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Editorial:
Bench to Bedside – the translation of intracortical inhibition marker to clinical practice

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Introduction

The history of Clinical Research went through an arduous and fascinating journey. From Austin Flin - having conducted the first study with a placebo - passing through the UK Medical Research Council's (MRC) trial of patulin for the common cold (the first double-blind controlled trial), until the iconic 1948 study for tuberculosis (the first randomized control trial), much has evolved. The result of this process is a structure that allows investigators to gradually apply, in a safe way, the data generated dur-ing laboratory and pre-clinical studies to the development of trials and studies in humans - commonly known as taking the knowledge from "bench to bedside."

Despite the growing number of noninvasive and technological therapies, some therapies conducted on the bench are sometimes challenging to translate to the bedside. For example, transcranial magnetic stimulation (TMS) is a safe and noninvasive way of stimulating the brain by electromagnetic induction that has been studied since 1985. However, 37 years later, aside from major depression and obsessive-compulsive disorder, the therapeutic use of this neuromodulation technique remains restricted to the off-label and experimental investigational research (Burke et al., 2019). Similarly, TMS can be used as an assessment tool to evaluate intracortical inhibitory and excitatory processes (Burke et al., 2019).

Considering that several neuropsychiatric conditions have shown altered patterns of the homeostatic control of excitatory and inhibitory networks (e.g., chronic pain and depression), the TMS assessments could help characterize the maladaptive neuroplasticity associated with multiple diseases. However, the translation of neurophysiological findings to the clinic depends on the reliability and validity of the marker, which requires proper test-retest and inter-rater correlations. Also, it depends on the sample sizes and the sample diversity in the studies; usually, validation studies require large samples and adequate representation of the target population (age, disease severity, and comorbidity frequencies).

Finally, a critical challenge for the clinical translation of neurophysiological markers is the construct validity, namely the biological plausibility and causality link between the marker and the clinical domain being assessed (correlation between the marker and the clinical feature at baseline and after follow-up)(Koch et al., 2020; Olbrich & Arns, 2013). All these factors are crucial for a successful translation and are progressively under assessment in the current TMS literature.

In this editorial, we will show examples of other promising clinical applications of TMS as assessment, particularly intracortical inhibition (ICI), a neurophysiological marker for studying the inhibitory tonus within the motor cortex and their associated networks.

Overview of TMS

TMS is a noninvasive brain stimulation technique (Wagle-Shukla et al., 2009), in which a magnetic stimulus is delivered to elicit cortical excitability changes due to an electromagnetic induction phenomenon (Klomjai et al., 2015). Hence, it can be used as an intervention, using repetitive pulses to induce long-lasting cortical changes (Bonin Pinto et al., 2019; Ekhtiari et al., 2019; Gershon et al., 2003); or as an assessment (Gunduz et al., 2020; Pacheco-Barrios et al., 2022; Uygur-Kucukseymen et al., 2020), through both single- and paired-pulses protocols that temporarily modulate the cortex.

The main parameters evoked by the TMS are motor-evoked potential (MEP), motor threshold (MT), ICI, intracortical facilitation (ICF), and cortical silent period (CSP). An MEP is an electromyography response elicited after delivering a single-pulse TMS stimulus in a motor cortex area that represents a target muscle. It is commonly used to estimate corticospinal tract excitability (Klomjai et al., 2015). On the other hand, paired-pulse TMS protocols use two consecutive pulses – a subthreshold conditioning stimulus (CS) followed by a suprathreshold test stimulus (TS) – with a short or long inter-stimulus interval (ISI) to measure inhibitory and excitatory intracortical networks, depending on the ISI (Kujirai et al., 1993; Valls-Solé et al., 1992) (Tokimura et al., 1996). Long ISIs (8-15 ms) are used to elicit an ICF, and short ISIs (1-4 ms) elicit an ICI (Chen et al., 1998; Kujirai et al., 1993).

This commentary focuses on the ICI – a marker that reflects a GABA-mediated inhibitory response of intracortical networks – which could be used as a surrogate or diagnostic marker in several neurological and neuropsychiatric diseases. This may be due to a deficit in the inhibitory responses within the somatosensory areas and other connected regions (frontal cortex and thalamic regions). The ICI – as a way to measure the level of motor cortex inhibition– is a promissory tool. We will briefly discuss the progress and challenges of using ICI in a clinical context for chronic pain conditions (osteoarthritis, phantom limb pain, and fibromyalgia) and depression as examples of an ongoing bench-to-bedside translation.

ICI and knee osteoarthritis (KOA) chronic pain

Knee osteoarthritis is a prevalent disease, with studies reporting a global prevalence of around 16% (Cui et al., 2020). Despite the disease itself having some known risk factors and triggers (Driban et al., 2020), the level of pain can vary among patients (Driban et al., 2016). The pain can occur independently of the severity of the peripheral injury (cartilage degeneration), being a major burden for patients (M. Simis et al., 2021). This could be explained by maladaptive neuroplasticity at the pain-related networks, which leads to an endurance of pain (Willett et al., 2020). In fact, current evidence has shown that in these patients the imbalance between excitatory and inhibitory circuits may be caused by an inefficient inhibitory system that is not able to compensate the increased peripheral nociception (M. Simis et al., 2021).

The ICI has been characterized as a marker of compensation for chronic pain on KOA (Marcel Simis et al., 2021). Simis et al. found not only associated ICI with KOA compensation, but also with demographic variables. The higher the cortical inhibition, higher the compensation of the chronic pain; also, the patients on the cohort that presented higher ICI were also younger, had greater cartilage degeneration and had less pain on the WOMAC scale (Marcel Simis et al., 2021).

Hence, transcranial magnetic stimulation represents a useful tool to assess the brain function and excitability, such as the ICI and ICF. It could be used to objectively measure this inhibitory dysfunction and potentially monitor treatment response. Although these results are promising, the ongoing clinical translation is still pending due to the need of larger sample sizes, inclusion of more diverse OA populations, and longitudinal explorations assessing test-retest reliability and changes after treatment (Hermsen et al., 2016).

ICI and phantom limb pain (PLP)

PLP is a pain perception that emerges from the representation of an amputated limb. Its prevalence can be high in this population (40 to 60%), with a great impact on their quality of life (Limakatso et al., 2020). Some studies have looked for risk factors associated with PLP, showing that phantom sensations, pain prior to the amputation, and use of prosthesis are some of its associated factors (Dijkstra et al., 2002; Münger et al., 2020). These patients are usually resistant to other forms of treatment, such as medications (Alviar et al., 2016), likely due to the lack of understanding of its pathophysiology.

Similarly to other chronic pain conditions, the development of PLP seems to be related to an impairment on the neuronal inhibitory system after sensorimotor reorganization (Pacheco-Barrios et al., 2020). Corroborating with this hypothesis, a systematic review reported that although only a few studies assessed cortical excitability, most studies showed a decrease in ICI in the affected hemisphere (contralateral to the amputation) (Candido Santos et al., 2020).

Similarly, TMS could be used to quantify the deficit in the inhibitory system as a predictor of PLP development or as biomarker of treatment response. The bench-bedside translation is still under development, similarly, the main challenges are the need for larger sample sizes and validation studies testing the predictive power of ICI to detect different symptoms trajectories (temporary PLP vs. chronic PLP). On the other hand, non-invasive treatment options, such as tDCS, showed reduction of ICI in a chronic PLP cohort, mostly on the affected hemisphere. These cortical changes were associated with less PLP as well (Gunduz et al., 2021). Likewise, validation studies are needed testing treatment response prediction via classical statistical analysis and statistical learning techniques (machine learning algorithms)(Pacheco-Barrios et al., 2021).

ICI, fibromyalgia (FM) and major depressive disorder (MDD)

FM and MDD are known to have overlapping clinical manifestations (Cardinal et al., 2019) and, in conjunction, represent a high disease burden (Marques et al., 2017). Therefore, it is imperative the development of an objective biomarker that could help to assess the endotype of these two pathologies. Different studies have already shown the efficacy of TMS in assessing the neurophysiology of both pathologies (Castricum et al., 2022; Caumo et al., 2016; Fidalgo et al., 2014)

One of these studies (Cardinal et al., 2019) evaluated motor cortex inhibition indexed by TMS measures, such as ICI and ICF, as well as the function of descending pain modulatory systems (DPMS) between FM and MDD. They used a multivariate analysis model to assess the relationship between variables: SICI, ICF, and CPM-test (independent variables) and FM and MDD (dependent variables), adjusting by the serum brain-derived neurotrophic factor (BDNF) - used as a surrogated marker of neuroplasticity. Their results showed an increased SICI, conversely correlated with the change in the Numerical Pain Scale (NSP) during the CPM, but only in the FM population. It suggests the presence of significant differences in the pathophysiological mechanisms between the two diseases, despising their overlapping clinical symptoms. With that in mind, TMS could assess MDD patients as having a more "functional" DPMS compared to FM patients, leading to better diagnosis and, consequently, better care between these two populations.

Among other clinical features, fibromyalgia is characterized by widespread pain, being in the top three most common musculoskeletal conditions. The findings are sometimes sparse and depend on self-reported scales since there are no images or direct clinical findings (Sarzi-Puttini et al., 2020). Consequently, there is a need for different assessment techniques helping to predict a correct diagnosis or clinical improvement. Therefore, the interaction between TMS and neural circuits, more directly than neuroimaging, could lead to a better correlation between brain area and behavior (Burke et al., 2019), potentially becoming an objective biomarker for FM.

Aligned with our hypothesis, Pacheco-Barrios et al. (Pacheco-Barrios et al., 2022) compiled 15 studies correlating TMS and fibromyalgia, finding that FM patients have an unbalanced inhibitory motor cortex regulation with less intracortical inhibition. FM patients seem to have a deficit in the GABAergic network, represented by central sensitization and altered motor cortical excitability. (Caumo et al., 2016; de Oliveira Franco et al., 2022). This inhibitory dysfunction seems to be modulated by some interventions such as exercise, pregabalin, and non-invasive brain stimulation, which can increase intracortical inhibition (Pacheco-Barrios et al., 2022). Therefore, TMS metrics that measure brain intracortical inhibition – such as the SICI – can potentially be a biomarker of clinical improvement in FM patients; according to Pacheco-

Barrios et al. and colleagues, changes in ICI and ICF are correlated with clinical improvements: higher inhibition moderately correlates with less pain, depression, and pain catastrophizing. These results confirmed the high potential utility of using TMS assessments for FM patients in clinics representing our examples' more advanced bench-bedside translation. Although, more validation studies are warranted before including paired-pulse protocols as a habitual neurophysiologic measurement for FM.

Conclusion

Most of the time, the neurophysiological findings go a long way until they can be applied in a clinical setting. Despite the last decade has been seen an increase in the application of TMS on the study of brain-behavior and Neurologic disorders, such as FS, MDD and PLP, there are still some challenges regarding the use of this device. For example, one of the greatest barriers to more widespread adoption of TMS in clinical practice would be the variability in each participant's response to stimulation, ranging from irregularity in pulse-to-pulse reactions within a single participant to inconsistent outcomes after therapies across patients. This variability contributes to the continued uncertainty regarding the more optimal TMS assessment protocol, which in turn offers a hindrance regarding the clinical application of the TMS. Still, it is essential that researchers try to maintain that goal in mind and constantly refine biomarkers for clinical use. As exemplified with ICI, the bench-bedside translation is a non-linear process that holds the promise of better diagnosis and prediction in the clinic.

Conflict of interest

The authors declare no conflict of interest. KPB and FF are members of the PPCRJ editorial board, they were not involved in the editorial process of the present manuscript.

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