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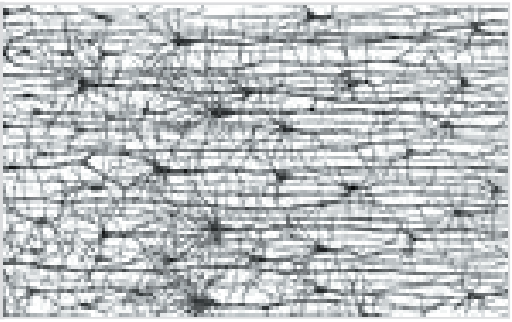
Neuromodulation and Neuroelectronics

Opportunities and challenges for the Catalan healthcare system and industry



Drawings by the neuroanatomist Ramón y Cajal showing the complexity of neural networks in the hippocampus, an area of the brain involved in memory and epilepsy.[1]

Introduction to neuromodulation

The brain and the peripheral nervous system form an enormous network of cells (thousands of millions of neurons) that generate and propagate electric signals that might be compared to an extremely complex matrix of biological computers.

Neurological pathologies such as Parkinson's disease, psychiatric disorders such as depression, and peripheral nervous system conditions such as chronic neuropathic pain all have in common the presence of erroneous electrical activity somewhere in that network.

Pharmacological treatments use molecules that enter the bloodstream and spread throughout the body, entering into contact with all its cells, including the neurons of the nervous system. There, they alter the patterns of electrical activity for therapeutic purposes.

On the other hand, neuromodulation[2] (also called neuroelectronics) corrects the pathological electrical activity selectively, only that the points in the neural network where correction is needed. It does so, however, with no use of drugs, by applying tiny electrical currents or magnetic fields that directly «modulate» (increasing or reducing) the neuronal electrical signals, to return them to levels that are considered normal.

Implantable pacemakers, which were developed in the mid-20th century, are a technological forerunner of today's neuromodulation systems for the nervous system and they provide a reference for understanding the functional basis of neuromodulation systems, which may, in a sense, be considered pacemakers for nervous system rather than for the heart.

Key concepts

- Neuromodulators are a new generation of pacemakers that act on the nervous system rather than on the heart.
- They correct the electrical activity associated with neurological and psychiatric disorders.
- They offer supplementary or alternative treatment to drugs, with fewer side effects and potential for greater efficacy.
- Opportunity for the Catalan economy.Rapidly growing new large-scale global industry.
- Challenge I for the Catalan healthcare system. High cost. Need for cost-benefit analysis.
- Challenge II for Catalan industry. Development of neuromodulation technology involves large investments and long turn-around times.

Types of neuromodulation: implantable (DBS), electrical non-implantable (tDCS) and magnetic non-implantable(TMS)

Unlike cardiac pacemakers, neuromodulation systems can act on the nervous system through surgery (implanted in the brain or spinal cord) or through external procedures (applying currents or magnetic fields to the skull, with no need for surgery).

Implantable

Neuromodulation systems using implants in the brain, known as DBS (deep brain stimulators) normally include one or more electrodes (conducting wires) that modulate electrical activity in specific parts of the brain where needed.

The electrodes apply weak electric currents controlled by an electronic system that is often implanted near the patient's collarbone.

The commonest DBS systems are those used to control motor symptoms (erratic movements) caused by Parkinson's disease, a neurodegenerative condition that affects 0.5% of people between the ages of 65 and 74 and 2% of people over 75. In this case, the electrodes stimulate the part of the brain known as the globus pallidus or the subthalamic nucleus to compensate for the lack of dopamine and the resulting alteration of electrical activity in the neural networks disconnected from those areas.

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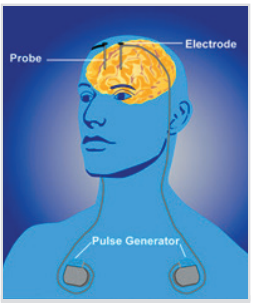

Illustration of a DBS-type (intracranial) neuromodulation system with two electrodes. (Source: Image del National Institute of Health - NIH)[2]

There are other indications for DBS systems, such as epilepsy, depression and obsessive-compulsive disorder, which require placement of the electrodes in other areas of the brain and different characteristics for the microcurrents applied through them.

Neuromodulators may also be implanted in the spinal cord. These are called SCS (spinal cord stimulators) and they are used, for example, to control chronic neuropathic pain caused by damage to or disorders of peripheral nerves.

External (non-implantable) neuromodulators

In the case of tDCS (transcranial direct current stimulation) and TMS (transcranial magnetic stimulation), currents or magnetic fields are applied using external electrodes or magnetic field generators placed on the skin, with no need for surgery.

The tDCS technique uses electric microcurrents applied through the skull (transcranially) via surface electrodes to the areas of the cortex (the outermost layer of the brain) affected by the pathology, while the TMS technique uses electromagnets.

Illustration of the application of TMS magnetic stimulation therapy to treat depression (Source: National Institute of Health - NIH)[2]

Both tDCS and TMS have given good results in the treatment of different neurological or psychiatric conditions, such as depression, tinnitus (persistent high-pitched sound of neurological origin), rehabilitation following a stroke and other conditions.

Of course, external neuromodulation systems cannot reach the inner parts of the brain and they act less intensely on brain activity, but their non-invasive nature makes them competitive with implantable devices, such as DBS and SCS.

Advantages of neuromodulation over treatment with drugs

Both the implantable and non-invasive systems of neuromodulation offer two advantages:

1. Selective modulation of electrical activity in the neural network, acting only where the electrodes or electromagnets are placed. This reduces side effects by eliminating or minimizing the use of drugs, which can often act on undesired targets.

2. The intrinsic flexibility of neuromodulation that allows the treatment to be increased, reduced or optimized simply by electronically adjusting the frequency and/or electromagnetic intensity of the stimulation.

Clinical acceptance

Around the world

In the last 10 years neuromodulation has become positioned internationally as a widely accepted and rapidly growing treatment strategy, easily seen from the fact that the number of medical publications on DBS increased from 114 in 2000 to 839 in 2012 (Font: PubMed).

DBS (intracerebral implants) were authorized for Parkinson's disease in 1997. They have also now been authorized in Europe for treatment of essential tremor, dystonia, obsessive-compulsive disorder, epilepsy and depression. Other applications are now at the R&D stage.

A total of approximately 75,000 patients around the world have a DBS[3] implant (figures for 2011). Most DBS devices are implanted to treat Parkinson's disease. For example, only 200 patients worldwide have been treated for obsessive-compulsive disorder with DBS.

Some 3,500 DBS implants are made each year in the United States (11.1 per million inhabitants), in comparison with 80 in Switzerland (10.1 per million inhabitants).[4]

Like DBS, SCS systems (spinal cord implants) for treatment of chronic pain have also been approved in Europe and they have been widely accepted. For example, the Neuromodulation Society of the United Kingdom and Ireland (NSUKI) reports that 1,000 SCS implants were made yearly in both countries in 2006[5] i.e. 10.5 implants per million inhabitants per year at 30 centres through Great Britain and Ireland.

The non-invasive (non-surgical) alternative using magnetic stimulation (TMS) received CE certification in 2012 for treatment of depression and chronic pain. On the other hand, non-invasive electric stimulation (tDCS) is awaiting approval for treatment of depression and other pathologies, although there are several tDCS devices on the market with CE certification strictly for R&D purposes.

In Catalonia

In Catalonia, DBS-type neuromodulators are now regularly implanted for treatment of the symptoms of Parkinson's disease and SCS-type devices are implanted for chronic pain control. No complete figures are available as of the date of this publication, but the available partial figures indicate that levels of acceptance of DBS and SCS in Catalonia are similar to those in other western countries.

For other pathologies with less validated neuromodulation therapies, such as obsessive-compulsive disorder (OCD), these systems have met with lower levels of acceptance. Bellvitge University Hospital recently announced (March 2013) the results obtained with 13 OCD patients fitted with DBS-type intracranial neuromodulators for the past 6 years: improvements were attained with 80% of the patients.[6]

Opportunities for Catalonia

For the Catalan healthcare system

Patients affected by neurological and psychiatric disorders that were previously difficult to treat could now have a new range of possible therapies with neuromodulation.

In the case of neurodegenerative diseases such as Parkinson's disease, neuromodulation improves or eliminates the symptoms and enhances the patient's quality of life, although it does not arrest the underlying degenerative process.

With conditions such as epilepsy and chronic pain that resist drug treatment and in general are not degenerative, neuromodulation has potential to become the reference therapy.

For Catalan industry. Neuromodulation as a new global manufacturing sector

The study *Making Perfect Life. European Governance Challenges in 21st Century Bio-engineering*,carried out by the Science and Technology Options Assessment (STOA) of the European Parliament, estimated a global market for neuromodulation in excess of $4,000 million in 2010, with annual growth of 18.6%.[7]

The table below shows certain figures for the four leading companies in terms of turnover. All four have non-European parent companies (Source: public corporate information).

Company (non-Catalan)	Products	Turnover	Year	Year-on-year growth
MEDTRONIC	DBS Parkinson's and other stimulators	$ 1.560 million	2009	+9%
BOSTON SCIENTIFIC	SCS stimulator (pain)	$ 285 million	2009	+17%
ST JUDE MEDICAL	DBS Parkinson	$ 330 million	2009	+30,2%
CYBERONICS	Stimulation of the vagus nerve (epilepsy)	$ 120 million	2010	+17%

This, then, is a large industrial sector with unusually rapid growth.

Challenges posed by neuromodulation in Catalonia and Europe

Challenges for the Catalan healthcare system: cost effectiveness, regulatory framework, clinical trials

Cost effectiveness

In general terms, the new therapies using neuromodulation enhance the quality and duration of the patient's life in comparison with strictly drug-based treatments. In some cases, however, they involve higher cost (e.g. DBS and SCS), while in others (tDCS and TMS) they can lead to reduced costs in comparison with the current alternatives.

To give just one example, according to the British healthcare system, DBS improves the quality of life of patients with Parkinson's disease by 30% in comparison with conventional drug treatment over the 5 years following the operation[5]. That improvement involved an additional cost of £147,079 per patient in 2008 in comparison with conventional drug treatment.

The cost of DBS treatment (surgery and implant) in Catalonia can be estimated at between €20,000 and €30,000.

Thus, to determine the level of financing or co-financing of these new therapies by the public health care system, the challenge is to establish objective criteria for cost effectiveness for each neuromodulation method and each pathology.

Regulatory framework

Neuromodulation devices and instruments require CE certification before they can be marketed in Europe. Obtaining CE certification requires compliance with a number of European directives, including electrical safety, electromagnetic accounting, the medical devices directive and particularly the directive on active implantable medical devices[8]. Together, those directives ensure that the product is safe and effective.

Rapid access by patients to the neuromodulation treatments now being researched and developed (for which CE certification is not required), particularly for pathologies with few therapeutic alternatives, would be facilitated by a specific regulatory framework.

In addition, possible off-label uses, mainly for non-implantable neuromodulation systems such as tDCS, TMS and others (EEG-biofeedback) will need specific oversight and regulation. Recreational uses and application in the area of competitive sports will require particularly close attention.

Challenges for Catalan industry: cost of R&D

If Catalan industry wishes to play a part in the global neuromodulation sector, it will have to overcome certain difficulties, due in part to the technological peculiarities of neuromodulation and in part to the characteristics of our social and economic environment.

The main obstacle to entry into the industry is the cost of R&D for development of a new neuromodulation therapy. The numerous start-ups working on new neuromodulation systems around the world provide a reference point. For example, in 2012 the Canadian company Functional Neuromodulation Inc. announced investment of $10.4 million in its DBS system for Alzheimer's disease; in 2011, the US company Nevro Corp. obtained $58 million for its pain treatment system, and also in 2011, Neuronetics, another American company, mobilized $30 million for its magnetic neuromodulation (TMS) system.

The leading sources of financing for these developments, which are often carried out by small and medium-sized enterprises of the start-up type, are venture capital investment funds and industrial partners interested in taking part in the growing neuromodulation therapies industry.

Access to such sources of financing in Catalonia, a regulatory framework to facilitate it and the co-operation of our research centres and hospitals with extensive know-how in the field will be crucial if Catalonia is to be present in this new industry.

The future of neuromodulation

Given the numerous clinical trials under way to assess new equipment, implantable devices and applications for neuromodulation, Catalan neurologists will foreseeably make increasing use of this therapy.

Thus, within the next decade the Catalan healthcare system will obtain new tools to deal with pathologies that have been difficult to treat. In addition, management of the associated cost will benefit from cost effectiveness studies on a pathology-by-pathology basis, to identify those cases where financial efficiency and the impact on the patient's health will justify the investment in neuromodulation.

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Abbreviations

DBS (Deep Brain Stimulation): Neuromodulation using one or two electrodes implanted in the train to treat neurological or psychiatric disorders with weak electrical currents.

OCD (Obsessive-Compulsive Disorder).

tDCS (trans-Cranial Direct Current Stimulation): Neuromodulation using electrodes attached to the skin (external) and weak electrical currents.

TMS (Transcranial Magnetic Stimulation): Neuro¬modulation using magnetic fields. Does not require physical contact between the device generating the electric field and the patient's body.

SCS (Spinal Chord Stimulation): Neuromodulation using electrodes implanted near the spinal cord. SCS devices can control chronic pain by preventing the neural electric signal communicating the sensation of pain from reaching the brain.