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Effects of Neuroplasticity and Neuromodulation on Brain Function

Marco Vinícios de Oliveira Santana[1], Carlos Henrique Marchiori[1*], Klebert de Paula Malheiros[1], Èrico Meirelles de Melo[1]
[1]Researchers of Instituto Marco Santana, Goiânia, Goiás, Brazil

Abstract: In this medical discipline, devices that record or produce electrical or magnetic activity are used to functionally explore the nervous system for diagnostic, prognostic, and therapeutic purposes. These techniques are fundamental to the practice of a wide range of specialties. Today, neurorehabilitation works closely with research in neuroscience, biomechanics, and other fields that encompass the study of human behavior, all in search of more targeted and effective treatments. The objective of this review is to understand how neuroplasticity and neuromodulation occur in the nervous system. This is a literature review, conducting research in the UpToDate, MEDLINE, Scielo, Google Scholar, and PubMed databases using the descriptors: Neurogenesis, neuroplasticity, neuromodulation, and rehabilitation. To highlight emerging and future research studies, a documentary search was conducted in the PubMed and Scopus databases. The total results obtained in the initial screening were counted, and the inclusion criteria were applied. Sixty articles were found in the database, of which only 47 met the requirements of having been published within the last 22 years and providing relevant information on the topic. Original articles, reviews, and case reports published in indexed national and international journals were selected.

Keywords: Electrophysiology, Neuropsychology, Neuropsychologists, Rehabilitation.

Research Paper

***Corresponding Author:**
Carlos Henrique Marchiori
Researchers of Instituto Marco Santana, Goiânia, Goiás, Brazil

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1.0.INTRODUCTION

When you meet someone or learn a new skill, your brain changes its structure and function. Our environment, our habits, and our learning can change our brains, even if we are not aware of it. Some events alter the way brain cells communicate with each other, strengthening or weakening this communication (Dobkin, 2003; Erickson *et al.*, 2011).

The nervous system is not only complex but also dynamic, and its functioning depends largely on an adequate supply of oxygen and glucose. This is why a lack of any of these elements leads to some disorders that are currently being addressed from various angles, including the use of the intrinsic neuroplasticity of the nervous system and the use of the neuromodulators specific to each cell group to help neurorehabilitation the affected individual (Prieto *et al.*, 2011; Lefaucheur *et al.*, 2020; García, 2022).

1.1. OBJECTIVE

The objective of this review is to understand how neuroplasticity and neuromodulation occur in the nervous system.

2.0. METHODS

This is a literature review, conducting research in the UpToDate, MEDLINE, Scielo, Google Scholar, and PubMed databases using the descriptors: Neurogenesis, neuroplasticity, neuromodulation, and rehabilitation. To highlight emerging and future research studies, a documentary search was conducted in the PubMed and Scopus databases. The total results obtained in the initial screening were counted, and the inclusion criteria were applied. Sixty articles were found in the database, of which only 47 met the requirements of having been published within the last 22 years and providing relevant information on the topic. Original articles, reviews, and case reports published in indexed national and international journals were selected.

3.0. SELECTED STUDIES

3.1. Neurogenesis

Synaptic plasticity is achieved through improved communication at the synapse between existing neurons; neurogenesis refers to the birth and proliferation of new neurons in the brain. But especially in recent years, the existence of neurogenesis has been scientifically proven, and we now know that it occurs when stem cells a special type of cell found in the dentate gyrus, hippocampus, and possibly the prefrontal cortex divide into two cells: a stem cell and a cell that will become a fully equipped neuron, with axons and dendrites (Figure 1) (Kolb *et al.*, 2010; Fernandes *et al.*, 2020).

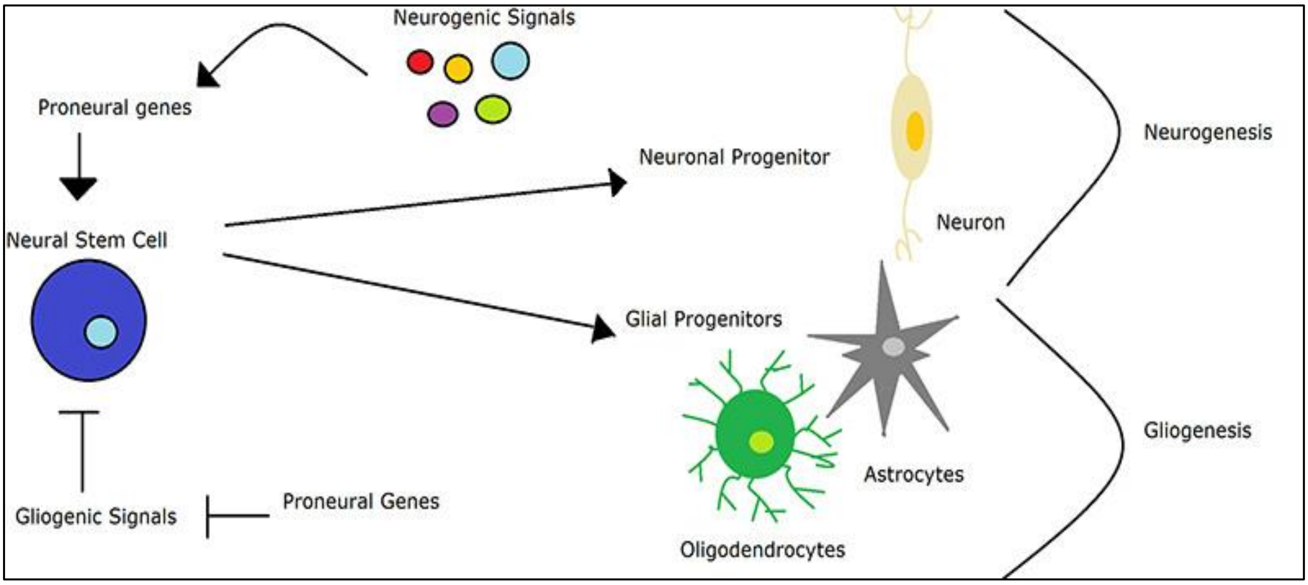

Figure 1: Neural stem cells have the potential to generate all neural cell types. They differentiate into neuronal progenitor cells, which give rise to neurons, or glial progenitors, which give rise to glial cells
Sources: Image Credit: NCD Project / CC BY-SA 3.0 via Commons and https://www.microscopemaster.com/neural-progenitor-cells.html

These new neurons then migrate to different, even distant areas of the brain where they are needed, thus allowing the brain to maintain its neuronal capacity. It is known that in both animals and humans, sudden neuronal death, such as a stroke, is a potent trigger for neurogenesis (Kolb *et al.,* 2010; Fernandes *et al.,* 2020).

3.2. Neuroplasticity

Neuroplasticity, one of the most revolutionary concepts in neuroscience, refers to the brain's marvelous ability to adapt and transform. This capacity is vital in neurorehabilitation, helping people recover from brain injuries and disorders. In recent years, neuromodulation has emerged as a promising technique to enhance this plasticity (Dobkin, 2003; Hummel *et al.,* 2008; Krakauer *et al.,* 2012; Laver *et al.,* 2017; García, 2022).

Neuroplasticity is the brain's incredible power to change and adapt throughout our lives. It is not a static capacity, but a dynamic one, and it comes in various forms: it can be the result of learning, experience, or recovery from brain injury. Neuroplasticity allows the brain to form new connections between neurons, allowing us to learn new skills, remember experiences, and adapt to new environments or situations (Krakauer *et al.,* 2012; García, 2022).

Neuroplasticity is popularly categorized into structural and functional categories. Structural neuroplasticity refers to physical brain tissue remodeling in response to learning and new experiences, whereas functional neuroplasticity occurs when existing neurons propagate and form new synaptic connections after functional loss following injury (Krakauer *et al.*, 2012; García, 2022).

3.2.1. There are two main types of neuroplasticity:

1. **Functional neuroplasticity.** This is the brain's ability to change the way functions are organized within different brain areas. For example, if one part of the brain is damaged, other areas can take over those functions to compensate for the loss.
2. **Structural neuroplasticity.** This type involves changes in the brain's physical structure, such as the growth of new neurons or the modification of the connections between nerve cells. Neurogenesis, or the creation of new neurons, is a clear example of this type of plasticity (Figure 2).

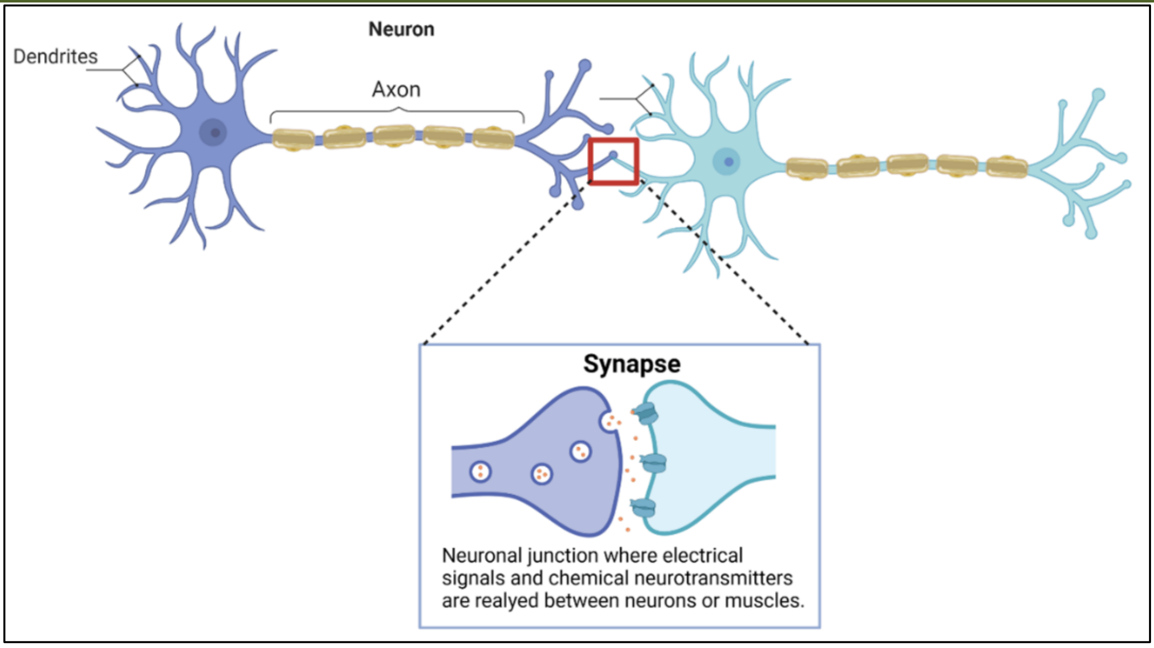

Figure 2: Structure of a neuron and synapses

Sources: Image created with Biorender.com, by Lalitha Ramasubramanian/December 09, 2022, and https://biotech.ucdavis.edu/blog/neuroplasticity

This ability is greatest during the neurodevelopment period, that is, during childhood, adolescence, and early adulthood. However, it is a capacity that is preserved even after this development; the important thing is the presence of some type of stimulus. It is because of this neuroplasticity that it is possible to recover functions after a neurological injury (Hummel *et al.*, 2008; Krakauer *et al.*, 2012; Lefaucheur *et al.*, 2020).

Neuroplasticity is considered the capacity of neural tissue to reorganize, assimilate, and modify the biological, biochemical, and physiological mechanisms involved in intercellular communication to adapt to the stimuli received, including axonal regeneration, neurogenesis, synaptogenesis, and functional reorganization (Figure 3) (Deer *et al.*, 2014).

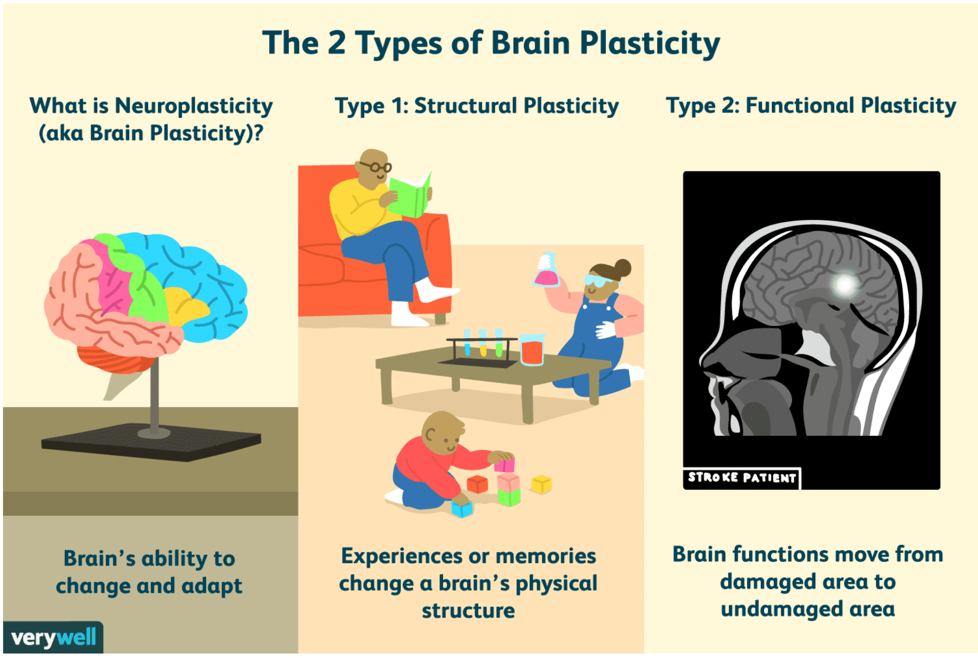

Figure 3: Today, it's understood that the brain's neuroplasticity allows it to reorganize pathways, create new connections, and, in some cases, even create new neurons

Sources: Verywell/JR Bee, Kendra Cherry, MSEd, and https://www.verywellmind.com/what-is-brain-plasticity-2794886

With the advent of new scientific technologies that have emerged in recent years, we have responded to and maintained this concept of plasticity of the nervous system as a basic premise for its susceptibility to external and dynamic changes. The experience of the phantom limb permanently reveals the existence of a mental map of the body that underpins and modifies our experience with our body, whose nervous system has the capacity for cortical reorganization through sensory, endocrine, and motor stimulation (Krakauer *et al.*, 2012; Deer *et al.*, 2014; Lefaucheur *et al.*, 2020).

3.3. Neuromodulation

Due to the lack of awareness that existed until very recently of the plastic capacity of the human nervous system, and therefore, the possibility of being neuromodulated, as we discussed previously, it was then considered for a long time that the clinical neurologist who dedicated himself to neurorehabilitation was concerned with activities devoid of glamour, given that the latter includes the use of elements such as stairs, access ramps and kitchen utensils (Sotero, 2008; Erickson *et al.*, 2011; Krakauer *et al.*, 2012; Lefaucheur *et al.*, 2020).

Neuromodulation can enhance neuroplasticity, which improves the effectiveness of rehabilitation. For example, it can be used to treat disorders such as depression, schizophrenia, and Parkinson's disease, or to restore motor, cognitive, or speech functions. To encourage neuroplasticity, you can do activities that challenge the brain, such as learning a new language or playing a musical instrument (Krakauer *et al.*, 2012; Lefaucheur *et al.*, 2020; Makowski, 2020).

It is possible to induce neuroplasticity in humans through neuromodulation, which consists of increasing or decreasing the excitability of a group of neurons or even of a complex system of connections. Changes in the expression of neuronal receptors have been observed, as well as changes in the kinetics, content, and release of neurotransmitters. Changes in the activity of astrocytes and microglia that monitor and regulate the environment close to neurons have also been reported (Figure 4) (Edwards *et al.*, 2017; Makowski, 2020).

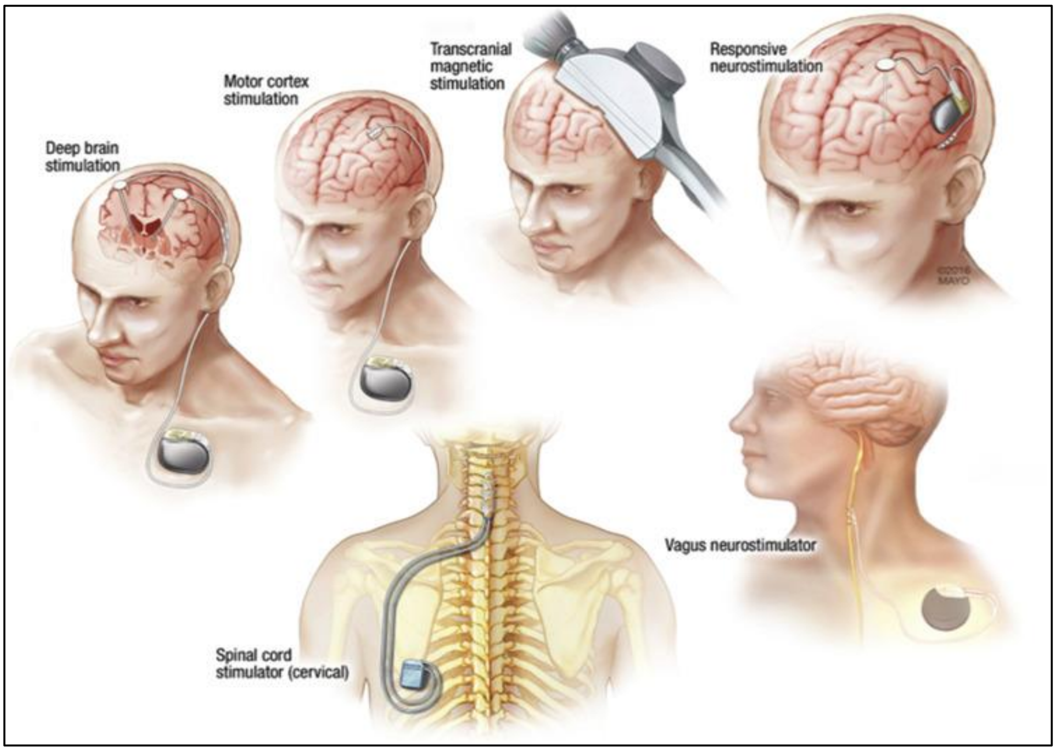

Figure 4: Neuromodulation devices for the treatment of neurologic disorders. Schematic summarizing of common neuromodulation devices and stimulation targets in the central and peripheral nervous systems
Sources: Doi: http://dx.doi.org/10.1016/j.mayocp.2017.05.005 and https://www.researchgate.net/figure/Neuromodulation-devices-for-the-treatment-of-neurologic-disorders-Schematic-summarizing_fig1_319423397

Recently, non-invasive neuromodulation has become an important ally in the treatment of several diseases, from depression, anxiety disorders, and obsessive-compulsive disorder to improving the recovery of motor sequelae after a stroke, chronic pain, fibromyalgia, Parkinson's, and multiple sclerosis, among others. One of the principles of neuromodulation is neuroplasticity (Krakauer *et al.,* 2012; Lefaucheur *et al.,* 2020).

The diversity of research focuses is further enlarged by a necessity to engage in both basic and translational research, clinical trials, and synthesis of the evidence in systematic reviews with meta-analyses, and by a methodologically sound link from evidence to the clinical decision via evidence-based practice recommendations (Platz and Sandrini, 2020).

3.4. Neuroplasticity and Neuromodulation

It has an increasing effect on the generation of new neural networks, and there is currently sufficient evidence to support the hypothesis that the stimuli lead to long-term changes in neuronal activity. It is important to emphasize that the effects of neuromodulation can be enhanced when combined with other treatments, such as rehabilitation (Lefaucheur *et al.,* 2020; García, 2022).

Making new neural connections depends on an individual's experience and environment. It is possible to improve neuroplasticity through exercise, balanced nutrition, and avoiding toxic agents, and neuromodulation acts to facilitate this process of forming new connections (Portera, 2002; Laver *et al.,* 2006; Krakauer *et al.,* 2012; Makowski, 2020).

3.4.1. It is important to emphasize that some factors are essential for neuroplasticity to occur:

1. **Specificity:** both in rehabilitation and during the use of neuromodulation, the target or task must be specific to a given function.
2. **Intensity:** Low-intensity stimuli do not produce the desired effect on the brain, as they do not promote significant changes. The greater the number of repetitions, the greater the learning, leading to new brain connections.
3. **Motivation:** to be able to walk again, to be able to change clothes by yourself, to go back to work, to go back to exercising. no matter what the motivation is, it must be present for the results to be positive.
4. **Time:** It is always possible to promote neuroplasticity, but the sooner, the better (Sotero, 2008; Prieto *et al.,* 2011; Krakauer *et al.,* 2012; Merzenich *et al.,* 2014; García, 2022; Rahman *et al.,* 2023).

Although it is a term that is almost always used positively, neuroplasticity can also occur after an injury. The brain is very intelligent and always seeks to save energy, so what is not used is lost. Establishing new brain connections is not a simple process, but it is possible! The help of a professional is extremely important, as they guide and direct which paths should be followed. Neuroplasticity, neuromodulation, and neurorehabilitation are areas that, in general, have provided significant benefits to clinical intervention programs that are carefully planned for each specific case. With this approach, we are managing to change the cruel fate established in some scientific and academic circles for people who suffer neurological injuries. In adult brains, the nerve pathways are fixed, finished, and immutable (Figure 5) (Portera, 2002; Erickson *et al.,* 2011; Merzenich *et al.,* 2014; García, 2022).

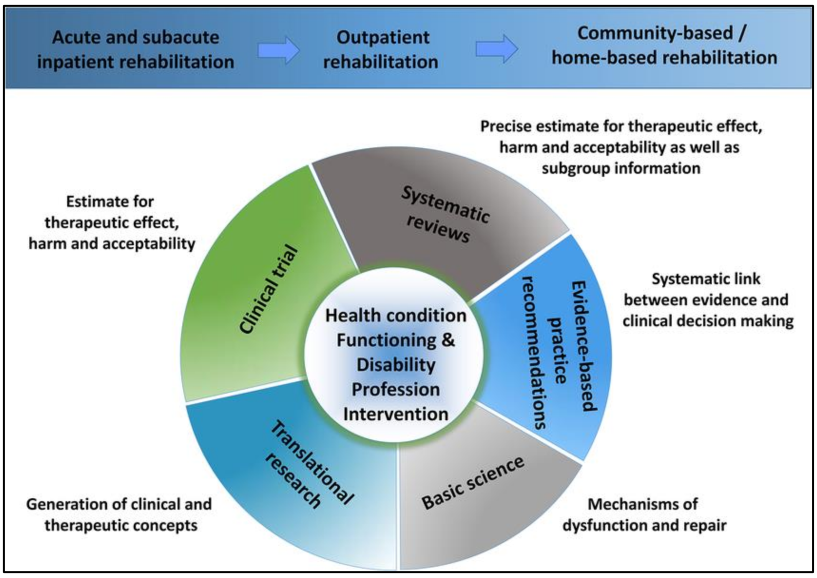

Figure 5: Neurorehabilitation research perspectives. The complexity is caused by the multitude of health conditions, alterations of functioning and disabilities, and of respective interventions as provided by different health care professions along a continuum of health care from acute rehabilitation to community-based rehabilitation
Sources: Doi: 10.3389/fneur.2020.00349 and https://www.researchgate.net/figure/Neurorehabilitation-research-perspectives-The-figure-shows-the-complexity-of-the_fig1_341584541

The approach to people suffering from a Central Nervous System (CNS) disease or with consequences for the CNS is multidisciplinary, but the professionals responsible for evaluating, diagnosing, and intervening on the impact of these events on cognitive functions, also known as mental or brain functions, are clinical neuropsychologists. The term neuropsychology refers, in general terms, to the study of behavior, the mind, and its relationship with the central nervous system. Neuropsychology is situated at the intersection between the neurosciences, including neurology, neuroanatomy, neurophysiology, psychiatry, and neuroimaging, and the behavioral sciences, such as psychology and linguistics, encompassing cognitive and emotional-motivational processes (Figure 6) (Portera, 2002; Laver *et al.*, 2017; Lefaucheur *et al.*, 2020; Makowski, 2020; García, 2022).

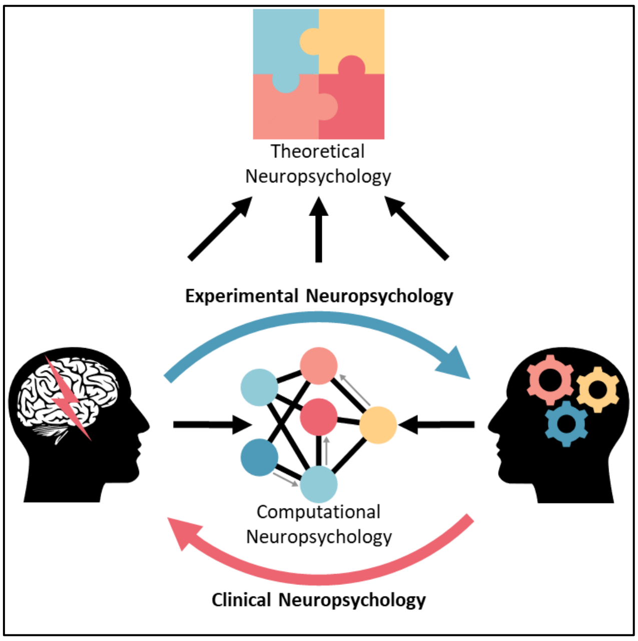

Figure 6: The fourfold structure of neuropsychology
Sources: Dominique Makowski, Sep 13, 2020, Neuropsychology and https://dominiquemakowski.github.io/post/2020-09-13-what_is_neuropsychology/

The primary role of clinical neuropsychologists is to assess cognitive function in individuals with known or suspected brain damage. Cognitive functions can be conceptualized as those processes by which an individual perceives external and internal stimuli; selects relevant stimuli and inhibits irrelevant stimuli; registers, retains, and retrieves information; forms associations between stimuli and manipulates information in pursuit of a goal; and emits information through the expression of overt behavior (Figure 7) (Schmitt *et al.*, 2005; Hummel *et al.*, 2008; Prieto *et al.*, 2011; Merzenich *et al.*, 2014; García, 2022).

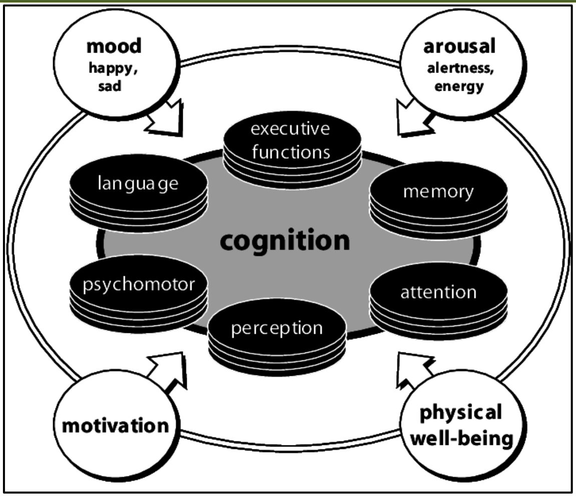

Figure 7: Schematic representation of the interaction between the cognitive functions in black and the factors that may modulate the efficiency of cognitive processing in white

Sources: Doi 10.1007/s00394-005-0585-4 and https://www.researchgate.net/figure/Schematic-representation-of-the-interaction-between-the-cognitive-functions-in-black_fig1_7438905

Neuropsychology allows us to quantify the changes that occur through the intervention of Transcranial Magnetic Stimulation (TMS). Another contribution of professionals is research, particularly magnetic resonance studies. Recent studies indicate that post-processing analyses of images performed by engineers, neuropsychologists, and radiologists are even more sensitive in identifying neuroplasticity changes that occur in the CNS (Portera, 2002; Laver *et al.,* 2017; Lefaucheur *et al.,* 2020; García, 2022).

Neuromodulation is one of the most interesting techniques currently used in neurorehabilitation. The use of technologies to influence the activity of the nervous system, either by stimulating or inhibiting it, to improve function and quality of life. There are several forms of neuromodulation, including Transcranial Magnetic Stimulation (TMS), Direct Electrical Stimulation (tDCS), and neuroimplants. These techniques can increase neuroplasticity, increasing the effectiveness of rehabilitation. TMS effectively improves mobility and speech recovery after a stroke (Figure 8) (Hummel *et al.,* 2008; Krakauer *et al.,* 2012; Lefaucheur *et al.,* 2020).

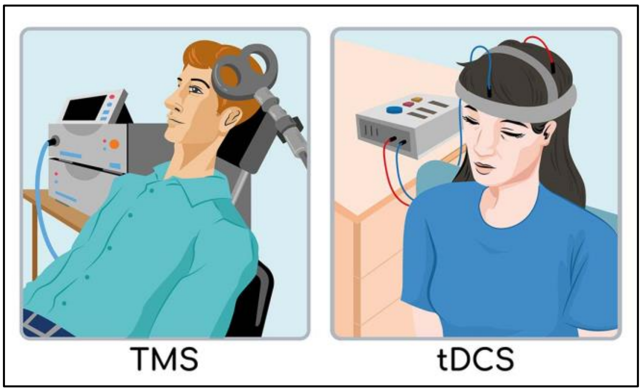

Figure 8: Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS) are noninvasive brain stimulation techniques that can produce lasting changes in mood and behavior. Although they share several common mechanisms and effects, there are also important differences

Sources: M. Neal Waxham, Ph.D., Department of Neurobiology and Anatomy, McGovern Medical School, and https://med.uth.edu/nba/nso/table-of-contents/cellular-and-molecular-neurobiology/ch-13-amino-acid-neurotransmitters/

The electrophysiological activity of the nervous system is present in all the functions we perform in our daily lives. A reflex, a memory, a thought, a dream, a spontaneous run. All these small activities are supported by a vast network of neural circuits that interact with each other using a wide variety of neurotransmitters (Figure 9) (Dobkin, 2003; Erickson *et al.,* 2011; Prinsloo *et al,* 2014; Sdrulla *et al.,* 2018; Fernández, 2021).

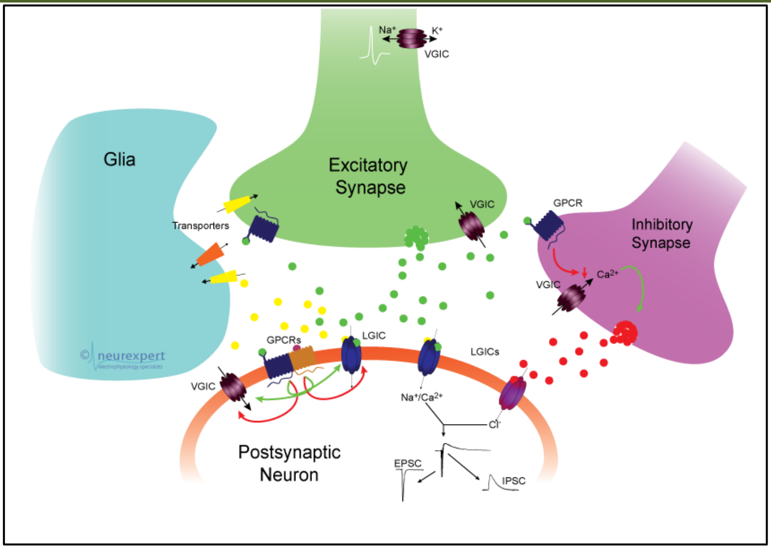

Figure 9: Electrical signals measured by electrophysiology are produced by the activity of VGICs and LGICs. This activity is modulated by many other targets, so although electrophysiology is often described as the "gold standard" when applied to ion channels, the technology is very applicable to targets such as GPCR and transporters
Sources: NEUREXPERT and the Neurexpert logo are trademarks of Neurexpert Ltd. ©2020 Neurexpert Ltd and https://www.neurexpert.com/neuronal%20electrophysiology.html

The neurophysiological activity of axonal synapses can generate both inhibition and potentiation in a neuronal network. Furthermore, the most interesting aspect of this situation is that this inhibition or enhancement responds to very well-described physiological processes. Thanks to the neuroplasticity of our nervous system, we can perpetuate the positive changes we induce in the short term and generate permanent changes in neuronal electrophysiology (Figure 10) (Bucher and Marder, 2013; Nadim and Bucher, 2014; Sdrulla *et al.*, 2018).

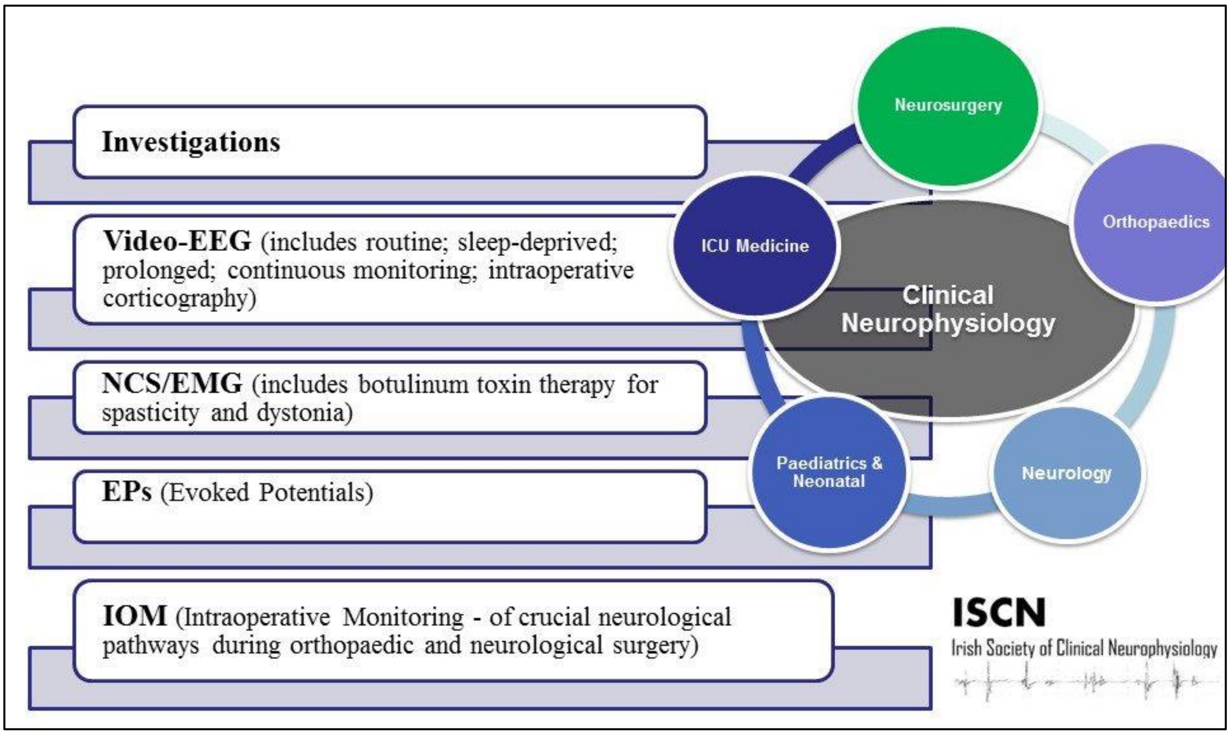

Figure 10: The specialty requires an intimate understanding of neurological disease, differential diagnosis, and pathophysiology, as well as an understanding of how electrophysiology may be used to resolve diagnostic questions in the area
Sources: © Irish Institute of Clinical Neuroscience, Irish Society of Clinical Neurophysiology (ISCN) and

Neuromodulation, brain plasticity, is emerging as a key element to improve treatments and revolutionize neurological rehabilitation. This surprising brain phenomenon becomes a beacon of hope for those seeking to improve the effectiveness of treatments and accelerate the neurological recovery process (EPTE 3, 2024; Footer, 2024).

3.4.2. These characteristics summarize the dynamic and highly adaptive nature of brain plasticity:

1. Continuous adaptability.
2. Structural and synaptic plasticity.
3. Activation principles.
4. Plasticity can occur in different ways (Kolb *et al.*, 2010; EPTE 3, 2024; Footer, 2024).

3.4.3. Examples: Some examples of when brain plasticity can be naturally enhanced are:

1. Learning New Skills.
2. Recovery After a Stroke.
3. Physical Exercise.
4. Enriched Sensory Experiences (EPTE 3, 2024; Footer, 2024).

3.4.4. Several neuromodulation techniques, tDCS and TMS, harness brain plasticity to positively influence different diseases:

1. Practical applications in neuromodulation.
2. Optimizing psychiatric treatments.
3. Specific neurological rehabilitation.
4. Pain Modulation. Personalized Treatments for Neurological Disorders (EPTE 3, 2024; Footer, 2024).

3.4.5. Researchers at the Institute of Physical Medicine and Rehabilitation (IMREA) of the Faculty of Medicine of the University of São Paulo (FMUSP) have successfully applied a set of innovative techniques, including the following:

1. Robotic Exoskeleton.
2. Transcranial Magnetic Stimulation (rTMS).
3. High-density Electroencephalography (EEG-HD).
4. To treat patients suffering from Cerebrovascular Accidents (CVA) or spinal cord injuries.

When attending to patients who suffer a cerebral vascular accident, there are two key points to identify the predictors of the motor response, which are only the signs captured from the recording of cerebral electrical activity, which indicates the capacity of each patient to recover two movements. This is carried out by a combination of two techniques: Reconfirmation of the Motor Evoked Potential (MEP), a test that does not include a magnetic stimulus applied to the brain and the motor response is validated, and the Measurement of Cerebral Electrical Activity with HD-EEG (Kolb *et al.*, 2010; Toledo, 2016; Footer, 2024).

Another approach within IMREA, also in collaboration with Harvard, combines tDCS with aerobic exercise designed to enhance the treatment of chronic pain in people with fibromyalgia. This method can also be applied to patients with incomplete spinal cord injury who complain of chronic pain. "During the exercises, use a device that produces electrical stimuli that are adequately tolerated by the brain and capable of controlling pain" [The group collaborates with the Neuromodulation Laboratory at Harvard Medical School, under the leadership of Professor Felipe Fregni. One of the main researchers at IMREA-FMUSP is Professor Marcel Simis.] (Lebedev and Nicolelis, 2006; Toledo, 2016; Footer, 2024).

The neurophysiological approach also includes the use of transcranial magnetic stimulation for diagnostic purposes, a study that indicates which areas of the brain should be stimulated and which should be inhibited to induce neuroplasticity and improve motor control (Lebedev and Nicolelis, 2006; Toledo, 2016; Footer, 2024).

Percutaneous neuromodulation is an invasive and safe procedure, performed with sterile needles and complete asepsis, under ultrasound guidance, using TENS-type current and under different treatment frequencies. Thus, the objectives sought with this technique in general and at a clinical level are to reduce pain and decrease dysfunction. Percutaneous neuromodulation is an invasive and safe procedure, performed with sterile needles and complete asepsis, under ultrasound guidance, using TENS-type current and at different treatment frequencies. Thus, the objectives sought with this technique in general and at a clinical level are to reduce pain and decrease dysfunction (Figure 11) (Lebedev and Nicolelis, 2006; Kolb *et al.*, 2010; Ortega, 2019; Footer, 2024).

Figure 11: Ultrasound-guided percutaneous neuromodulation as a tool in physiotherapy. The field of physiotherapy has evolved considerably in recent years following the emergence of new techniques and the technological development of devices that contribute to improving intervention and evaluation of patients with a variety of pathologies

Sources: ASSA Insurance, Javier Valero Ortiz - Physiotherapist and Director at Valero Clinic, and https://www.asssa.es/en/ultrasound-guided-percutaneous-neuromodulation-as-a-tool-in-Kolbt-physiotherapy/

The treatment should be administered tangentially under ultrasound guidance, as it is effective and improves and prepares the neuromuscular system. Additional studies are necessary and are carried out in conjunction with a multidisciplinary team. Plasticity works when complemented by the application of percutaneous neuromodulation techniques. The neuroplasticity changes in the brain, such as recovery from injuries to the central nervous system (Lebedev and Nicolelis, 2006; Ortega, 2019; Hernández and Pérez, 2020; Footer, 2024).

Neuroplasticity or brain plasticity, which includes synaptic and non-synaptic plasticity; the former is related to the functional modification of ion channels in the neuronal axon, dendrites, and cell body, which gives rise to the modification of the intrinsic excitability of the neuron. In the case of plasticity, no synaptic plasticity fundamentally affects the mechanisms of neuronal functioning at the cellular level (Kolb *et al.,* 2010; Ortega, 2019; Hernández and Pérez, 2020; Footer, 2024).

The nervous system is a dated, more highly complex system that assimilates, reorganizes, and modifies its biological, biochemical, and physiological mechanisms. This capacity is called neuroplasticity and involves alterations in neural tissue that include axonal regeneration, collateralization, neurogenesis, synaptogenesis, and functional reorganization, among other mechanisms (Bayona *et al.,* 2011; Hernández and Pérez, 2020; Footer, 2024).

These mechanisms use neurotransmitters such as N-methyl-D-aspartate (NMDA), Gamma-Aminobutyric Acid (GABA), acetylcholine, or serotonin, involved in short- or long-term synaptic potentiation or depression, which can last hours or days, supported by second messengers such as cyclic AMP, whose effects can be transient or permanent. These effects are based on neuromodulation. The latter is a long-term change in neuronal metabolic activity and its response to various electrical, magnetic, or chemical stimuli used in clinical neurorehabilitation (Figure 12) (Bayona *et al.,* 2011; Hernández and Pérez, 2020; Waxham, 2020; Footer, 2024).

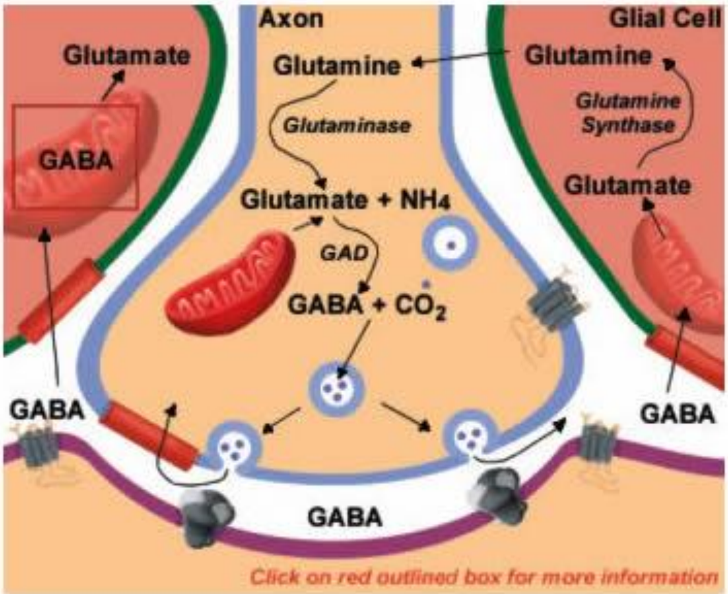

Figure 12: GABA mediates the majority of inhibitory synaptic actions in the central nervous system (CNS). GABA is synthesized from glutamate in a reaction catalyzed by glutamic acid decarboxylase

Sources: © Copyright 2008-Present | The University of Texas Health Science Center at Houston (UTHealth Houston) and https://med.uth.edu/nba/nso/table-of-contents/cellular-and-molecular-neurobiology/ch-13-amino-acid-neurotransmitters/

Tinnitus is a hearing disorder that has challenged medicine for decades. For those who suffer from it, the constant ringing in the ears can become an unwelcome companion in everyday life. However, today, we are witnessing an exciting advance in the treatment of tinnitus based on two fundamental pillars: neuromodulation and neuroplasticity (Bayona *et al.*, 2011; Olmo, 2023).

Neuroplasticity is the reason why bimodal neuromodulation therapy for tinnitus has such revolutionary potential. By combining sound therapy with electromagnetic therapy, this therapy stimulates the brain in specific ways to rewire the neural connections altered by tinnitus. This can help reduce the perception of tinnitus and, in some cases, even eliminate it (Bayona *et al.*, 2011; Olmo, 2023; Footer, 2024).

Neuromodulation is a therapeutic approach that seeks to alter neural activity in specific areas of the brain. In the context of tinnitus, bimodal neuromodulation therapy acts as a catalyst to induce beneficial neuroplastic changes. Sound therapy provides specific sounds that help mask the ringing of tinnitus, thereby alleviating discomfort. Electromagnetic therapy, on the other hand, works at deeper levels, influencing neuronal activity in a non-invasive manner. Together, these therapies open the door to a positive reconfiguration of damaged auditory pathways (Bayona *et al.*, 2011; Olmo, 2023; Footer, 2024).

Bimodal neuromodulation offers new hope for those suffering from tinnitus. By harnessing the brain's neuroplasticity, this therapy is at the forefront of tinnitus research. While it is important to remember that each case is unique, this innovative therapy is effective in a significant proportion of patients. On the path to eliminating tinnitus, neuromodulation and neuroplasticity are leading the revolution, offering hope to those seeking a life without constant ringing (Figure 13) (Bayona *et al.*, 2011; Olmo, 2023; Footer, 2024).

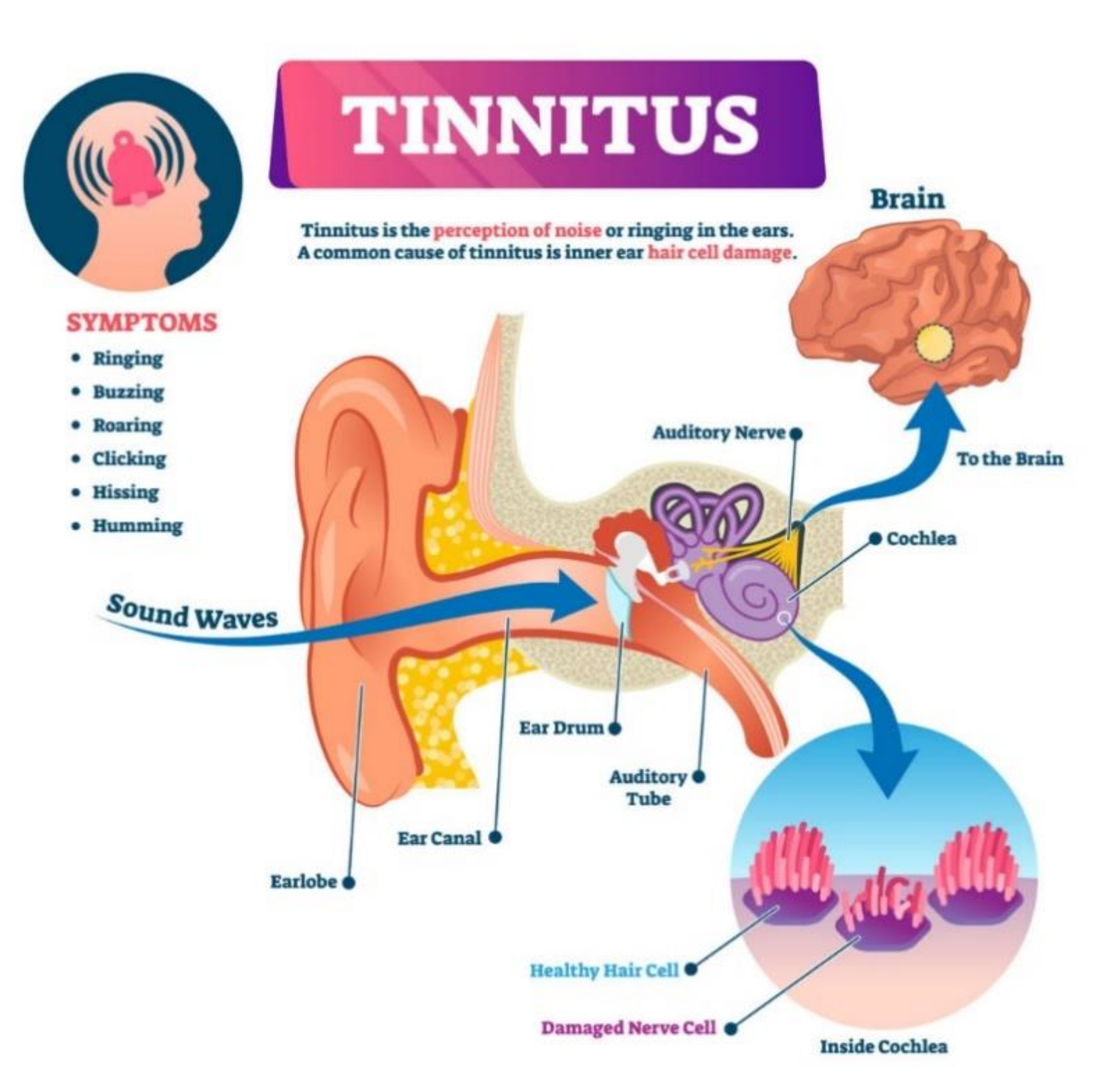

Figure 13: At Hermitage Audiology, the impact that tinnitus can have on your quality of life
Sources: Hermitage Audiology and https://hermitageaudiologypa.com/tinnitus-treatment/

Neuromodulation can act globally in the body, generating adaptations in the Nervous System through the application of intelligent electrical patterns through peripheral nerves. This technology promotes impulses that activate neuromodulatory and neurotransmitter systems through afferent and efferent pathways:

1. This technique is being researched and used in several therapeutic areas.
2. Sleep regulation: Improves sleep quality by promoting a parasympathetic state of relaxation.
3. Reduction of stress and anxiety: helps to modulate stress levels by regulating autonomic tone.
4. Control of chronic pain: This can be useful in cases of chronic pain by influencing pain-processing circuits (Figure 14) (Bayona *et al.*, 2011; Olmo, 2023; Rahman *et al.*, 2023).

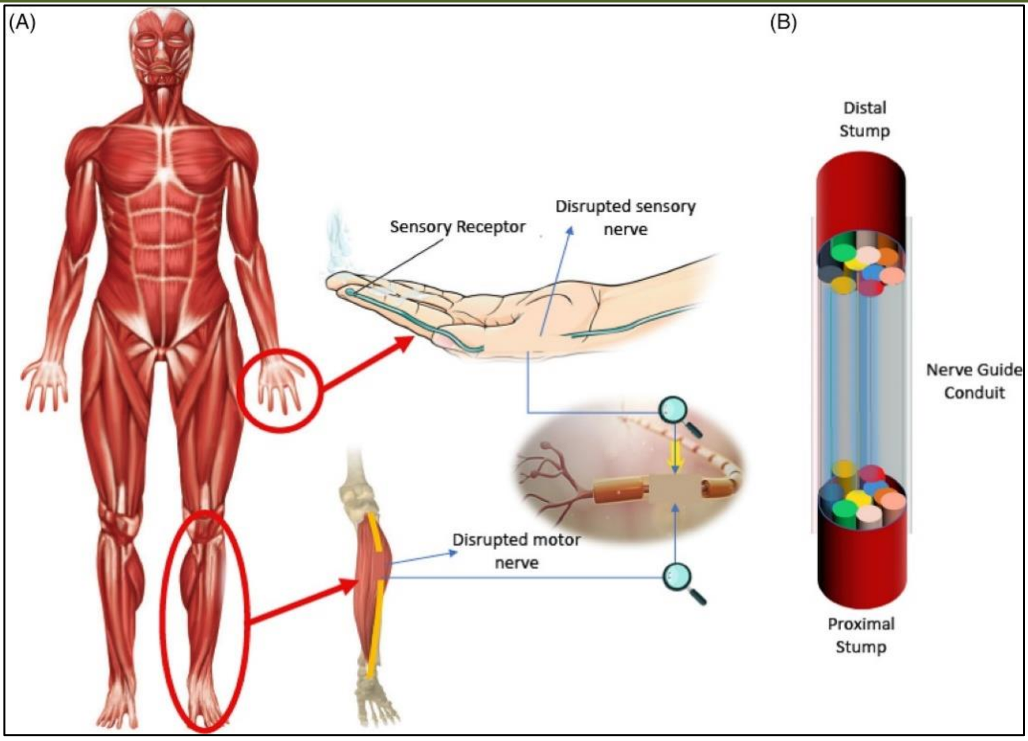

Figure 14: (A) Destructive effect of peripheral nerve injury on patients' bodies, and (B) the most promising treatment option is an artificial nerve guide conduit
Source: Doi: 10.1002/jbm.a.37595

Neurological rehabilitation: This has been explored in patients with mild or moderate neurological dysfunctions, such as movement disorders or injuries to the nervous system: synaptopathy, fibromyalgia, spinal cord injury, and Parkinson's disease (Casal-Beloy *et al.*, 2020; González *et al.*, 2020; Hernández and Pérez, 2020)

It has been demonstrated that the results of a large series of patients who, after failing to respond to conservative treatment, benefited from a neurostimulator implanted in the gluteus that delivers current pulses to the sacral roots and is not only effective in treating severe fecal incontinence but consequently improves quality of life (Figure 15) (Casal-Beloy *et al.*, 2020; González *et al.*, 2020; Hernández and Pérez, 2020; Summa Health, 2025).

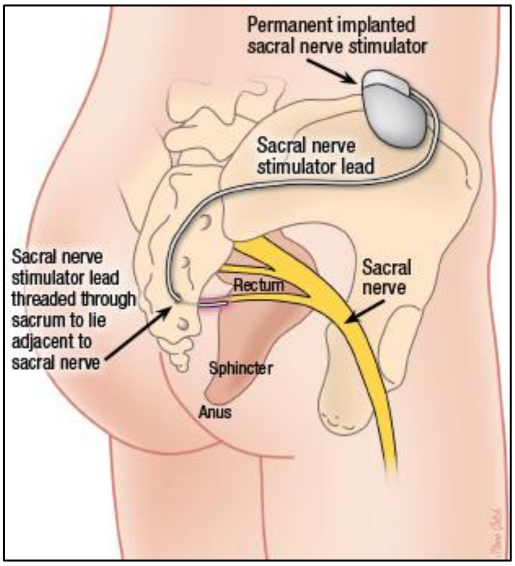

Figure 15: A sacral nerve stimulator is a surgically implanted device used to help a patient reduce the number of bowel accidents and fecal incontinence

Source: https://www.summahealth.org/about-us/publications-and-reports/thrive/sacralnerve

3.5. Morphological Processes in Neuromodulation

Nerve cells can have their activity modified through different morphological processes, classified as follows:

1. Neurogenesis: Producing new cells.
2. Collateralization: Forming branches from intact axons or synaptogenesis, creating new synapses.
3. Axonal Regeneration: Growth and repair of damaged axons.

3.6. Forms of Neuroplasticity

Two forms of plasticity can be distinguished:

1. Short-Term plasticity: After injury, due to changes induced in the injured area and facilitated by exercise, there is an activation of silent synapses before the injury.
2. Long-Term Plasticity: Stable changes in synapse efficacy through new neuronal growth and reorganization, sprouting, dependent on the frequency with which that axon is stimulated. In this process, new pathways emerge from healthy areas to reach the injured area.
3. Changes in Neuromodulatory Circuits: Control of pre- and post-synaptic activity.

Neurorehabilitation focuses on the recovery and rehabilitation of brain and spinal cord functions in people who have suffered injuries to the CNS. It encompasses a wide range of therapies and techniques, one of the most revolutionary and promising neuromodulations, which is used to treat various conditions, including neurological and psychiatric disorders (Casal-Beloy *et al.*, 2020; González *et al.*, 2020; Immedico, 2024).

With the advent of new scientific technologies that have emerged in recent years, we have responded to and maintained this concept of plasticity of the nervous system as a basic premise for its susceptibility to external and dynamic changes. The experience of the phantom limb permanently reveals the existence of a mental map of the body that underpins and modifies our experience with our body, whose nervous system has the capacity for cortical reorganization through sensory, endocrine, and motor stimulation (Huertas, 2014; Casal-Beloy *et al.*, 2020; González *et al.*, 2020).

Neuromodulation is always used before neurofeedback sessions; you'll likely encounter these different devices during your treatment. They stimulate the vagus nerve parasympathetic system, the brain, and also the body, often in the gut:

1. Electrical stimulation.
2. tDCS.
3. Transcranial Alternating Current Stimulation (tACS).
4. Transcranial Random Noise Stimulation (tRNS).
5. Low-Intensity Magnetic Stimulation (pEMF).
6. Formerly called Low-Level Phototherapy (LLLT), it is now called Photobiomodulation (PBM).
7. Auditory stimulation.
8. Visual Stimulation (AVE).
9. Repetitive Transcranial Magnetic Stimulation (rTMS).
10. Electroconvulsive Therapy (ECT).
11. Microcurrent for Pain Relief (MENS).
12. Transcutaneous Electrical Nerve Stimulation (TENS or TNS).

Neurofeedback training enables learning and change through neuroplasticity and conditioning. Stimulation amplifies these phenomena: the session is easier because the brain learns more quickly and easily. It is in a plastic state, ready to change. Furthermore, stimulation allows for longer, more effective sessions without side effects: 1 + 1 = 3! (Figure 16) (Edwards *et al.*, 2011; Casal-Beloy *et al.*, 2020; González *et al.*, 2020; Barbosa, 2024).

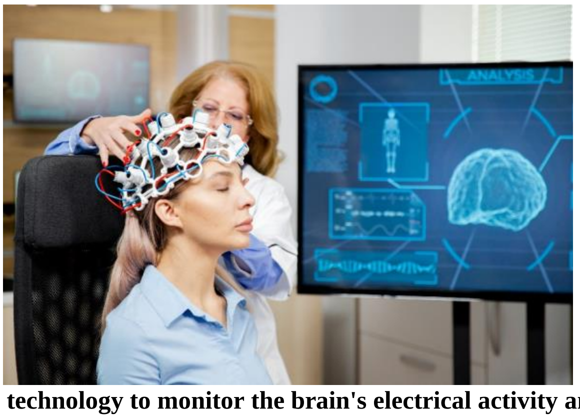

Figure 16: Neurofeedback uses technology to monitor the brain's electrical activity and provide real-time feedback. Improved Emotional Self-Regulation: By learning to adjust brain waves, patients acquire skills to deal with stress and improve emotional control. Reduced Symptoms of Mental Disorders: Many patients experience reduced symptoms of

ADHD, anxiety, and depression, complementing other forms of treatment. Improved Quality of Life: With proper training, neurofeedback promotes better sleep quality, greater focus, and mental well-being
Source: https://draanabeatriz.com.br/neurofeedback-como-o-treinamento-cerebral-ajuda-na-saude-mental/

Neuroplasticity is the brain's ability to reorganize neuronal activity or readjust its functionality. This is due to neuronal connections that respond to environmental factors, sensory stimulation, or consequences in normal development. These brain capacities are most favored at an early age as they allow for better information absorption and regeneration in neurons through rapid synapse response (Casal-Beloy *et al.,* 2020; Delgado *et al.,* 2022).

There are various mechanisms of neuroplasticity, and these depend on the process that originates it, the location where it develops, and the mechanism by which it occurs, among other aspects (Casal-Beloy *et al.,* 2020; Delgado *et al.,* 2022):

1. Branching or reactive synaptogenesis.
2. Denervation hypersensitivity.
3. Behavioral compensation.
4. Non-synaptic diffusion neurotransmission.
5. Unmasking.
6. Trophic factors.
7. Synapses and neurotransmitters.
8. Regeneration of nerve fibers and cells.
9. Diaschisis.
10. Neurotransmitters.
11. Long-term potentiation.

3.6.1. Brain complications

1. Stroke.
2. Alzheimer's disease.
3. Multiple sclerosis.

3.7. The Laboratory of Neurology and Translational Neurophysiology, led by Dr. José Manuel Matamala at the University of Chile School of Medicine

It is dedicated to translational research in neuromuscular and neurodegenerative diseases, such as Amyotrophic Lateral Sclerosis (ALS). (PETNODO Lab, 2024).

This laboratory seeks to identify biomarkers and develop new treatments by exploring the neuroplastic reserve in the brains of ALS patients. This approach could revolutionize our understanding and treatment of this devastating disease. According to Dr. Matamala, "understanding how the brain adapts under these conditions is key to designing future interventions that can slow its progression" (Ayaan *et al.,* 2023; PET NODO Lab, 2024).

The use of a robotic exoskeleton, in addition to assisting with walking and arm movement, also provides researchers with objective measurements of each patient's functional performance. Using sensors located in the upper and lower extremities, this device calculates the force that the individual exerts during the execution of the movement (Toledo, 2016; Casal-Beloy *et al.,* 2020; PET NODO Lab, 2024).

3.8. Neuromodulation Laboratory at Harvard Medical School, led by Professor Felipe Fregni. One of the lead researchers at IMREA-FMUSP is Professor Marcel Simis

Also, in collaboration with Harvard, it combines tDCS with aerobic exercises designed to enhance the treatment of chronic pain in people with fibromyalgia. This method can also be applied to patients suffering from incomplete spinal cord injury who complain of chronic pain. "During the exercises, we use a device that produces electrical stimuli that are adequately tolerated by the brain and capable of controlling pain (Toledo, 2016; Casal-Beloy *et al.,* 2020; PEAT NODO Lab, 2024).

A group of patients who underwent only a conventional rehabilitation program was compared with another group that, in addition to exercises, received magnetic stimulation to promote cortical balance. The second group showed significantly greater improvement. Thus, it can be stated that this technique can indirectly influence the processes of neuroplasticity and, consequently, improve motor control (Toledo, 2016; Casal-Beloy *et al.,* 2020; PET NODO Lab, 2024).

3.9. Changes in Somatosensory System Plasticity after NPM Application - FYD 2020

Ultrasound-guided percutaneous neuromodulation is defined as electrical stimulation, using an ultrasound-guided needle, of a peripheral nerve at some point along its path or of a muscle at a motor point for therapeutic purposes. It is a safe and non-invasive procedure that is generally used with TENS current. Neuromodulation is a technique that physiotherapists use to intervene in the functioning of the nervous system, both peripheral and central. The treatment should be administered tangentially under ultrasound guidance, as it is effective and improves and prepares the neuromuscular system (Figure 17) (Toledo, 2016; Casal-Beloy *et al.,* 2020; NODO Lab, 2024).

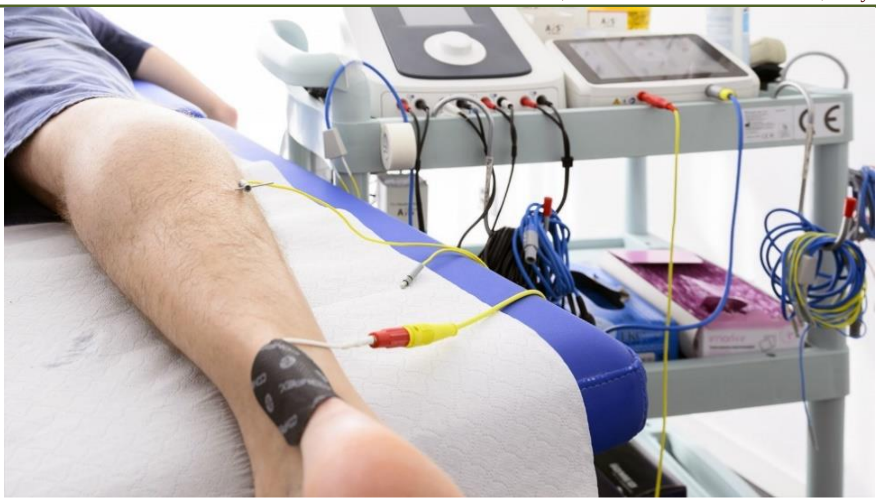

Figure 17: Ultrasound-guided percutaneous neuromodulation

Sources: © 2025 ASFI. Designed By JoomShaper - Webmaster Reality Design and https://www.fisioinvasiva.ch/index.php/en/techniques/invasive-techniques/ultrasound-guided-percutaneous-neuromodulation-nmp-e-r

3.9.1. Pathologies that can be treated with NMP:

1. Frequent injuries in the clinic.
2. Achilles tendinopathy.
3. Plantar fasciitis.
4. Tibial periostitis.
5. Metatarsalgia.

3.9.2. Application effects:

1. Mechanical afference.
2. Motor awareness.
3. Pattern changes.

3.9.3. It has no side effects:

1. Pharmacological neuromodulation.
2. Transcutaneous Spinal Cord Stimulation (tSCS).
3. Botulinum toxin.
4. Vagus Nerve Stimulation (VNS).
5. Endogenous neuromodulation (Toledo, 2016; Casal-Beloy *et al.*, 2020; NODO Lab, 2024).

3.10. Neuromodulation has been shown to have a significant impact on neurorehabilitation outcomes

Numerous scientific studies have supported the effectiveness of these techniques in improving physical function, reducing symptoms, and significantly improving patients' quality of life. (Toledo, 2016; Casal-Beloy *et al.*, 2020; PET CENNODO Lab, 2024). Neuroscience Centre (CEN+) continues to innovate in neurorehabilitation with CEN+, its new specialized service that incorporates neuromodulation techniques. The European Neuroscience Centre (CEN), a pioneer in the field of intensive neurorehabilitation in Spain, now includes innovative new techniques by inaugurating the European (CEN+), which specializes in neuromodulation therapies (Toledo, 2016; CEN, 2024).

Neurorehabilitation focuses on the recovery and rehabilitation of brain and spinal cord functions in people who have suffered injuries to the CNS. It encompasses a wide range of therapies and techniques, one of the most revolutionary and promising being neuromodulation, to treat various conditions, including neurological and psychiatric disorders (Toledo, 2016; CEN, 2024).

"Through this innovative technique, our patients will have a wider variety of options to obtain rehabilitation appropriate to their personal needs and achieve their goals more efficiently," [José López Sánchez, Co-Founder and Technical Director of the European Neuroscience Centre] (Lebedev and Nicolelis, 2006; Toledo, 2016; CEN, 2024).

At CEN+, various cutting-edge neuromodulation techniques are implemented to maximize neurorehabilitation outcomes. These methods include pharmacological neuromodulation, botulinum toxin, VNS, electrical stimulation (spinal, peripheral nerve, and transcranial direct current), transcranial magnetic stimulation, and endogenous neuromodulation, among others (Raven *et al.*, 2018; Stee and Peigneux, CEN, 2024).

As can be seen, physical exercise, exposure to an enriched environment, diet or our quality of rest, act through complex modifications of microglial cells, which alter their phenotype and functional activity, thus translating lifestyle events into the remodeling of cerebral homeostasis balance and the remodeling of neuronal networks, ultimately improving neuroprotection and cognitive longevity (Raven *et al.*, 2018; Stee and Peigneux, 2021).

3.11. Brain diseases have long been a challenge for medicine due to the complexity of the nervous system Innovations such as neuroscience:

1. Neurotechnology and Brain-Computer Interfaces (BCIs).
2. Psychedelics in the treatment of mental illness.
3. Neuroplasticity and brain training.
4. Artificial intelligence and neuroscience data analysis.
5. Neuroethics and social implications.
6. Biomarkers and personalized medicine.
7. The future of human cognition: "Neuroenhancement".
8. Artificial intelligence applied to neurological diagnostics.
9. Gene therapy for neurodegenerative diseases: This involves modifying defective genes in diseases such as Alzheimer's and Huntington's.
10. Implants that send electrical impulses to the brain to treat Parkinson's disease, epilepsy, and drug-resistant depression.
11. Algorithms capable of detecting early signs of Alzheimer's and Parkinson's.
12. Stem cell research has shown advances in the regeneration of damaged neurons.
13. Use of drugs to stimulate neuroplasticity and aid in the recovery of brain injuries.
14. Applications for patients with paralysis, allowing them to control robotic prostheses with their minds.
15. More advanced neural implants allow the restoration of speech and mobility in patients with paralysis.
16. Greater integration between neuroscience and virtual reality for neurological rehabilitation.
17. Personalized therapies based on genetic analysis and neuroimaging.
18. The development of smart drugs that act precisely on the brain without side effects (Arora and Baldi, 2024; Sur Noticias, 2025).

3.12. Expected Outcomes

1. Longer life expectancy and improved quality of life for patients with neurological diseases.
2. Improved accuracy of early diagnoses, enabling more effective interventions.
3. New therapies that could replace invasive treatments or those with serious side effects.
4. Increased independence for patients with disabilities through advanced neural interfaces (Arora and Baldi, 2024; Sur Noticias, 2025).

4. CONCLUSION

The technological revolution is creating unprecedented opportunities and challenges in the fields of medicine and healthcare. Continuous technological advances are transforming the structure, organization, and workflow, and this is particularly notable in specialties such as neurophysiology, whose clinical practice is heavily reliant on technology. In this medical discipline, devices that record or produce electrical or magnetic activity are used to functionally explore the nervous system for diagnostic, prognostic, and therapeutic purposes. These techniques are key to the practice of a wide range of specialties. Today, neurorehabilitation works closely with research in neuroscience, biomechanics, and other fields that comprise the study of human behavior, all in pursuit of more targeted and effective treatments.

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