Talking to the brain – An introduction to non-invasive brain stimulation techniques
Conversando com o cérebro – Uma introdução a técnicas de estimulação cerebral não invasivas

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Abstract
Over time, various types of stimuli, such as visual, auditory, chemical, and physical, have been used to investigate neurological responses to decipher the mechanisms of brain function. Non-invasive brain stimulation techniques have been gaining popularity, both for their therapeutic potential for neurological disorders and as tools to enhance our understanding of the human brain. This review article aims to introduce three modalities of non-invasive brain stimulation: transcranial magnetic stimulation, transcranial electrical stimulation, and low-intensity focused ultrasound. Methods commonly used for recording and analyzing brain responses provoked by these techniques are also discussed throughout the text. By exploring magnetic fields, electrical currents, and ultrasonic waves, these stimulation methods offer new perspectives for intervening in brain functions, standing out as tools with great potential for both scientific advances and clinical applications in brain manipulation.

1. Introduction
Knowledge of how the brain works represents one of science’s greatest challenges, triggering both practical and philosophical questions, from understanding basic processes to even issues such as the possibility of a brain knowing itself. There are great advances in this aspect, but there is still a lot to know about one of the most complex organs in the human body. Thinking of the brain as a plausible physical system of investigation, like a “black box”, scientists have been studying this system and, through responses, seek to understand how it operates. The classic method has been to apply a stimulus, which can be visual1, auditory2, olfactory3, electrical4, magnetic5, mechanical6, pharmacological7, and observe the responses from the body itself through the brain accessed by instruments or the subject’s behavior. In this case, the measuring instrument and the object of study are the same.

According to current knowledge, the fundamental structure of the brain is the neuron. The study of this fundamental entity, which would be the analog of the hydrogen atom for quantum mechanics or the silicon atom for solid-state physics, has allowed enormous advances. In addition to neurons, the brain comprises so-called glial cells. Their occurrence in the brain is estimated to be as much as three times greater than the neurons. Classically, the basic functions of glial cells are considered to be support, nutrition and repair of nervous tissue. In recent studies, they have been considered important “partners” of neurons in noble functional tasks8. Chemical and physical agents can stimulate neurons, resulting in an electrical impulse propagating along the axon, which works like an
electrical cable connecting several neurons. Chemical agents, or drugs, that can alter neurotransmission are used to treat various diseases and manipulate some brain states and generally act at the contact between neurons or synapses. With this, electrical impulses can be modulated, and the entire functioning of the brain can be changed. Another possibility is to intervene directly in the electrical currents. It can be done by introducing devices directly into the brain through surgical procedures to map certain regions, the well-known technique called deep brain stimulation. On the other hand, to stimulate the brain externally, the electrical current must overcome biological resistive barriers, such as the skin, the skull, and the dura mater.

The electroshock technique, modernly known as electroconvulsive therapy, presents several drawbacks, but it’s part of a search for non-invasive physical methods to directly stimulate neurons, or more precisely, a set of them, and observe the responses without the subject’s intervention. With this approach, it is possible to answer questions related to the outermost layer of the brain, which is, therefore, closest to the cortex, the neocortex. The neocortex is a thin layer of nerve cells that covers the brain and is highly folded, with gyri and sulci, to fit into the space available in the skull. From an evolutionary point of view, the neocortex is the most recent part of the human brain. From a functional point of view, it is believed that the neocortex is also the most crucial part of the brain, being associated with practically all the “noble” functions, such as sensory and motor processing, memory, planning, and reasoning, among others.

Therefore, stimulating neurons in the neocortex requires a change in the electrical balance, or resting potential of the cells, which can be done by chemical/pharmacological methods and physical methods such as electrical, magnetic and, more recently, optical and ultrasound stimuli. This review will address in more detail three relatively recent physical methods that have great scientific and clinical potential regarding brain stimulation:

- Transcranial magnetic stimulation (TMS): induction of electrical currents in the brain through the use of rapid, high-intensity magnetic pulses, resulting in evoked neuronal responses;
- Transcranial electrical stimulation (TES): application of low-intensity currents (up to 2 mA) through the cortex from surface electrodes to modulate brain activity;
- Low-intensity transcranial focused ultrasound (LIFU): stimulate the brain via ultrasonic waves in constructive or destructive combinations, producing a focused stimulus in the desired brain region.

2. Transcranial magnetic stimulation

TMS uses pulses of magnetic fields that penetrate the skull and the brain. An electrical current of 2,000 to 8,000 amperes in approximately 100 microseconds is generated, producing a short-lived magnetic field that induces an electrical field and a current in the cerebral cortex. The equipment used in this process is a coil coupled to a capacitor bank, initially charged, which discharges when generating pulses. Depending on the configuration of these coils, the magnetic field, and consequently, the electric field, have different geometries. Figure-8 coils, widely used in TMS applications, present an electric field peak below the junction point between both windings.

The biological principle associated with TMS is the change in cell membrane potential, arising from the difference in concentration of positive ions in the extracellular environment and negative ions in the intracellular environment. The electric field induced by the magnetic stimulus triggers the membrane depolarization process, which returns to the resting potential within tens of microseconds. This change in polarity, in turn, induces currents capable of triggering action potentials, which can function in an excitatory or inhibitory manner.

When applied to the primary motor cortex, TMS generates an action potential that propagates through the corticospinal tract, reaching the target muscle corresponding to the brain region, resulting in involuntary contractions of muscle fibers. Such evoked muscle electrical activity is called motor evoked potential (MEP) and can be recorded with electromyography devices. The information most commonly extracted from the MEP is its amplitude and latency. The amplitude represents the signal intensity and, therefore, characterizes the excitability of the corticospinal system. In turn, latency is the time interval between applying the TMS pulse and the MEP onset, being associated with the neural conduction speed. These two characteristics are important because they contain information about cortical structures, the integrity of the corticospinal tract, and the recruited muscle fibers. For that reason, the electrode placement protocol should be carefully considered.

Figure 1 shows the configuration of a TMS motor experiment, emphasizing the observed MEP parameters. These experiments have important applications in evaluating the decrease or increase in MEP amplitude, which can be a proxy of inhibition or excitation of the cortical activity in different TMS protocols. TMS motor applications are also widely used in assessing preoperative motor maps, the influence of drugs on cortical excitability, cortical representations of muscle groups and cortical and corticospinal excitability and plasticity.
necessary to evoke a consistent MEP with minimal amplitude in the designated muscle\textsuperscript{13}.

![Figure 1 - Schematic of a motor mapping experiment using TMS, highlighting the MEP response.]

Major depressive disorder, a well-established TMS application approved by regulatory bodies in various countries, including Brazil, is usually associated with hypoactivity in the left dorsolateral prefrontal cortex (DLPFC) and hyperactive right DLPFC. In these cases, stimulation of either the right DLPFC with low frequency, the left DLPFC with high frequency, or both is typical\textsuperscript{25}. High frequency on the left DLPFC increases cerebral blood flow, while the mechanism of low-frequency rTMS on the right DLPFC remains unclear. Thus, the right prefrontal cortex inhibition and/or excitation of the left potentially correct the interhemispheric imbalance associated with depression\textsuperscript{26}. Furthermore, TMS has clinical applications for treating other neuropsychiatric disorders such as obsessive-compulsive disorder, schizophrenia, bipolar disorder\textsuperscript{27} and neurodegenerative diseases such as Alzheimer’s and Parkinson’s\textsuperscript{28}.

Due to the variability and lack of precise assessment of the induced current’s reach in the brain, it is challenging to determine which cortical neurons and how much cortical area is affected by each TMS pulse. Some tools, such as the induced electric field simulation, can potentially improve cortical targeting\textsuperscript{28}. Another limitation of TMS comes from the physical nature of the stimuli. Considering the head as a conductive sphere, the induced current is restricted to the surface, which means that TMS targets are cortical, and not able to affect deeper brain regions directly. The depth depends on the characteristics of the coil and the intensity of the pulses. Figure-8 coils can reach 2.5 cm below the skull with an intensity of 150% rTMS, while the H-coils have been reported to effectively activate brain regions at depths greater than 6 cm\textsuperscript{30}. However, a relationship exists between depth and focality\textsuperscript{31}, meaning avoiding cortical stimulation by targeting subcortical regions is impossible. Some studies use this principle to study brain connectivity\textsuperscript{32}. However, these indirect effects complicate the determination of which brain areas are actually linked to certain functions or behaviors\textsuperscript{33}. Another delicate aspect of TMS is the positioning of the stimulation coil over the brain structures, which is fundamental to the technique\textsuperscript{34}. Neuronavigation systems guided by magnetic resonance imaging (MRI) are a relevant tool for defining targets in the brain with greater spatial precision and better knowledge of the areas stimulated by TMS\textsuperscript{35}. Usually, the anatomical T1 images are used as a reference for navigation, however, other techniques such as functional (fMRI) and diffusion MRI are used both to determine the stimulation site\textsuperscript{36} and to evaluate the effects of TMS\textsuperscript{37}.

Another important advance for more precise control of TMS is new coil conformations capable of controlling the stimulation site without the need to move the coil. The technique is called multi-locus TMS, also called mTMS\textsuperscript{38} and is based on different coil geometries combined, allowing the location of the pulses to be changed on the microsecond scale\textsuperscript{38} by electronic adjustments made to each of the coil layers\textsuperscript{40}. Another major improvement in the automated use of TMS can be achieved by using collaborative robotic arms to precisely position the stimulation coil over target structures in the brain. Thus, any displacements made by the patient during a session are quickly corrected automatically, minimizing the dependence of the technique on the operator, and resulting in greater standardization between sessions\textsuperscript{41}, especially combining it with the mTMS\textsuperscript{42}.

### 3. Transcranial electrical stimulation

Transcranial electrical stimulation (tES) involves applying a low-intensity electrical current to the scalp that can generate changes in brain excitability. tES includes the modalities of transcranial direct current stimulation (tDCS), alternating current stimulation (tACS) and random noise stimulation (tRNS)\textsuperscript{43}. Despite the differences in the temporal behavior of the currents, as shown in Figure 2, they are typically generated in the same way: through two or more electrodes of opposite polarities placed on the scalp. The distribution of the currents depends on the intended therapeutic application and follows the usual electrode positioning system 10–20\textsuperscript{44}. Although the procedures of the three tES techniques are very similar, their mechanisms and effects differ and will be discussed below.

Standard tDCS protocols are typically based on applying direct currents of up to 2 mA for tens of minutes. The short-term effects of tDCS are classified according to the polarity of the electrodes. The anodic effects, which occur in the region where the anode is placed (adopted by convention in tDCS as the positive pole), lead to excitation of the site through an increase in the rate of neuronal activations due to the decrease in the excitability threshold caused by the
depolarization of the membrane potentials. In regions below the cathode (negative pole), they suffer inhibition due to the hyperpolarization of the site and an increase in the excitability threshold\(^45\).

**Figure 2** – An example of the positioning of the electrodes in tES and the current pattern used in each modality: transcranial direct current, transcranial alternating current and transcranial random noise stimulation.

These results were confirmed based on the perception of a decrease in MEP amplitudes with cathodal IDCS and an increase with anodal IDCS\(^46\). Despite this, particularities depend on the subtype of neuron involved, as cases described in the literature of interneuron inhibition due to the combination of low anodic and cathodic currents\(^47\). The electrode positioning can be guided with structural and/or fMRI\(^48\). The targets depend on the region associated with the task or function of interest. Similar to the TMS application for major depressive disorder described above, applying anodal current in the left DLPFC is a way to increase its activity and cathodal current on the right to balance the hemispheres\(^48\).

Concerning the long-lasting effects of IDCS, even with results regarding the recovery and improvement of motor functions and post-stroke aphasia\(^49\), the exact mechanisms are still not completely understood. It is known that these effects are related to changes in neuronal excitability associated with modifications in synaptic connections\(^50\). These post-session effects depend on both the duration of the pulse application and the magnitude of the applied current. They can last hours after the end of the current application and occur even after a single session\(^51\). Typically, durations range from 5 to 30 minutes, with intensities between 1 and 2 mA\(^52\), replicating analogous protocols targeting the same brain region as the proposed experiment. However, the nonlinear relationship between duration and intensity of current with the post-session effects warrants further investigation\(^52,53\).

For tACS applications, fixed frequency sine waves are used, with a large range varying from 0.1 Hz to 200 kHz according to the application purpose\(^54\). A study by Moliadze\(^55\) showed the dependence of the effects of tACS on the intensity of the current used. A 140 Hz current was applied to the primary motor cortex during the experiment, and a single TMS pulse was applied to the same site. In low current intensity ranges, around 0.2 mA, a decrease in the amplitude of MEP was observed with an increase in the rMT, while at higher intensities, around 1 mA, the effect was the opposite. No threshold changes were observed for intensities of 0.6 to 0.8 mA.

Another aspect of tACS is its ability to modulate brain oscillatory activity. Because different frequencies of brain oscillations are associated with cognitive functions, tACS has been aimed at modulating these oscillations based on the applied frequency\(^56\). Observations also suggest that these responses to tACS stimuli depend on the brain state in which the stimuli were applied\(^45\). This type of effect allows the application of tACS to study cognitive functions such as memory, attention and decision-making\(^56\).

Remarkable similarities are observed between tACS and tRNS, with the most significant difference being that in tRNS, no specific frequency is applied but rather a range of frequencies and amplitudes that change randomly during the procedure. The frequency range is divided between low (0.1 Hz to 100 Hz) and high (101 Hz to 640 Hz). Compared to tACS, tRNS showed greater excitability of the motor cortex\(^43\). Other studies have shown how low and high frequency tRNS applications can decrease or increase the duration of motion aftereffects, where prolonged exposure to a moving stimulus leads to an illusion of motion even after the stimuli, showing its influence on visual perception\(^57\). Other studies with tRNS focus on its ability to enhance learning tasks and cognitive processes, such as attention and memory, showing a performance improvement, mainly when it’s applied online, i.e. during the task\(^58\).

As discussed, tES techniques are widely used for neuropsychiatric disorders, but there are other applications, such as aphasia\(^59\), epilepsy\(^60\), chronic pain\(^61\) (migraine, fibromyalgia) and motor rehabilitation\(^52\). Compared to TMS, the advantages of tES include lower cost, greater portability, pharmacological compatibility, and greater ease in producing long-lasting modulatory responses of cortical functions\(^53\). Furthermore, a challenge of the technique is determining the focus of the targets, given the difficulty of modeling the path of the applied currents. Factors such as age, gender, and head composition of the electrode positioning region, such as skin, skull and hair thickness, and technical application parameters such as current amplitude, frequency, and phase influence the results obtained\(^43\).
4. Transcranial low-intensity focal ultrasound

Ultrasonic waves are mechanical waves that produce vibrations in the molecules of the incident medium with a frequency composition above the audible sounds by humans. When interacting with matter, waves can be absorbed, reflected, transmitted, or scattered. Its diagnostic capacity has been explored since the 20th century, but in recent decades, the possibilities of therapeutic applications have been studied, emphasizing brain applications. The technique is transcranial focused ultrasound and can be divided into two categories: high intensity (HIFU) and low intensity (LIFU). In diagnostic ultrasound applications, the intensity is below 0.1 W/cm², while HIFU uses values above 100 W/cm², and LIFU varies in the range of 0.125 to 3 W/cm².

A transducer is used to generate ultrasonic waves. It consists of a single or multiple piezoelectric elements. These crystals dilate in response to electrical stimuli and generate electrical responses to vibrations, which means they can convert electrical energy, that is, electrical signals, into mechanical energy, sound waves, and vice versa. It is possible to obtain constructive and destructive interference from the emitted waves, focusing the point of maximum energy on a single point in the brain, as illustrated in Figure 3.

Figure 3 – Representation of a LIFU application scheme.

High-intensity focal ultrasound causes rapid heating of the region of interest, reaching approximately 60 °C, triggering a tissue ablation process, resulting in localized irreversible lesions. This type of treatment has a greater focus on applications involving tumors of the kidney, liver, uterus, breast, pancreas, bone and prostate. However, there are applications for brain conditions, such as neurosurgery to treat essential tremors and Parkinson's disease.

Because of the biological effects discussed above, HIFU is not used as a brain stimulation technique. However, if applied at low intensities, focal ultrasound allows modulation of the permeability of cell membranes and thus interacts with the functioning of the brain, proving, in recent years, to be a promising technique for neuromodulation. In this case, unlike HIFU, the nature of LIFU effects is non-thermal. It is known that cavitation does not occur at the intensities used in LIFU, and hypotheses suggest that modulation occurs through changes in the permeability of neuronal membranes through pressure-sensitive ion channels and sodium, calcium, and potassium channels. Furthermore, there is the possibility that ultrasonic waves affect the tension of the membrane with the plasma or the structure of the lipid bilayer, altering neuronal activity.

LIFU has already been demonstrated to be a technique capable of facilitating or inhibiting MEP activations, altering parameters of EEG signals, such as wave frequency and phase, in addition to having already observed an increase in blood flow in the region of stimulus application through MRI. One advantage that LIFU has over other stimulation techniques discussed throughout the text is its compatibility with MRI. Although possible, integrating MRI with tES and TMS brings artifacts and experimental difficulties. The application of LIFU locally varies the blood-brain barrier, whose properties are related to the pathology and progression of different neurological diseases. This has been used for therapeutic applications, such as enhancing brain drug delivery. Additionally, when combined with MRI, especially fMRI, it has been proposed to functionally map the brain and help diagnose some neurological disorders through the evaluation of transient modulations of brain regions.

One characteristic that drives LIFU as a promising approach for neuromodulation is its stimulus range. While the exact depth of the stimulation in tES is practically immeasurable due to current modulation difficulties and TMS has a limited range in the order of 2.5 cm below the surface of the head, without the use of H coils, LIFU can stimulate depths greater than 10–15 cm, opening up a range of possibilities for reachable brain regions. Furthermore, it presents higher spatial resolution than other techniques discussed in this review due to the focusing of the pulses.

LIFU still lacks established dose–response curves for desired neurophysiological effects, with a vast number of parameters including fundamental frequency, pulse repetition frequency, duty cycle, sonication duration, and intensity, necessitating systematic examination of parameter alterations. Besides that, the relationship between the effects of LIFU administration and brain state during sonication remains unclear. Furthermore, variable skull anatomy among individuals poses an important issue in LIFU research, affecting ultrasound conduction and delivery. While LIFU has often been applied over the temporal bone to mitigate skull effects, the impact of skull variability on focal ultrasound delivery remains unknown.
uncertain, prompting the development of modeling approaches to address individual skull characteristics.62

5. Measuring brain responses to applied stimuli

Physical sciences have contributed significantly to developing methods that allow recording the brain’s functioning from different aspects, such as when performing stimulation. Some examples of these techniques are electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and near-infrared diffuse optical tomography (NIR-DOT). Each of these modalities uses a different physical property to study the brain function. Multimodal approaches of combining two or more techniques allow more robust information and have gained attention.

Figure 4 – Techniques for detecting brain changes. The contrast mechanism of each method is: EEG: electrical currents spread through the volume; MEG: resulting magnetic signal from currents generated inside the neurons; fMRI: BOLD signal originated by the differences in oxy and deoxyhemoglobin; PET-FDG: detects both photons generated after electron-positron annihilation related to radiopharmaceutical metabolism; NIRS: infrared light emitted penetrate and spread through tissues and oxyhemoglobin concentration is assessed by optical spectroscopy.

Like EEG, MEG is widely used to study brain functionality and the location of areas of activation in specific tasks. Neuroradiological measurements are used to overcome the instrumental difficulties embedded in electrical EEG measurements, such as electrical attenuation of the signal in the presence of the skull and tissue layers above the signal source while still maintaining high temporal and spatial resolution. However, due to the magnitude of the biomagnetic signals, these measurements require strong magnetic shielding, making the technique more expensive. Innovative strategies have been presented for studying the human brain using MEG and low-field MRI systems. Combining anatomical and functional images in a single system allows localizing neuronal electrical activity with greater precision and accuracy. fMRI is a method capable of indirectly mapping brain electrical activity by measuring changes in oxygenation levels in certain regions. The evaluated effect is called blood oxygenation level-dependent (BOLD), based on the principle that deoxyhemoglobin and oxyhemoglobin activity, sweat, movement, or by the environment, such as the power grid (60Hz), poor electrode contact, broken electrodes, impairing its spatial resolution and making it difficult to identify the epileptogenic focus. To be seen on the scalp’s surface, the small EEG voltages generated by cortical neurons must pass through several biological barriers that reduce the signal’s amplitude and divert the currents from their sources. Action potential fields must pass through the brain, cerebrospinal fluid, meninges, skull, and skin, as well as structures of different electrical conductivity, before reaching the location where they can be detected. EEG can be combined with TMS, a technique known as TMS–EEG. TMS–EEG simultaneously provides recordings of TMS-evoked potentials and cortical oscillations and is a valuable tool for investigating brain state dependency on pulses. Processing EEG data is already challenging in itself and gets more complicated when combining both techniques, given the need to clean the signals obtained by the small contractions that can occur on the scalp due to the TMS pulses and the evoked auditory stimulus by the sound of pulse firing.

Magnetoencephalography (MEG) records the magnetic fields generated by ionic currents resulting from neuronal electrical activity. This electrical current along a bundle of neurons generates magnetic fields about hundreds of femto Tesla, a billion times weaker than the earth’s magnetic field. The detected signal can be the result of evoked responses, visual and auditory stimulation, for example, or spontaneous brain activity, which produces rhythmic oscillations in different frequency bands (alpha, theta, delta, etc.). MEG uses highly sensitive biomagnetic sensors, such as superconducting quantum interference devices (SQUIDs) or optical magnetometers operating in the spin exchange relaxation-free regime.

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have distinct magnetic characteristics, the first being paramagnetic and the second diamagnetic. It is known that local cerebral blood flow increases during neural activity, leading to an increase in the ratio between oxy and deoxyhemoglobin, which decreases the local magnetic susceptibility, increasing the local brightness of magnetic resonance images. fMRI makes it possible to evaluate brain activity at rest or while performing motor, visual, auditory, and cognitive tasks. Compared to EEG, fMRI has greater spatial resolution and allows the region of increased cerebral oxygenation to be identified more precisely. However, temporal resolution is limited to the hemodynamic response, and the BOLD contrast peak normally occurs around 5 seconds post-stimulus, reducing the temporal information acquired.

Positron emission tomography (PET) is an imaging modality that provides physiological information about the patient. The exam captures images of the organ’s activity after absorbing radioactive tracers (radiopharmaceuticals) into the bloodstream. These markers are linked to compounds metabolized by the organ of interest. The operating principle is to detect radiation and reconstruct the radiopharmaceutical distribution captured in the target region. PET imaging is a standard component in diagnosis and staging in oncology but is also used for cardiovascular and neurological indications. In the case of the brain, its primary fuel is glucose, so PET is performed after the insertion of a glucose-based radiopharmaceutical, usually fluorodeoxyglucose (FDG). Active brain areas will utilize glucose faster than inactive areas, highlighting which brain regions are recruited in a given task. PET provides an in vivo functional image, so it is limited to effects that alter the metabolism of the region. To accurately identify the structures of physiological processes, it is necessary to combine PET imaging with another imaging modality, such as computed tomography or magnetic resonance. Unlike the other techniques mentioned above, PET imaging has an important radiation dose absorption, so it is necessary to justify its use. Because of that, it is normally used in diagnoses such as brain tumors, strokes, epilepsy and neurodegenerative disorders.

Finally, near-infrared spectroscopy (NIRS) investigates the absorption and scattering properties of light in biological tissues. Diffuse optical tomography (DOT) is a tomographic imaging modality carried out through the different behaviors of a beam of light as it passes through the human body. The infrared optical tomography (NIR-DOT) technique was created by combining an infrared light beam with diffuse optical tomography. This technique is used to investigate the oxygenation level of hemoglobin. For example, when a specific brain area is activated, the blood volume in that area changes rapidly. Optical imaging can measure the location and activity of specific brain regions, continuously monitoring blood hemoglobin levels by determining the optical absorption coefficients of infrared light.

However, the spatial resolution of this technique is limited when compared to other imaging modalities, such as magnetic resonance imaging (MRI) or X-ray computed tomography. fNIRS has limited clinical use due to the lack of anatomical precision, low temporal resolution, and limitations in the consistency of individual results since characteristics such as ambient light, hair type, and skull thickness affect the measurements. Furthermore, its spatial resolution is lower than that of fMRI due to its dependence on the number of detectors and the dispersion of light between the emitter and the detector. Strategies such as anatomical co-registration with another imaging modality, such as MRI, the precise positioning of detectors in relation to individuals, and new signal processing techniques can improve the results obtained by this technique.

### 6. Final considerations

In short, the non-invasive brain stimulation techniques discussed throughout this review offer advances in understanding and modulating brain responses, in addition to their strong therapeutic potential. While TMS and tES are well-established techniques, having already demonstrated their effectiveness in various clinical applications and experimental conditions, LIFU emerges as a promising technique, although still in early stages of development, being able to contribute with new possibilities such as deep target range and high focusing of stimulation targets. Each technique has its particularities, and therefore, they are not exclusive. Something they all have in common is the potential for developing new tools to improve the stimulation and new protocols for other conditions.

The measurement of brain responses to these techniques has evolved, relying on advanced methods such as fMRI, EEG, MEG, and optical techniques, such as NIRS, to help observe and analyze the neurophysiological changes associated with these interventions. These complementary technologies and approaches offer exciting prospects for future advances in understanding and treating neurological and psychiatric conditions.

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