



## Brain Imaging and neurostimulation in health and disorders: status report

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**ABSTRACT | INTRODUCTION:** Despite being considered least important for clinical practice in the pyramid of evidence for recommendations, sometimes scientists' expert opinions could help to better understand the summarization of updated publications. **OBJECTIVE:** To provide a major summarized update about brain imaging and stimulation of the nervous system in health and disease. **METHODS:** Comprehensive review developed by experts in each subarea of knowledge in neuroimaging and non-invasive stimulation of the nervous system. A team of researchers and clinic experts was invited to present an update on their area of expertise. **RESULTS:** In basics on brain imaging techniques, we approach general and quantitative electroencephalography, functional magnetic resonance imaging, functional near-infrared spectroscopy, and experimental paradigms in brain imaging studies. Were included associations between transcranial magnetic stimulation and electromyography, electroencephalography, and functional near-infrared stimulation to evaluate brain activity. Furthermore, we showed several actualized central and peripheral neuromodulation techniques. And finally, we presented different clinical and performance uses of non-invasive neuromodulation. **CONCLUSION:** To our knowledge, this is a major summarized and concentrated update about brain imaging and stimulation that can benefit neuroscience researchers and clinicians from different levels of experience.

**KEYWORDS:** Neuromodulation. Brain Stimulation. Brain Image. Neuroimage. Neuroscience.

## 1. Introduction

Basic science, clinical research, technological development and health policies in non-invasive stimulation of the nervous system have grown considerably in recent decades across countries.<sup>1-4</sup> The theoretical basis to support clinical application comes from brain imaging in different health and disease conditions.<sup>5-8</sup>

Brain imaging comprises several techniques to understand the neurobiological substrates and circuits enrolling different neurostructures and has helped to search for a specific brain signature for psychiatric, musculoskeletal, metabolic, neurologic, and other diseases.<sup>9,10</sup> Recently, meta and mega-analyses of brain imaging studies, and the use of computational modeling, have deciphered some consistent changes in the brain of people with different motor, cognitive and behavioral disorders<sup>1</sup>, and offer support for the theoretical rationale to propose interventions as non-invasive neuromodulation. Also, brain imaging techniques have increasingly been used as the basis for the so-called intelligent, individualized, and/or closed-loop neuromodulation, probably the future of the field.<sup>11-13</sup>

On the other hand, security, efficacy, and effectiveness for the clinical use of non-invasive stimulation of the nervous system require up-to-date scientific evidence from randomized clinical trials, meta-analyses and umbrella reviews.<sup>14-16</sup> With the accelerated science development in the area of brain imaging and stimulation it is increasingly difficult to keep up to date in various sectors of contemporary science. Despite being considered least important for clinical practice in the pyramid of evidence for recommendations, sometimes scientists' expert opinions can help to better understand the summarization of updated publications<sup>17,18</sup>, which can benefit researchers and clinicians from different levels of experience. The content of this article may provide knowledge of how brain imaging techniques support a deeper understanding of brain structure and/or dynamics in health and disease, and also to identify targets for non-invasive stimulation of the nervous system. Hence, the aim of this study is to provide a major summarized update about brain imaging and stimulation of the nervous system in health and disease.

## 2. Methods

This is a comprehensive review developed by experts in each subarea of knowledge in neuroimaging and non-invasive stimulation of the nervous system. The criteria to choose experts were to have a significant scientific production (minimum of 5 articles) in their subareas and be inserted in a research institution or in an editorial team of a journal in brain imaging or neurostimulation. A team of researchers and clinic experts was invited to present an update on their area of expertise. All contributions were organized into a single document that is separated into different parts, approaching the basics of brain imaging and non-invasive neuromodulation techniques.

## 3. Results

### 3.1. Basics on brain imaging techniques

#### 3.1.1. Electroencephalography (EEG)

In neuroscience, human brain activity is one of the main sources of information that can be used both in clinical and research environments. In this context, electroencephalography (EEG) is a brain imaging technique widely used to understand and assess the dynamics of human brain activity during resting or task brain states, the latter can be done in different approaches (i.e, cognitive, motor, sensorial stimulus, and others).<sup>19</sup> The EEG signal is a graphic representation of the potential difference between two different cerebral locations plotted in the time scale of milliseconds.<sup>20</sup>

The source of the EEG signal arises from the synchronized synaptic activity of pooled cortical neurons, mainly near the scalp electrodes.<sup>21</sup> The electrical postsynaptic synchronous activity from thalamocortical and corticocortical connections are spread by volume conduction that crosses dura, and skull layers, and scalp until reaching the EEG electrodes. These signals are interpreted in terms of frequency bands, which have specific classifications, such as delta (0.5Hz - 4Hz), theta (4Hz - 8Hz), alpha (8Hz - 12Hz), beta (13Hz - 30Hz), and gamma (above 30Hz).<sup>22</sup>

EEG signals can be used to investigate the presence of altered brain activity as a biomarker of pathologic conditions, such as the increase in the power density of theta band in chronic neuropathic pain<sup>23</sup>, the reduction of the alpha and beta power density, as well as the increase in the theta and delta power density in Alzheimer disease (AD)<sup>20</sup> and the increase in the beta power density in Parkinson disease (PD).<sup>21</sup> EEG broad temporal resolution makes it the gold standard for the evaluation of electrical brain activity with high temporal resolution. This technique may also be relevant to guide and understand the effects of the neuromodulatory techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation/transcranial alternating current stimulation/transcranial random noise stimulation (tDCS/tACS/tRNS).<sup>21,24,25</sup>

#### 3.1.2. Quantitative Electroencephalography (qEEG)

Data obtained by EEG has also been used in the analysis of brain connectivity.<sup>21,26</sup> In these studies, EEG electrodes are considered the nodes of the network, while the edges represent the connection between the nodes. Brain connectivity can be classified as functional or effective. Functional connectivity captures the statistical dependence between dispersed node rhythms and, sometimes distant, computing their correlations, in the time or frequency domain.<sup>21,26,27</sup> Effective connection describes how rhythms recorded at one node affect rhythms at another distant node, reflecting a causal interaction between two cortical generators.<sup>28</sup>

In this way, the study of brain connectivity helps to understand how the healthy human brain works in the resting state and through cognitive and/or motor tasks. The resting network is known as the default mode network and includes the medial and lateral parietal, medial prefrontal, and medial and lateral temporal cortices.<sup>16</sup> Knowledge of the healthy functioning of the brain allows identifying changes in brain connectivity in various disease conditions, such as migraine, and sickle cell disease.<sup>29-31</sup> A representative example of the potential of qEEG in the assessment of disease is the evaluation of brain activity in AD, which is the most common neurodegenerative disease among the elderly, with a progressive decline in cognitive function, significantly affecting quality of life. New international research criteria allow the diagnosis of AD in vivo, based on the identification of cerebral amyloidosis and tauopathy, using analysis of cerebrospinal fluid (CSF) and positron emission tomography (PET).<sup>32</sup> Lewy bodies are abnormal aggregations (or clumps) of the alpha-synuclein protein in neurons. When they develop in the cerebral cortex, it can result in dementia, known as dementia with Lewy bodies (DLB).

In comparison with image and CSF analysis techniques, resting-state EEG (rsEEG) is non-invasive, affordable, easy to implement, has high repeatability and is well tolerated by patients, in addition to being widely used worldwide.<sup>33</sup> rsEEG can be used to measure the timing of neural activity in cortical and subcortical neural networks<sup>34</sup>, offering the unique potential to identify subtle disease-related abnormalities in upward

oscillatory systems that regulate brain excitation and vigilance in AD and in DLB.<sup>34,35</sup> However, it should be noted that rsEEG markers do not directly measure the neurodegenerative processes that occur in AD and DLB. Thus, although it is not recommended to use rsEEG markers to provide a conclusive diagnosis of AD or DLB, rsEEG may be useful for early case differentiation and for stratifying and selecting patients for more invasive, time-consuming, and expensive investigations such as CSF and PET.

Previous rsEEG studies have shown that, compared to healthy elderly (HE), patients with AD dementia have a lower interrelation of alpha (8-12 Hz) and beta (13-20 Hz) rhythms between sensors in the occipital<sup>34-36</sup>, temporoparietal<sup>34-37</sup>, frontal and central<sup>38</sup> regions of the scalp. When compared to HE, DLB patients exhibit a greater global interrelationship of EEG activity between sensors for delta rhythms, but a lower global interrelationship for alpha rhythms.<sup>39</sup> Likewise, compared with AD, DLB patients showed greater overall interrelationship between sensor pairs in the temporal, frontal, and central regions for delta and theta rhythms, while the interrelationship ratio for beta rhythms was lower in DLB compared AD in the occipital, temporal and between pairs of centroparietal electrodes.<sup>40</sup>

These EEG markers have been used to discriminate between AD and DLB and also to differentiate them HE. Bonanni et al. reported a classification accuracy of 80-84% when comparing AD vs. DLB using rsEEG spectral measurements<sup>41</sup> and our own research group at UFABC, in collaboration with Prof. Claudio Babiloni from Sapienza University of Rome, achieved an accuracy of 94.8% in the classification between ADD, DLB and HE.<sup>42</sup>

### **3.1.3. Functional Magnetic Resonance Imaging (fMRI)**

Functional magnetic resonance imaging (fMRI) is a non-invasive and safe imaging technique that uses magnetic fields and radio waves to detect which areas of the brain are activated while a person performs different tasks or is at rest. It was first introduced in the early 1990s. Since then, fMRI has become a widely used method in neuroscience research to study brain

function and to investigate the neural basis of various cognitive and behavioral processes, such as memory or motor control. It is a powerful method to monitor the effects of interventions such as drug treatments or behavioral therapies, and can also be used clinically to help diagnose, monitor neurological disorders and plan neurosurgeries.<sup>43</sup>

fMRI measures changes in blood oxygen level-dependent (BOLD) signals, which refers to physiological modifications in blood flow and oxygenation that occur in response to increased neural activity. When neurons in the brain are activated, they increase metabolic activity. As a result, blood flow to the activated area also increases to supply the extra energy needed. fMRI measures the ratio of oxygenated to deoxygenated hemoglobin in the blood. The increased blood flow brings more oxygenated hemoglobin to the area, which affects its magnetic properties. This, in turn, alters the magnetic resonance signal detected by the fMRI scanner.<sup>44</sup>

By examining the BOLD response in different brain regions during specific tasks or conditions, researchers can gain insight into how the brain processes information and how different areas of the brain interact with each other. Besides the applications during external stimulation or tasks, fMRI can also scan brain activity at rest. Even when someone rests quietly the brain is still highly active, and the patterns of activity in this resting state are thought to reveal particular networks of areas that often act together. Resting-state fMRI can therefore be used to identify functional networks in the brain and investigate how they are disrupted in different neurological and psychiatric disorders, for example.<sup>43,45</sup>

fMRI has revolutionized our understanding of the human brain, but it is important to note that it also has some limitations that need to be considered when interpreting results. For instance, it is an indirect measure and there can be confounding factors, such as changes in blood pressure, that affect blood flow in the absence of changes in neural activity. Furthermore, as fMRI is a noise signal there is the need for rigorous statistical analyses before interpreting the results.<sup>46</sup>

### 3.1.4. Functional Near-Infrared Spectroscopy (fNIRS)

Functional Near-infrared Spectroscopy (fNIRS) is a non-invasive neuroimaging technique that measures changes in the concentration of oxy and deoxyhemoglobin in the brain. In fNIRS, light emitters and detectors in the near-infrared spectrum (between 650 and 1000 nm) are placed on the participant's scalp using a cap or headband.<sup>47</sup> Because human tissue is partially translucent to infrared light<sup>48</sup>, it is possible to penetrate the outermost cortical gyri and quantify its absorption. The extinction coefficient curves of oxy and deoxyhemoglobin molecules in the blood differ in the infrared spectrum, making it possible to estimate the concentration of both using the modified Beer-Lambert equation.<sup>49</sup>

The distance between emitters and detectors in fNIRS is usually about 3 cm. Too short a distance would only allow for a superficial measurement without reaching the cortex, and too long a distance would result in signal loss. Therefore, an optimized spatial grid that interleaves emitters and detectors (optodes) can cover many regions of interest in the brain.<sup>50</sup> By taking into account the neuro-hemodynamic coupling process and some assumptions, the estimated hemodynamic states, such as oxy and deoxyhemoglobin concentration, could be considered as an indirect measure of local neuronal activity<sup>48,50</sup>, similar to the BOLD signal in fMRI.

Compared to other neuroimaging techniques such as EEG and fMRI, fNIRS is less susceptible to motion artifacts and less restrictive in terms of environmental conditions (e.g., electrical interference).<sup>51</sup> This makes it a promising tool for experiments involving movements, children, and speech, enabling studies that more closely resemble real-life situations. Hyperscanning protocols that involve the interaction between subjects with simultaneous brain signal acquisition are also easier to implement using fNIRS.<sup>52</sup> However, fNIRS has some limitations, such as its low spatial resolution, inability to reach subcortical and deep brain structures, and sensitivity to systemic artifacts. For the latest research and applications in fNIRS, a review by Ayaz et al. (2022) provides an up-to-date in clinical conditions.<sup>53</sup>

### 3.1.5. Data science applied to brain imaging studies

The Brain Imaging field is facing a substantial renewal in the Big Data era. On one hand scientists have confronted new challenges in data curation for creating, organizing and maintaining a huge amount of information.<sup>54</sup> On the other hand the scientific community can benefit by collaborative data exchange, integration and interpretation, improving learning capabilities and leading to potential new findings, insights and diagnostics about the human brain.<sup>55,56</sup>

There is an increasing need for novel Brain Imaging methods in automating scalable data analysis within the FAIR paradigm (findability, accessibility, interoperability and reuse) and Data Science is the key pathway to address Big Data issues in global scientific research. Data Science is a convergent field that integrates expertise from Mathematics, Physics, Statistics and Computer Science areas. Although Data Science fundamentals are from the second half of the 20th century, it's gaining enormous importance and has been rapidly evolving in the last decade, together with the conceptual shift in brain structure and function characterization, considering the network-based rather than region-based approaches.<sup>54,57</sup>

One of the most remarkable approaches in the Data Science framework is the Machine Learning method for data mining. This algorithm allows meaningful feature extraction from raw data through a progressive "learning process" sensible to abstract patterns embedded in the data set. Brain Imaging applications lie in the intersection between Machine Learning and Radiomic fields, obtaining valuable information from medical imaging using Convolutional Neural Networks, a class of Deep Learning techniques which involves a complex architecture of "learning layers" capable of notable image classification and segmentation.<sup>58</sup>

Artificial Intelligence systems use the knowledge obtained from Machine Learning methods to perform tasks in real-world environments, emulating human decision making. In the Brain Imaging field, several clinical aspects can be improved with Artificial Intelligence support, such as image quality enhancement, salient feature highlighting, pathology detection and treatment response prediction.<sup>59,60</sup>

## 3.2. Transcranial magnetic stimulation techniques to evaluate brain activity

### 3.2.1. Transcranial Magnetic Stimulation and Electromyography (TMS-EMG)

TMS is a safe, non-invasive method to investigate brain function and mechanisms in awake humans. The combination of TMS with surface electromyography (TMS-sEMG) allows the evaluation of the motor system by measurement of cortical excitability.<sup>61</sup> The coil of TMS generates a magnetic field that penetrates the brain and induces an electric current, causing rapid depolarization of neurons and generating action potential that propagates along the motor pathways. Recordings of the phasic electrical circuit may be registered at a peripheral muscle targeted by the stimulated region.<sup>62,63</sup>

TMS approaches can be applied either as single-pulse or paired-pulse protocols. Single-pulse protocol enables cortical mapping of muscles and connections of motor pathways, nerve roots and peripheral nerves, while paired-pulse reveals the excitatory and inhibitory function of the brain, through intracortical facilitation and intracortical inhibition, respectively.<sup>64</sup>

The main method to evaluate cortical excitability is by single-pulse using the motor-evoked potential (MEP) (i.e., an indirect measure of corticomotoneuronal excitability) and the motor threshold (i.e., minimal intensity stimulation needed to induce a MEP). Both measures are a consequence of this interaction between induced electrical current and neuronal excitation.<sup>65</sup> Changes in parameters such as MEP amplitude, motor threshold and cortical silent period in response to a single constant-intensity stimulus infer information regarding the density of corticomotor projections to the spinal cord.<sup>14,62</sup>

Paired-pulse TMS techniques have a conditioning stimulus delivered over the motor cortex followed by a test stimulus after a given interval (interstimulus interval, ISI), so two pulses. The mean amplitude of the resulting conditioned MEP is then compared against the mean amplitude of the MEP induced by a test stimulus to assess the excitatory or inhibitory effects of the conditioning stimulus on the test stimulus. Short-interval intracortical inhibition (SICI) is a measure of excitability of cortical GABA A energetic inhibitory interneurons. By convention, intensity of the TMS conditioning and test stimuli were kept constant

and the changes in averaged MEP amplitude were used as outcome measure. Typically, the intensities of the first and second pulses will be set to 80 and 110% of resting motor threshold (RMT).<sup>66</sup> The test MEP amplitude is reduced in inter-stimulus intervals (ISI) of between 1 and 5 ms. In contrast, test MEP amplitude is increased when the ISI is between 7 and 30 ms, indicating intracortical facilitation (ICF).<sup>14</sup>

Neurophysiological measures of MT, MEP, SICI, ICF are able to provide information on changes in the nervous system related to diseases.<sup>67,14</sup> Therefore, TMS-EMG is useful in diagnostic approaches and monitoring of therapeutic proposals. However, a major limitation of this conventional constant-stimulus technique is the large variability in MEP amplitude between trials.<sup>68-71</sup> A threshold-tracking TMS (TT-TMS) technique was developed to overcome this limitation.<sup>72</sup> In contrast to conventional methods, TT-TMS tracks the stimulus intensity required to produce a predetermined MEP amplitude (e.g., 0.2mV).<sup>72</sup> As such, SICI is reflected by an increase in the test stimulus intensity required to elicit the target MEP amplitude when compared to the unconditioned stimulus. The opposite, i.e., a decrease in test stimulus intensity when compared to the unconditioned stimulus, reflects ICF. TT-TMS has recently been reported to be more reliable than the conventional constant stimulus technique<sup>73-75</sup> and has been increasingly utilized to explore disease pathophysiology in clinical neurology including stroke<sup>76</sup>, amyotrophic lateral sclerosis (ALS)<sup>77</sup>, Alzheimer's disease (AD)<sup>78</sup> and multiple sclerosis.<sup>79</sup> In particular, TT-TMS has been demonstrated to have significant diagnostic utility in ALS patients.<sup>80</sup>

### 3.2.2. Transcranial Magnetic Stimulation and Electroencephalography (TMS-EEG)

Transcranial magnetic stimulation combined with electroencephalography (TMS-EEG) is one of the most powerful non-invasive techniques for imaging brain activity at high temporal resolution.<sup>81</sup> By recording the brain's response to a direct, focal and controlled cortical stimulation, TMS-EEG allows measuring the excitability of thalamocortical circuits underlying the stimulated area<sup>82</sup>, as well as the effective connectivity between different brain regions that are directly or indirectly connected to the target of stimulation.<sup>83</sup>

Over the last two decades, TMS-EEG has been used to investigate the neural mechanisms of several neurological and psychiatric conditions.<sup>84</sup>

Among its various clinical applications are studies of neurodegenerative diseases<sup>85,86</sup>, brain lesions<sup>87</sup>, epilepsy<sup>87,88</sup>, schizophrenia<sup>89</sup> and depression.<sup>90</sup> TMS-EEG can also be employed to investigate the neural correlates of consciousness<sup>91</sup> and to extract perturbational complexity metrics<sup>92,93</sup>, which have been recently highlighted by clinical guidelines as promising tools for improving the diagnosis of disorders of consciousness.<sup>94</sup>

Despite the potential applications of TMS-EEG in research and clinical studies, its use in the clinical environment is still hindered by high costs, technical challenges and lack of standardization. The correct application of TMS-EEG depends on several experimental and technical procedures, which include the use of neuronavigation systems<sup>95</sup>, TMS-compatible EEG amplifiers and real-time response monitoring systems<sup>95,96</sup>, as well as the crucial control of stimulus-related EEG artifacts, both during the execution of the experiments<sup>97</sup> and in offline stages of processing.<sup>97,98</sup>

Anticipated advances in the standardization of experimental protocols and analysis procedures through multicentric validations<sup>99,100</sup>, should result in a better assessment of the clinical reliability of TMS-EEG and eventually pave the way for its use in clinical practice.

### **3.2.3. Transcranial Magnetic Stimulation and functional Near-Infrared Stimulation (TMS-fNIRS)**

The integration of TMS with fNIRS enables researchers to directly study brain metabolism and connectivity.<sup>101</sup> Pulses fired from TMS evoke changes in oxygenation, volume and blood flow of cortical tissue exposed to infrared light from fNIRS, hence fNIRS could measure the immediate effects of TMS in different areas of the brain. The first use of TMS-fNIRS was reported by Oliveira et al.<sup>102</sup> that repetitive TMS induces metabolic activation of the cerebral cortex together with an increase in cerebral blood flow detected by fNIRS. The quantitative and qualitative evaluation of these changes allows understanding the mechanisms of: (1) changes in neuronal activity linked to changes in concentration of blood oxygenation; (2) cortical brain activation and connectivity that could be useful in studying brain disorders as well as cortical changes induced by TMS.<sup>103</sup> In recent years, TMS-fNIRS has been used to investigate both experimental and clinical conditions.

However, there are methodological inconsistencies in existing studies and also different experimental protocols of TMS parameters.

According to the systematic review of Curtin et al.<sup>104</sup>, studies have observed central fatigue in exercise tasks and induced hypoxia in healthy individuals, which reduces muscle performance and corticospinal excitability. Most studies investigated the metabolism of motor cortex and dorsolateral prefrontal cortex after TMS single-pulses and repetitive pulses, in different frequencies and motor thresholds. Jiang et al.<sup>105</sup> showed in a narrative review the use of TMS-fNIRS system to verify the effect in brain metabolism of repetitive TMS in dorsolateral prefrontal cortex in neuropsychiatric conditions such as depression and panic disorders.

## **3.3. Neuromodulation through brain stimulation techniques**

### **3.3.1. Classical Repetitive Transcranial Magnetic Stimulation (rTMS)**

rTMS is a non-invasive technique for cortical stimulation that involves trains of magnetic pulses. In contrast to single-pulse TMS, rTMS is performed at frequencies usually between 1Hz and 50Hz for changing the brain activity and metabolism that outlast the period of stimulation.<sup>105,106</sup> Since Barker and colleagues described the first device of modern TMS in 1985<sup>107</sup>, rTMS has been widely used both as an investigational tool to explore cortical functions (e.g., by virtual lesion) and as a treatment tool for a variety of neurologic and psychiatric disorders.<sup>107,108</sup>

Repetitive TMS can activate or inhibit the cortical activity of a targeted brain area, depending on stimulation frequency. Low-frequency trains (~ 1Hz) tend to induce suppression of the activity of the cortex and high-frequency stimulation (usually above 5 Hz) tends to increase cortical activation.<sup>106</sup> Thus far, the mechanisms behind such effects remain to be understood in detail. Presumably, rTMS exerts its effects on the brain through the activation of networks by phenomena similar or closely related to long-term depression (LTD) and potentiation (LTP). Furthermore, studies suggest that modulation of neurotransmitters and changing gene expression of growth factor proteins like BDNF may contribute to the long-lasting modulatory effects of rTMS.<sup>109</sup>



The combination of a variety of parameters (intensity and frequency of stimulation, duration of each train, total number of trains, inter-train interval, site of stimulation, and coil orientation) determines therapeutic protocols of rTMS. These are considered safe and generally very well tolerated. *Common side effects include scalp discomfort, headache, and fatigue during or after treatment.* Inductions of psychiatric symptoms and seizures are also possible.<sup>14</sup> In view of these risks, safety guidelines have been issued regarding stimulus frequency, intensity, and inter-train interval.<sup>110</sup> Although considerable questions still exist regarding the mechanism of action and how protocols *should* be adequately prescribed, a large and substantive academic literature has clearly established the therapeutic efficacy of rTMS for several neurologic and psychiatric disorders.<sup>111</sup> In this context, rTMS has progressively been approved for clinical use in a substantial number of countries.

### **3.3.2. Patterned Repetitive Transcranial Magnetic Stimulation**

Theta-Burst Stimulation (TBS) is a type of TMS-patterned stimulation extensively studied for its ability to induce neuroplastic changes in disease and healthy conditions.<sup>112</sup> Huang and colleagues first introduced TBS in 2005, inspired by the theta frequency paradigm observed in animal studies.<sup>113,114</sup> This pattern of rhythmic neural activity occurs in the brain at a frequency of 4-8 Hz. TBS was created to improve the magnitude and duration of excitability changes induced by a single traditional rTMS session.<sup>115</sup> TBS has advantages over rTMS, such as a shorter session duration, which makes the treatment more tolerable for patients, reduces treatment costs and clinic visits, and increases the number of patients per hour and it also allows for accelerated protocol creation.<sup>116</sup>

There are two traditional types of TBS: intermittent theta-burst stimulation (iTBS) and continuous theta-burst stimulation (cTBS).<sup>113</sup> In iTBS, bursts of stimulation are delivered at 50 Hz for 2 seconds, followed by an 8-second rest period, which is repeated for a total of 600 pulses.<sup>113</sup> In contrast, in cTBS, bursts of stimulation are delivered at 50 Hz for 40 seconds, followed by a 20-second rest period, which is repeated for a total of 600 pulses. Studies show that iTBS can increase cortical excitability and enhance synaptic plasticity, while cTBS can decrease cortical excitability and induce long-term depression.<sup>117,118</sup>

TBS has different protocols with varying frequency and duration.<sup>119,120</sup> Attention should be given to the extended TBS protocols with 1200 or 1800 pulses per session, which have shown good results in accelerated depression protocols.<sup>121</sup> TBS is also used to treat chronic pain, neurological, and psychiatric conditions.<sup>122-125</sup> However, more research is needed to determine the optimal TBS parameters and the long-term effects of TBS treatment. Despite earlier beliefs, TBS is a safe non-invasive neuromodulation method having similar contraindications and side effects to classical rTMS.<sup>126,127</sup>

### **3.3.3. Transcranial electrical stimulation (tDCS)**

tDCS approach was much less developed than invasive cranial electrotherapy stimulation techniques, although it was experimentally proven that the application of polarizing direct current to the cerebral cortex can modulate brain neural activity with significant after-effects.<sup>128</sup> tDCS effects are mainly related to: (a) changes in resting-state membrane potential (short-term effects) and increased synaptic efficiency (long-term effects). Such changes induce neurotransmitter release, spike timing and brain plasticity. There is a possibility that short and long-term therapeutic effects could be related to neurogenesis and cortical reorganization associated with synaptic plasticity.

Clinical applications with encouraging results have been reported in several studies, but the optimal stimulation protocols remain to be determined. It is important to understand neuroplastic effects for the stimulation parameters duration and intensity.

The most currently used montage of tDCS is a bipolar montage using two electrodes (anode and cathode) on the scalp or with one electrode on extra-cephalic location. However, there are other types of montage, including high-definition and multifocal montage. In general, in a bipolar montage, the anode (positive red electrode) is thought to excite or hyperpolarize the underlying cortex, whereas the cathode (negative black electrode) is thought to produce inhibitory hyperpolarization.<sup>128</sup> However, substantial inter-individual variability in current direction can occur.<sup>128,129</sup>

A study comparing encephalographic results between high-definition tDCS (HD-tDCS) conventional tDCS showed that HD-tDCS induced an alpha power reduction in participants with lower alpha at baseline. On the other hand, participants with higher beta at baseline experienced a reduction in beta power through conventional tDCS. Moreover, there was a tendency towards improved behavioral response times through HD-tDCS in individuals with lower beta at baseline. The modulation of cortical activity differed between conventional and HD-tDCS, highlighting the significance of considering state dependence in evaluating the impact of tDCS on individuals.<sup>130</sup>

### 3.3.4. High-definition tDCS (HD-tDCS)

HD-tDCS stands for High Definition tDCS. The term and the acronym were created by a research group of the Biomedical Engineering Department of the City College of New York, led by Prof. M. Bikson, Dr. Abhishek Datta and others, after computerized modeling studies<sup>131</sup> with the aim of optimizing the traditional tDCS montages, which employs 2 relatively big conductive sponges ( $\approx 25\text{cm}^2$ ) and are known to spread electric current broadly within the brain.<sup>132</sup> Currently, HD-tDCS may indicate any tDCS multielectrode montage using small size electrodes intended to confine the resulting E-field within a restricted brain region.

The 4X1, which is by far the most used montage, is composed of a central electrode surrounded by 4 return electrodes, thus restricting the resulting electrical field within the area demarcated by the external-most electrodes.<sup>131-133</sup>

The first clinical test of HD-tDCS was performed in 2009 at Eric Wassermann's Brain Stimulation Lab at NINDS-NIH, and published in 2012.<sup>134</sup> The study was a proof of concept, intended to demonstrate that in normal subjects, the montage was capable of induce an increase on the TMS motor evoked potential. Further study of the same group, with EEG, supported the provisions made with the modeling studies<sup>135</sup>, showing an EEG effect restricted to the 4x1 area, but not on other sampled brain regions.

Because of its focal quality the usefulness of a focused tDCS approach is granted on cognitive studies where a direct neuromodulatory effect is required in approaches where specific brain regions are to be up or down-regulated in order to determine its role on a specific cognitive process.<sup>136</sup>

Although level A evidence of therapeutic efficacy has not been attained yet, for any indication, clinical studies with HD-tDCS have gathered some promising results.<sup>137</sup> On critically ill patients from COVID-19, it was shown that HD-tDCS decreased time of weaning from mechanical ventilation.<sup>138</sup> Studies on the effect of HD-tDCS on fatigue have been published on athletes<sup>137,139</sup> and on pathological population.<sup>140</sup>

### 3.3.5. Transcranial Alternating Current Stimulation (tACS)

Transcranial alternating current stimulation (tACS) is a powerful non-invasive tool to investigate the neural correlates of cognition in humans<sup>140-142</sup> but also a neuromodulatory intervention technique to enhance brain functions.<sup>142,143</sup> Basically, tACS is based on the application of weak sinusoidal electrical currents (1 - 2 mA) to the scalp in the conventional EEG range (0.1 - 80Hz), which are expected to entrain with intrinsic brain oscillations and to synchronize neuronal networks.<sup>144</sup> In this regard, it has been suggested that tACS may induce changes in cortical excitability by forcing the membrane potential to oscillate from its resting state to a hyperpolarized or depolarized state.<sup>141</sup> Furthermore, it has been shown that tACS can modulate brain activity at the level of large-scale network dynamics.<sup>145</sup> However, due to difficulties in removing stimulation artifacts from ongoing EEG activity, there are still controversies about the electrophysiological mechanisms by which the induction of these low-intensity oscillating electrical currents modulates endogenous brain activity.<sup>145,146</sup> Regarding the methodology, the tACS protocols are not yet standardized and vary significantly depending on the cognitive processes and/or clinical symptoms that are to be modulated.<sup>142,145,146</sup> Thus, for instance, it has been observed that 4 Hz tACS may improve auditory detection, whereas 40 Hz tACS may facilitate attention and speech perception.<sup>142</sup> Research on tACS over primary motor cortex revealed that gamma band entrainment enhances movement velocity<sup>147</sup>, whereas 20 Hz tACS facilitates sensorimotor integration and 10 Hz tACS improves motor learning.<sup>141</sup> Furthermore, frontal alpha and theta tACS seems to improve clinical symptoms in schizophrenia and depression, whereas frontal gamma tACS would be helpful in Alzheimer patients.<sup>148</sup> In addition, specific methodological recommendations for tACS have been proposed such as the use of active-sham control conditions (for example, changing only the electrode montage or the stimulation frequency), experimental control of the

environment during stimulation (given the influence of sensory inputs on oscillatory EEG activity), or selection of stimulation frequency based on individual EEG power spectra.<sup>143</sup>

In summary, tACS can induce neuroplastic changes and thus provide a deeper understanding of the causal explanation of brain activity in cognitive processes, as well as contribute to reversing plastic changes underlying neurological and psychiatric disorders by modifying or resetting anomalous brain oscillations.<sup>148</sup>

### 3.3.6. Transcranial Random Noise Stimulation (tRNS)

The technique of transcranial Random Noise Stimulation (tRNS) comprises the use of alternate balanced sinusoidal or square electrical currents applied with low amplitude to the scalp through surface electrodes.<sup>149</sup> tRNS frequencies vary randomly over time, ranging from 0.1 to 700Hz, and can be classified as Low- (<100Hz) and High-frequency (100Hz to 700Hz) tRNS.<sup>150</sup> Changes in frequencies vary between tRNS dispositive, but in general happen each second. The majority of studies that evaluated the effects of tRNS used 1mA of amplitude, during seven to 30 minutes (10 minutes more frequent), and its after-effects were maintained for at least 60 minutes.<sup>149</sup> The technique has been shown to be safe and tolerable<sup>151</sup>, and avoid the electrolytic effects seen in tDCS.

The rationale behind the effects of tRNS is the introduction of “white-noise” into the stimulated neuronal network. As a non-polarizing technique, the first question about the mechanisms by which tRNS acts was answered through its effects on cortical excitability, assessed through single- and paired-pulse TMS. In general, tRNS decreases motor threshold<sup>152</sup>, and increases motor cortex excitability<sup>153</sup>, which may facilitate synaptic transmission.<sup>150</sup> Applied in conjunction with motor tasks, tRNS may have additive effects if done before, or during the tasks, but not after.<sup>154</sup> This effect may also depend on the nature of the motor task, either “inhibitory” or “excitatory”.<sup>155</sup> Also, a meta analysis has confirmed the effects of tRNS in increasing motor cortex excitability, but with an effect size almost half than anodal tDCS<sup>156,157</sup>, and this effect in increasing task performance has not been seen when the technique was applied to the parietal cortex in a cognitive task<sup>156</sup>, what raises questions

about the effectiveness of tRNS regarding the cortical target. From the clinical point of view, there is not still support to apply tRNS in clinical populations.

### 3.3.7. Transcranial Focused Ultrasound (tFUS)

The non-invasive method of neurostimulation called transcranial focused ultrasound (tFUS) is a developing technique that offers greater spatial resolution and deeper structure accessibility in comparison to non-invasive brain stimulation techniques such as magnetic or electric stimulation.<sup>158</sup> Its mechanism of action is based on two distinct ways: i) it modifies the membrane gating kinetics through the action on sodium and calcium voltage-gated channels and ii) it has a mechanical effect that induces cavitation into the cellular membrane, which changes the membrane permeability.<sup>158,159</sup> Similar to rTMS, during the stimulus duration two paradigms of sonication are used: continuous or pulsed, the latter being the most applied for focal neuromodulation.

Preliminary animal studies suggest that tFUS can target superficial brain regions such as primary motor cortex<sup>160</sup> or frontal eye field<sup>161</sup>, and more deep areas like hippocampus, amygdala, or thalamus.<sup>162</sup> Additionally, this technique has a high spatial resolution and can modulate very small areas such as the lateral geniculate nucleus or the Edinger-Westphal nucleus.<sup>158,162</sup>

The application of tFUS on healthy individuals supports its ability to modulate the brain's functions. For instance, tFUS induced different types of tactile sensations in the opposite hand region following primary and secondary somatosensory stimulation.<sup>158,162</sup> Additional research has shown that tFUS applied to the primary motor cortex and basal ganglia can alter brain activity, causing distinct patterns of blood oxygen level dependent signals in fMRI.<sup>163</sup>

Therapeutic applications of tFUS were analyzed in a small number of patients so far. Few trials showed that it can alleviate chronic pain when applied over the posterior frontal cortex<sup>164</sup> and can also improve minimally conscious state after thalamic stimulation.<sup>165</sup> In four patients with Alzheimer's disease, tFUS of the hippocampus improved memory, executive, and global cognitive function.<sup>166</sup> Finally, patients with drug-resistant epilepsy had their seizures reduced after delivery of tFUS to the seizure onset zone.<sup>166,167</sup>

One potential application of tFUS is to temporarily open the tight junctions of endothelial cells at specific locations in the blood-brain barrier, thereby allowing drugs to be delivered to a particular region of the brain. The most extensively researched applications thus far involve the delivery of chemotherapy and gene therapy utilizing recombinant adeno-associated virus.<sup>166,168</sup> As it is still in phase one and two studies, there is no evidence to recommend its clinical use.

### 3.3.8. Photobiomodulation

Photobiomodulation (PBM), a nomenclature that started to be used from 2014 and included as a keyword in MESH searches in 2015, refers to the use of light, both in the older form with the so-called low-power or low-intensity LASERS (there are several other ways to refer to these sources), but also LEDs (Light Emitting Diodes) as a means of conducting electromagnetic energy within the visible and near infrared range for the treatment of various pathophysiological conditions.<sup>169</sup>

The PBM technique consists of directing beams of light to the target tissue, like neurons to achieve effects such as increased ATP, improved microcirculation through release of nitric oxide, reduced apoptosis, and improved neuroinflammation.<sup>170</sup>

A new approach to make neuromodulation is the use of PBM with different wavelengths of near infrared (NIR) or red, to treat by transcranial irradiation of the skull. It is important to note that these wavelengths were analyzed when penetrating the cranial vault and on the possibility of light reaching the target, which is the cerebral cortex, which was confirmed in an experiment with cadaver and neurosurgery patients.<sup>171</sup> This is called transcranial PBM (tPBM) and it is safe to the patients and therapists, easy to administer and low cost.

Based on animal experiments with encouraging results, clinical studies were carried out showing that in fact there is neuromodulation by tPBM and clinical results have already been described in several conditions such as Major Depressive disorders, Traumatic brain injury, Treatment of anxiety and depression, improvement of attention and cognitive disorders, stroke recovery, among others.<sup>172</sup>

In a clinical trial our group showed improvement of cognitive function, pain relief, greater manual

dexterity, enhancement of physical and social-emotional health which led to better quality of life and well-being in the post-stroke patients treated with tPBM associated with neuromuscular electrical stimulation (NMES).<sup>173</sup>

### 3.3.9. Transcutaneous and Percutaneous Peripheral Electrical Stimulation (tPES and pPES)

Peripheral electrical stimulation (PES) is the application of low-frequency and -intensity electrical currents through transcutaneous or percutaneous electrodes to recruit afferent and efferent neural pathways and has been used in research and clinical rehabilitation.<sup>174</sup> Electrical stimulators used for PES provide monophasic (constant or pulsed) or biphasic electrical currents, that area applied via many different types of surface electrodes and by needles into the tissues. The techniques are used in different levels of amplitude, frequency and duration to exercise muscles, induce a muscle response to nerve stimulation, relieve pain, alleviate incontinence, and assess nerve or muscle activation. Electrical stimulators generally have controls for setting pulse duration, pulse repetition frequency, pulse amplitude, and current trigger modes. The electrodes for such devices can be permanent, percutaneously or surface implanted.

Although these electrical currents and devices are generally known by their commercial names (e.g. TENS or FES), by the effects associated with those commercial names (e.g. analgesia, muscle contraction), the electrical stimulation of tissues promotes quite wide effects on the organism, ranging from the classical ones to anti-inflammatory<sup>175,176</sup>, anti-tumoral<sup>177</sup>, cognitive<sup>178</sup>, and emotional<sup>179</sup> effects. Stimulating peripheral nerves may also change somatosensory and primary motor cortex excitability, similar to what is achieved with central nervous system stimulation such as tDCS and rTMS. If applied transcutaneously, tPES parameters seem to promote central neuromodulation according to the parameters used. It is generally accepted that low-frequency (<10Hz), tPES at the motor threshold amplitudes, during more than 45 minutes have an excitatory cortical effect, while high-frequency (>10Hz), tPES at the sensory or nociceptive threshold amplitudes, during around 30 minutes may have opposite effects.<sup>180-182</sup> These effects are addictive to the classical effects of tPES, and are changed when PES is made via percutaneous electrodes, i.e. pPES.

Percutaneous peripheral nerve stimulation (pPES) is a type of neuromodulation therapy where the electrode is placed (implanted or acupuncture needle) near a peripheral nerve (i.e., nerve located outside the brain and spinal cord) that innervates the painful dermatome. The electrodes deliver electrical impulses to the affected nerve to interrupt the transmission of pain signals, thereby reducing the pain level.<sup>183</sup> pPES modulation of the primary motor cortex is dependent on the parameters used. Stimulation at the sensory threshold and 100Hz frequency increases the corticospinal excitability, differently from tPES.<sup>184</sup>

Pain relief induced by PES treatment is mediated both by modulation of A $\beta$  fibers and the local release of biochemical mediators such as neurotransmitters and endorphins, reducing the pain response.<sup>185</sup> More specifically, an orthodromic stimulus applied to non-nociceptive A $\beta$  nerve fibers activates the respective interneurons in the dorsal horn and transmits nociceptive information to peripheral A $\beta$  and C fibers.

### **3.3.10. Transcutaneous Auricular Vagus Nerve (taVN)**

Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive neuromodulation technique in the auricular branch of the vagus nerve.<sup>186,187</sup> Tragus and cyma conchae are the main targets of the stimulation. This stimulation can be bilateral (both ears) or unilateral, monophasic or biphasic. Current's parameters may differ between studies, typically the current is pulsed (5-25 Hz,  $\leq$  500  $\mu$ S pulse width, and  $\leq$  10 mA).<sup>178-187</sup> Safety and tolerability studies showed minimal side effects.<sup>188-190</sup> Potential use and therapeutic benefits of the taVNS include neuropsychiatric disorders such as depression<sup>191,192</sup>, rehabilitation<sup>193</sup>, neurological conditions, such as chronic pain<sup>194,195</sup>, epilepsy<sup>195</sup>, and tinnitus.<sup>196</sup> Furthermore, taVNS has been used in neurodevelopmental pediatric disorders, for example to modulate the motor learning during suckling in neonates born preterm.<sup>197</sup>

Neuroprotective treatment by taVNS for inflammation conditions has been investigated<sup>198</sup> and improved the autonomic function.<sup>194,199</sup> Also, taVNS can influence cognition in healthy individuals.<sup>200</sup> In recent years, systematic reviews have been performed in order to examine the potential clinical effects of taVNS; however, more studies are needed to determine the neurophysiological effects of this stimulation on brain activity<sup>201</sup> using EEG and new

technologies. Furthermore, the combination of this type of stimulation and other neuromodulatory interventions such as tDCS and TMS also need to be better explored.

### **3.3.11. Peripheral Magnetic Stimulation (PMS) and Repetitive Peripheral Magnetic Stimulation (rPMS)**

Peripheral magnetic stimulation (PMS) involves delivering pulsed, high-intensity magnetic fields to peripheral tissues. It has gained significant attention in research and clinical settings over the past few decades due to its perceived advantages, including its painless and straightforward application for many different conditions.<sup>202</sup>

The PMS device is composed of a high current pulse generator, which can generate large electric discharge currents through a stimulating coil, thereby producing magnetic pulses. The focality and depth of penetration on the target depend on the type of coil used, with the round coil and figure-8 coil being the most common types. Both coils have air- or oil-cooling systems in place to prevent heating. While the round coil is less focused, it produces a deeper magnetic field with a stimulated area equal to its diameter. On the other hand, the figure-8 coil generates a stronger magnetic field at the center with a precise focus.<sup>203</sup>

In contrast to TMS, there is still insufficient safety data and parameters regarding PMS. The duty cycle, total number of magnetic pulses, frequency, and intensity for PMS have yet to be established. Nonetheless, studies have shown that PMS can be beneficial for conditions such as myofascial pain syndrome<sup>204</sup>, traumatic brachial plexopathy<sup>204,205</sup>, post-traumatic peripheral neuropathic pain<sup>204-206</sup>, acute and chronic low back pain<sup>207</sup>, spasticity reduction<sup>208</sup>, increase muscle strength<sup>209</sup>, and dysphagia.<sup>209,210</sup>

Repetitive peripheral magnetic stimulation (rPMS) is a technique that elicits muscle contraction by stimulating action potential in motor axons, making it a potential neuromodulatory approach for motor recovery. The advantage of rPMS is that it can penetrate deeper regions of muscles without causing discomfort.<sup>202</sup> rPMS was applied to the wrist extensor muscles at different frequencies (50, 25, and 10 Hz), with the total number of stimuli set constant to examine the physical effects of stimulus frequency. The application of rPMS to wrist extension at 25 Hz or higher for 15 minutes can increase cortical excitability

at the irradiated site and improve motor output from the motor cortex, rather than changing the excitability of the spinal cord circuitry.<sup>202,211</sup>

### **3.4. Clinical uses of Noninvasive Brain Stimulation (NIBS)**

#### **3.4.1. Cardiorespiratory disorders**

The breathing is controlled by the autonomic nervous system and the structures of the main center are located in the medulla. The control of this system is dynamic in response to necessary adjustments to keep the homeostasis. The system is provided of special cells differentiated to act as pacemaker to control the respiratory cycle. The system is modulated by peripheral and central chemoreceptors and mechanoreceptors.<sup>212</sup>

Mechanical ventilation is a procedure commonly used as a life support in Intensive Care Units (ICU), and the diaphragm dysfunction is a frequent condition either as pre-existent or acquired in the ICU.<sup>213</sup> The inhibition of the diaphragm corticospinal pathway of these patients due to the mechanical ventilation.<sup>214</sup>

As the diaphragm is the most important respiratory muscle, its dysfunction compromises the breathing itself and also the efficient cough to the clearance of the air pathways. This functional condition is a challenge to restore the spontaneous respiration free of mechanical ventilation.

A protocol with anodal tDCS in the supplementary motor area, associated with peripheral stimulation, has been an optimistic protocol to the weaning and decannulation of high level spinal cord injury patients as well as difficult weaning of complex coronavirus pandemic patients.<sup>215,216</sup> HD-tDCS also seems to be promising for this purpose.<sup>138</sup> Transpinal Magnetic Stimulation may also appears as a possibility as a diaphragm contraction in response to these stimulations were shown by ultrasound assessment.<sup>217</sup>

#### **3.4.2. Communication disorders**

##### **3.4.2.1. Aphasia**

Aphasia is an acquired language disorder caused typically by left-hemisphere injury to brain networks implicated in language processing. The main etiology of aphasia is stroke; however, other conditions may

also cause aphasia, including neurodegenerative diseases.<sup>218</sup> Persons with aphasia (PWA) present with mild to severe difficulties understanding and/or expressing language across all input and output modalities (oral, written, signed) due to phonological, morphosyntactic and/or lexical-semantic deficits. Aphasia can co-occur with speech disorders such as oral apraxia and dysarthria.

The most effective treatment for aphasia is speech and language therapy (SLT)<sup>218</sup> which facilitates behavioral improvements and neural reorganization mechanisms underlying functional recovery such as reactivation or compensation.<sup>219-221</sup> Recent research has attempted to shed light into factors that increase the efficiency of SLT for PWA such as the optimal intensity, dosage and frequency of treatment<sup>222</sup> and the add-on effects of NIBS to potentiate SLT effects.<sup>223,224</sup> The latter research has mostly employed tDCS and rTMS<sup>223-226</sup> based on two theories of neural reorganization of language recovery in PWA: the interhemispheric inhibition theory and the laterality shift hypothesis.

The first theory postulates that following an injury affecting the language network, the cortical excitability is reduced in the LH and increased in the RH. According to this theory, neuromodulation can help restore interhemispheric balance and facilitate reactivation or intra-hemispheric compensation for language recovery by: a) inhibiting maladaptive neural activity of homologous contralateral lesion sites (cathodal TDCs, low-frequency rTMS applied to RH regions); b) increasing neural excitability in left hemisphere regions (anodal tDCS and high-frequency rTMS applied to LH regions) and; c) combining these two approaches (Dual tDCS). On the other hand, based on the laterality shift hypothesis, neuromodulation protocols should target the stimulation of regions of the RH to facilitate language recovery through compensation (i.e., language function shifted to the RH).

Numerous studies have reported benefits of the abovementioned neuromodulation protocols in language recovery of PWA.<sup>223-226</sup> However, the evidence of the effectiveness of rTMS and tDCS to treat aphasia is of low-moderate quality, as most studies have included small and heterogeneous samples and applied multiple trial designs with few randomized controlled trials. Lefaucheur et al.<sup>227</sup> reported level B (probable efficacy) of low-frequency-rTMS applied to the right inferior gyrus (homologous

to Broca's area) for the treatment of chronic post-stroke non-fluent aphasia. Elsner et al.<sup>224-231</sup> reported moderate quality of evidence of tDCS to improve noun naming in PWA. Treatment parameters such as the polarity, intensity and stimulation sites need more systematic investigation.<sup>224</sup> Moreover, therapeutic protocols need improvements to maximize clinically relevant gains (improvements in quality of life and functional communication).<sup>223,231</sup> Individualized neuromodulation according to age, aphasia type and brain injury features and the combined use of neuroimaging and electrophysiological to evaluate treatment effects are promising approaches for the rehabilitation of PWA.

#### **3.4.2.2. Apraxia of speech**

Apraxia of speech (AoS) is a disturbance in the planning and motor programming of the speech and represents a poor prognostic factor for the rehabilitation outcome.

Patients with AoS present articulatory and prosodic alterations, identified as an overall slow rate of speech, segmentation of syllables, distorted sounds, consistent error type, abnormal prosody. The greater the complexity of the utterances, the greater the difficulty presented by the patient.<sup>228</sup>

Anatomically, AoS symptoms have been associated with these regions: left inferior frontal gyrus (IFG); parietal lobe, the basal ganglia, cerebellum, pre-supplementary motor area and the insula under the left IFG. All these areas are part of the circuit involved in the speech programming and motor planning function.

Studies have shown beneficial effects of tDCS in patients with AoS. They point out that the concomitant association of NIBS stimulation with speech therapy has a better effect on the patient's speech performance. Furthermore, the effects were sustained for more than two months after treatment, both for the sounds trained during the research and for the untrained sounds.<sup>229</sup> Therefore, tDCS can facilitate speech production<sup>227-230</sup> maximizing the efficacy of speech therapy in patients with AoS.

One study, which used the anode electrode protocol positioned over Broca's area and the cathode over the contralateral supraorbital region, demonstrated that there was an improvement in articulatory accuracy and also in speech rate.<sup>231</sup>

Presenting another montage, this study concludes that bihemispheric stimulation may be a highly indicated alternative for the treatment of patients with AoS after stroke.<sup>232</sup> Patients who were stimulated anodic stimulation in the left frontal hemisphere and cathodic stimulation in the right frontal hemisphere demonstrated a significant recovery of speech quality, both in relation to accuracy and articulatory speed, as well as in relation to other areas related to language. Such improvement in performance was maintained over time and was generalized to other linguistic tasks.

The benefit of bihemispheric stimulation may occur through interhemispheric interaction, which potentiates the effects of anodic stimulation in the lesional hemisphere.<sup>232</sup> The improvement in speech production is closely related to the improvement in neural connectivity in the left hemisphere, both in specific areas of speech and in areas of general domain.<sup>228,232</sup>

#### **3.4.2.3. Dysarthria**

Dysarthria refers to phonetic alterations in speech, with neurological origin and impairment of one of the motor bases: breathing, phonation, resonance, articulation and prosody.

The application of NIBS as a neuromodulation strategy aims to modulate the neural circuits of certain regions of the brain, through the modification of cortical excitability. As the etiologies of dysarthrias can be multiple, the stimulation target will depend on the topography and pathophysiology of the underlying disease.

A comparative study between dysarthric patients who received stimulation compared to the sham group concluded that there was an improvement in articulatory movements produced in syllables and sentences, as well as a reduction in vocal range perturbation.<sup>233</sup> In an analysis of studies involving patients with cerebellar ataxia, an improvement in the clinical condition was observed in 12 of the 13 studies analyzed.<sup>234</sup>

A controlled study showed positive changes in the group of patients diagnosed with Parkinson's disease who received high frequency rTMS stimulation (5Hz) for 10 minutes a day (3,000 pulses) for 10 days.

Patients were reassessed two and twelve months after stimulation and improvements were observed in intelligibility, communication efficiency, maximum velocity of tongue movements and amplitude of tongue movements.<sup>235</sup>

In post-stroke patients, changes in the corticobulbar pathways (referring to tongue innervation) are frequent; however, using TMS as an evaluation tool, it was observed that the ability of the unaffected hemisphere to respond to stimuli seems to be related to the presence or absence of dysarthria in patients.<sup>235,236</sup>

The results are still unable to establish a robust conclusion on effectiveness, due to the high risk of bias, the heterogeneity of the techniques and respective parameters and the heterogeneity of the sample of the analyzed studies, both in relation to severity and etiology.<sup>237</sup>

In general, studies show that neuromodulation associated with therapy (exercise) can improve motor functions, showing a synergistic effect between brain stimulation and speech therapy.<sup>237,238</sup>

Neuromodulation can also be used as a tool to better understand the pathophysiology of the neural pathways involved in the process of speech articulation, through understanding the connectivity of the pathways. TMS has been described as a sensitive technique for investigating the corticobulbar tracts, with a temporal precision character.

### **3.4.3. Mental disorders**

#### **3.4.3.1. Depression**

Depression is one of the most important global health problems, affecting at least 264 million people worldwide, and ranking third in years lived with disability.<sup>239</sup> Current psychiatric guidelines for the treatment of depression recommend antidepressants and cognitive-behavioral therapy as first-line interventions.<sup>240</sup> However, pharmacotherapies are associated with modest remission rates and discontinuation due to side effects,<sup>241</sup> while psychotherapy has a modest effect size and is not readily available for the majority of the world's population.<sup>242</sup>

Brain stimulation techniques are non-pharmacological and non-psychotherapeutic interventions that could fill the gaps in mainstream treatments.<sup>243,244</sup> These techniques consist of applying electrical current or magnetic fields to modulate neural networks and affect neural plasticity in order to restore or enhance brain function.

In a recent umbrella review, which included seven meta-analyses evaluating the effects of 12 brain stimulation techniques for depression treatment in 5,615 patients, revealed that a large body of data supports high frequency rTMS to the left DLPFC, theta burst rTMS, and tDCS at the highest level of evidence, based on large sample sizes and with very consistent effects across the most recent randomized clinical trials.<sup>239</sup> The certainty of evidence of most interventions was downgraded as a result of small sample sizes. The quality of evidence for electroconvulsive therapy (ECT), an established technique for depression, was considered moderate, while two Food and Drug Administration (FDA) approved techniques intermittent theta burst (iTBS) and deep transcranial magnetic stimulation (dTMS) had low quality of evidence. Therefore, our findings confirm that brain stimulation techniques have matured, becoming important treatment alternatives in the treatment of depressive disorders, and could soon join pharmacological treatments and psychotherapy as standard intervention options.

#### **3.4.3.2. Anxiety**

Anxiety disorder is a big public health concern that generates disability. Its prevalence varies from 3.0% to 22.1%.<sup>245</sup> According to the eleventh version of the International Classification of Diseases (ICD-11)<sup>246</sup> and the Diagnostic and Statistical Manual of Mental Disorders (DSM-5),<sup>247</sup> mental disorders are classified as disorders of mood, behavior or neurodevelopment. Mental disorders are syndromes characterized by a clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects dysfunction in the psychological, biological, or developmental processes that underpin mental and behavioral functioning. These disturbances are usually associated with distress or impairment in personal, family, social, educational, occupational, or other important areas of functioning. However, only a low percentage of the patients respond to the first-line treatments that include pharmacological and psychotherapies approaches.<sup>248</sup>



NIBS are low-cost, easy to apply and tolerable interventions. NIBS interventions have been preferentially applied over the prefrontal cortex (PFC) for the neuropsychiatric population. The PFC is the brain region primarily involved in more complex psychobiological processes, including cognitive and emotional domains.<sup>249</sup>

Recently we developed an umbrella review in this theme, and we found several systematic reviews with meta-analyses including a high level of randomized clinical trials sham controlled.<sup>250</sup> From these umbrella review results, there are evidence to recommend low frequency rTMS to treat Generalized Anxiety Disorder and Obsessive Compulsive Disorder, and high frequency rTMS to treat Posttraumatic Stress Disorder, with large effect sizes. There is no evidence to apply NIBS to treat Panic Disorder or to use tDCS in anxiety disorders. Future studies need to improve evidence level through qualified RCTs. Available evidence reveals NIBS is safety and effective to treat Generalized Anxiety Disorder<sup>251</sup>, PostTraumatic Stress Disorder<sup>252</sup>, and Obsessive-Compulsive Disorder<sup>252,253</sup>, but not yet to treat panic disorder.<sup>254</sup>

#### **3.4.3.3. Craving**

Dependence on psychoactive substances and food is considered a worldwide public health problem. Both can be described as brain disorders included in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).<sup>255</sup> Such disorders may be associated with other pathologies such as cardiovascular, metabolic and psychiatric diseases.

Both licit and illicit drugs are included in this context, as well as food. In general, refined products such as sugars, fats, salts, caffeine, among others, are the most frequent causes of dependence.<sup>256</sup> In this context, both categories are considered addictive and their excessive and uncontrolled consumption can be treated as chemical dependence, despite their particularities and different forms of management. Thus, the desire for consumption, or craving, is a sensation that precedes the search behavior and may be associated with a past experience that one intends to repeat and generate a reward or, failing that, the feeling of abstinence. This behavior is related to the inability to stop consuming the substance, demonstrating a deregulation in the inhibitory control.

Treatments usually include pharmacotherapy and psychological therapies, mainly Cognitive Behavioral Therapy with techniques focused on psychoeducation, coping and systematic desensitization. However, not everyone adheres to first-line treatments for different reasons. Thus, non-invasive neuromodulation can be an additional and very promising resource.

Imbalance in the limbic system and in the prefrontal cortex region can be identified as relevant in the study of substance dependence, food and desire control. In this sense, neural networks linked to executive functions such as cognitive flexibility, inhibitory control and decision making have been targets in treatment with neuromodulation.<sup>257</sup> There is efficacy of excitatory protocols of rTMS and tDCS to control craving in illicit/licit drugs and food consumption, being the major effect size with high frequency (10Hz) of rTMS protocols over the left DLPFC applying around 1,500 pulses during 30 sessions.<sup>258</sup>

The study of addictions associated with the use of neuromodulation needs more, since the heterogeneity of studies is still high. There is a need for more specific investigations on the different substances used in combination or separately and with a larger number of participants.

#### **3.4.3.4. Schizophrenia**

Schizophrenia is a psychotic disorder with multifactorial causes and according to the World Health Organization has a prevalence of 0.32%. There are two subtypes of schizophrenia: type I or with positive symptoms including tactile, auditory or visual hallucinations; and type II or with negative symptoms including affective dullness and speech poverty. In addition, many patients have persecutory hallucinations (DSM-5). All symptoms have a detrimental impact on functional outcomes and quality of life in people with schizophrenia, and few therapeutic options are considered effective for this disorder.<sup>259</sup> The more recognized assessment instruments are the Auditory Hallucinations Rating Scale (AHRs) and the Positive and Negative Symptoms Scale (PANSS). They are important to measure the effect of therapeutic resources applying pre and post interventions.

The brain of schizophrenic people has structural and functional alterations with reduction of its size and weight, enlargement of the ventricles, increase in cortical sulci and consistent aberrant activity on hypo campo, hippocampal gyrus, superior and medial temporal gyrus, thalamus, base ganglions, and corpus callosum.<sup>260</sup> Those brain alterations justify the non-invasive brain stimulation.

Studies have suggested that noninvasive brain stimulation interventions may be effective in treating negative and positive symptoms, and hallucinations. There is evidence level C to auditory hallucination and to negative symptoms, and there is no recommendation for positive symptoms yet.<sup>249</sup> The main stimulation targets are frontal cortex (left prefrontal dorsolateral, ventromedial and supraorbital cortex), and left temporoparietal junction. The techniques that show the best results are HF-rTMS to treat negative symptoms and hallucinations, and tDCS to treat negative symptoms.<sup>261</sup> Several trials evaluated the efficacy of rTMS, theta-burst stimulation, transcranial random noise stimulation, transcutaneous vagus nerve stimulation, and tDCS on negative, positive symptoms and hallucinations in schizophrenia.<sup>111</sup>

Excitatory non-invasive brain stimulation protocols over the left dorsolateral prefrontal cortex were associated with significantly large improvements in the severity of negative symptoms.<sup>259</sup> There is reasonable evidence that rTMS is an efficient treatment for hallucinations and negative symptoms.<sup>249</sup> There is insufficient evidence for conclusions to be drawn about the efficacy of tDCS for the treatment of hallucinations and negative symptoms. However, both stimulation methods are safe and largely without side-effects<sup>261</sup>.

### **3.4.4. Musculoskeletal disorders**

#### **3.4.4.1. Non-inflammatory musculoskeletal disorders**

Neuroplastic changes have been observed in conditions of non-inflammatory musculoskeletal disorders. There are neurophysiological changes across the central and peripheral nervous system described in a range of musculoskeletal conditions.<sup>262-264</sup> These changes are not only a consequence of peripheral alterations, but may also be involved in the pathophysiological mechanisms of musculoskeletal disorders.<sup>262</sup> It is crucial that healthcare professionals, including those on the

rehabilitation team, are aware of these changes and are able to adopt the best treatment practices for musculoskeletal disorders. A variety of interventions can influence the peripheral and central nervous system and can promote targeted neuroplastic changes for each musculoskeletal disorder.<sup>265,266</sup> These techniques can influence different parts of the nervous system and contribute to electrophysiological and clinical changes.<sup>262</sup>

Electrical currents can be used in central and peripheral regions of the body in order to promote plastic changes in the nervous system and clinical changes. tDCS applied in the M1 area for 5 consecutive days can improve pain in people with chronic musculoskeletal pain secondary to chikungunya<sup>267</sup> and improve pain, anxiety and contributes to quality of life in people with temporomandibular dysfunction.<sup>268,269</sup> Another type of brain stimulation is rTMS, which induces magnetic fields in the brain with the aim of promoting neuroplasticity. Low frequency Dorsolateral Prefrontal cortex can significantly reduce pain and associated symptoms of Fibromyalgia and mechanisms are probably related to top-down pain modulation.<sup>266</sup>

Peripheral neuromodulation techniques have also contributed to the treatment of musculoskeletal disorders. pPES promotes pain improvement and function in soft tissue injuries.<sup>270</sup> Other results support these findings in a case report of a patient with lateral elbow pain. Two sessions of ultrasound-guided pPES of the radial nerve and 4-weeks of a low-load concentric-eccentric exercise program of the wrist extensors resulted in improvement of pain and function that were maintained after a two-year follow-up.<sup>265,271</sup> Also, tPES<sup>265</sup> and cryotherapy have been shown to be the best techniques to improve arthrogenic inhibition in the knee and improve quadriceps femoris activation.<sup>271</sup> All of these interventions should be explored as potential forms of treatment for musculoskeletal disorders. The choice should be based on scientific publications and the experience of healthcare practitioners.

#### **3.4.4.2. Inflammatory musculoskeletal disorders**

Musculoskeletal diseases comprise a variety of inflammatory and noninflammatory diseases. In the first case, it was very common in the context of systemic autoimmune rheumatic diseases that course through a chronic inflammatory process.

Patients with these diseases frequently present with symptoms such as chronic pain and fatigue, resulting in decreased functional capacity.<sup>272,273</sup>

Pain and fatigue may not be exclusively related to possible peripheral injury-nociceptive and neuropathic pain.<sup>271</sup> In addition, central sensitization may or may not be influenced by various substances found in autoimmune conditions.<sup>272</sup> Central sensitization, in turn, corresponds to a change in the functional state of neurons triggered by an increase in the excitability of the neuronal membrane, efficiency of synaptic transmission, or reduction of inhibition in this system.<sup>274</sup>

The applicability of NIBS has shown positive and promising results for the management of pain (e.g., osteoarthritis)<sup>275</sup>, and fatigue (e.g., fibromyalgia)<sup>276</sup> in patients with noncommunicable musculoskeletal diseases, inflammatory processes that primarily affect the central sensitization mechanism. However, studies on the impact of this modality on inflammatory conditions.<sup>276,277</sup>

Pinto et al.<sup>277</sup> demonstrated that tDCS (with anode and cathode, respectively, in the right and left dorsolateral prefrontal cortex; 2 mA, 5 consecutive sessions, 20 min) was able to reduce symptoms of fatigue in patients with Sjögren's syndrome.

Studies by our group have shown that tDCS is safe in patients with dermatomyositis, without promoting disease reactivation or significant adverse events.<sup>277-279</sup> Furthermore, tDCS improves skeletal muscle strength<sup>278</sup>, and significantly reduces refractory postherpetic neuropathy.<sup>279,280</sup> In this context, additional studies with larger sample sizes and several other inflammatory musculoskeletal diseases are necessary to strengthen our data.

### 3.4.5. Neurological disorders in adults

#### 3.4.5.1. Stroke

Clinically, stroke characterizes a syndrome of acute, focal neurological signs caused to vascular injury in the central nervous system. It is a leading cause of acquired permanent mental and physical disability worldwide with a considerable impact on daily functioning and quality of life.<sup>281</sup> The major determinant of functional recovery post-stroke is the reparatory and regenerative processes that occur following ictus.

During recent decades, NIBS techniques, including rTMS, tDCS, tACS, tFUS, and tVNS, have been applied to enhance adaptive or suppress maladaptive processes of post-stroke neural reorganization. NIBS has provided novel insight into the physiology of neural circuits underlying motor dysfunction, and brain reorganization during the motor recovery after stroke. Particularly, TMS is an important tool to quantify the corticomotor excitability properties of clinically affected and unaffected muscles, and probe local cortical networks, as well as remote but functionally related areas.<sup>282</sup> Compared to rTMS and tDCS, tACS, tFUS, and tVNS are less studied but have also emerged as a potential add-on tool to post-stroke rehabilitation interventions.<sup>282</sup> In recent preclinical study, another NIBS technique, the suprathreshold HF-rTMS was implicated in activate the genetic cascade B-RAF- MEK1/2 signaling in the sensorimotor cortex neurons, promoting axon regeneration in mature corticospinal tract and sprouting after injury, as well as regeneration and functional recovery in mice.<sup>283,284</sup>

Thus far, the use of NIBS techniques in the stroke population has been relatively safe and well tolerated.<sup>285,286</sup> Studies show that NIBS combined with traditional rehabilitation treatment effectively improves motor<sup>287</sup>, speech<sup>288</sup>, swallowing<sup>289</sup>, cognitive impairment<sup>290,291</sup>, and depression<sup>292</sup> in patients with acute, subacute, and chronic stroke. However, despite its great therapeutic potential, NIBS is not an one-size-fits-all treatment and inter-individual variability in response to therapy limits its implementation in routine clinical care. The high variability in stimulation protocols and in demographic, clinical, and neurobiological characteristics of subjects involved in the studies may be associated with the degree of NIBS response in stroke patients.<sup>292</sup> There is insufficient evidence for recommending specific stimulation protocols or cutoffs for specific stroke impairments. Furthermore, disappointments in NIBS results of clinical trials may be also related to the unequivocal choice of stimulation protocol based on an oversimplified model of the normalization of interhemispheric balance. Indeed, NIBS application guided by this model may be inappropriate in patients with greater cortical damage and more severe motor impairment.<sup>293</sup> Using biomarkers for a better understanding of the reorganization of neural networks, future research should focus on developing the personalized protocol to increase the efficacy of NIBS in stroke rehabilitation.<sup>294,295</sup>

Identifying biomarkers of responsiveness may also be key to enhance the probability of NIBS therapeutic success.

### 3.4.5.2. Parkinson

Parkinson's disease is now viewed as a slowly progressive neurodegenerative disorder that begins years before diagnosis, involves multiple neuroanatomical areas, results from a combination of genetic and environmental factors, and manifests with a wide range of motor symptoms that include bradykinesia, muscle rigidity, tremor at rest, postural instability and gait changes.<sup>296</sup> Even before the motor symptoms are visible to the eyes, the subject may already have presented several non-motor symptoms that may accompany throughout the course of the disease, such as: hyposmia, constipation, REM sleep disorders, depression and/or anxiety, pain, fatigue, among others. And yet, after a long period of being medicated with a dopaminergic precursor, the patient may develop dyskinesias.

Faced with this complex picture, NIBS has a lot to offer and research in this field has shown increasing progress. What hinders the best interpretation of the results of this technique is exactly the clinical diversity of this population versus the range of possibilities of NIBS parameters. The main scientific evidence found involves cardinal signs, specific outcomes for gait and gait freezing, dyskinesias induced by Levodopa, cognitive deficits and depression. Bradykinesia, rigidity and tremor are usually evaluated together using the UPDRS-III and, thus, to date, evidence indicates that transcranial electrical stimulation (tES) does not show significant improvements in this scale<sup>297</sup> and both high-frequency and low-frequency rTMS were effective, especially when applied on motor cortex (M1), supplementary motor area (SMA), DLPFC or M1+DLPFC<sup>298,299</sup>, in addition to bilateral applications on M1 with the patient in the ON-state seem to be even more promising.<sup>299</sup> Gait: studies with tDCS point to an improvement in gait parameters also when associated with motor intervention.<sup>300</sup> HF-rTMS presents promising results, including for patients with frozen gait.<sup>300,301</sup> Levodopa-induced dyskinesia: there are few studies with NIBS on this condition, those with the best results used LF-rTMS on SMA or M1 or cTBS in the cerebellum.<sup>302</sup> Cognitive deficits: HF-rTMS has shown promising results in the treatment

of these disorders<sup>300</sup>, as well as anodic tDCS<sup>301,303</sup>, with the greatest effectiveness occurring when applying NIBS in the DLPFC.<sup>304</sup> Depression: some studies show positive effects of rTMS in the treatment of depression versus sham<sup>303</sup>, but others do not identify superior effects of rTMS when compared to antidepressants.<sup>305</sup>

Treatments are more efficient stimulating left DLPFC, inhibiting right DLPFC or when applied to both cortices.<sup>297</sup> Remembering that work in this area is still on the rise and the subject with PD presents multiple symptoms concomitantly, thus, nothing will replace the supremacy of clinical reasoning to define the best technique and parameters for the benefit of the patient.

### 3.4.5.3. Dysphagia

Neurogenic oropharyngeal dysphagia refers to the alterations in the processes of mastication and swallowing, secondary to neurological lesions. Dysphagia can have respiratory and nutritional consequences, compromising the safety of and life of the patient.

The role of the pharyngeal motor cortex in controlling the muscles that participate in swallowing is recognized and, more recently, the role of the cerebellum in that brain circuit has been reported. Such regions have been the target of NIBS. TMS and tDCS<sup>306</sup> have been indicated as an auxiliary resource in the treatment of dysphagia. When associated with the exercises and maneuvers prescribed in swallowing therapy, there is the report of benefits and clinical improvement for the patient.<sup>307</sup>

TMS has been used in scientific research as: (1) an instrument that evaluates physiological mechanisms, in healthy subjects, to better understand the biomechanics of swallowing<sup>308,309</sup>; (2) diagnostic resource, which evaluates the effectiveness of the therapeutic strategies adopted for the treatment of the studied group, by measuring the PEM (potential evoked motor) amplitude, at pre and post intervention, in order to evaluate possible changes in cortical excitability; and (3) therapy resource, in the treatment of dysphagia.<sup>310</sup>

tDCS has been used as a stimulation tool. Studies show that the use of anodal tDCS applied to regions

of the cortex responsible for swallowing (pharyngeal motor cortex and cerebellum) can increase cortical excitability, stimulating the functionality of the neuronal circuits involved.<sup>311</sup>

The broad spectrum of etiological possibilities of neurogenic dysphagia causes significant variability in relation to clinical responses. This is an important factor to be considered, as it means that there is no consensus on establishing a single protocol, both in relation to the site of stimulation (anode) or inhibition (cathode), as well as in relation to the intensity and to frequency (number of sessions).<sup>310</sup> Each treatment plan must be drawn up individually by the therapist, considering all the patient's clinical variables.

#### **3.4.5.4. Tinnitus**

Tinnitus is a phenomenon of perception of sound without any external sound source<sup>312</sup> and affects between 10-20% of the population.<sup>313</sup> Chronic tinnitus is a clinical condition that can interfere with the quality of life<sup>312,313</sup> and has comorbidities with depression, anxiety, and emotional concerns.<sup>313</sup> We yet don't have a causal cure for tinnitus, and the pharmacologic and psychosomatic treatment modalities aim to diminish tinnitus' impact on the quality of life.<sup>312</sup> The mechanisms underlying tinnitus have a neurophysiological model as the principal model demonstrating structural and functional disorders in the cochlea, nerves, and the brain, showing suboptimal or maladaptive neuroplasticity in the correspondent areas.<sup>314,315</sup> Two principal neuronal networks are described, one involving the auditory cortex and one involving frontal areas.<sup>314</sup> Non-invasive brain stimulation techniques are a great option in the treatment of tinnitus, such as TMS, transcranial electrical stimulation such, as tDCS, transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS), neurofeedback and transcutaneous vagus nerve stimulation<sup>313</sup>, also transcutaneous electrical nerve stimulation (tens).<sup>316</sup> rTMS is the most studied procedure for tinnitus non-invasive brain stimulation treatment, especially low frequency (1Hz) protocols<sup>314</sup> with 10 (ten) consecutive sessions<sup>315</sup>, with efficacy been observed in the difference between sham and active protocols<sup>314</sup>, with one or more target areas for each protocol. The auditory cortex (AC) is the target most used in the studies.<sup>315</sup> Also, frontal areas are chosen as targets, especially the DLPFC, and

also in the parietal region, the left temporoparietal junction cortex is considered.<sup>315</sup> The auditory cortex seems to modulate the insula cortex, representing a fine modulatory mechanism of the neural network involved in tinnitus.<sup>314</sup> The rTMS is considered a promisor<sup>315</sup> and an effective procedure to treat tinnitus.<sup>317</sup> Burst TMS was also investigated in the treatment of tinnitus with good responsivity in the management of this symptom.<sup>318</sup>

The effect of tDCS is yet controversial, some studies show its efficacy in different protocols<sup>313</sup>, but others show no effect in comparing sham and active protocols<sup>314</sup>, and more studies can increase the level of confidence in this procedure. The potential of non-invasive brain stimulation techniques to induce neuroplasticity in brain areas and networks makes them a promissory treatment for tinnitus.<sup>313-315</sup> Most studies showing neuromodulatory effects on tinnitus are presented with few individuals in each group and varying protocols applied, no consensus is reported, and no indication for clinical intervention is already established. Lefaucheur<sup>111</sup> present two based targets in tinnitus treatment with rTMS, in auditory cortex, and DLPFC, and consider the studies leading to a level C of evidence ("possible effect of repeated sessions of low frequency-rTMS of the temporoparietal cortex (on the left hemisphere or contralateral to the affected ear) in tinnitus"). From what we know at this moment, non-invasive brain stimulation techniques, especially TMS, are recommended for complimentary attendance for tinnitus patients, but more studies are needed in this field, if possible, to form consent. Only one of the studies mentioned<sup>317</sup> shows safety in using TMS for tinnitus treatment, and more studies are required now.

#### **3.4.5.5. Vestibular disorders**

Vestibular Disorders have common complaints such as dizziness and impaired postural balance or disequilibrium. Most of the major causes that lead to vestibular disorders can come from peripheral diseases affecting the vestibular and nerve apparatus or central reasons with lesions in the brain stem, cerebellum, or the brain. NIBS can increment neuronal activity through different techniques. Little is known about the use of NIBS in vestibular disorders. From what we know until now, only one systematic review<sup>319</sup> has analyzed the effect of NIBS

on vestibular disorders, and only two articles are cited on it. Two main protocols are described, both with tDCS. The first one described the use of anodal cerebellar tDCS with the intensity of 2 mA associated with vestibular rehabilitation therapy and shows that the association of tDCS and vestibular rehabilitation therapy is better than vestibular rehabilitation therapy alone. The other used bifrontal positioning of electrodes, being, the anode electrode over the right (F4) DLPFC side and the cathode on the left side (F3), with 2 mA of intensity. This last study also associates tDCS with vestibular rehabilitation therapy. The two studies were randomized controlled designed studies and could show the beneficial effect of tDCS on dizziness and disequilibrium. Different pathologies were included in those studies with common features of the patients being chronic vestibular patients with little response through therapeutics until the time of the studies.<sup>317,319</sup>

Among otoneurologic patients, the elderly with disequilibrium are of the most importance. Saki et al (2022)<sup>320</sup> showed a positive response in treating chronic vestibular dysfunction among old persons. They used the same bifrontal position of the electrodes. That way of positioning the electrodes is of particular interest because the DLPFC is involved in multiple functions such as planning motor commands, and executive functions, having a property in the treatment of depression and anxiety.<sup>321,322</sup> Persistent Postural-Perceptual Dizziness (PPPD) is also investigated about the use of tDCS with some evidence of its use in anodal F3 positioning improving dizziness, balance, and confidence and the neural activity on right superior temporal and left hippocampus observed with neuroimage techniques. PPPD was also treated with neurofeedback with good quality response in the management of its symptoms.<sup>323</sup> One important issue in the treatment of NIBS of vestibular disorders is the use of Galvanic Vestibular Stimulation (GVS), involving different current features such as noise and sinusoidal.<sup>321,322</sup>

There are many studies that show the effects of this stimulation on the vestibular system in animals models<sup>323</sup> and clinical studies<sup>324</sup> improving vestibular-ocular reflex<sup>325</sup>, vestibular-spinal reflex<sup>326</sup>, activation of brain areas<sup>325</sup>, and improvements of the concentration of neurotransmitters such as GABA.<sup>326</sup> On the other hand, little is already proposed for clinical applications such as time of exposure, sessions per week, and duration of the protocols. And

only the study from Saki<sup>320</sup> reported that tDCS is safe application on the elderly in this context.

### **3.4.5.6. Spinal cord injury**

Transcutaneous spinal direct current stimulation (tsDCS) was first described in 2008 as a non-invasive, non-expansive, and simple method to modulate the spinal circuitry through an electrical field induced in the spinal cord (SC) tissue.<sup>327</sup> Similarly to transcranial application, these electrical fields induced may contribute to inhibiting or facilitating neuronal responses influenced by polarity (anodal/cathodal), current intensity, electrode number, location, and design (shape and structure).<sup>328</sup> For polarity dependence, the current applied in the spinal cord interacts with the terminal axon and not with soma like in tDCS. In this way, the cathodal application seems to result in a depolarization of neurons, while anodal may result in a hyperpolarization in the postsynaptic potential.<sup>329</sup>

Indeed, some studies with anodal tsDCS depress ascending spinal pathway conduction and decrease post-activation depression of soleus H-reflex<sup>326-330</sup>, while cathodal tsDCS increase corticospinal output.<sup>331</sup> With regard to the location of the electrode, a modeling study investigated the position of the electrode over the spinous process of the vertebra, and the reference electrode in the region not located over SC: right shoulder, umbilicus, iliac crest, and cervicomentral angle. The location of electrodes is able to induce an electrical field to stimulate several sensorimotor functional areas (upper and lower extremities, neck, thorax, pelvic floor, and abdominal organs).<sup>328</sup> Furthermore, given the several interactions between the brain and the SC, the SC is seen as a “highway” to the brain. In this way, tsDCS is able to module the supraspinal activities.<sup>332</sup> Indeed, tsDCS has been used for treating different neurological diseases and injuries<sup>333-335</sup> and for pain control.<sup>336</sup>

### **3.4.5.7. Dementia**

Dementia has no known cure, and the few successful treatments now available are ineffective in many cases. The potential of non-invasive neuromodulation in the treatment of dementia has been investigated in several articles. For instance, a recent meta-analysis of randomized controlled studies discovered that both TMS and tDCS can enhance cognitive function

in individuals with Alzheimer's disease and mild cognitive impairment.<sup>337</sup> There were 882 participants in 26 randomized controlled trials that were part of the meta-analysis. The studies comprised both single-session and multi-session therapies, and they were carried out between 2010 and 2020. The meta-findings analysis demonstrated that both TMS and tDCS were efficient at enhancing cognitive function in those with moderate cognitive impairment and Alzheimer's disease. TMS had a moderate overall effect size with a standardized mean difference of 0.51 while tDCS had a small overall effect size with a standardized mean difference of 0.26.

The findings held across a range of cognitive functions, such as memory, executive function, and attention. Another investigation has shown that tACS can improve memory function in healthy older persons.<sup>338</sup> Promising outcomes for non-invasive neuromodulation in dementia have also been documented in other trials. For instance, tDCS increased working memory and attention in patients with mild cognitive impairment, according to a 2017 study (3) that was published in the *Journal of Alzheimer's Disease*.<sup>339</sup> Another study found that TMS enhanced cognitive function and decreased neuropsychiatric symptoms in dementia patients, which was reported in the *Journal of Neurology, Neurosurgery, and Psychiatry* in 2020.<sup>340</sup> A network meta-analysis with 19 RCTs showed evidence of the benefits of NIBS, especially tDCS, for beneficial effect on cognition in patients with AD.<sup>341</sup> The studies used different targets of stimulation with different protocols. More homogenous studies are necessary.

### **3.4.6. Neurological disorders in children and adolescents**

#### **3.4.6.1. Neurodevelopmental disorders**

Neurodevelopmental disorders (NDDs) are defined as a group of conditions with onset in the developmental period, inducing deficits that produce impairments of functioning. NDDs comprise intellectual disability (ID); Communication Disorders; Autism Spectrum Disorder (ASD); Attention-Deficit/Hyperactivity Disorder (ADHD); Neurodevelopmental Motor Disorders, including Tic Disorders; and Specific Learning Disorders. These disorders commonly appear during early developmental stages, frequently before the child begins formal education, and are identified by developmental shortcomings that

lead to limitations in personal, social, academic, or occupational activities.<sup>342</sup>

The impact of NDDs is well-known, while the efficacy of the current standard behavioral treatment and drugs medication is still controversial. Promising results in adult neurologic and psychiatric disorders have elicited interest in NIBS, particularly TMS and tDCS, in childhood and adolescent syndromes.<sup>343,344</sup> Several thorough recent reviews summarize the applications of these techniques in pediatric patients<sup>345-349</sup> attempting to induce functional plastic changes not only in sensorimotor processing, but also in higher-level functions (e.g. executive functions, attention, and memory), with the aim to boost rehabilitation.<sup>350</sup> NIBS seems to play a crucial role also in addressing impairment in social cognition and behavior.<sup>351</sup>

Studies examining NIBS as a novel treatment option in NDDs (specially ASD, ADHD, dyslexia and cognitive impairments)<sup>352</sup> have demonstrated positive effects of these treatments supporting its use as a treatment tool for NDDs, particularly when combined with functional training. However, efficacy and safety of using these techniques in the pediatric population is still debated. There is great variability in the methodology of the studies, which precludes any conclusion on optimal stimulation parameters. Gold-standard assessments must be used in the evaluation of the effects and larger randomized double-blind sham-controlled designs are imperative. Also, we need more information about safety, long-term effects of the treatment and potential harm of its application.

#### **3.4.6.2. Autism spectrum disorder**

Autistic spectrum disorder (ASD) is a prevalent neurodevelopmental disorder marked by the presence of restricted or repetitive behavioral patterns, interests or activities and persistent deficits in communication and social interaction in various contexts which begin early in life and may produce lifelong functional impairments.<sup>351,353</sup> ASD is clinical and etiologically heterogeneous, covering a wide range of cognitive and verbal difficulties, sensory abnormalities and behavioral symptoms. Its causes and pathophysiology are not yet clear. Structural and functional abnormalities throughout the development of the nervous system have been proposed in individuals with ASD, such as the presence of a larger number of neurons (it would make it difficult

to activate and inhibit brain areas); changes in the frontotemporal gray matter, cerebellum, amygdala, hippocampus, corpus callosum and cingulate cortex<sup>353</sup>, right brain lateralization; abnormal brain connectivity; altered synaptic maturation and mirror neuron system dysfunction.<sup>354,355</sup>

Recently, noninvasive brain stimulation (NIBS) methods, particularly tDCS and TMS, have been investigated as possible therapeutic options for modifying the pathological neuroplasticity involved in ASD. Recent systematic reviews demonstrate that NIBS methods could be helpful for treating some dimensions of ASD such as repetitive behavior, sociability or some aspects of executive and cognitive functions.<sup>356-358</sup> The most frequently studied targets include dorsolateral prefrontal cortex; medial prefrontal cortex; superior temporal sulcus; temp-paroparietal junction; motor cortex; and frontal cortex.<sup>356</sup>

Regarding TMS, low frequency stimulation has been used for dorsolateral prefrontal targets while medial prefrontal targets and other non frontal targets are preferably stimulated at higher frequencies (5-10 Hz).<sup>359</sup> The tDCS studies point to positive effects with anodic stimulation, with 1-2 mA, for 10-40 min, in up to 28 sessions.<sup>351,359</sup> Despite being optimistic and growing, the evidence is still preliminary and needs to be interpreted with caution, due to the clinical and methodological variability of the studies. More studies are needed to allow clinicians and researchers to base NIBS protocols on robust evidence and lower risk of bias for the treatment of clear and specific outcomes in ASD.

#### **3.4.6.3. Attention deficit hyperactivity disorder**

Attention-deficit/hyperactivity disorder (ADHD) is a worldwide neurodevelopmental disorder characterized by symptoms of age-inappropriate inattention and/or hyperactivity/impulsivity (DSM-5) with a prevalence of around 7%.<sup>255</sup> Neuropsychological functions are frequently impaired in ADHD children mainly deficits in so-called executive functions.<sup>360</sup> The most effective treatment is with psychostimulant medication which enhances dopamine levels in the brain, but longer-term efficacy has not been demonstrated in epidemiological studies.<sup>361,362</sup>

Modern neuromodulation, as a complementary treatment, can directly target the key brain

neurophysiological deficits, mainly in cortical areas such as DLPFC. Brain stimulation has been applied to ADHD mainly using rTMS or tDCS.<sup>363,364</sup> rTMS has shown mostly negative findings on improving cognition or symptoms.<sup>365</sup> Transcranial currents induce plasticity by causing subthreshold polarity-dependent increases (anodal stimulation) or decreases (cathodal stimulation) in membrane potentials that can modify spontaneous discharge rates and cortical excitability, thus increasing/decreasing cortical function and synaptic strength. Side effects are minimal in children.<sup>366,367</sup>

Combining cognitive training with tDCS over a cortical area that mediates the cognitive function being trained<sup>368</sup> (presumably via a synergistic effect of training-induced and stimulation-induced plasticity).<sup>369</sup> A larger meta-analysis of 12 tDCS studies (232 children) found that one to five sessions of anodal tDCS over mainly left DLPFC led to small, trend-level significant improvements in cognitive measures of inhibition ( $g = 0.21$ ) and of processing speed ( $g = 0.14$ ) but not of attention ( $g = 0.18$ ).<sup>370</sup> Although most studies used very small session numbers and tested different cognitive functions, recent meta-analyses found that tDCS may improve ADHD symptoms and cognition including long-term neuroplasticity, work memory, and selective attention. However, only minimal effect sizes were observed.<sup>319,370</sup>

### **3.4.7. Pain disorders**

#### **3.4.7.1. Peripheral neuropathic pain**

Pain is defined by the International Association for the Study of Pain (IASP) as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".<sup>371</sup> Pain may arise from different sources in the body, and when it comes from lesion or dysfunction in the somatosensory system it is called peripheral neuropathic pain (PNP).<sup>372</sup> The most common diseases associated with PNP are diabetic neuropathy, post-herpetic neuralgia, trigeminal neuralgia, peripheral polyneuropathy and radiculopathy syndromes.<sup>372,373</sup> The actual recommendations of IASP to the diagnosis of neuropathic pain in general, that may be used for PNP include a three level categorization into possible, probable and confirmed neuropathic pain.<sup>374</sup> People with PNP may feel spontaneous or evoked pain, aftersensations, hyperpathia and referred pain<sup>371</sup>,



and those symptoms are associated with potential targets for NIBS such as central sensitization<sup>375</sup>, altered expression of neuromediators<sup>376</sup>, disinhibition of synaptic transmission<sup>377</sup>, and alterations in brain organization and connectivity.<sup>374</sup>

Non-invasive stimulation of the nervous system has been extensively investigated in the control of PNP in the last decades, mostly tDCS and rTMS. The main cortical target to treat PNP is the primary motor cortex, which is generally under activated in this condition.<sup>378</sup> Hence, stimulation protocols are used to increase primary motor cortex excitability through anodal tDCS or HF-rTMS. The results of meta analysis and recommendations of guidelines suggest anodal tDCS or 10Hz-20Hz HF-rTMS to be used over a five to 10 days period of induction.<sup>111,379,380</sup> It is expected a moderate reduction of pain intensity, between 30% and 50% and with moderate effect sizes.<sup>381</sup> rTMS has higher effect sizes than tDCS, but with higher cost.<sup>382</sup> The effects are more pronounced weeks after the induction period, and responders are prone to respond to invasive neuromodulation techniques.<sup>382</sup>

### 3.4.7.2. Central neuropathic pain

Central neuropathic pain (CNP) is a chronic painful condition generated by lesion (s) of the spinal-thalamocortical somatosensory pathways in the central nervous system.<sup>383</sup> Caused by stroke, demyelinating, inflammatory, traumatic, or other disease that affect the brain or the spinal cord, it is commonly refractory to current pharmacological treatments.<sup>384</sup>

Repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex (M1) have shown analgesic effect since the first single-session studies with post-stroke CNP patients, more than 20 years ago.<sup>385</sup> Transient analgesic effects, lasting up to three hours after stimulation, were demonstrated with higher ( $\geq 5$  Hz) frequencies over M1.<sup>384-387</sup> A placebo-controlled study of four daily sessions of high-frequency (20Hz) navigation guided M1 rTMS have shown analgesic effect lasting up to three weeks in 47% of the sample of CNP patients.<sup>388</sup>

Systematic reviews<sup>380,389</sup> and an expert's Consensus<sup>380,390</sup> showed evidence of moderate to high analgesic effects but low to moderate after maintenance sessions of M1 rTMS (10-20 Hz, 1500-3000 pulses per session) in CNP. Other targets such as the prefrontal dorsolateral cortex did not show

significant analgesic effect in this group of patients so far.<sup>380</sup> Recent multimodal treatment guidelines for neuropathic pain included M1 rTMS and medullary epidural stimulation as third lines of recommendation for CNP along with classical medications, respectively, for encephalic or medullary CNP.<sup>380,390</sup>

rTMS, as well as other neuromodulation techniques, have increasingly been considered as an option for patients who are resistant or intolerant to current medications. Patients may experience relief of CNP with rTMS on M1. However, long-term stimulation protocols have not been well established. New prospective clinical studies are necessary to establish ideal individualized maintenance phase protocols in this condition. Non-invasive brain stimulation may play a role as an effective and safe option to treat CNP patients.

### 3.4.7.3. Fibromyalgia

Fibromyalgia is a highly prevalent chronic pain disorder characterized by widespread musculoskeletal pain, fatigue, sleep disturbances, and other functional symptoms ranging from depression to somatic and cognitive disorders. Although its etiopathogenesis is not yet fully understood, a complex interplay of genetic, environmental, and neurological factors has been involved.<sup>391,392</sup> There is also evidence that alterations in brain information processing could play a relevant role in the maintenance of symptoms in fibromyalgia. In this sense, chronic pain in fibromyalgia is fundamentally associated with the concept of nociplastic pain (pain derived from altered nociception)<sup>392,393</sup>, as there is evidence of functional changes in the somatosensory system. Furthermore, it is hypothesized that these plastic alterations may be involved in the increased sensitivity for pain detection, as well as the abnormal information processing of bodily signals and proprioception that characterize fibromyalgia.<sup>392</sup> Thus, studies have shown that individuals with fibromyalgia display an increased activation and connectivity within pain-related brain areas<sup>394-397</sup>, as well as a reduced brain activation associated with endogenous inhibitory pain processing<sup>398</sup>, anticipatory pain signaling<sup>399</sup>, and affective stimuli associated with pain perception.<sup>400</sup> This imbalance between the facilitatory (nociceptive) and inhibitory (antinociceptive) brain systems involved in central pain processing appears to extend to neurotransmitter systems. Thus, it has shown that patients with fibromyalgia display elevated levels of excitatory neurotransmitters mediating pain

facilitation<sup>393</sup>, together with decreased availability of  $\mu$ -opioid receptors in brain regions involved in pain modulation (including the nucleus accumbens, amygdala, and dorsal cingulate)<sup>401</sup> and reduced levels of noradrenergic, serotonergic and dopaminergic neurotransmitters during painful stimulation.<sup>393</sup>

According to recent recommendations, pain management in fibromyalgia should begin with patient education and focus on non-pharmacological therapies.<sup>402</sup> Additional therapies should be tailored to the specific needs of the individual and include psychological therapies, pharmacotherapy, and a multimodal rehabilitation program. In the last decade and building on previous findings of central sensitization in fibromyalgia, neuromodulatory brain techniques such as tDCS and rTMS have also been shown to be effective for fibromyalgia.<sup>380,402</sup>

#### **3.4.7.4. Low-back pain**

Treating low back pain is a challenging condition, especially when it becomes chronic. The advancement of brain imaging opened up new possibilities based on structural and functional changes associated with pain persistence.<sup>403</sup> Regardless of whether neuronal activity is increasing or decreasing, evidence of cortical and subcortical dysfunctions may lead to important impairments in processing, perception and regulation of pain signals.<sup>404</sup> The evidence of brain alterations in chronic pain states expanded chronic low back pain (CLBP) treatment options beyond the traditional biomechanical approaches.

NIBS techniques such as rTMS and tDCS have emerged as promising strategies for treating CLBP patients by targeting dysfunctional brain area.<sup>111,227</sup> The rationale for using NIBS techniques is the ability to induce positive neuroplastic changes (normal excitability patterns) and, as a result, pain relief, via (most evidence) primary motor cortex (M1) stimulation. It has been shown that M1 stimulation activates pain processing structures such as the thalamus through cortico-thalamic projections<sup>404</sup> and facilitates descending pain inhibitory controls.<sup>405</sup>

However, randomized trials investigating the clinical benefits of NIBS techniques are urgently needed to validate its recommendations for treating chronic low back pain. There have been few studies on the efficacy of rTMS, with one randomized trial (not

blinded) showing that long-term repeated sessions reduce pain perception in CLBP patients.<sup>403</sup> The use of tDCS as a single therapy appears insufficient to produce clinical benefits.<sup>406</sup> Nevertheless, when combined with exercise therapy<sup>407</sup> or peripheral electrical stimulation (sensory level)<sup>408</sup>, tDCS showed promising results for pain relief.

#### **3.4.7.5. Cancer pain**

Pain is one of the symptoms that commonly leads to cancer diagnosis.<sup>409</sup> Although it can be present during the course of disease, pain usually increases intensity as the lesions progress, so that 75-90% of patients with metastatic or late-stage cancer will experience pain.<sup>410</sup> Most of what we know about the mechanisms that generate cancer-related pain is concentrated in changes in the primary afferent sensory and sympathetic nerve fibers that innervate the organ with tumor lesion.<sup>411</sup> However, new perspectives on the biology of pain caused by tumor invasion have emerged. Cancer pain must be understood as a result of processes that involve complex interactions between neoplastic cells and host's immune and peripheral and central nervous systems.<sup>411,412</sup> Intolerance to side effects, use of polypharmacy, high cost and difficulty of access are important barriers to the treatment of cancer-related pain.<sup>380</sup> In this context, there is growing interest in non-pharmacological treatments, such as NIBS.

Recent guidelines concluded that rTMS of M1 is probably effective for the treatment of neuropathic pain and fibromyalgia.<sup>380</sup> Anodal tDCS applied to the motor cortex contralateral to the pain side have been shown to be effective for various neuropathic pain syndromes.<sup>303</sup> However, although promising results, studies using TMS and Tdcs and patients with cancer-related pain are rare and there are no randomized controlled trials. These therapy as an adjunctive treatment for cancer pain may prove to be beneficial.<sup>412</sup> However, more studies are needed to determine more specifically in which situations these therapies would be indicated.

#### **3.4.8. Physical and cognitive performance**

##### **3.4.8.1. Physical performance**

Knowledge of the effects of "brain focused recovery strategies" on elite athletes is still limited.<sup>413</sup> The stress from competition can result in fatigue, perceptions of

soreness, decreased alertness and motivation to train during days postexercise.<sup>414</sup> Changes in decision-making, mood, and motivation<sup>414,415</sup> suggest that brain-related fatigue should be addressed in sports. It is reasonable therefore to consider that recovery strategies that can influence psychophysiological dimensions, notably regarding brain modulation, could offer an effective alternative in sport.

The use of tDCS as a recovery strategy emerges as a promising alternative. For example, positive impacts (improvement) on reaction time, response time, vigilance and mood, after being negatively influenced by fatigue, were demonstrated in military personnel after the use of tDCS over the DLPFC.<sup>416</sup> Indeed, Mehrosfar et al.<sup>417</sup> demonstrated that the application of tDCS over the DLPFC [anode electrode (+) over the left DLPFC and the cathode over the right DLPFC (-) (+F3/-F4 montage)] increased the athletes' perception of vigor and reduced the perception of fatigue, tension, and cognitive and somatic anxiety. Studies with team sport athletes have also shown the potential of using the tDCS technique over the DLPFC (+F3/-F4 montage) as a recovery strategy in professional male and female soccer athletes.<sup>414,417</sup> Changes in well-being and autonomic activity were demonstrated in these studies, suggesting the potential use of tDCS for recovery in sports as well.

If tDCS can improve athletes' recovery from competition, it can also be used during the training process, not only focused on improving short-term recovery, but also to counteract the sport-related stress and the non-sport environment to which athletes are constantly subjected.

#### **3.4.8.2. Cognitive performance**

Cognitive performance has been the target for the creation and intervention of different technological strategies for its improvement, changing the way "our cognition shapes and is shaped by technology".<sup>418</sup> In this scenario, we can see the relevance of the use of NIBS techniques that explore neuroenhancement in complex learning tasks, modulating neural networks underlying cognitive and motor performance.<sup>418,419</sup>

In the search for improvement, different techniques have been applied, and although studies have explored the application of photobiomodulation for neuroenhancement<sup>420,421</sup>, currently the studies use, eminently, repetitive electrical and magnetic

stimulation techniques, which can be done as a tool for cognitive improvement, evidenced, for example, when used with physical training.<sup>420</sup>

Regarding the use of magnetic stimulation, the accelerated theta-burst stimulation protocols show better results when compared to the use of repetitive high-frequency stimulation, although its standardization is necessary<sup>420</sup>, which also occurs with electrical stimulation, widely used by amateur and professional athletes, increasing the interest in the ethical regulation of its use<sup>422</sup>, besides the investigation of how to restrict the variability of its application through self-directed devices, and also the need to monitor the growing number of new devices promising neuroenhancement that have not been submitted to controlled tests.<sup>422,423</sup>

Despite all this, one can see the increasing interest in the use of NIBS techniques for neuroenhancement, both in controlled environments such as laboratories, and in more naturalistic environments such as those used in sports, the arts, and education. We still need to know the long-term effects of its use and the relationship between dose and appropriate response, key elements for the survival of these interventions in science and everyday life.

## **4. Final remarks**

The purpose of this present review is to give the reader an overview of neuromodulation, showing the non-invasive assessment and treatment through neurostimulation techniques and pointing out their clinical applicability in various segments of the health area. We believe that this material can support deeper understanding of brain structure and to identify types of techniques and targets for non-invasive stimulation of the nervous system in different functions and diseases.

The development of brain imaging techniques aims to provide professionals with a dimension of the brain dynamics involved in the most diverse activities and tasks. A better understanding of brain connectivity mechanisms is the basis for the development of broader and more varied therapeutic techniques, aiming at better rehabilitation of functions altered by certain clinical conditions/diagnoses or even improved performance in healthy subjects.

In general, there is a consensus among authors about the need to conduct more studies, involving a larger number of subjects and a carefully elaborated methodology, with well-defined and controlled criteria. Moreover, the concomitant performance of NIBS with clinical therapeutic strategies has been indicated by most studies, showing better results when there is a brain activity of elaboration, association and/or execution happening simultaneously with the external stimulus promoted by the neuromodulation techniques.

The substantial increase in investigations using neurostimulation supports the idea that those techniques can be a very effective treatment option for children or adults patients, who have deficits related to the brain's interface with sensory, motor, cognitive, emotional and/or psychological aspects. With the advancement of research in the field of neuromodulation, it will be possible to find answers to the many questions that continue to be formulated in line with research and clinical practice.

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## 6. Authors contributions

Baptista AF, Oda AL and Sá KN were responsible to coordinate this work and get together each part sent by authors, writing abstract, methods, introduction, and final remarks. Zana Y reviewed all parts and has contributed with improvement of alignment of all intellectual contributions. Fonseca A, Rodrigues EC, Fraga F, Santana JE, Sato JR, Trambaiolli L, and Oliveira TL wrote updates about basics on brain imaging techniques. Baptista AF, Casalli AG, Fernandes AM, Caparelli-Dáquer E, Silva JRT, Monte-Silva KK, Sá KN, Silva ML, Lee M, Parizotto NA, Montoya P, Duarte-Moreira RJ and Cury R wrote neuromodulation techniques. Oda AL and Carthery-Goulart MT wrote about application of neuromodulation in communication disorders. Brunoni A, Sá KN and Baptista RF wrote about mental disorders. Santana MV and Shinjo SK wrote in musculoskeletal disorders. Oda AL, Fontana AP, Boffino CC, Oliveira CEN, Monte-Silva KK and Brito RM wrote in neurological adult disorders. Valiengo L wrote in dementia and Angelis EC, Goulardins JB and Muszkat M in neurological disorders in children and adolescents. Baptista AF, Oliveira RAA, Montoya P and Hazime FA wrote about pain disorders. Okano AH

and Moreira A wrote about physical performance, while Tanaka C wrote about cardiorespiratory disorders and Maia Maércio about cognitive performance.

## 7. Conflicts of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Abrahão Fontes Baptista, Adriana Leico Oda, Katia Nunes Sá, André Fonseca, Francisco Fraga, Clarice Tanaka, Maria Teresa Carthery-Goulart, André Brunoni, Michael Lee, Samuel Katsuyuki Shinjo, Ana Paula Fontana, Katia Karina Monte-Silva, Fuad Ahmad Hazime, Alexandre Hideki Okano, Alexandre Moreira, Mauro Muszkat, Egas Caparelli-Dáquer, Erika Carvalho Rodrigues, Pedro Montoya, João Ricardo Sato, Nivaldo Antonio Parizotto, Yossi Zana, Josie Resende Torres da Silva, listed as co-authors, are section editors in the Journal of Brain Imaging and Stimulation.

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