Artigo Original

Revista Brasileira de Física Médica (2024)18:762

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

Thais C. Marchetti[1], Renan H. Matsuda[1,2], Victor H. Souza[2], Antonio C. Roque[3], Oswaldo Baffa[1]

[1]*Laboratório de Biomagnetismo, Departamento de Física da Faculdade de Filosofia Ciências e Letras da Universidade de São Paulo, Ribeirão Preto, Brasil*

[2]*Department of Neuroscience and Biomedical Engineering, Aalto University School of Science (AALTO), Espoo, Finland*

[3]*Laboratório de Sistemas Neurais, Departamento de Física da Faculdade de Filosofia Ciências e Letras da Universidade de São Paulo, Ribeirão Preto, Brasil*

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.

Keywords: Non-invasive brain stimulation; transcranial magnetic stimulation; transcranial electrical stimulation; low-intensity focused ultrasound.

Resumo

Ao longo do tempo, diferentes estímulos, tais como visual, sonoro, químico, físico, entre outros, foram empregados para investigar as respostas neurológicas, com o objetivo de decifrar os mecanismos subjacentes ao funcionamento cerebral. As técnicas de estimulação cerebral não invasivas vêm ganhando espaço tanto no aspecto de estratégias terapêuticas para distúrbios neuronais como ferramenta para aumentar a nossa compreensão acerca do cérebro humano. O intuito deste artigo de revisão é fornecer uma introdução à compreensão de três modalidades, sendo elas a estimulação magnética transcraniana, a estimulação elétrica transcraniana e o ultrassom focalizado de baixa intensidade. Esses métodos, ao explorar campos magnéticos, correntes elétricas e ondas ultrassônicas, oferecem novas perspectivas para a compreensão e intervenção nas funções cerebrais, destacando-se como potenciais ferramentas tanto para avanços científicos quanto para aplicações clínicas na manipulação cerebral, principalmente com o desenvolvimento de novas tecnologias. Ao longo do texto, também são abordados os métodos de registro das respostas cerebrais provocadas por essas técnicas.

Palavras-chave: *Estimulação cerebral não invasiva; estimulação magnética transcraniana; estimulação elétrica transcraniana; ultrassom focalizado de baixa intensidade.*

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 stimulating this system and, through responses, seek to understand how it operates. The classic method has been to apply a stimulus, which can be visual[1], auditory[2], olfactory[3], electrical[4], magnetic[5], mechanical[6], pharmacological[7], 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 tasks[8]. 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[9]. 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[10]. 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[11]. 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[12].

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[13].

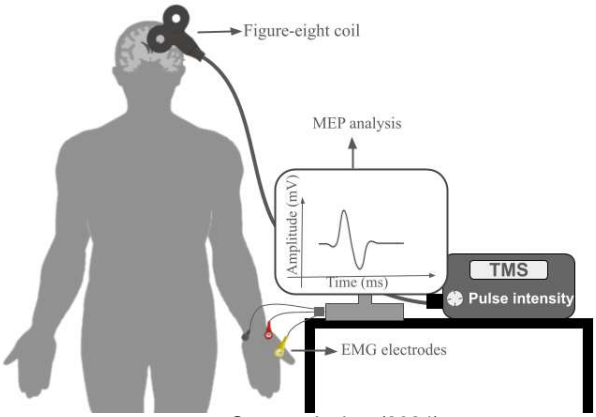
The biological principle associated with TMS is the change in cell membrane potential, arising from the difference in concentration of positive ions in the extracellular environment and negative ions in the intracellular environment. The electric field induced by the magnetic stimulus triggers the membrane depolarization process, which returns to the resting potential within tens of microseconds[14,15]. This change in polarity, in turn, induces currents capable of triggering action potentials, which can function in an excitatory or inhibitory manner[16].

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[17]. 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[13]. 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[18,19]. 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[20]. TMS motor applications are also widely used in assessing preoperative motor maps[21], the influence of drugs on cortical excitability[22], cortical representations of muscle groups[23] and cortical and corticospinal excitability and plasticity[24].

The therapeutic modality of TMS is repetitive TMS (rTMS), and the protocol's parameters, such as frequency, target localization and pulse intensity, vary with the intention of treatment. In these clinical applications, the intensity of the pulses is unique for each individual, since it is given as a percentage of the resting motor threshold (rMT), defined as the minimum intensity of motor cortex stimulation

necessary to evoke a consistent MEP with minimal amplitude in the designated muscle[13].

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



Source: Author (2024).

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[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[26]. Furthermore, TMS has clinical applications for treating other neuropsychiatric disorders such as obsessive-compulsive disorder, schizophrenia, bipolar disorder[27] and neurodegenerative diseases such as Alzheimer's and Parkinson's[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[29]. 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% rTM, while the H-coils have been reported to effectively activate brain regions at depths greater than 6 cm[30]. However, a relationship exists between depth and focality[31], meaning avoiding cortical stimulation by targeting subcortical regions is impossible. Some studies use this principle to study brain connectivity[32]. However, these indirect effects complicate the determination of which brain areas are actually linked to certain functions or behaviors[33].

Another delicate aspect of TMS is the positioning of the stimulation coil over the brain structures, which is fundamental to the technique[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[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[32] and to evaluate the effects of TMS[36,37].

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[38] and is based on different coil geometries combined, allowing the location of the pulses to be changed on the microsecond scale[39] by electronic adjustments made to each of the coil layers[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[41], specially combining it with the mTMS[42].

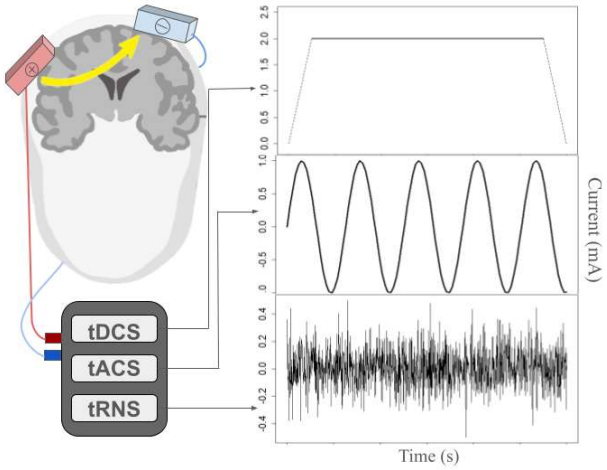
3. Transcranial electrical stimulation

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)[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[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.



Source: Author (2024).

These results were confirmed based on the perception of a decrease in MEP amplitudes with cathodal tDCS and an increase with anodal tDCS[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 tDCS, 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[43]. 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].

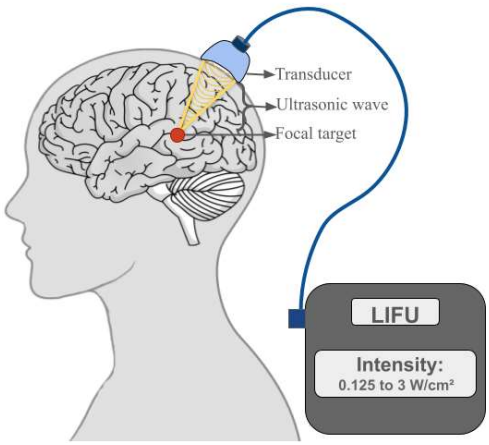
As discussed, tES techniques are widely used for neuropsychiatric disorders, but there are other applications, such as aphasia[59], epilepsy[60], chronic pain[61] (migraine, fibromyalgia) and motor rehabilitation[62]. Compared to TMS, the advantages of tES include lower cost, greater portability, pharmacological compatibility, and greater ease in producing long-lasting modulatory responses of cortical functions[63]. 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[64], 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 [65].

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[66], 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[65], as illustrated in Figure 3.

Figure 3 – Representation of a LIFU application scheme.



Source: Author (2024).

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[67]. This type of treatment has a greater focus on applications involving tumors of the kidney, liver, uterus, breast, pancreas, bone and prostate[68]. However, there are applications for brain conditions, such as neurosurgery to treat essential tremors[69] and Parkinson's disease[70].

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[71], 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[72]. 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[72].

LIFU has already been demonstrated to be a technique capable of facilitating or inhibiting MEP activations[73], altering parameters of EEG signals[74], such as wave frequency and phase, in addition to having already observed an increase in blood flow in the region of stimulus application through fMRI[73]. One advantage that LIFU has over the 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[75,76], whose properties are related to the pathology and progression of different neurological diseases[77]. This has been used for therapeutic applications, such as enhancing brain drug delivery[76]. Additionally, when combined with MRI, especially fMRI, it has been proposed to functionally map the brain[78] and help diagnose some neurological disorders[79] through the evaluation of transient modulations of brain regions[78,80].

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[71], 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[71].

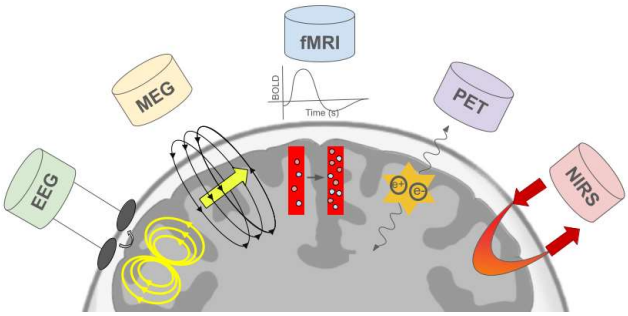
LIFU still lacks established dose–response curves for desired neurophysiological effects, with a vast number of parameters including fundamental frequency, pulse repetition frequency, duty cycle, sonication duration, and intensity, necessitating systematic examination of parameter alterations[72]. Besides 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[81] to mitigate skull effects, the impact of skull variability on focal ultrasound delivery remains

uncertain, prompting the development of modeling approaches to address individual skull characteristics[72].

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.



Source: Author (2024). Adapted from (Min, 2020)[82].

EEG is an electrophysiological technique for recording the electrical activity of the human brain. Given its temporal sensitivity, the main use of EEG is the assessment of the dynamic functioning of the brain[83]. The electrical activity is acquired by multiple electrodes positioned on the patient's scalp. The detected activities result from the depolarization groups of cerebral cortical neurons close to the scalp, where the acquisition electrodes are positioned. The intensity of the measured electrical activity has an order of magnitude of microvolts. EEG uses the principle of differential amplification, using a pair of electrodes that compares an active scanning electrode site with a neighboring reference electrode[84].

Despite the high temporal resolution, allowing, for example, identification of the onset of epileptic seizures, the main limitation of EEG is that brain activity can be overloaded by other electrical activities generated by the body such as heart pulse, muscular activity, sweat, movement, or by the environment, such as the power grid (60Hz), poor electrode contact, broken electrodes, impairing its spatial resolution[84] 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[85]. TMS–EEG simultaneously provides recordings of TMS-evoked potentials and cortical oscillations[86] and is a valuable tool for investigating brain state dependency on pulses[87]. 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[88].

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[89], 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 (SERF)[89].

Like EEG, MEG is widely used to study brain functionality and the location of areas of activation in specific tasks. Neuromagnetic 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[90]. 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

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[91]. 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[92].

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[93] and neurological[94-96] 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)[97]. 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[98]. 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[98].

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[99].

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[100]. 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[100]. 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.

Acknowledgments

The authors acknowledge financial support from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for financing the Scientific Initiation scholarship (2022/15500-8), to the Center for Research, Innovation and Diffusion in Neuromathematics (CEPID NeuroMat process 2013/07699-0), the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and the Research Council of Finland (Decision No. 349985).

References

1. Lutzenberger W, Pulvermüller F, Elbert T, Birbaumer N. Visual stimulation alters local 40-Hz responses in humans: an EEG-study. Neurosci Lett. 1995 Jan 2;183(1):39–42.
2. Luke R, Larson E, Shader MJ, Innes-Brown H, Van Yper L, Lee AKC, et al. Analysis methods for measuring passive auditory fNIRS responses generated by a block-design paradigm. Neurophotonics. 2021 Apr;8(2):025008.
3. Sobel N, Prabhakaran V, Desmond JE, Glover GH, Sullivan EV, Gabrieli JDE. A method for functional magnetic resonance imaging of olfaction. J Neurosci Methods. 1997 Dec 30;78(1):115–23.
4. Garcia-Cossio E, Witkowski M, Robinson SE, Cohen LG, Birbaumer N, Soekadar SR. Simultaneous transcranial direct current stimulation (tDCS) and whole-head magnetoencephalography (MEG): assessing the impact of tDCS on slow cortical magnetic fields. NeuroImage. 2016 Oct 15;140:33–40.
5. Siebner HR, Hartwigsen G, Kassuba T, Rothwell J. How does transcranial magnetic stimulation modify neuronal activity in the brain? - Implications for studies of cognition. Cortex J Devoted Study Nerv Syst Behav. 2009 Oct;45(9):1035–42.
6. Kasuba KC, Buccino AP, Bartram J, Gaub BM, Fauser FJ, Ronchi S, et al. Mechanical stimulation and electrophysiological monitoring at subcellular resolution reveals differential mechanosensation of neurons within networks. Nat Nanotechnol. 2024 Feb 20;1–9.
7. Ziemann U, Lönnecker S, Steinhoff BJ, Paulus W. The effect of lorazepam on the motor cortical excitability in man. Exp Brain Res. 1996 Apr 1;109(1):127–35.
8. Jessen KR. Glial cells. Int J Biochem Cell Biol. 2004 Oct 1;36(10):1861–7.
9. Kandel ER, Koester J, Mack S, Siegelbaum S, editors. Principles of neural science. Sixth edition. New York: McGraw Hill; 2021. 1646 p.
10. Perlmutter JS, Mink JW. Deep Brain Stimulation. Annu Rev Neurosci. 2006;29(1):229–57.
11. Singh A, Kar SK. How Electroconvulsive Therapy Works?: Understanding the Neurobiological Mechanisms. Clin Psychopharmacol Neurosci. 2017 Aug;15(3):210–21.
12. Rakic P. Evolution of the neocortex: a perspective from developmental biology. Nat Rev Neurosci. 2009 Oct;10(10):724–35.
13. Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol Off J Int Fed Clin Neurophysiol. 2015 Jun;126(6):1071–107.
14. Matsuda RH, Tardelli GP, Guimarães CO, Souza VH, Filho OB. Estimulação magnética transcraniana: uma breve revisão dos princípios e aplicações. Rev Bras Física Médica. 2019 Sep 1;13(1):49–56.
15. Ruohonen J. Basic Physics and Design of Transcranial Magnetic Stimulation Devices and Coils. In: Magnetic Stimulation in Clinical Neurophysiology. 2005. p. 17–30.
16. Di Lazzaro V, Rothwell JC. Corticospinal activity evoked and modulated by non-invasive stimulation of the intact human motor cortex. J Physiol. 2014 Oct 1;592(Pt 19):4115–28.
17. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet Lond Engl. 1985 May 11;1(8437):1106–7.
18. Garcia MAC, Souza VH, Lindolfo-Almas J, Matsuda RH, Nogueira-Campos AA. Motor potential evoked by transcranial magnetic stimulation depends on the placement protocol of recording electrodes: a pilot study. Biomed Phys Eng Express. 2020 Jun 12;6(4):047003.
19. Garcia MAC, Souza VH, Vargas CD. Can the Recording of Motor Potentials Evoked by Transcranial Magnetic Stimulation Be Optimized? Front Hum Neurosci [Internet]. 2017 Aug 15 [cited 2024 Mar 11];11. Available from: https://www.frontiersin.org/articles/10.3389/fnhum.2017.00413
20. Sondergaard RE, Martino D, Kiss ZHT, Condliffe EG. TMS Motor Mapping Methodology and Reliability: A Structured Review. Front Neurosci [Internet]. 2021 Aug 19 [cited 2024 Mar 11];15. Available from: https://www.frontiersin.org/journals/neuroscience/articles/10.3389/fnins.2021.709368/full
21. Raffa G, Scibilia A, Conti A, Ricciardo G, Rizzo V, Morelli A, et al. The role of navigated transcranial magnetic stimulation for surgery of motor-eloquent brain tumors: a systematic review and meta-analysis. Clin Neurol Neurosurg. 2019 May 1;180:7–17.
22. Paulus W, Classen J, Cohen LG, Large CH, Di Lazzaro V, Nitsche M, et al. State of the art: Pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. Brain Stimulat. 2008 Jul 1;1(3):151–63.
23. Tardelli GP, Souza VH, Matsuda RH, Garcia MAC, Novikov PA, Nazarova MA, et al. Forearm and Hand Muscles Exhibit High Coactivation and Overlapping of Cortical Motor Representations. Brain Topogr. 2022;35(3):322–36.
24. Ziemann U, Paulus W, Nitsche MA, Pascual-Leone A, Byblow WD, Berardelli A, et al. Consensus: Motor cortex plasticity protocols. Brain Stimulat. 2008 Jul 1;1(3):164–82.
25. Gross M, Nakamura L, Pascual-Leone A, Fregni F. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. Acta Psychiatr Scand. 2007;116(3):165–73.
26. Klein E, Kreinin I, Chistyakov A, Koren D, Mecz L, Marmur S, et al. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. Arch Gen Psychiatry. 1999 Apr;56(4):315–20.
27. Luber B, McClintock SM, Lisanby SH. Applications of transcranial magnetic stimulation and magnetic seizure therapy in the study and treatment of disorders related to cerebral aging. Dialogues Clin Neurosci. 2013 Mar;15(1):87–98.
28. Rawji V, Latorre A, Sharma N, Rothwell JC, Rocchi L. On the Use of TMS to Investigate the Pathophysiology of Neurodegenerative Diseases. Front Neurol. 2020 Nov 3;11:584664.
29. Daneshzand M, Makarov SN, de Lara LIN, Guerin B, McNab J, Rosen BR, et al. Rapid computation of TMS-induced E-fields using a dipole-based magnetic stimulation profile approach. NeuroImage. 2021 Aug 15;237:118097.
30. Roth Y, Amir A, Levkovitz Y, Zangen A. Three-Dimensional Distribution of the Electric Field Induced in the Brain by Transcranial Magnetic Stimulation Using Figure-8 and Deep H-Coils. J Clin Neurophysiol. 2007 Feb;24(1):31.
31. Deng ZD, Lisanby SH, Peterchev AV. Electric field depth–focality tradeoff in transcranial magnetic stimulation: simulation comparison of 50 coil designs. Brain Stimulat. 2013 Jan;6(1):1–13.
32. Luber B, Davis SW, Deng ZD, Murphy D, Martella A, Peterchev AV, et al. Using diffusion tensor imaging to effectively target TMS to deep brain structures. NeuroImage. 2022 Apr 1;249:118863.
33. Bolognini N, Ro T. Transcranial Magnetic Stimulation: Disrupting Neural Activity to Alter and Assess Brain Function. J Neurosci. 2010 Jul 21;30(29):9647–50.
34. Conforto AB, Z'Graggen WJ, Kohl AS, Rösler KM, Kaelin-Lang A. Impact of coil position and

electrophysiological monitoring on determination of motor thresholds to transcranial magnetic stimulation. Clin Neurophysiol Off J Int Fed Clin Neurophysiol. 2004 Apr;115(4):812–9.
35. Souza VH, Matsuda RH, Peres ASC, Amorim PHJ, Moraes TF, Silva JVL, et al. Development and characterization of the InVesalius Navigator software for navigated transcranial magnetic stimulation. J Neurosci Methods. 2018 Nov 1;309:109–20.
36. Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. Eur J Neurosci. 2004 Apr;19(7):1950–62.
37. Hawco C, Voineskos AN, Steeves JKE, Dickie EW, Viviano JD, Downar J, et al. Spread of activity following TMS is related to intrinsic resting connectivity to the salience network: A concurrent TMS-fMRI study. Cortex J Devoted Study Nerv Syst Behav. 2018 Nov;108:160–72.
38. Koponen LM, Nieminen JO, Ilmoniemi RJ. Multi-locus transcranial magnetic stimulation—theory and implementation. Brain Stimulat. 2018 Jul 1;11(4):849–55.
39. Souza VH, Nieminen JO, Tugin S, Koponen LM, Baffa O, Ilmoniemi RJ. TMS with fast and accurate electronic control: Measuring the orientation sensitivity of corticomotor pathways. Brain Stimul Basic Transl Clin Res Neuromodulation. 2022 Mar 1;15(2):306–15.
40. Nieminen JO, Sinisalo H, Souza VH, Malmi M, Yuryev M, Tervo AE, et al. Multi-locus transcranial magnetic stimulation system for electronically targeted brain stimulation. Brain Stimulat. 2022 Jan 1;15(1):116–24.
41. Matsuda R, Souza VH, Marchetti T, Araki V, Caurin G, Machado H, et al. An open-source platform for robotized transcranial magnetic stimulation. Brain Stimulat. 2021 Nov 1;14:1659.
42. Matsuda RenanH, Souza VH, Marchetti TC, Soto AM, Kahilakoski OP, Zhdanov A, et al. Robotic–electronic platform for autonomous and accurate transcranial magnetic stimulation targeting. Brain Stimulat [Internet]. 2024 Apr 4 [cited 2024 Apr 9]; Available from: https://www.sciencedirect.com/science/article/pii/S1935861X24000585.
43. Reed T, Cohen Kadosh R. Transcranial electrical stimulation (tES) mechanisms and its effects on cortical excitability and connectivity. J Inherit Metab Dis. 2018;41(6):1123–30.
44. Zhao H, Qiao L, Fan D, Zhang S, Turel O, Li Y, et al. Modulation of Brain Activity with Noninvasive Transcranial Direct Current Stimulation (tDCS): Clinical Applications and Safety Concerns. Front Psychol. 2017;8:685.
45. Arul-Anandam AP, Loo C. Transcranial direct current stimulation: a new tool for the treatment of depression? J Affect Disord. 2009 Oct;117(3):137–45.
46. Paulus W. Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods. Neuropsychol Rehabil. 2011 Oct;21(5):602–17.
47. Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport. 1998 Jul 13;9(10):2257–60.
48. Sreeraj VS, Arumugham SS, Venkatasubramanian G. Clinical Practice Guidelines for the Use of Transcranial Direct Current Stimulation in Psychiatry. Indian J Psychiatry. 2023 Feb;65(2):289–96.
49. Vestito L, Rosellini S, Mantero M, Bandini F. Long-term effects of transcranial direct-current stimulation in chronic post-stroke aphasia: a pilot study. Front Hum Neurosci. 2014;8:785.
50. Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol. 2003 Nov 15;553(Pt 1):293–301.
51. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000 Sep 15;527(Pt 3):633–9.
52. Thair H, Holloway AL, Newport R, Smith AD. Transcranial Direct Current Stimulation (tDCS): A Beginner's Guide for Design and Implementation. Front Neurosci. 2017 Nov 22;11:641.
53. Elsner B, Kugler J, Pohl M, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving activities of daily living, and physical and cognitive functioning, in people after stroke. Cochrane Database Syst Rev [Internet]. 2020 [cited 2024 Mar 22];(11). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD009645.pub4/full
54. Antal A, Paulus W. Transcranial alternating current stimulation (tACS). Front Hum Neurosci [Internet]. 2013 Jun 28 [cited 2024 Mar 8];7. Available from: https://www.frontiersin.org/articles/10.3389/fnhum.2013.00317.
55. Moliadze V, Atalay D, Antal A, Paulus W. Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. Brain Stimulat. 2012 Oct;5(4):505–11.
56. Herrmann CS, Rach S, Neuling T, Strüber D. Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes. Front Hum Neurosci [Internet]. 2013 Jun 14 [cited 2024 Mar 8];7. Available from: https://www.frontiersin.org/articles/10.3389/fnhum.2013.00279
57. Campana G, Camilleri R, Moret B, Ghin F, Pavan A. Opposite effects of high- and low-frequency transcranial random noise stimulation probed with visual motion adaptation. Sci Rep. 2016 Dec 9;6(1):38919.
58. van der Groen O, Potok W, Wenderoth N, Edwards G, Mattingley JB, Edwards D. Using noise for the better: The effects of transcranial random noise stimulation on the brain and behavior. Neurosci Biobehav Rev. 2022 Jul 1;138:104702.
59. Elsner B, Kugler J, Mehrholz J. Transcranial direct current stimulation (tDCS) for improving aphasia after stroke: a systematic review with network meta-analysis of randomized controlled trials. J NeuroEngineering Rehabil. 2020 Jul 8;17(1):88.
60. Sudbrack-Oliveira P, Barbosa MZ, Thome-Souza S, Razza LB, Gallucci-Neto J, da Costa Lane Valiengo L, et al. Transcranial direct current stimulation (tDCS) in the management of epilepsy: A systematic review. Seizure. 2021 Mar;86:85–95.
61. Pinto CB, Costa BT, Duarte D, Fregni F. Transcranial Direct Current Stimulation as a Therapeutic Tool for Chronic Pain. J ECT. 2018 Sep;34(3):e36–50.
62. Elsner B, Kugler J, Mehrholz J. Transcranial direct current stimulation (tDCS) for upper limb rehabilitation after stroke: future directions. J NeuroEngineering Rehabil. 2018 Nov 15;15(1):106.
63. Fregni F, Boggio PS, Nitsche MA, Marcolin MA, Rigonatti SP, Pascual-Leone A. Treatment of major depression with transcranial direct current stimulation. Bipolar Disord. 2006 Apr;8(2):203–4.
64. Jensen JA. Medical ultrasound imaging. Prog Biophys Mol Biol. 2007 Jan 1;93(1):153–65.
65. Elhelf IAS, Albahar H, Shah U, Oto A, Cressman E, Almekkawy M. High intensity focused ultrasound: The fundamentals, clinical applications and research trends. Diagn Interv Imaging. 2018 Jun;99(6):349–59.
66. Zhou Q, Lam KH, Zheng H, Qiu W, Shung KK. Piezoelectric single crystals for ultrasonic transducers in biomedical applications. Prog Mater Sci. 2014 Oct 1;66:87–111.

67. Ter Haar GR. High Intensity Focused Ultrasound for the Treatment of Tumors. Echocardiography. 2001;18(4):317–22.
68. Haar GT, Coussios C. High intensity focused ultrasound: physical principles and devices. Int J Hyperth Off J Eur Soc Hyperthermic Oncol North Am Hyperth Group. 2007 Mar;23(2):89–104.
69. Elias WJ, Lipsman N, Ondo WG, Ghanouni P, Kim YG, Lee W, et al. A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. N Engl J Med. 2016 Aug 25;375(8):730–9.
70. Bauer R, Martin E, Haegele-Link S, Kaegi G, von Specht M, Werner B. Noninvasive functional neurosurgery using transcranial MR imaging-guided focused ultrasound. Parkinsonism Relat Disord. 2014 Jan;20 Suppl 1:S197-199.
71. Rezayat E, Toostani IG. A Review on Brain Stimulation Using Low Intensity Focused Ultrasound. Basic Clin Neurosci. 2016 Jul;7(3):187–94.
72. Arulpragasam AR, van 't Wout-Frank M, Barredo J, Faucher CR, Greenberg BD, Philip NS. Low Intensity Focused Ultrasound for Non-invasive and Reversible Deep Brain Neuromodulation-A Paradigm Shift in Psychiatric Research. Front Psychiatry. 2022;13:825802.
73. Legon W, Bansal P, Tyshynsky R, Ai L, Mueller JK. Transcranial focused ultrasound neuromodulation of the human primary motor cortex. Sci Rep. 2018 Jul 3;8(1):10007.
74. Mueller J, Legon W, Opitz A, Sato TF, Tyler WJ. Transcranial Focused Ultrasound Modulates Intrinsic and Evoked EEG Dynamics. Brain Stimulat. 2014 Nov 1;7(6):900–8.
75. Burgess A, Nhan T, Moffatt C, Klibanov AL, Hynynen K. Analysis of focused ultrasound-induced blood–brain barrier permeability in a mouse model of Alzheimer's disease using two-photon microscopy. J Controlled Release. 2014 Oct 28;192:243–8.
76. Conti A, Kamimura HAS, Novell A, Duggento A, Toschi N. Magnetic Resonance Methods for Focused Ultrasound-Induced Blood-Brain Barrier Opening. Front Phys [Internet]. 2020 Sep 30 [cited 2024 Mar 25];8. Available from: https://www.frontiersin.org/articles/10.3389/fphy.2020.547674.
77. Daneman R, Prat A. The Blood–Brain Barrier. Cold Spring Harb Perspect Biol. 2015 Jan 1;7(1):a020412.
78. Yoo SS, Bystritsky A, Lee JH, Zhang Y, Fischer K, Min BK, et al. Focused ultrasound modulates region-specific brain activity. NeuroImage. 2011 Jun 1;56(3):1267–75.
79. Baek H, Pahk KJ, Kim H. A review of low-intensity focused ultrasound for neuromodulation. Biomed Eng Lett. 2017 Jan 9;7(2):135–42.
80. Meng Y, MacIntosh BJ, Shirzadi Z, Kiss A, Bethune A, Heyn C, et al. Resting state functional connectivity changes after MR-guided focused ultrasound mediated blood-brain barrier opening in patients with Alzheimer's disease. NeuroImage. 2019 Oct 15;200:275–80.
81. Legon W, Ai L, Bansal P, Mueller JK. Neuromodulation with single-element transcranial focused ultrasound in human thalamus. Hum Brain Mapp. 2018;39(5):1995–2006.
82. Min BK, Hämäläinen MS, Pantazis D. New Cognitive Neurotechnology Facilitates Studies of Cortical–Subcortical Interactions. Trends Biotechnol. 2020 Sep 1;38(9):952–62.
83. Light GA, Williams LE, Minow F, Sprock J, Rissling A, Sharp R, et al. Electroencephalography (EEG) and Event-Related Potentials (ERP's) with Human Participants. Curr Protoc Neurosci Editor Board Jacqueline N Crawley Al. 2010 Jul;CHAPTER:Unit-6.2524.
84. Michel CM, Brunet D. EEG Source Imaging: A Practical Review of the Analysis Steps. Front Neurol. 2019;10:325.
85. Ilmoniemi RJ, Virtanen J, Ruohonen J, Karhu J, Aronen HJ, Näätänen R, et al. Neuronal responses to magnetic stimulation reveal cortical reactivity and connectivity. NeuroReport. 1997 Nov 10;8(16):3537.
86. Cao KX, Ma ML, Wang CZ, Iqbal J, Si JJ, Xue YX, et al. TMS-EEG: An emerging tool to study the neurophysiologic biomarkers of psychiatric disorders. Neuropharmacology. 2021 Oct 1;197:108574.
87. Tremblay S, Rogasch NC, Premoli I, Blumberger DM, Casarotto S, Chen R, et al. Clinical utility and prospective of TMS–EEG. Clin Neurophysiol. 2019 May 1;130(5):802–44.
88. Rogasch NC, Biabani M, Mutanen TP. Designing and comparing cleaning pipelines for TMS-EEG data: A theoretical overview and practical example. J Neurosci Methods. 2022 Apr 1;371:109494.
89. Singh SP. Magnetoencephalography: Basic principles. Ann Indian Acad Neurol. 2014 Mar;17(Suppl 1):S107–12.
90. Vesanen PT, Nieminen JO, Zevenhoven KCJ, Dabek J, Parkkonen LT, Zhdanov AV, et al. Hybrid ultra-low-field MRI and magnetoencephalography system based on a commercial whole-head neuromagnetometer. Magn Reson Med. 2013 Jun;69(6):1795–804.
91. Gore JC. Principles and practice of functional MRI of the human brain. J Clin Invest. 2003 Jul 1;112(1):4–9.
92. Glover GH. Overview of functional magnetic resonance imaging. Neurosurg Clin N Am. 2011 Apr;22(2):133–9, vii.
93. Nayfeh M, Ahmed AI, Saad JM, Alahdab F, Al-Mallah M. The Role of Cardiac PET in Diagnosis and Prognosis of Ischemic Heart Disease: Optimal Modality Across Different Patient Populations. Curr Atheroscler Rep. 2023 May 10;1–7.
94. Foster NL, Heidebrink JL, Clark CM, Jagust WJ, Arnold SE, Barbas NR, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. Brain J Neurol. 2007 Oct;130(Pt 10):2616–35.
95. Rinne JO. Positron emission tomography in the differential diagnosis of parkinsonism. J Mov Disord. 2009 Oct;2(2):53–7.
96. Kreisl WC, Kim MJ, Coughlin JM, Henter ID, Owen DR, Innis RB. PET imaging of neuroinflammation in neurological disorders. Lancet Neurol. 2020 Nov;19(11):940–50.
97. Davis KM, Ryan JL, Aaron VD, Sims JB. PET and SPECT Imaging of the Brain: History, Technical Considerations, Applications, and Radiotracers. Semin Ultrasound CT MRI. 2020 Dec 1;41(6):521–9.
98. Tai YF, Piccini P. Applications of positron emission tomography (PET) in neurology. J Neurol Neurosurg Psychiatry. 2004 May;75(5):669–76.
99. Lima A, Bakker J. Espectroscopia no infravermelho próximo para a monitorização da perfusão tecidual. Rev Bras Ter Intensiva. 2011;341–51.
100. Chen WL, Wagner J, Heugel N, Sugar J, Lee YW, Conant L, et al. Functional Near-Infrared Spectroscopy and Its Clinical Application in the Field of Neuroscience: Advances and Future Directions. Front Neurosci. 2020;14:724.

Contact:

Thais Cunha Marchetti
Universidade de São Paulo
Rua Prof. Aymar Batista Prado, S/N - Campus da USP - Vila Monte Alegre, Ribeirão Preto - SP, 14040-900
thaismarchetti@usp.br