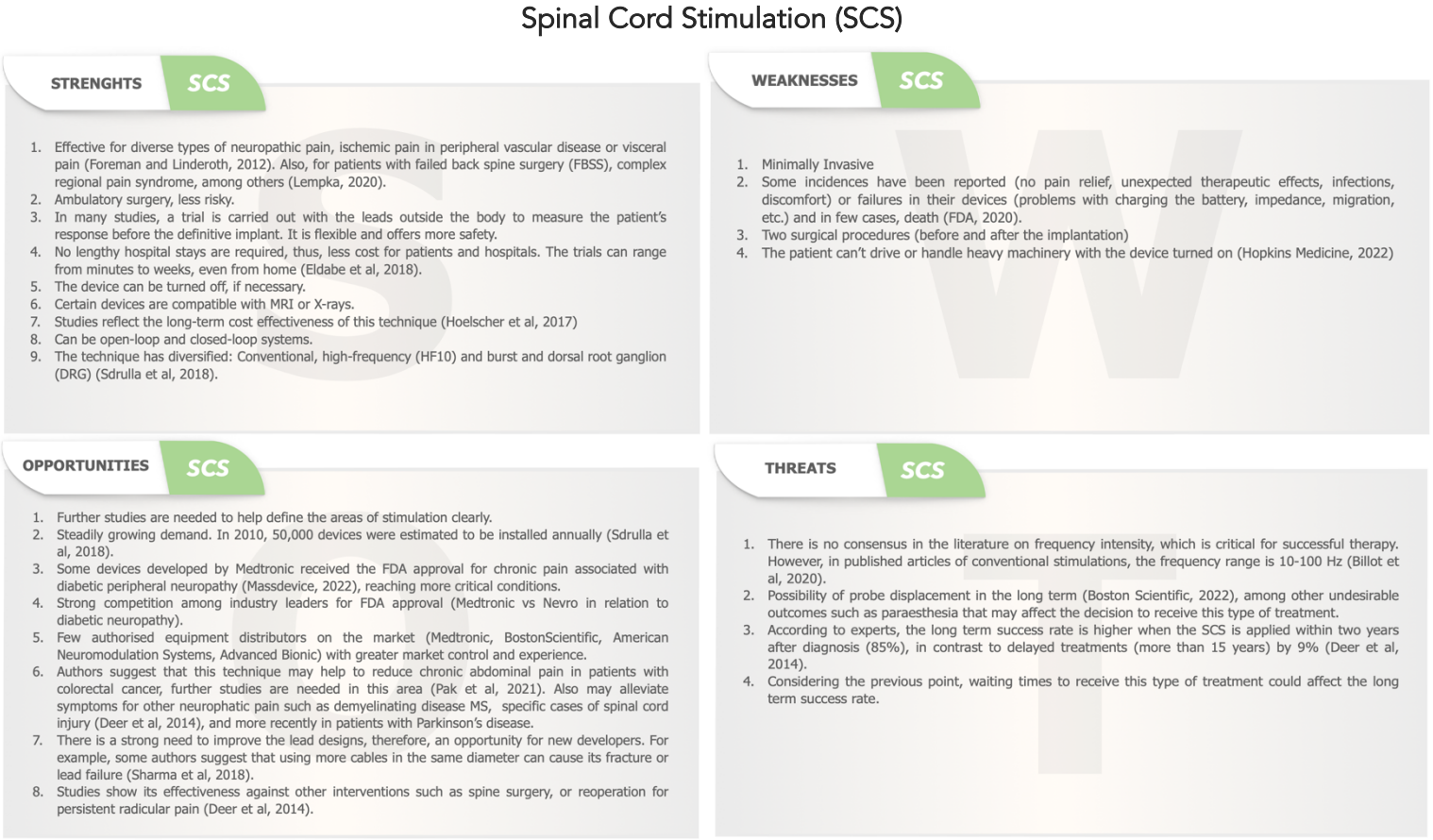


Figure 85.SWOT analysis for SCS neurostimulation technique (source: own elaboration)

The technology is highly effective in patients with Failed Back Surgery Syndrome (FBSS), Neurophatic Pain, Ischemic Pain, Visceral Pain, Complex Regional Pain Syndrome (CRPS), as the main strength. The procedure is done on an ambulatory basis, without the need to spend long periods in hospital, saving costs for both the health system and the patient. Also, a trial is performed before the final implant to provide greater safety in therapy. Among the most important companies offering the device are Boston Scientific, Medtronic, Nevro Corp, Globus Medical, Abbott and subsidiaries.

On the other hand, the impact of the pandemic also has also had an impact on patients with chronic pain: in a survey of 810 affected adults in the United States and conducted by the company Medtronic, 9 out 10 people worsened their condition since the beginning of the pandemic, in addition to the delay in receiving a specialised medical evaluation (Warwic Beacon, 2022). Situation that would impact on the number of affected and those who fail to relieve their symptoms with the available medications. These are situation that are undoubtedly an opportunity for these companies to continue investing resources in innovative solutions for the

benefit of these patients. Another aspect to highlight is the growing demand for these therapies, which already reach other critical conditions such as chronic pain associated with diabetic peripheral neuropathy, disputing not only the control of innovations among the few distribution companies but also the approval of FDA.

There is also an opportunity for new companies and developers who want to improve the design, given the current weaknesses of the device (see matrix). As for the threats, the lack of consensus on the intensity of the frequency for therapies are concerns that may affect their long-term effectiveness, in addition to the possibility of devices and other adverse effects that may affect the decision to choose therapy. They are still expensive procedures: from 10,000 euros in Italy (Zucco, 2015), while in the United States the device alone can cost up to 19,000$ (Lee, 2015).

Vagus Nerve Stimulation (VNS)

STRENGHTS VNS

1. Applied for a diverse neurological diseases (epilepsy, headache and migraine, depression, heart failure, stroke, among many others).
2. Less side effects for the patient, considering that the frequency can be changed non-invasively (Farmer et al, 2016).
3. The technique allows to choose between five stimulation parameters, which can be of low-frequency (1-10 Hz) mostly applied in inflammatory diseases, and 10-30 Hz in epilepsy and depression (Bonaz et al, 2017).
4. Can be open and closed-loop systems.
5. Secondary benefits associated (in brain plasticity, inflammatory responses)
6. FDA approval for drug-refractory epilepsy and depression (in the USA only for partial epilepsy), also in children over 12 years old. (Nune et al, 2015)

WEAKNESSES VNS

1. Invasive
2. General anaesthetic is used (Farmer et al, 2016).
3. Less or minor side effects. In some cases paraesthesia, dysphonia, cough, etc. (Wheless et al, 2018)
4. Better definition of stimulation areas.
5. The mechanism that explains its effectiveness remains unclear in the literature. This makes it difficult to establish clear stimulation strategies.
6. Expensive procedure.
7. It has a positive delayed effect: Up to 2 years after therapy (AANS, 2021).
8. Compatible with MRI scans under certain conditions. In some cases the VNS generator should be removed to obtain a MRI (Couch et al, 2015)

OPPORTUNITIES VNS

1. Is a technique that keeps growing given the functional properties. The VN is considered one of the longest cranial nerves and connects with various organs, including the digestive system, immune response and heart rate (Breit et al, 2018).
2. When combined with alternative therapies such as meditation, improved effects on anxiety, post-traumatic stress and inflammatory disorders are obtained. (Ibíd, 2018).
3. Studies suggest that children may have better outcomes than adults after VNS but more side effects (minor and transitory) (Rossignol et al, 2009).
4. Attractive market: In 2018 more than 100,000 devices were implanted worldwide (Wheless et al, 2018).
5. Few models and authorised distributors (Cyberonics was the pioneer), however, there are limited device developments in this area, especially in Europe. An opportunity for start-ups.
6. Interesting positive effects in plasticity combined with motor rehabilitation (in rats). (Brougher et al, 2021).

THREATS VNS

1. In the field of epilepsy, in some studies the VNS reduces the frequency of crises by 50%, while RNS has 62% median reduction and DBS 70% respectively. (Jamy et al, 2019).
2. The non-invasive method is showing increasingly better results in different neurological diseases. There may be a preference for it in the long term (see nVNS below)
3. According to some distributors, the battery is offered with a lifetime of 4.9-10 years depending on models (VNS Therapy, 2018). However, in some retrospective studies (Couch et al, 2015), nearly half of the patients (46%) who received VNS therapy underwent surgery at least once per replacement, revision or removal. The temporary nature of the battery may lead to a preference for a non-invasive option of this method (nVNS).

Figure 86.SWOT analysis for VNS neurostimulation technique (source: own elaboration)

Market reports project a CAGR of 10.5% on VNS devices between 2021-2028 (Verified Market Research, 2022). As for the procedures, scientific studies share positive results if VNS in a wide range of diseases and with fewer secondary effects for patients -including children over 12 years old-. Among other aspects, benefits related to brain plasticity, attenuation of the inflammatory response and motor rehabilitation have also been reported. It has FDA approval for epilepsy and depression, with few agents authorised for distribution, with Cyberonics being the pioneer company. Among the companies that dominate the distribution of this equipment are the following: Boston Scientific and subsidiaries, ElectroCore, LivaNova and subsidiaries, Setpoint Medical, Parasym. As for the matrix of opportunities, the possibilities of growth of the techniques stand out, considering

the amplitude of the vagus nerve and its connection with other organs of the human body. Another aspect is the benefit reported in paediatric patients, although with more side effects than adults -minor and transient- they have better outcomes. In 2018, more than 100,000 devices were implanted globally (see matrix).

As for weaknesses, it is still an invasive procedure with general anaesthesia, unlike other methods. Some publications report adverse effects on the patient (although minor), the positive effects of which could be delayed up to about two years after therapy. It also remains an expensive procedure: Implanting the device costs 26,543 € -e.g. in Italy- and in the United States around 30,000$ (Marras et al, 2020; Dickson, 2018). As for the threats, depending on the medical condition and frequency of therapies, other techniques are competitive, such as RNS or DBS for epilepsy, reducing seizures by up to 50% and 70%. Other similar but non-invasive procedure are also competitive (nVNS), for which patients would not have to undergo further surgery to replace the device's battery.

3.4 The creation of open innovation brain ecosystems

There are many ***factors that hamper the growth of the neuromodulation device market***. The major restraint for the market is the high investment in capital needed. The high investment in neuromodulation devices is creating a problem for the new key players, mainly technology-based start-ups, and it has become a major restraint for the market. Apart from that, the use of neuromodulation devices requires highly skilled professionals, and the lack of trained professionals is a constraint for the market of neuromodulation devices.

From our point of view, this is one of the areas where ***the creation of a targeted open innovation ecosystem can accelerate innovation***. The term is applied to those cases where several types of actors (large companies, SMEs, universities, research centres, hospitals, business incubators, capital risk entities, public administrations, foundations, patients' associations, etc.) work together in a single location or in a wider region. The emphasis on the term ***"open"*** refers to the need that the innovation ecosystem stimulates the dynamic cooperation among to address specific technological and production challenges.

Usually, these ecosystems should ***attract a critical mass of actors and talented people*** to be effective. For that reason, many of the innovation ecosystems created until now feel that "neurostimulation" is too narrow; the same could happens with brain domain, and they like to focus on wider domains as health to ensure sufficient deal flow and investments.

The ***"openmind consortium"*** (see box 27) is one of the examples of brain-based ecosystems located in the USA. It is focused on implantable neurostimulation hardware platforms looking for de facto industry standards shared by several companies and research groups.

Box 27.

"The "Open Mind" neural communications consortium was formed to accelerate cooperation and innovation in the use of implantable neurostimulation hardware platforms. These next generation devices incorporate sensing of cortical and subcortical field potential activity, with the capability for wireless streaming from the internal device to external computers over years. Our founding team represents the major clinical areas of interest in neuromodulation: movement disorders (UCSF), epilepsy (Mayo Clinic), and psychiatry (Brown/Baylor), and includes experts in the design and dissemination of implantable devices (Oxford), and in neuroethics. This consortium will facilitate already funded proposals, as well as entry of new investigators, in the rapidly evolving ecosystem of implantable wireless neural interfaces.

Our goal is to provide investigators with critical elements to the launch of their own clinical studies: A "turnkey" user interface to get started, a library of more sophisticated, open-source software elements for neural sensing at home paired with peripheral monitors, and streamlined regulatory pathway for FDA approval of investigational protocols, which we call the "Open Source Quality Management System". We will disseminate education and resources through biannual workshops and a web-based library of regulatory documents, software, and the Quality Management System.*

***Source**: https://openmind-consortium.github.io/post/resources/*

In Europe, similar initiatives can be found around large brain initiatives like EBRAINS, EIT Health or others, specific focus on neurostimulation can be created on the bases of European research groups and companies in the field.

Europe´s equivalent endevour to that of OpenMind is the research project financed under the European funding program EXCELLENT SCIENCE - Future and Emerging Technologies (FET), named "Ionic Neuromodulation For Epilepsy Treatment" (IN-FET).

Box 28.

"This research project started in 2020 and is expected to finalize in 2024. The total cost of the programme come to 3 369 758,75 €, entirely EU funded and coordinated by Scuola Internazionale Superiore di Studi Avanzati di Trieste. This EU-funded consortium aims to elaborate a totally new, proof-of-principle approach for neuromodulation technology and use it in order to built future brain implants for epilepsy treatment.

The technology behind this project rests under a new way to tamper neural cell excitability, applying neuronal firing by direct ionic actuation at the microscope scale and monitoring cell responses by nanoscale transistors. In order to achieve this goal, the multidisciplinary consortium brings together electrochemistry, 3D nano fabrication, nanoelectronics, numerical simulations and neural biophysics.

This project integrates the participation of different actors across Europe aiming to combine its knowledge and know-how to accelerate the transfer of research and innovation results in neuromodulation technology and its use for epilepsy treatment. The entities cooperating range from knowledge provider institutions, such as Université de Genève (Switzerland), The University of Sheffield (United Kingdom) and the Consorzio Nazionale Interuniversitario per la Nanoelectrica in Italy to technology providers such as IBM research GMBH in Switzerland or Multi Channel Systems MCS GMBH in Germany."

Health start-ups face great challenges when seeking large sums of money, even during the first phases before scaling-up. The risks involved are not negligible and share with other large companies. Pharmaceutical companies, for example, need, after researching and developing the drug in question, to organize and fund clinical trials. They must also pass the regulatory approvals of federal agencies such as the US Food & Drug Administration (FDA), in the case of the US, the European Medicines Agency (EMA) in the EU, and similar agencies ion other countries. All of this considerably increases the amount of time it takes for a product to reach the market and start generating revenue. Figure 87 provides us with an overview of how the differences between biotechnology and technology start-ups can be distinguished.

Figure 87. Differences between biotechnology and technology start-ups (source: https://www.airswift.com/blog)

A singular aspect of health innovation (brain innovation has also inherited this challenge) that collides with the usual start-up methodology used in other domains like ICT is the ***impossibility of producing a Minimum Viable Product (MVP) in the short-term***, to test it in the market (with exploratory users), and then to refine it by adding additional features.

In the brain domain, the development of a new product takes time and reduces the possibility that business angels and independent risk management entities can

invest in it. The only area where the situation is like ICT is the development of non-invasive mental health products based on wearables if they are not considered as medical devices. In this case, many products collecting behavioural data are processed by using individual smartphones and are marketed as another type of app.

It is interesting to note how the characteristics of newly created brain-based companies have attracted ***venture capital investment from corporate funds launched by large companies***. This is because the institutional VC investors are the ones who most identify with the proposals of these science start-ups: they see an incredible capital return opportunity with a moon-shot.

3.5 The regulatory challenge for neurostimulation devices

3.5.1 The precautionary principle in the health sector

One well-accepted role of the public administrations is to provide a context where citizens are protected against bad effects of product and services marketed in the environmental, energy, health, or industrial contexts. Then, they assume the ***"precautionary principle",*** well rooted in the behaviour of public administrations[36].

Precautionary principle can be defined as *"When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause-and-effect relationships are not fully established scientifically."* (Wingspread Conference, 1998)[37].

In a document presented to the European Parliament (Bourguignon, 2015) its author claims that *"Most experts agree that the precautionary principle does not call for specific measures such as bans or reversing the burden of proof. However, experts and institutions do not agree on the method for determining when to apply precautionary measures (cost-benefit analysis, risk trade-off analysis, cost-effectiveness analysis, pros and cons analysis of action and inaction, etc.).* The underlying goal is to deal with the "uncertainty" (a situation where environmental and/or human health impacts are likely, but the probabilities are unknown may lead

[36] In 1982 the World Charter for Nature, which was adopted by the UN General Assembly in 1982, was the first international endorsement of the precautionary principle. By the late 1980's the principle was being incorporated into European environmental statements. It was subsequently incorporated into a number of international conventions, but the most widely cited is the 1992 Rio Declaration on Environment and Development. The Maastricht Treaty of 1992 and the later EC Treaty noted that European Union environmental policy would be *"based on the precautionary principle and on the principles that preventive action should be taken, that environmental damage should as a priority be rectified at source and that the polluter should pay"*.https://www.sourcewatch.org/index.php/Precautionary_principle

[37] A difficulty in studying the precautionary principle is that it has been formulated in a variety of ways with varying implications for when and how precautionary action should be implemented. No single formulation has been universally adopted. These references discuss influential statements that include definitions of the precautionary principle and analyses of various definitions. https://www.oxfordbibliographies.com/view/document/obo-9780199756797/obo-9780199756797-0046.xml

to precautionary measures to reduce exposure to certain hazards) in measuring the consequences of applying new technological advances.

If the application of an international law for the precautionary principle is disputed, countries will make their own decisions, with a patched scenario where some countries will become more permissive than others. It is happening today in many S&T areas where innovators could find easier to enter their products in the market.

Within this context, there is a strong debate about the desired balance between precaution and innovation. The concept of *'responsible research and innovation'*[38], stated in H2020 and Horizon Europe, framework programmes for research and innovation of the EU try to get a balance to protect citizens (in the health area with a focus on patients) and, simultaneously promote innovation in this area. An excessive over protectionist regulation can avoid or delay the launching of very innovative products when other regulations in third countries can allow it[39]; on the contrary, a permissive legislation could provoke undesirable side-effects to citizens.

For that reason, when EU or national institutions develop, discuss, or approve policy or regulatory proposals linked to the precautionary principle, the impact on innovation should be fully assessed and addressed. This issue is even more relevant in the context of its consequences on technology sovereignty.

Figure 88 see how the implementation of the precautionary principle could help in making the wiser decisions on behalf of citizens. If we stay forever in the *"high confidence"* quadrant, no innovation is possible. Then, society (citizens and administrations) should accept some level of uncertainty. Decisions framed in the ambiguity and complexity quadrants require specific political will and appropriate regulatory frameworks.

[38] Responsible research and innovation is a cross-cutting issue in Horizon 2020, the EU research and innovation framework programme which aims to foster social and environmental responsibility and ethics in the governance of science and technology.

[39] Do not forget that technology markets are global. A very strict regulation can isolate the EU with respect to other countries.

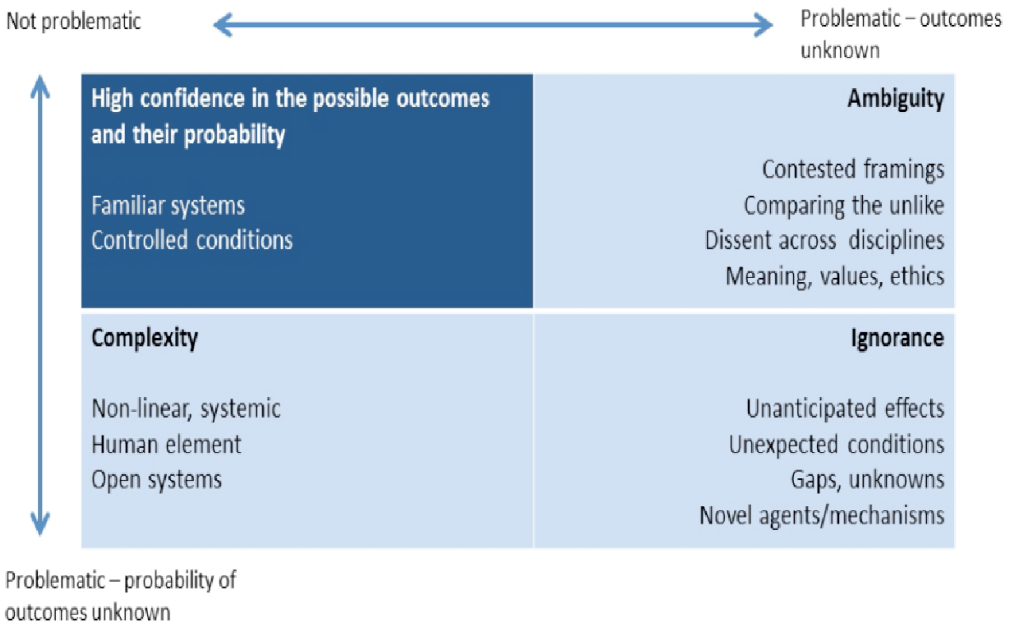


Figure 88. Framework for the implementation of the precautionary principle (source: Bourguignon, 2015)

Central components of the implementation of the precautionary principle (https://www.sourcewatch.org/index.php/Precautionary_principle) are:

- Setting goals (Health indicators).
- Taking preventive action in the face of uncertainty.
- Shifting the burden of responsibility to the proponents of an activity (Who benefits?).
- Exploring a wide range of alternatives to possibly harmful actions (Is it necessary?).
- Increasing public participation in decision making (transparency of information and environmental justice).

Patient-reported outcomes in the regulatory approval of medical devices (FDA, 2020; Rivera et al., 2021).

Box 29.
Bourguignon (2015)
Antimicrobials as growth promoters: Since the late 1940s, antibiotics have been added to feed to accelerate the growth of livestock and productivity. Antibiotic resistance in bacteria was observed in the 1950s and the possibility of transferring resistance to other species of bacteria was documented in the 1960s. In 1985, Sweden banned this use of antibiotics because of its uncertain long-term effects. In 1998, the European Union took the precaution of prohibiting the use of four antibiotics for this purpose. This decision was challenged by Pfizer in 1999 in the EU Court of Justice. The application was rejected in 2002 (case T-13/99).

One of the most relevant areas where the *precautionary principle* directly applies is ***health***. Practically, all areas of human (and animal) health are affected. To find the right balance in the health area depends on the type of regulations derived from

the regulatory principle. The well-known mechanisms of clinical trials in drug development reflect this view. When applied for medical devices, similar processes are set.

3.5.2 Regulation of medical devices: the case of neurostimulators

Then, neurostimulation systems and devices described in this report require the approval of regulatory agencies as ***"medical devices".*** To get the approval of a new medical device is a lengthy process to ensure that it is safe for patients, and it produces clear cost-benefits with respect to pre-existent methods (even to do nothing as an option!!). Then, the innovation rate could be lower than in other sectors, even when pressures from patients (families, associations, etc.) to the administrations are growing to accelerate the use. The example of COVID-19 vaccines and associated treatments clearly demonstrates during the peak of pandemic in 2020 and 2021 the possibility to shorten the time required for approval processes when regulatory agencies were looking for accelerating procedures.

There are two approaches to regulate medical technologies depending on the point in time when regulation applies relative to market authorization.

- The first approach concerns pre-market evaluations, which cover safety and performance aspects. An additional demonstration of efficacy can be required de- pending on the authorization system and the risk of the device.
- The second approach encompasses post-market evaluation systems that additionally aim to consider effectiveness in the usage context, cost-effectiveness and other domains potentially relevant for coverage decision making, such as legal, ethical, socio-cultural, and organisational consequences. Health Technology Assessment (HTA) considerations belong to this approach.

Unfortunately, the broad range of products under the general category of "medical device" precludes the use of a single regulation to obtain the maximum level of flexibility in launching trials.

Figure 89 presents a ***"taxonomic model"*** to classify medical devices according to their HTA relevance (Henschke et al., 2015). The risk-based level (from low risk to high risk) used in the EU directives should be applied differently considering the primary objective of the medical device: diagnostic or therapeutic use. Then, three types of medical device types are identified for each use. Notice that according to this taxonomy, ***neurostimulator medical device*** appears in the high-risk active row, both for diagnostic (B1 artificial body parts (implanted by medical procedures), and for therapeutic (B2).

Following Henschke et al, (2015) *"High HTA-relevance of different device categories is highlighted green, low relevance red. Cells marked yellow include groups where*

relevance is context-sensitive. Grey fields denote cells for which no medical devices were identified (29 of the 54 cells)". Neurostimulators are coded in green.

Classification criteria of EU Directives according to risk aspects		Classification according to the relevance of product and service/ and reimbursement characteristics + HTA logic					
		Diagnostic			Therapeutic		
		(A1) Assistive technology devices (directly used by patients)	(B1) Artificial body parts (implanted by medical procedure)	(C1) Medical devices for the assistance of medical professional	(A2) Assistive technology devices (directly used by patients)	(B2) Artificial body parts (implanted by medical procedure)	(C2) Medical devices for the assistance of medical professional
93/42/EEC and 90/385/EEC	(I) Low risk	manual blood pressure meter intermittent electronic patient thermometer		ophtalmoscope stethoscope	walking frame orthosis conventional wheelchair		slit lamp spatula
	(IIa) Medium risk, non-active	pulse oximeter		ultrasonic device clinical thermometer	contact lenses hearing aid device	dental crown	tracheal tube infusion cannula
	(IIb) Medium risk, active			x-ray machine PET, CT	insulin pen long term corrective contact lenses	dental implant bone prosthesis	laser radio-therapy unit
	(III) High risk			neuro-endoscope intracardiac catheter	concom with spermicide	hip/ knee joint replacement cardiac stent breast implant	stent delivery catheter/ system angioplasty ballocn catheter
	(IV) High risk, active implantable		ICD: heart monitor unit neurostimulator: monitor unit			ICD: defibrillator unit neurostimulator: active unit cardiac pacemaker	
98/79/EC (in vitro diagnostic)	V			ABO/Rh(D) blood grouping analyser			
	VI	glucose strip		Trisomy 21 IVD			
	VII	pregnancy test		blood coagulation selftest			
	VIII			Ebola virus antigen IVD			

Figure 89.Taxonomic model to classify medical devices according to their HTA relevance. (Source Henschke et al., 2015)

Due to scientific and technological advances, and the social perception of health risks, the regulations for medical devices cannot be static. The USA through the **FDA** (Food and Drug Administration) and the European Union through the **EMA** (European Medical Agency) have approved specific regulatory procedures to approve a new medical device for clinical use. Both the FDA and EMA have recently started the modification of the procedures to cope with new requirements: speed-up procedures for breakthrough devices, better connections to other regulated areas like artificial intelligence, electromagnetic or nuclear radiation, etc.

Since May 2021 (see box 30), all new medical devices must meet the EU Medical Devices Regulation requirements[40]. This marks the beginning of a new era for the industry with additional requirements.

[40] Some medicines are used in combination with a medical device, usually to enable the delivery of the medicine. If the principal intended action is achieved by the medicine, it is considered a medicinal product that includes a medical device. The entire product is regulated under EU pharmaceutical legislation

Box 30.
Medical devices are products or equipment intended for a medical purpose. In the European Union (EU) they must undergo a conformity assessment to demonstrate they meet legal requirements to ensure they are safe and perform as intended. They are regulated at EU Member State level, but the European Medicines Agency (EMA) is involved in the regulatory process.
The Regulations on Medical Devices (Regulation (EU) 2017/745) and on In-Vitro Diagnostic Devices (Regulation (EU) 2017/746) changed the European legal framework for medical devices, introducing new responsibilities for EMA and national competent authorities in the assessment of certain categories of medical device.
The Medical Devices Regulation applies from 26 May 2021, following a four-year transition period. Manufacturers must comply with the Regulation when placing new medical devices on the market. It repeals Directive 93/42/EEC on medical devices and the Directive 90/385/EEC on active implantable medical devices.
The In-Vitro Diagnostic Devices Regulation will apply from 26 May 2022, following a five-year transition period. In the meantime, manufacturers can opt to place in-vitro diagnostic devices on the market under Directive 98/79/EC or under the new Regulation if they fully comply with it.
***Source**: Bourguignon (2015)*
https://www.ema.europa.eu/en/human-regulatory/overview/medical-devices

As reviewed in this report, the field of **BCI** (Brain Computer Interface) devices is progressing rapidly from fundamental neuroscience discoveries to translational applications and market access. The need to review the current regulatory processes to approve a new BCI device comes from the development of new types of neurostimulation devices (invasive or not) capable of modifying the human brain functions. Combined with powerful artificial intelligence algorithms to process brain signal and to generate closed-loop systems, with wireless control, and with smart robotics, it is also raising an ethical debate about the consequences for human beings and the need to anticipate consequences.

On May 20, 2021, the FDA issued the final *guidance on Implanted Brain-Computer Interface (BCI) Devices for Patients with Paralysis or Amputation – Non-clinical Testing and Clinical Considerations*[41] (non-implanted BCI devices are outside the scope of this guidance). It deals with one specific area: BCI for patients with paralysis or amputation. For the guidance, implanted BCI devices are neuroprostheses that interface with the central or peripheral nervous system to restore lost motor and/or sensory capabilities in patients with paralysis or amputation. This guidance provides general recommendations for non-clinical testing and study design considerations for IDE feasibility and pivotal clinical studies.

(Directive 2001/83/EC or Regulation (EC) No 726/2004) and must obtain a marketing authorisation for a medicinal product.

[41] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/implanted-brain-computer-interface-bci-devices-patients-paralysis-or-amputation-non-clinical-testing

Non-clinical testing methods may not be available or may not sufficiently provide the information needed to advance to a final version of an implanted BCI device under development. Therefore, if your device is still under development, we recommend that you consider performing an early feasibility study through an IDE[42] to collect an early clinical evaluation of your device to provide proof of the principle and initial clinical safety data. As with all clinical studies, initiation of an early feasibility study must be justified by an appropriate benefit-risk analysis and adequate human subject protection measures.

Box 31.
"Complete description of every module of the device. For example, BCI systems typically consist of several modules including but not limited to the following modules:
a) Signal acquisition (e.g., leads and recording electrodes);
b) Signal processing that includes software for decoding and encoding signals and providing stimulation (in some cases) and associated hardware;
c) Stimulation delivery (internal/external stimulator and stimulating electrodes);
d) Assistive effector component (e.g., a prosthetic limb, wheelchair, functional electrical stimulators applied to intact limbs, exoskeletons or robotic systems, or communication devices and computers);
e) Sensor component for neural feedback (e.g., sensors for restoring touch or reporting other information), if applicable; and
f) Programming module that consists of an operating protocol to control functions, such as turning the device on and off and switching between various outputs and programs.
A general overview of the BCI device as a whole system including a description of how the different modules are configured to comprise the whole system and if applicable, a description of the different system configurations (e.g., programming, calibration, or testing configurations).
A complete description of key components of the device including its function, relevant model numbers, materials, location (implanted or external component) and dimensions or sizes that a user would need to know to use the device properly." ***Source****: https://www.fda.gov/media/120362/download*

3.6 Ethical considerations

The report has addressed the field of neurostimulation from a technological perspective and the related market evolution. Some aspects related to regulation were also considered because they affect the evolution of the market and the play field among countries when regulations significantly differ.

Nevertheless, there is also a key dimension in this analysis which deserves more attention: the ethical aspects related to neurostimulation and the inputs that this discussion could provide for future regulations.

[42] IDE refers to Investigational Device Example. See https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-device-exemptions-ides-early-feasibility-medical-device-clinical-studies-including

According to San-Agustin and Camilo (2021), the introduction of this dimension appeared in 1998 linked to TMS (Transcranial Management Stimulation), see box 32. Probably, the rationale behind can be also applied to many of the techniques described in this report.

Box 32. *San Agustin, A., Camilo, I. (2021).*
"The application of TMS has gone hand in hand with a consensus on the ethics of its application since at least 1998, when a report and suggested guidelines were defined for the correct application of TMS (Wassermann, E. M., 1998). In this way, consensus conferences have been established on several occasions in 2008 and 2018 to update these guidelines, resulting in a series of ethical points around this stimulation. The most up-to-date guidelines at this time are those specified in the article "Safety and recommendations for TMS use in healthy subjects and patient populations, with updates on training, ethical and regulatory issues: Expert Guidelines" still in press, based on the meeting promoted and supported by the International Federation of Clinical Neurophysiology (IFCN), which took place in Siena (Italy) in October 2018 (Rossi, S. et al., 2020).

At that time, the ethical aspects of the application of TMS were focused on the risk that the patient could suffer and their ability to understand the risk (close similar to other medical interventions like surgery). The proposal to do an ethical TMS therapy was based on the gain that the patients had in relation to the damages that they could suffer, which with the application of TMS were few although existing.

There were three ***fundamental ethical pillars*** on which the basic and clinical application of TMS is based.

The first was based on ***informed consent***, where the subject to whom the TMS is applied must give voluntary consent when participating in the experimental procedures. In addition, the volunteer to be considered suitable to accept participation must be duly informed about the procedures to be carried out, as well as the possible risks and discomfort that she or he could feel. This is a common procedure used in many medical acts which implies the signature of a discharge responsibility document.

The second and third concepts are in regard to the ***risk and benefit of the application of TMS***. Not only is it necessary that the subject is willing and has understood the risks involved in participating in brain stimulation processes, but it is also a requirement to demonstrate that the gain should be greater than the risk in applying TMS. In addition, there should be no other alternatives of scientific methodology by which to obtain the same data, for instance, non-invasive techniques.

The application of those criteria did not create any specific problem beyond the usual ethical principles in medicine… until now.

Possibly, one of the most critical ethical issues on neurostimulation is related to the concept of ***neuroenhancement*** and its consequences. Neuroenhancement is

defined (Luber, B., & Lisanby, S. H.,2014) as *''Any augmentation of core information processing systems in the brain, including the mechanisms underlying perception, attention, conceptualization, memory, reasoning and motor performance"*

In other terms, the evolution of the technology related to neurostimulation could imply an ***augmentation of mental capacities*** (neuroenhancement) which affects the whole individual. If in 2014, this possibility was perceived as a long-term and future problem, the fast evolution of the field made it in 2022 closer to reality. Do we have regulations to deal with?

Notice that regulation on neurostimulation, as described in this section, came from the application of the precautionary principle which in this context, could be understood as risk of losing mental capacities or other derived physical problems. Some questions are relevant to frame the discussion: Is the enhancement of those functions a risk to be considered and regulated? Why should we be worried about the improvement of our memory or concentration? Is it relevant to the funding agency? Is it a dual use technology?

3.6.1 Consequences of Ethics and Regulation from the Market Perspective

This report does not intend to develop in detail all technical and philosophical problems related to the regulatory and ethical issues of neurostimulation, but to analyse how they can impact on the development and commercialization of products and services and on the structure of the international market.

We assume as a starting point that changes in the regulatory framework to adopt legislative consequences of neuro-rights will condition decision making in stakeholders with consequences in the way that new neurostimulation products and services are adopted in the market.

To set-up an analysis framework, the relationships with market evolution will be described by using the ***PESTLE*** (Political, Economic, Social, Technology, Legal and Environmental dimensions) analysis approach combined with ***triple helix*** (industry, academia, administration) impact considerations; then, estimations about future evolution scenarios will be presented.

The next table describes the most important relationships between ***PESTLE*** dimensions and triple helix perspectives in relation to ethics and regulations. Both the industry and the administrations' perspectives are divided into two groups to enrich the analysis with different visions. Distinction is made between large companies and SMEs, and an additional sub-column for the clinical (hospital) administration was included to deal with the specificity of the analysis in the field of neurostimulation.

There is little evidence in legislation to reduce greenhouse gas emissions in the medical device industry in neurostimulation. However, in some reports, big players such as Abbott, Boston Scientific, for example, share some of the guidelines and

policies they apply both in their distributors and internally for their own supply chains. These standards facilitate the licence acquisition, certificates and permits, considering the best practices in recycling, waste management, emissions, water, and energy.

Relationships, dimension and perspectives	Triple helix perspectives				
	Industry		*Academia*	*Administration*	
	Large	*SME*		*Government*	*Hospitals*
Political	*Pressures to enforce regulatory changes to speed-up approval processes*	*Focus on tech-based start-ups.*	*Increasing support to public-private cooperation.*	*Priority in responsible research and innovation neuro programmes .*	*Competition between private and public hospitals.*
Economic	*Uncertainty will postpone investments decisions*	*Lack of clear positioning of capital risk in neurostimulation projects*	*Higher industry investments in universities and research centres*	*Additional resources to research and innovations (e.g., Next Generation Funds).*	*Investments in specialised services should compete with other areas like primary health services.*
Social and cultural	*Lack of confidence in pharma companies.*	*Risk aversion and need to address short-term needs will be a barrier.*	*Increased public-private cooperation is clearly noticed.*	*Growing ethical concerns in citizens impacts governmental policies' design.*	*Growing role of patients' associations to block some uses.*
Technological	*Lack of standards could slow-down the adoption of digital twins of human brains.*	*TRL increase of emerging products is conditioned by the evolution of capital risk.*	*Breakthrough innovations start to move from the lab to the market*	*Priorities on neurology are set in funded research programmes*	*Resistance to changes in current procedures (lack of confidence in the technology).*
Legal	*Regulations on neuro-devices differ*	*Control of international acquisition*	*Research cannot be hindered by*	*Regulatory sandboxes to test new*	*Impact on regulation in clinical trials*

	between countries provoke market fragmentation	*of neuro start-ups*	*precautionary principles*	*medical devices*	*and data privacy to preserve neuro-rights*

Table 2. Relationships between PESTLE Dimensions and Triple Helix perspectives in relation to ethics and regulation (source: own elaboration)

A preliminary analysis of Table 1 indicates three main conclusions:

- Industrial decisions are strongly dependent on the speed and type of regulatory changes.
- Risk of market fragmentation and delays in adopting new products due to a combination of factors.
- Governmental priorities imply to pay more attention for responsible research and innovation principles.

Based on this analysis two ***simplified scenarios*** (named as "optimistic" and "pessimistic") on the evolution of neuro-rights seem possible towards 2030:

Scenario 1: Optimistic

Description. Neuro-rights legislation and regulations are adopted in all advanced countries, institutions and companies, and citizens are aware of its need and consequences.

Driving forces.

- Growing awareness of the need to protect individual minds from abuses in a fully digitised society.
- The adoption of technological advances is well-balanced with the precautionary principles adopted by society.
- Citizens are confident in the use of neurostimulation as medical devices.
- Companies (both large and SMEs) have a stable scenario to adopt their decisions.

Scenario 2: Pessimistic

Description. Patched scenario with fragmented social views of consequences and lack of a shared vision on the need to adopt common regulatory frameworks.

Driving forces.

- No agreement on the consequences of the regulation of neuro-rights creates a very fragmented legislative framework with a national bias constrained by national interests.

- Reluctance to adopt neurostimulation devices in society due to a poor understanding of effects and effective control
- Very limited adoption in public institutions.

PART 4.

4. Relationships of neurostimulation with the research activities in HBP and EBRAINS

4.1. HBP activities in neurostimulation

The development of the *Human Brain Project, HBP (https://www.humanbrainproject.eu/en/)* started in 2013 was funded by the European Commission to put in place a cutting-edge research infrastructure that will allow scientific and industrial researchers to advance our knowledge in the fields of neuroscience, computing, and brain-related medicine. Then, its goals are broader than simply neurostimulation as addressed in this report.

Furthermore, as stated in the initial section of this report, the *EBRAINS Research Infrastructure (https://ebrains.eu/)*, which is being created by the HBP, gives access to research data, models, and software shared by researchers worldwide, as well as computational resources provided by the FENIX infrastructure through the EU Human Brain Project.

One of the key issues in HBP and the services to be provided by EBRAINS is related to the capture of detailed information on the human brain. Specifically, many of the activities associated with capturing detailed information on human brain microstructure or brain activity are related to the use of microscopy and brain imaging (RMA, MEG, PET, etc.). These are techniques that cannot be considered pure *'neurostimulation' techniques* (unless combined with other techniques) because they do not act directly on brain activity but obtain brain data that could be useful to provide advances in neurostimulation devices.

However, *some HBP research can boost the use of neurostimulation by providing information to medical areas such as neurosurgery.* Specifically, four research activities carried out in HBP have been identified for this purpose:

- Neuromorphic Computing (NP)
- Perturbational Complexity Index (PCI)
- Virtual Epileptic Patient (VEP)
- Photoneuromodulation (PNM).

The intention is not to describe in detail these HBP research results but to analyse their *potential usefulness to accelerate or accelerate future neurostimulation*

advances. In all these cases, emerging neurostimulation techniques can take advantage of these results when used by external companies or research groups.

4.1.1 Applications of neuromorphic computing (NP)

Neuromorphic computing systems, inspired by the biological concepts of the human brain, has the potential to be used for the storage and processing of large amounts of digital information with ***much lower power consumption than conventional processors***. Among their potential future applications, an important niche is moving the control from data centres to edge devices. (Christensen et al., 2022).

Neuromorphic systems can offer higher speed (real-time or accelerated) and lower energy consumption than traditional High-Performance Computing (HPC) resources. The accelerated systems are particularly suited for research projects of brain plasticity and learning, enabling simulation of hours or days of biological time in only seconds or minutes. This section summarizes its potential use in relation to neurostimulation.

Box 33.
The next generation computer technology is expected to solve problems at the exascale with 1018 calculations each second. Even though these future computers will be incredibly powerful, if they are based on von Neumann type architectures, they will consume between 20 and 30 megawatts of power and will not have intrinsic physically built-in capabilities to learn or deal with complex data as our brain does. ***Source****: Christensen et al., 2022*

The ***relevance of neuromorphic computing for neurostimulation*** comes from its potential use in the development of a new generation of ***smart micro brain implants with embedded processing capabilities***. NP approach can be very useful when it is necessary to move intelligence "*to the edge*" (in this case to the brain implant itself). This could be the case of smart medical devices with NPs capabilities.

The main advantages of neuromorphic chips are the low consumption of energy and the efficient execution of deep learning algorithms. As implanted devices for closed loop neurostimulation required more processing capabilities and less consumption of energy the use of NPs is a natural approach.

Human Brain Project (HBP) has developed two specific neuromorphic architectures integrated in a simulation platform. The ***Neuromorphic computing platform of the HBP*** allows users simulate experiments on two different systems:

- *BrainScaleS-2*
  https://wiki.ebrains.eu/bin/view/Collabs/neuromorphic/BrainScaleS/
  It is the Heidelberg system based on the concept of "Neuromorphic Computing with Physical Emulation of Brain Models" (see figure 89). The current technology implements analogue electronic models of 4 million

neurons and 1 billion synapses on 20 silicon wafers. The ***next generation BrainScaleS-2 single chip system*** with 512 point neurons or a lower number combined to structured neurons and with programmable plasticity is accessible for usage via PyNN both for batch submissions and (since October 2021) for interactive use via the EBRAINS Collaboratory. The system runs 1000x faster that biological real time.

Figure 90. BrainScaleS-2 (source: EBRAINS)

- *SpiNNaker 2*.
  https://wiki.ebrains.eu/bin/view/Collabs/neuromorphic/SpiNNaker/
  The Manchester system based on "Neuromorphic Computing with Digital Many-core implementation of Brain Models" (see figure 90) connects 1 million ARM processors with a packet-based network optimized for the exchange of neural action potentials (spikes) (Farber and Bogdan, 2020). ***SpiNNaker is a digital neuromorphic architecture, designed specifically for the low power simulation of large-scale spiking neural networks at speeds close to biological real-time***. Unlike other neuromorphic systems, SpiNNaker allows users to develop their own neuron and synapse models as well as specify arbitrary connectivity. SpiNNaker has been used for neurostimulation (Mitaikis et al., 2018)

Figure 91.SpinNNaker-2 system (left) and chip (right) (source: EBRAINS)

Box 34.

"A number of demonstrations of the benefits of neuromorphic technology are beginning to emerge , and more can be expected in the short to medium term. Various start-up companies are emerging, in the USA and elsewhere, to exploit the prospective advantages of neuromorphic and similar technologies in these new machine learning application domains. In the HBP, small and large-scale demonstration systems are available and attract an increasing number of users from industry and academia. While these systems are primarily made for basic research on understanding information processing in the (human) brain, efforts are being made to also implement machine learning tasks on them.

The HBP-NP platform also offers industry researchers and technology developers the possibility to experiment with and test applications based on state-of-the-art neuromorphic devices and systems. Both systems offer the possibility of performing single simulations via the web browser, scripted or the HBP Portal. Likewise, they provide alternatives to deploy simulations in less time compared to traditional HBP computers, as well as batch-mode and closed-loop experiments in dynamic virtual scenarios. It also allows identifying errors during the simulation, guides and technical support to run the models. A platform aimed mainly at neuroscientists and technicians related to the computer and robotics field.

***Source**: https://www.humanbrainproject.eu/en/silicon-brains/*

Some research on this field has been published with ***experimental neuromorphic chips***. One relevant case (Yoo and Shoaran, 2021) describes the architecture of a ***neural CMOS microchip*** integrating conventional processing pipeline versus on-chip computing (see figure 92). The whole implant is a chip that allows real-time prediction of disease symptoms (e.g., epileptic seizures, Parkinson's tremor, mood change or anxiety) to trigger therapeutic stimulation in a closed-loop system, or to enable motor decoding for prosthetic control in a brain machine interface.

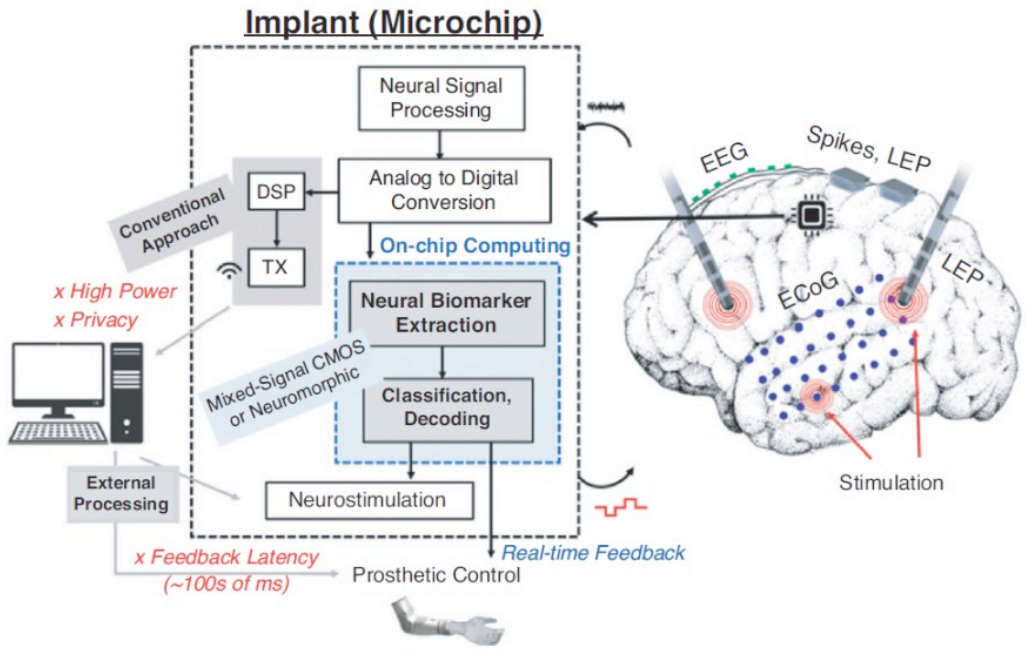


Figure 92.Neural microchip integrating conventional processing pipeline versus on-chip computing (source: Yoo and Shoaran, 2021)

Box 35.

"The advancement of implantable medical devices for the treatment of neurological disorders demands energy-efficient, low-latency processors for responsive, safe, and personalized neuromodulation. A 130-nm CMOS neural interface processor is presented to perform the brain-state classification and closed-loop control using programmable-waveform electrical stimulation.

The architecture features an autoencoder neural network for both spatial filtering and dimensionality reduction. Dedicated feature extraction blocks are implemented for univariate (signal-band energy) and multivariate (phase locking value, and cross-frequency coupling) neural signal processing. The proceeding exponentially decaying memory support vector machine (EDM-SVM) accelerator employs these features for hardware-efficient brain-state classification with a high temporal resolution. An integrated digitally charge-balanced waveform generator enables flexibility in finding optimal neuromodulation paradigms for pathological symptom suppression.

The system on chip (SoC) is validated using the EU human intracranial electroencephalography epilepsy data set, achieving a seizure sensitivity of 97.7% and a false detection rate of 0.185/h while consuming 169 μJ per classification.

***Source**:*

https://www.researchgate.net/publication/328242245_NURIP_Neural_Interface_Processor_for_Brain-State_Classification_and_Programmable-Waveform_Neurostimulation

Another relevant approach is the ***BrainChip integrated circuit technology of Akida***[43]. It is an ultra-low power, high performance, minimum memory footprint, event domain neural processor targeting Edge AI applications. The Akida neuromorphic framework by Brainchip implements these core concepts in the form of a digital neuromorphic system-on-a-chip (NSoC). Figure 93 shows the main components.

[43] https://brainchipinc.com/wp-content/uploads/2020/03/BrainChip_tech-brief_What-is-Akida_v3-1.pdf

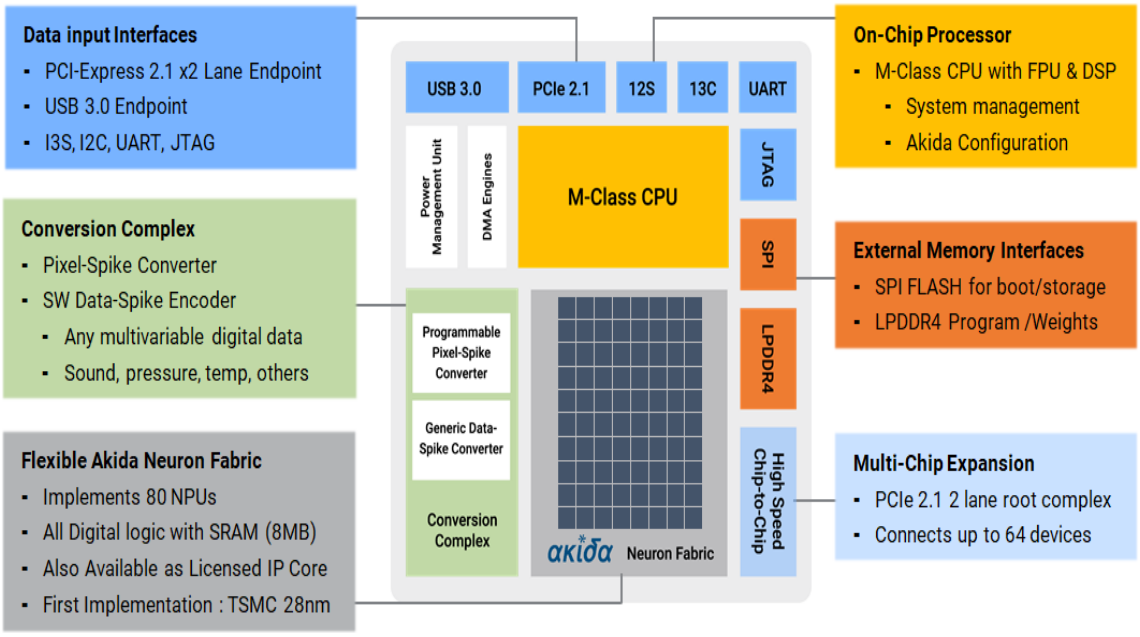


Figure 93.BrainChip Akida processor (source: https://doc.brainchipinc.com/)

It is complemented by the ***Akida Execution Engine (AEE),*** a Python-based chip emulator and key component of the Akida MetaTF ML framework (see Figure 94) for development and simulation of the behaviour of the SNNs supported by the event domain neural processor.

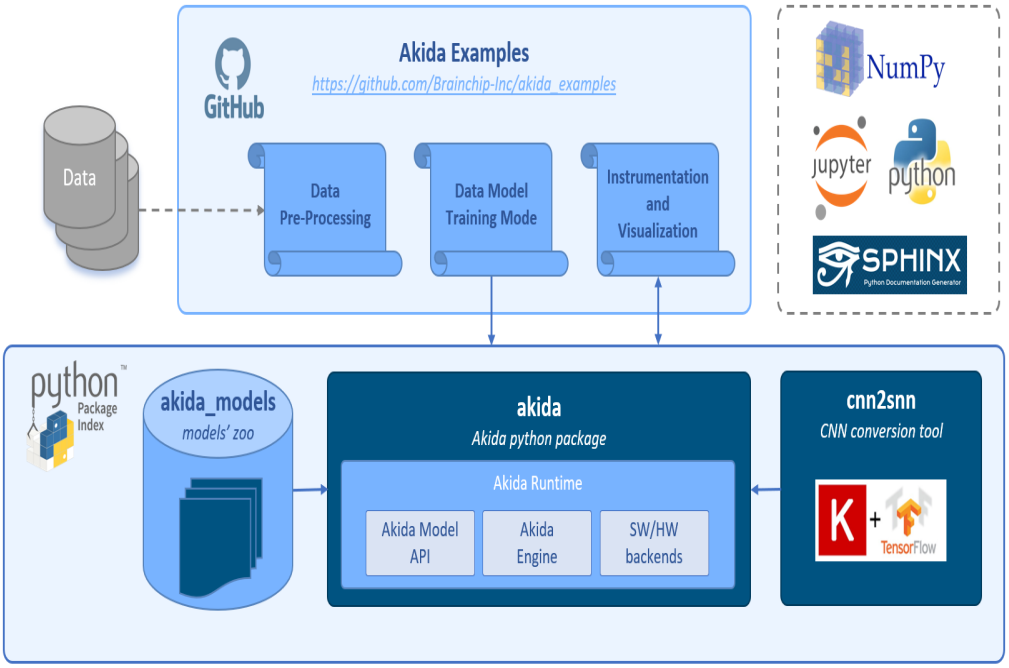


Figure 94.Akida MetaTF ML Framework (source: https://doc.brainchipinc.com/)

The latest avenue for biomedical applications is ***neuromorphic-based functional biohybrids for brain regeneration***. These are hybridized brain tissue grafts (Figure 95), wherein the neuromorphic counterpart(s) emulate and integrate brain function, aiming at guiding the integration of the biological graft into the host brain.

Functional biohybrids merge concepts from regenerative medicine (rebuild of brain matter) and neuromorphic neuroprosthetics (adaptive control of brain function). The symbiotic interaction between the biological and artificial counterparts is expected to achieve a controlled brain regeneration process.

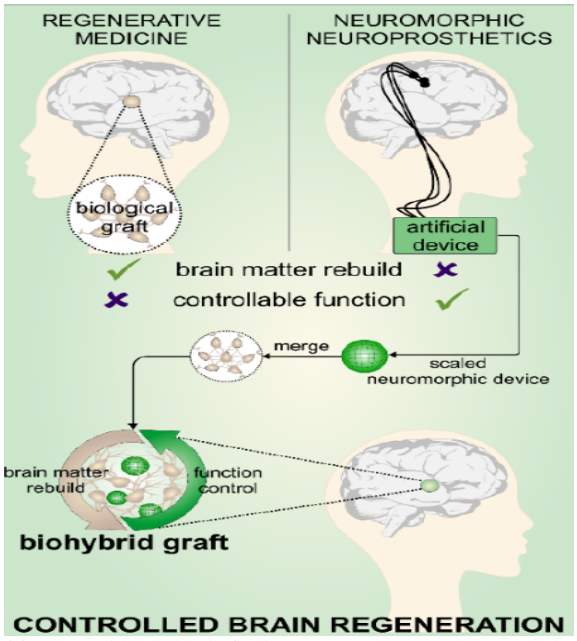


Figure 95.Concept of functional biohybrids for brain regeneration (source: Christensen et al., 2022).

Box 36.
"Biohybrid systems are established by biological and artificial components interacting in a unidirectional or bidirectional fashion. In this section, we specifically refer to neurons or brain tissue as the biological component of biohybrid systems for brain repair. A key feature of such systems is the real-time processing and decoding of neural signals to drive an actuator for brain function modulation or replacement. To this end, enhancement of biohybrid systems with artificial intelligence is the emerging strategy to achieve an adaptive interaction between the biological and artificial counterparts."
***Source**: Christensen et al., 2020).*

The integrated neuromorphic counterpart(s) must not perturb the mechanical equilibrium of the biological neurons; hence, depending on the intended application (i.e., extracellular or intracellular biosensing from neurons and their networks), these must be scaled down to meet the size of a small neuronal ensemble (<150 μm) or even to achieve intracellular residency (<3 μm).

In both cases, the primary challenge, and the pre-requisite, is the ***aggressive miniaturization of the integrated neuromorphic devices(s) without compromising their computational capability***. Novel materials for improved performance are expected to emerge in the near future to enable higher computational capability within smaller sizes. Organic materials hold great promise to merge advanced computation with extreme miniaturization

Further challenges arise due to the physical confinement of the neuromorphic counterparts within the biohybrid graft, stemming in the requirement of:

- *Power-autonomy*: device powering cannot rely on a wired power supply unit, such as commonly used subcutaneous batteries: while continuous device operation without the need of battery replacement is of utmost importance in brain regeneration, wiring neural dust is unfeasible (the devices are ultrasmall and physically inaccessible). Further, the operation of an autonomous system, by definition, should not depend on external components.
  Energy harvesting from the human body may represent the strategy of the future, wherein ATP seems to be the most promising solution to a long-standing issue. However, caution must be made to avoid negative physical effects on the patient, as the amount of harvested energy must be much less than what available.

- *Wireless operation*: this is required to follow the graft's evolving function during the regeneration process, to enable wireless device re-programming and hardware failure monitoring. dedicated integrated circuits are required, which must be ultrasmall so not to introduce bottlenecks in device miniaturization.
  As stated above, advanced CMOS technology holds promise to enable these wireless features in neuromorphic dust. Further, protocols tailored to energy efficient wireless communication are needed.

- *On-chip learning*: supported by application-specific integrated circuits for advanced signal processing, to follow the evolving temporal dynamics of the graft during its integration within the host brain, without the aid of an external controller.
  Understanding spatiotemporal patterns is a key feature to address the evolving dynamics of neuronal networks and reverse-engineer brain dysfunction. So far, these features have been achieved by pre-programming and the use of a microcontroller (Wang et al., 2018). Further advances must be made in order to achieve the same level of performance through on-chip learning. This would enable to address the inter-individual variability of the human brain while overcoming the drawbacks of trial-and-error (re)programming and of the need of a wired controller.

- *Bioresorbable property:* In aiming at healing brain damage, the neuromorphic counterparts should be regarded as a temporary aid in the process. Thus, they should be removable upon completion of brain repair. While non-invasive micro-surgery techniques, such as high-intensity focused ultrasound, may permit removal of mm-sized devices, this is not technically feasible in the case of ultrasmall (and, even more so, intracellular) devices.

Thus, particularly relevant to functional biohybrids is that the neuromorphic counterparts should be bioresorbable.

The device materials must be fully biocompatible so not to release cytotoxic compounds in the patient's brain. While outstanding advances have been made in the biosensors field (Huang, 2019), a major effort must be put in the field of neuromorphic engineering, where the performance of the device strongly depends on materials. In this regard, organic materials may present the key to beat this challenge.

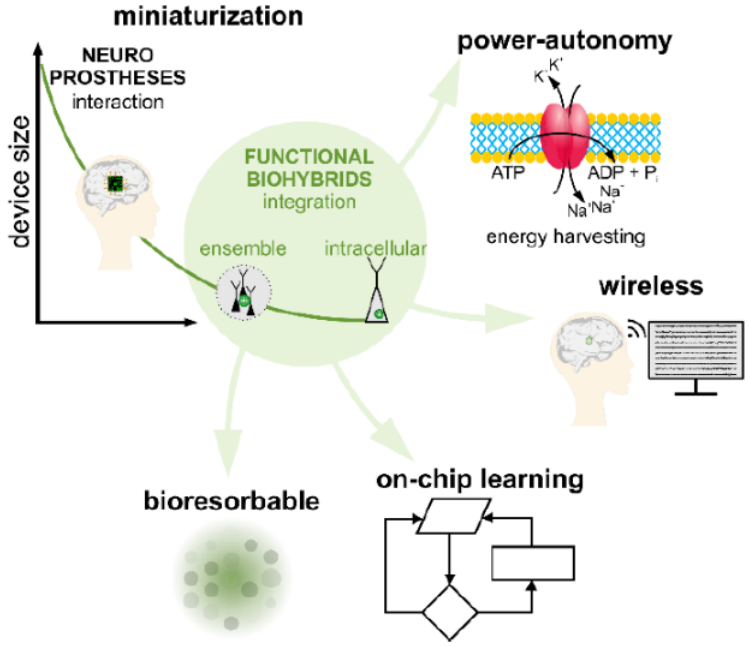


Figure 96.Challenges to achieve functional biohybrids for brain regeneration (source: Christensen et al., 2022).

As a summary, ***neuromorphic processing could become a key approach for smart brain micro-implants with embedded edge computing processor capabilities***. Some experimental devices have been tested with associated platforms to simulate these systems.

The two NP systems developed in the HBP context (SpiNNaker and BrainScaleS) and specifically novel chip architectures could be used for developing very advanced smart brain devices. Miniaturization and energy harvesting from the human body are still a challenge to see these disruptive devices very soon in the market.

4.1.2 Application of perturbational complexity index (PCI)

Understanding how network activity in the brain generates different states of consciousness is a major challenge – with implications for the clinic. Every year, millions of patients are sent to emergency services after loss of consciousness following a brain injury, e.g., from accidents or a stroke. Treating these patients and assessing their inner state is difficult.

Measures of brain complexity have recently begun to move from the realm of theoretical neuroscience into the field of experimental neurophysiology to study differences between global brain states, from wakefulness to sleep and anesthesia. Further, measures of brain complexity have been considered as useful paraclinical indices to assess consciousness at the bedside of brain-injured patients.

This approach is motivated by the general theoretical principle that a ***brain's capacity for conscious experience relies on its ability to integrate information***. In this view, a key mechanism of consciousness is the ability of different neural elements to engage in complex patterns of causal interactions such that the whole system generates information over and above its parts.

Then, ***the use of controlled "perturbations" by using TMS of specific areas of the brain and the processing of the EEG responses received*** can be used as a method to assess the level of consciousness.

The technique has been developed some years ago (Sarasso et al, 2014; Comolatti et al., 2019) and it is now part of HBP developments. The ***PCI is an index developed in HBP*** that measures the algorithmic complexity of electroencephalographic (EEG) responses to Transcranial Magnetic Stimulation (TMS), a method that has been validated in conditions such as comma and other critical conditions related to the brain response after injury (see figure 97).

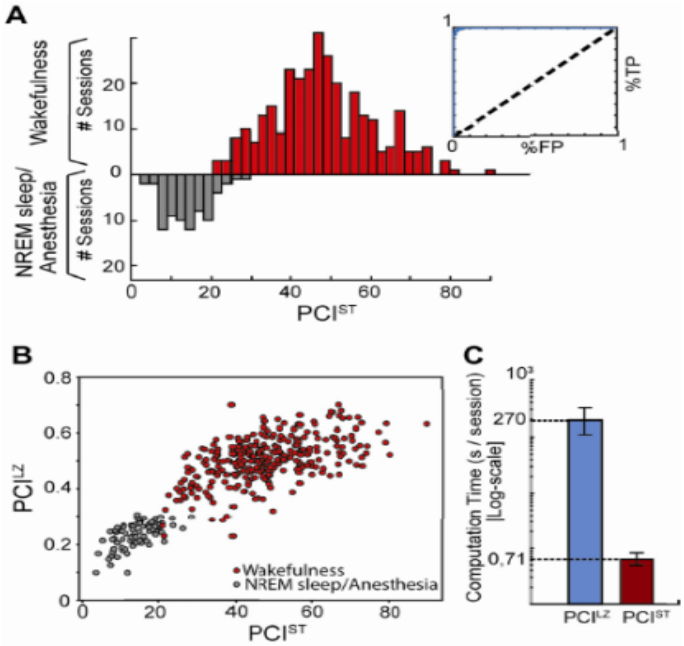


Figure 97.PCIST discriminates between consciousness and unconsciousness healthy individuals faster than PCILZ (source: Comolatti et al., 2019)

Box 37.

A general procedure was implemented based on two steps: (i) locally perturbing the system in a controlled and reproducible way to trigger a cause-effect chain and (ii)

quantifying the spatiotemporal complexity of the ensuing deterministic response to estimate information.
The original implementation of this perturb-and-measure approach involved (i) stimulating the brain with transcranial magnetic stimulation (TMS) and (ii) computing the algorithmic (Lempel-Ziv) complexity of the resulting patterns of activations at the level of cortical sources derived from the inverse solution of high-density electroencephalographic (hdEEG) responses; this metric will be henceforth referred to as Lempel-Ziv Perturbational Complexity Index (PCILZ). Comolatti et al., 2019

Current version of PCI measures the dynamics of the cortical neural networks faster, considering simultaneously the real-time information provided by the EEG and NBS, overcoming some of the difficulties that previous studies have presented TMS-EEG. (Goldman et al., 2020).

HBP researchers have built models of the brain networks associated with different states of consciousness, systematically connecting the microlevel of nerve cells, the intermediate-scale of neuronal circuits, and the whole brain-scale. The first two states that were modelled are wakefulness and slow-wave sleep. The theorists used high-quality data to build network models from the ground up. Scientist Marcello Massimini and colleagues were able to create an experimental set to test the PCI with patients (see Figure 98).

To build the neuronal level, recordings from microelectrodes became the basis of spiking neural network models. Next was the level of neural populations, corresponding to what is measured with larger scale, lower-resolution methods. This level was captured in so called mean-field models, each representative of a tiny area of brain tissue, which were then connected based on micro-circuit connectivity data

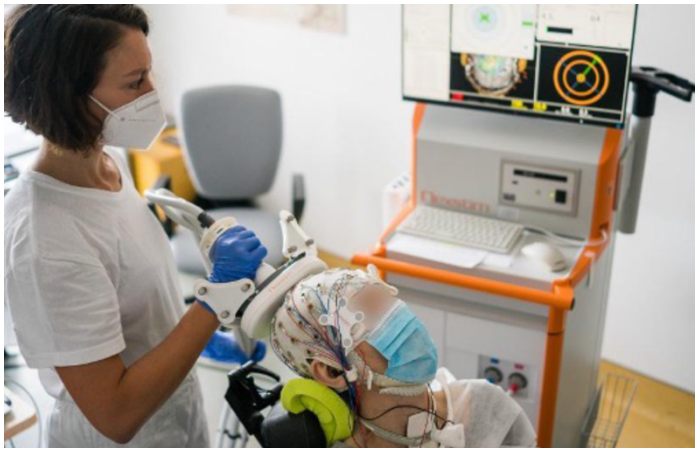


Figure 98.Experimental setup of PCI Perturbational complexity index measurements (Picture: Russ Juskalian)

Figure 99 shows the functional connectivity in synchronized and desynchronized states. A. Asynchronous state, B. Synchronized slow-waves. The person correlation between brain regions is shown for excitatory activities (left) and between inhibitory populations (middle). The structural connection weights (extracted from the connectome) are shown for comparison (right).

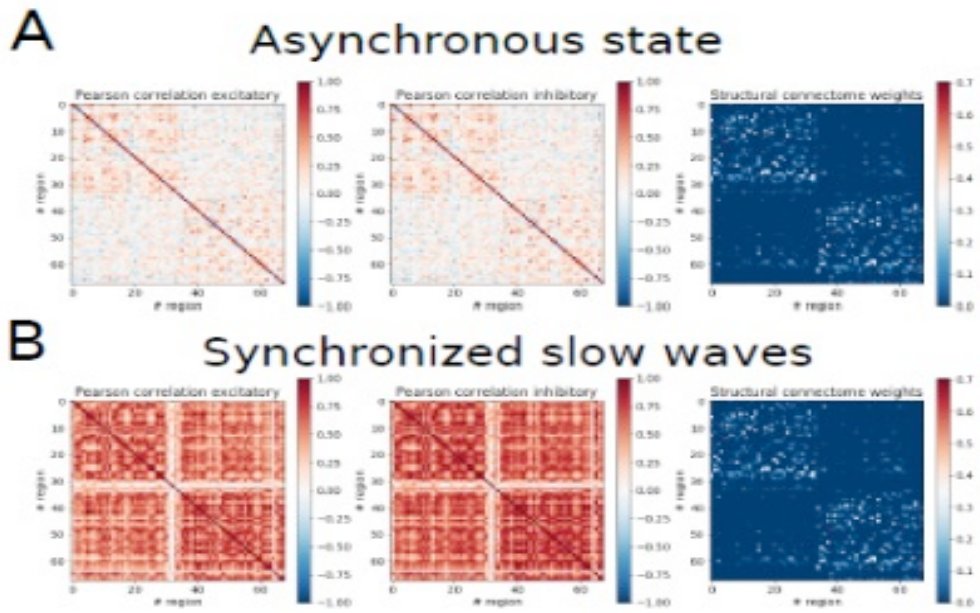


Figure 99.Functional connectivity in synchronized and desynchronized states

Its ***relevance for advancing the neurostimulation field***, and specifically for deep brain stimulation, is the possibility to have a continuous monitoring of the consciousness level in cases where the patient cannot interact with his/her environment. It could require minimising and simplifying the perturbations, if possible, outside the clinical setting.

4.1.3 The application of the Virtual Epileptic Patient (VEP)

In millions of epilepsy patients, pharmacological treatment is not effective and surgical intervention is a possibility. HBP scientists from France have developed personalised brain models to identify the areas where seizures emerge in a patient's brain. A 400-patient clinical trial (EPINOV) is currently ongoing in France with the aim of providing surgeons with a precise tool to help individual surgery decisions and improve outcomes. The EBRAINS human brain atlas built by the HBP now serves to further enhance accuracy.

The VEP is a simulation tool with the potential to identify the zones susceptible to surgical intervention in those patients with refractory epilepsy. The model uses structural data of individual patients (from MRI, EEG, SEEG mainly) and mathematical modelling of brain dynamics (Jirsa et al, 2017). The team behind this innovation is integrated by medical doctors and engineers of the HBP who have been working on the for the last decade, which is currently in a clinical trial in around 400 patients in France.

The software allows, though a 3D model, to represent the neuronal networks of the cerebral cortex for diagnostic support and to offer predictions in those areas to be intervened. This facilitates surgical planning not only in possible tissue resections, but also in minimally invasive neurostimulation techniques, allowing the medical

team to take precautions in treatments and in a subsequent evaluation. Likewise, the software stands out for its readiness to adapt to each patient, that is, it considers the data from presurgical evaluations and offer prognosis based on empirical data, combining the technology base of the human brain atlas provided by EBRAINS (see figure 100)

Figure 100. The Virtual Epileptic Patient

In other words, it offers in the same virtual brain the ability to modulate the Epileptic Zones (EZ), and the Propagation Zones (PZ) in the absence of seizures, even for the most complex cases in epilepsy: "In patients with non-lesional MRI, localization and surgical success in seizure control are more challenging" (Jeha et al, 2007, mentioned by Jirsa et al, 2017). Although MRI lesions data can be incorporated into the software, additional effort is required given the complexity of reflecting these parameters.

Another aspect to highlight is the inclusion of ML algorithms to adapt anatomical and functional data such as the Markov chain Monte Carlo (MCMC) that, according to Wang et al, 2022: "generates many random samples of the model parameters and virtual brain simulations and evaluates these for consistency with empirical data (Ibid, 2022). Other algorithms such as such as No-U-Turn Sampler (NUTS) and Automatic Differentiation Variational Inference (ADVI) based on the probabilistic programming languages and parameterization processes are applied, resulting in a probabilistic framework called Bayesian Virtual Epileptic Patient (BVEP) developed by the team (Hashemi et al, 2020). The last helps to infer the spatial map combining the structural data of each patient, and testing hypothesis of epileptogenic areas in terms of origin and propagation, according to authors.

For development of the software, in addition to the resources of the HBP/EBRAINS project, the collaboration is also managed between AIX- Marseille Université (AMU), le Centre National de la Recherche Scientifique (CNRS), Institut National de la Sant et de la Recherche Medicale (INSERM) and the Assistance Publique – Hôpitaux

de Marseille (AP-HM). It is a technology with seven registered patents and an ongoing clinical trial involving 13 hospitals in France for a four-year period. It has the advantage of not requiring additional IT resources to run the simulations.

4.1.4 Photo-pharmacology in HBP

The use of light to control functions of biomacromolecules has become an active field of research over the last decades. Reversibly photoisomerizable (i.e. photoswitchable) compounds have already demonstrated great promise in medicinal chemistry and materials science (Pianowski Z.L, 2019). Drugs that contain synthetic light-switching molecules could help target therapies to particular parts of the body, limiting side effects.

The most advanced photopharmaceutical research and development is being carried out by California-based company Photoswitch Biosciences. Set up in 2008 by a team including Trauner and Berkeley neuroscientists, the company is developing a light-responsive drug that could restore sight. The first successful candidate, published in 2012 (Polosukhina A, 2012), was the molecule diethylamine-azobenzene-quaternary ammonium (DENAQ), which replicates the light switching function of opsins, blocking the cell potassium-ion channels when activated by light and unblocking the channels in the dark.

HBP has also included in its research agenda activity on this field.

A study led by researchers from IBEC and IDIBAPS achieved, for the first time, the control of brain state transitions using a molecule responsive to light, named PAI. The results could lead to the development of photomodulated drugs for the treatment of brain lesions or diseases such as depression, bipolar disorders or Parkinson's or Alzheimer's diseases.

Figure 101 depicts a situation where the 3D structure of a molecule changes depending on the light intensity[44]. PAI is light responsive and allows a spatiotemporally controlled modulation of brain neurons, binding and controlling the activity of muscarinic cholinergic receptors, key receptors on neuronal interaction and communication. By using this approach, the cholinergic-innervation dependent brain state transitions can be controlled by light using drugs chemically designed to be photosensitive.

[44] The molecule used, named PAI (for Phthalimide-Azo-Iper) can specifically and locally control the muscarinic cholinergic receptors, that is, the acetylcholine receptors, a brain neurotransmitter very important in several processes as learning attention or memory. https://medicalxpress.com/news/2021-06-brain-states-ray.html

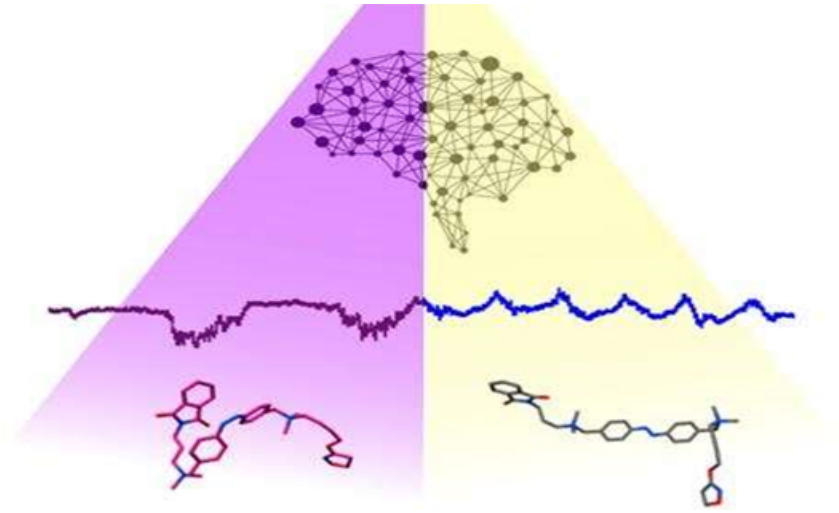


Figure 101.Effect of light on the PAI molecule. Source: https://www.humanbrainproject.eu/en/follow-hbp/news/controlling-brain-states-with-a-ray-of-light/

Relevance for the neurostimulation field. The drug could reach one area of the brain by using other invasive or minimally invasive techniques like the use of Strentode through the brain vessels. One placed on the right place of the brain is ready to be light-activated externally.

In this context, **Lumobiotics**, a USA based university Spin-off, develops light-controllable peptide drugs as safe cytolytic agents for treatment of solid cancers and localized infectious diseases.

The European Commission has also implemented some EU-funded projects in this area (**RET PHOTOSWITCH**). The principal objective of this project is to develop novel photoswitchable kinase inhibitors (PKIs), targeting on REarrange during Transfection (RET) for use in the treatments of neurodegenerative disorders. The ability to manipulate the activity of RET using light would result in temporal control of enzymatic activity, thus serving as a valuable molecular tool to study the function of RET in microglia cells and further our understanding of AD.

4.2 Potential interaction with EBRAINS services

EBRAINS will capitalise on the work performed by the Human Brain Project teams in digital neuroscience, brain medicine, and brain-inspired technology and will take it to the next level. It can help to find, analyse, share, and integrate neuroscience data, and perform modelling and simulation of brain function.

EBRAINS aims to collect and integrate specialised software and workflows, and scale these to meet the needs of the wider neuroscience community. Platforms, tools, and technologies are available for further collaborative research and data sharing aiming at accelerating research and innovation.

The next figure 102 presents a general view of the current EBRAINS services and their potential interaction with the area of neurostimulation (both invasive and non-invasive approaches). Services were grouped in five main areas: data and

knowledge, atlases, simulation, brain-inspired technologies, and medical data analytics[45]. Researchers (in their role as users of EBRAINS) can select some of these services adapted to their specific needs.

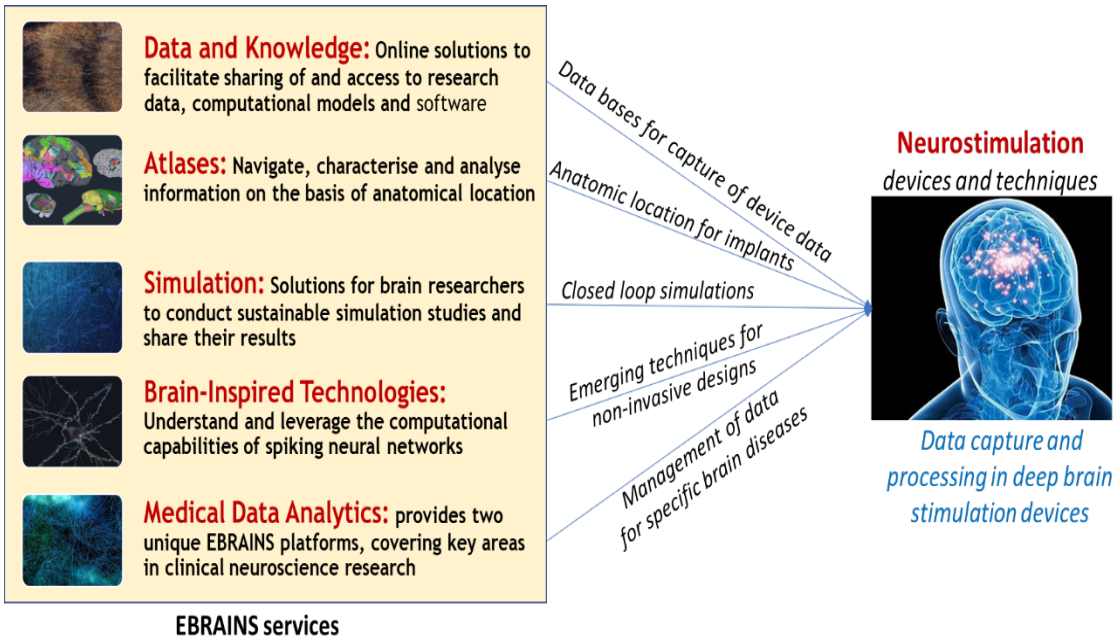


Figure 102.EBRAINS types of services (Source: EBRAINS and own elaboration)

Not all EBRAINS services will have the same relevance for neurostimulation. At least, not specifically for it. Even when the activities in HBP are non-invasive, it only affects the way to capture data.

Some relationship areas between neurostimulation and the types of EBRAINS services are described as follows (possible applications have been found among the EBRAINS technologies with invasive and non-invasive neurostimulation techniques, detailed in the next section):

- Relationships with the data and knowledge services
    - EBRAINS can provide support or managing databases of information captured by neurostimulation devices: From the Knowledge Graph tool, data and metadata can be accessed and shared. Although at present it is possible to Access some datasets related to neurostimulation -for example, intracranial electrophysiological recordings (iEEG)-, it is expected that in the near future new models and data can be incorporated at the willingness of its participants. The use of these requires attribution to their authors and being registered on the platform. See more at: https://ebrains.eu/service/share-data/

[45] The list of EBRAINS services provided by national nodes is very dynamic and they will be consolidated in 2022 and 2023. Anyway, as it happens in all European research infrastructures, services should evolve to accommodate new technologies and users' needs.

- Data from several devices can be curated and shared: In an effort to standardize, organize, and integrate data so that other researchers can find and use it following FAIR principles, EBRAINS facilitates this service to the researcher. The integration process requires following a series of simple steps to provide information about the research group, the study and specific data that will be published only with the consent of the authors. See more at: https://ebrains.eu/service/share-data#share

- **Relationships with atlases and navigation services**
  - Anatomic support for intelligent implants: Technologies such as Personalized in-silico Brain Networks allows modelling the human brain on a large-scale by combining probabilistic parameters or mathematical models, along with patient-specific metrics, facilitating a personalised simulation. In the future, these technologies could support surgical planning in implants with the ability to modulate brain areas according to the neurological condition of each patient.
  - Multilevel navigation with implanted electrodes: EBRAINS has an atlas of the human brain called The Multilevel Human Brain Atlas which could be useful for neurostimulation techniques. One of the tools with the greatest integration in EBRAINS for the visualization, analysis and simulation of the different organization of the human brain, reflecting its functional structure and connectivity, at a macroscopic and microscopic scale through the "BigBrain" model along with complementary maps. While for microanatomical analysis, it facilitates the visualisation of resources such as MNI Colin27 and ICBM 152, as nonlinear atlases. See more at: https://ebrains.eu/service/human-brain-atlas

- **Relationships with simulation services**
  - Application for neurostimulation/neuromodulation surgery planning and closed-loop simulations platforms. For more details go to section 3.3 and tables for each neurostimulation technique in the next section.

- **Relationships with brain-inspired technologies**
  - Emerging techniques for non-invasive designs.
  - Robotic platforms for the placement of neurostimulation devices. EBRAINS has the Neurorobotics NRP platform, open access and robots with skills with cognitive skills related to decision making, exploration, collaborative, etc. Other such as Neuromorphic Computing simulates spiking neural networks through SpiNNaker and

BrainScaleS, described in the section 4.1.1. See more at: https://ebrains.eu/service/neurorobotics-platform

- **Relationships with medical data analysis**.
    - Management of data captured in deep brain stimulation and their integration in databases for specific diseases.
    - Interoperability platforms
    - Proposals for industry standards.

Regarding the technical capabilities of the tools that have been developed in the six services offered by HBP/EBRAINS -Data & Knowledge, Atlases, Simulation, Neuromorphic and Neurocomputing, Medical Informatics Platform and Collaboratory-, besides a comprehensive review of innovative European start-ups in the field of neuroscience, short-term online sessions have been organised, called Solution Workshops. In these meetings, the most experienced researchers of HBP/EBRAINS establish a first approach with the start-ups, where presentations, concerns, and ideas about how their technologies would help these companies achieve their objectives in the scientific field are shared. These initiatives have attracted new users in the industrial field, receiving feedback and various requests that make it possible to improve technologies, considering the real scenarios faced by these experts.

4.2.1 Relationships of HBP and EBRAINS with invasive neurostimulation techniques

After the generic description made in previous sections, it is possible to deep into detailed assessment of the way that EBRAINS/HBP technologies are related to the neurostimulation techniques described in this report. More specifically, tables were elaborated in relation to Deep Brain Stimulation (DBS), SCS (Spinal Cord Stimulation), Vagus Nerve Stimulation (VNS), Chronic Subthreshold Cortical Stimulation (CSCS), Responsive Neurostimulation (RNS), and NIBS.

Each table presents the stage of the use, the clinical assessment, the HBP/EBRAINS support, and the main software used, or company involved. Clinical assessment or technology regularly in each stage was obtained from some of the references contained in the last section of the report.

Table 3. Some tools in DBS and EBRAINS/HBP technologies (source: own elaboration)

Stage	Clinical assessment or technology regularly used according to literature (related to the brain)	EBRAINS/HBP closest or supporting technology for neurologists	Main software used/Company
	Biomarkers	AI-MINDS, MIP	

Trial period (if needed, between 3-10 days)	Stereoencephalography (sEEG)	HIP, SWAP, VEP, NeuroFeatureExtract, (TVB-NEST-Elephant), PCI, ViSimpl	
	Positron emission tomography (PET)	LivingBrain, Neuro-Connect	
	Electroencephalography (EEG)	HIP, NeuroFeatureExtract, (TVB-NEST-Elephant), AI-MINDS, PCI	
	Magnetoencephalography (MEG)	AI-MINDS, Neuro-Connect	
	Functional magnetic resonance (fMRI)	Individual Brain Charting project (IBC), DISCO, HiBoP, Neuro-Connect	
Preoperative	Anatomico-clinical atlases (ACA) (Predictive maps, a gray scale 3D image)	Multilevel Human Brain Atlas, VEP, TVB, Bayesian model	
	Magnetic Resonance Imaging (MRI)	Individual Brain Charting project (IBC), DISCO, Neuro-Connect	Lead DBS/**Matlab** - DBSproc/**NIMH**, Stealth/**Medtronic** - Amira, Avizo software/**ThermoFisher**- DBSmapping/**Matlab -** PyDBS - PaCER/**Matlab** - Vercise Genus/**Boston Scientific** - GUIDE XT/**Brainlab & Boston Scientific** - DBStar
	White-matter attenuation inversion recovery (WAIR)	Simulator to generate ultra-realistic white matter virtual tissues, Individual Brain Charting project (IBC)	
	Commercial planning software/mapping software	Multilevel Human Brain Atlas, VEP, TVB, Bayesian model	
	Deterministic tractography	Multilevel Human Brain Atlas	
Intraoperative	Commercial planning software/mapping software	Multilevel Human Brain Atlas, VEP, TVB, Bayesian model, ViSimpl, Neuro-connect	
	Electrophysiology system for microelectrode recording and stimulation tests	HIP, NeuroFeatureExtract, Elephant, PCI, SWAP	
	Stimulation maps	TVB, VEP, PISBN, Bayesian model, ViSimpl	
	Electromyography (EMG)	Elephant, PCI	
Data analytics & integration	Anonymisation & Integration	AnonyMI, MIP Data Factory, Neuro-connect	-
	Cloud storage, data warehouses	FENIX, MIP	-

Table 4. Some tools in Spinal cord stimulation (SCS) and EBRAINS/HBP technologies.

Stage	Clinical assessment or technology regularly used according to literature (related to the brain)	EBRAINS/HBP closest or supporting technology for neurologists	Main software used/Company
Intraoperative (Limited number of publications)	Somatosensory evoked potentials (SSEPs)	HIP, NeuroFeatureExtract, Elephant/Viziphant, Visimpl, PCI	Precision Spectra System, mySCS, Spectra WaveWriter/**Boston Scientific -** ProclaimTM SCS System, Neurosphere, MyPath/**Abbott** - DTM, Intellis - Senza/**Nevro** - VANTA/**Medtronic**- Evoke/**Saluda Medical - Nalu**
	dermatomal somatosensory evoked potential (dSSEP)		
	Motor evoked potentials (MEP) or transcranial motor evoked potentials (tcMEPs)		
	Transcranial Magnetic Stimulator (TMS)		
	Laser evoked potentials (LEPs)		
	Sympathetic Skin Reponse (SSR)		
	Contact Heat Evoked Potential (CHEP)		
	Galvanic vestibucal stimulation (GVS)		
Data analytics & integration	Anonymisation & Integration	AnonyMI, MIP Data Factory	-
	Cloud storage, data warehouses	FENIX, MIP	-

Table 5. Some tools in Vagus Nerve Stimulation (VNS) and EBRAINS/HBP technologies.

Stage	Clinical assessment or technology regularly used according to literature (related to the brain)	EBRAINS/HBP closest or supporting technology for neurologists	Main software used/Company
Preoperative	Biomarkers	AI-MINDS, MIP	Aspire SR/**LivaNova - Cyberonics** - Vivistim/**Microtransponder**
	Electroencephalography (EEG)	AI-MINDS, (TVB-NEST-Elephant)	
	Magnetoencephalography (MEG)	AI-MINDS, Neuro-Connect	
	Magnetic Resonance Imaging (MRI)	Individual Brain Charting project (IBC), DISCO, HiBoP, Neuro-Connect	

	Functional magnetic resonance (fMRI)	Individual Brain Charting project (IBC), DISCO, HiBoP, Neuro-Connect	
	Positron emission tomography (PET)	Living Brain, Neuro-Connect	
	Electroencephalography (EEG)/video EEG	AI-MINDS, (TVB-NEST-Elephant)	
	Slow Cortical Potential (SCP)	HiBoP	
	Somatosensory evoked fields on MEG (SSEFs)	AI-MINDS	
Data analytics & integration	Anonymisation & Integration	AnonyMI, MIP Data Factory, Neuro-Connect	-
	Cloud storage, data warehouses	FENIX, MIP	-

Table 6. Some tools in Chronic Subthreshold Cortical Stimulation (CSCS) and EBRAINS/HBP technologies.

Stage	Clinical assessment or technology regularly used according to literature (related to the brain)	EBRAINS/HBP closest or supporting technology for neurologists	Main software used/Company
Trial period (if needed, between 3-20 days)	iEEG/Electrocorticography (ECoG)	HiBoP, HIP	NeuroPace
Preoperative	Magnetic Resonance Imaging (MRI)/ Functional magnetic resonance (fMRI)	Individual Brain Charting project (IBC), DISCO, HiBoP, Neuro-Connect	
	Electroencephalography (EEG)	AI-MINDS, (TVB-NEST-Elephant)	
Intraoperative	iEEG/Electrocorticography (ECoG)	HiBoP, HIP	
	Magnetic Resonance Imaging (MRI)	Neuro-Connect	
	Functional magnetic resonance (fMRI)	HiBoP, Neuro-Connect	
	stereoencephalography (sEEG)	HIP, SWAP, VEP, NeuroFeatureExtract, (TVB-NEST-Elephant), PCI, ViSimpl	
Data analytics & integration	Anonymisation & Integration	AnonyMI, MIP Data Factory, Neuro-Connect	-

	Cloud storage, data warehouses	FENIX, MIP	-

Table 7. Some tools in Responsive Neurostimulation (RNS) and EBRAINS/HBP technologies.

Stage	Clinical assessment or technology regularly used according to literature (related to the brain)	EBRAINS/HBP closest or supporting technology for neurologists	Main software used/Company
Trial period	Magnetoencephalography (MEG)	AI-MINDS, Neuro-Connect	**NeuroPace - Medtronic - Cyberonics - LivaNova**
	Magnetic Resonance Imaging (MRI)	Individual Brain Charting project (IBC), DISCO, HiBoP, Neuro-Connect	
	Electroencephalography (EEG)	AI-MINDS, (TVB-NEST-Elephant)	
	iEEG/Electrocorticography (ECoG)	HiBoP, HIP	
	Magnetic Resonance Imaging (MRI)	Neuro-Connect	
	Functional magnetic resonance (fMRI)	Individual Brain Charting project (IBC), DISCO, HiBoP, Neuro-Connect	
	Positron emission tomography (PET)	Living Brain, Neuro-Connect	
Preoperative	Electroencephalography (EEG)/video EEG	AI-MINDS, (TVB-NEST-Elephant)	
Intraoperative	iEEG/Electrocorticography (ECoG)	HiBoP, HIP	
Data analytics & integration	Anonymisation & Integration	AnonyMI, MIP Data Factory, Neuro-Connect	-
	Cloud storage, data warehouses	FENIX, MIP	-

Table 8. Some tools in NIBS and the relationship with EBRAINS/HBP technologies.

Non-invasive neurostimulation method (NIBS)	Stage	Clinical assessment or technology regularly used according to literature (related to the brain)	EBRAINS/HBP closest or supporting technology for neurologists
	Preassessment	Neuropsychological screening (IQ, cognitive tests, etc)	
		Cortical mapping (3D navigation software)	
		Robotics arms in TMS practice	
		Magnetic Resonance Imaging (MRI)	

No gold standards for NIBS protocols	During therapy	Functional magnetic resonance (fMRI)	TVB, VEP, PCI, tPCS, tDCS & apomorphine, Multilevel Human Brain Atlas, Bayesian model
		Language mapping	
		Fiber tractography (FT)	
		Positron emission tomography (PET)	
		Facial electromyography (fEMG)	
		Electroencephalography (EEG) (not for tSMS)	
		Data analysis software	
	Data analytics & integration	Anonymization	AnonyMI, MIP Data Factory, Neuro-Connect
		Cloud storage, data warehouses	FENIX, MIP

PART 5

5 Conclusions and future work

5.1 Main conclusions of the report

This report has presented a global view of ***neurostimulation technology and its clinical use*** today and in the coming years with an eye on the possible interaction with the results of the Human Brain Project (HBP) and the services offered by the European Brain Research Infrastructure EBRAINS.

Neurostimulation is one of the most active fields in health as the number of articles, patents, projects, and devices in the market clearly demonstrate. It is also a very active field in the creation of technology-based start-ups where investments from capital risk and corporate funds are growing. The consequence is a high rate of innovation in clinical use where trials on disruptive medical devices related to neurostimulation techniques are growing.

Nevertheless, from a scientific perspective, ***more research is needed*** because the biological and molecular mechanisms underlying neurostimulation therapies are not well understood; however, such approaches seem the only effective treatment option for several refractory neurologic disorders and are rapidly expanding to other clinical application domains (e.g., pain retrieval). Its uses in the cases of epilepsy, Parkinson's disease, neural tremors, and other neuro diseases are clearly in the clinical focus of these techniques, with outstanding published results in selected patients around the world.

Today, a ***more complete understanding of the therapeutic mechanisms of neurostimulation for various neurologic disorders is required***, allowing the discovery of biomarker feedback signals that effectively inform the closed-loop system, to extend these approaches in clinical neurology services.

The development of neurostimulation techniques is based on and driven not only by theoretical research but also by ***technological advances***.

Today, we are surfing a ***wave of technology convergence*** when the combination of techniques such as artificial intelligence, nanoelectronics, new biomaterials, low energy consumption for wireless communications, and smart sensors will offer additional neurostimulation functionalities that were unthinkable only a few years ago. From this perspective, decades of advances in neural activity monitoring technologies have resulted in powerful research and clinical tools that are providing remarkable non-invasive, in vivo, multimodal views of the brain.

Box 37. Own elaboration

During this decade, new electrodes must be designed to minimise the extent of postoperative electrode migration; new stimulation coils must reach deeper targets in the brain; longer lasting rechargeable generators must be used to reduce battery cost; miniaturisation of stimulation systems must decrease adverse effects after implantation; secure wireless remote communication would allow clinicians to easily modify the

stimulation program easily; household devices could facilitate long-term treatment outside the hospital, etc.

Progressive innovation in neurostimulation technologies is promising and is expected to continue. Researchers, engineers, and clinicians will need to communicate with each other and make efforts to offer the best stimulation therapy to drug-resistant epilepsy patients in open innovation ecosystems as described in the text.

This document has also discussed the ***structure and evolution of the neurostimulation market***, where high CAGR are forecast. The relative reduction of investments from large pharmaceutical companies in the last ten years (mainly due to lack of success of new drugs for neurodegenerative diseases) is being compensated by the irruption of consolidated ICT companies (even the largest ones) and a numerous group of brain-technology start-ups with disruptive products which have attracted the interest of venture capital and pharmaceutical companies.

With a lot of progress being made in the neurostimulation market, we see ***plenty of open areas for innovation***. With the rapid development of new electrodes, complex stimulation algorithms, and electrical field steering technology, research will have to focus on the dynamics and kinetics of electrical fields applied to the brain and how they affect physiological and pathological network activity, as well as various states of cortical excitability.

Even when start-ups face ***regulatory barriers*** to approve their medical devices, we are confident that ***many of the start-ups presented in this report will consolidate in the future***. It will not be an easy and fast way and it will take some years to obtain commercial profits. Fortunately, VC is betting for them.

Finally, the report has analysed the potential interaction with some research activities in HBP and the way that EBRAINS services can take advantage of it in the future.

5.2 Future work

Neurostimulation field is very dynamic and new scientific and technological breakthroughs, patents, products., start-ups and clinical use will rapidly evolve. Despite the effort made with the elaboration of this report, ***it will be necessary to provide regular updates of the present report.*** Specifically, an update will be presented in Q2 of 2023.

From the perspective of the usefulness for ***HBP*** tools and ***EBRAINS*** services in the future, we propose to conduct some activities related to the area of neurostimulation techniques:

- To ***monitor the evolution of the companies and the marketed medical devices identified in this report*** and to analyse how their products entered in the market.

  - Focus on European companies.
  - To collect data on investments (source and volume) and mergers and acquisitions.

- To launch a ***more comprehensive market analysis focused on Europe*** in the areas of neurostimulation and neuromodulation ***supported by a survey to existing companies in the field***. The emphasis on start-ups will continue and complete the work carried out in HBP during 2021.

  The objective of this market analysis is threefold:

  - To obtain clear indication about the product areas covered by start-ups in Europe and the roadmap of new products.
  - To understand the barriers and drivers of their development and access to venture capital.
  - To provide a basis for increasing the industrial use of HBP and EBRAINS.

- To make a ***specific analysis of publications, patents and R&D projects*** on several sub areas of the neurostimulation field that can condition the emergence of future breakthroughs. More specifically:

  - To compare EPO patents with USPTO and triadic families to obtain a more complete perspective of the evolution and trends.
  - To obtain a taxonomy of scientific articles in subfields related to neurostimulation.
  - To generate technology roadmaps.

- To analyse the current ***regulation on medical devices and clinical trials*** to assess the relationships with innovation.

  - To assess the ethical aspects related to neurostimulation, mainly in relation to neurorights and dual use.
  - To propose some changes in European regulation to accelerate the introduction of advanced neurostimulation techniques in clinical practice. Specifically, it is relevant to propose modifications to accelerate the launching of clinical trials.

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Annex 1. Glossary of terms and acronyms

ABPI: Association of the British Pharmaceutical Industry

AI: Artificial Intelligence

BMS: Bristol-Myers Squibb

BWD: Brain Wireless Device

CNS: Central Nervous System

DBS: Deep Brain Stimulation

DNP: Depth Neural Probe

EBRAINS: European Brain Research Infrastructure

EEG: Electroencephalogram

ESFRI: European Strategic Forum for Research Infrastructures.

EU: European Union

FAGMA: Facebook, Amazon, Google, Microsoft, Apple

FDA: Food and Drug Administration

fMRI: functional Magnetic Resonance Imaging

gDNP: graphene Depth Neural Probe

GSK: Glaxo SmithKline

HBP: Human Brain Project

HIFU: High Intensity Focal Ultrasound

HTA: Health Technology Assessment

ICREA: Catalan Institution for Research and Advanced Studies

ICT: Information and Communications Technology

MCS: Motor Cortex Stimulation

MND: Mental and Neurological Disorder

MTL: Medial temporal lobe (MTL)

MTLE: Mesial temporal lobe epilepsy (MTLE)

NIH: National Institutes of Health

PCI: Perturbational Complexity Index

PBM: Photobiomodulation

rTMS: repetitive Transcranial Magnetic Stimulation

RNS: Responsive Neurostimulation

SCS: Spinal Cord Stimulation

SGA3: Specific Grant Agreement 3

SME: Small and Medium Enterprise.

SWOT: Strengths, Weaknesses, Opportunities, Threads

TES: Transcranial Electrical Stimulation

TMS : Transcranial Magnetic Stimulation

tDCS: transcranial Direct Current Stimulation

tVNS: Transcutaneous VNS

VEP: Virtual Epileptic Patient

VNS: Vagus Nerve Stimulation

WHO: World Health Organisation

Annex 2. Companies Marketing Products and Services in the Neurostimulation field

Table: Neurostimulation market: MAIN PLAYERS (DEEP BRAINS STIMULATION).

	Webpage	*Country*
Abbott Laboratories	*https://www.abbott.com/*	*USA*
Boston Scientific Corporation	*https://www.bostonscientific.com/*	*USA*
Medtronic plc	*https://www.medtronic.com/us-en*	*Ireland*
NeuroPace, Inc.	*https://www.neuropace.com/*	*USA*
DBI Deep Brain Innovations	*https://www.deepbraininnovations.com*	*USA*
Aleva Neurotherapeutics	*https://www.aleva-neuro.com/*	*Switzerland*
Newronika	*www.newronika.com*	*Italy*
REBRAIN (DBS)	*https://rebrain.eu/en/home*	*FRANCE*
NI20	*https://ni2o.com/*	*UK*
Nuviant Medical Inc.	*http://nuviantmedical.com/*	*USA*

Table: Neurostimulation market: MAIN PLAYERS (MCS, RNS, SCS, VNS).

	Webpage	Country
Abbott Laboratories	https://www.abbott.com/	USA

Boston Scientific Corporation	https://www.bostonscientific.com/	USA
Medtronic plc	https://www.medtronic.com/us-en	Ireland
LivaNova PLC	https://www.livanova.com/en-US/	UK, Italy, USA
ElectroCore	https://www.electrocore.com	USA
Axonics Modulation Technologies, Inc.	http://www.axonics.com	USA
Nalu Medical	http://nalumed.com	USA
SzeleSTIM	https://www.szelestim.com/?page_id=1041	Austria
Saluda Medical	https://www.saludamedical.com/	UK, Netherlands, USA

Table: Neurostimulation market: MAIN PLAYERS (non-invasive).

	Technology	Webpage	Country
ElectroCore	tVNS	https://www.electrocore.com	USA
Halo Neuroscience	tDCS	https://www.haloneuro.com	USA
STARLAB/ NeuroElectrics	tDCS/tACS/tRNS	https://www.neuroelectrics.com	Spain
NeuroCare Group	TENS/TMS	https://www.neurocaregroup.com/home.html	Germany

Flow Neuroscience	tDCS	https://flowneuroscience.com	Sweden
Soterix Medical	tSDCS/TMS	https://soterixmedical.com/	USA
Ybrain	tDCS	https://www.ybrain.com/	Korea
Nexstim Plc	TMS	https://nexstim.com/	Finland
Magstim Company Limited	TMS	https://www.magstim.com/row-en/	UK
NeuroStar	TMS	https://neurostar.com/neuronetics/	USA
NeuroSigma	eTNS	https://www.neurosigma.com/	USA
DEYMED Diagnostic	TMS	https://deymed.com/	Czech Republic
BrainsWay	TMS	https://www.brainsway.com/	Israel
Foc.us	tDCS	https://foc.us/	UK
eNeura	TMS	http://www.eneura.com	USA
tVNS Technologies	tVNS	https://t-vns.com/	Germany
SzeleSTIM	arVNS	https://www.szelestim.com/?page_id=1041	Austria

BOTTNEURO AG	tCS	https://bottneuro.ch/wp/	Switzerland
PlatoScience's	tDCS	https://www.platoscience.com/	Denmark
Neuronetics	TMS	https://neurostar.com/neuronetics/	USA
Neuro Device Group SA	tES	https://neurodevice.pl/en/main-page/	Poland
NEUREK	tSMS	https://www.neurek.com/	Spain
Actipulse Neuroscience	rTMS	https://actipulse.com/	France Mexican

Abbreviation: *Transcutaneous Electrical Nerve Stimulation (TENS); Transcranial Magnetic Stimulation (TMS); Transcutaneous Spinal Direct Current Stimulation (tSDCS); Sacral Neuromodulation system (SNS); eTNS external Trigeminal Nerve Stimulation (eTNS).*