

## *Estimulación cerebral no invasiva combinada con neuroimagen: Hacia una medicina de precisión en el tratamiento de las adicciones*

Neuroimaging studies have shown that two of the different existing brain networks are particularly involved in addictive behaviour (Dunlop, Hanlon & Downar, 2017). The first is the salience network (SN), which has several key nodes: the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex, and the anterior fraction of the insulae. This system, which is central to cognitive control and response inhibition (Dosenbach et al., 2006; Menon & Uddin, 2010), has been identified as a common pathophysiological substrate of various psychiatric illnesses

(e.g., addiction, depression, and obsessive-compulsive disorder; Goodkind et al., 2015). In addictive disorders, this circuit is hypoactive. Abnormal functioning of this network could be behind the difficulty experienced by addicted people of curbing the impulse to consume when exposed to drug-related stimuli. The second brain network of key interest in addictions is the ventromedial network (VMN), which primarily encompasses the ventromedial prefrontal cortex (VMPFC), orbitofrontal cortices, and nucleus accumbens. This circuit is known as the brain's dopaminergic reward pathway. In addition, the network is hyperactive, thereby governing craving, i.e., the powerful need to consume the addictive substance (Volkow, Michaelides & Baler, 2019; Volkow, Wang, Fowler, Tomasi & Telang, 2011). In addictive disorders, not only is the intrinsic functioning of these networks altered, but the functional dynamics between them are also compromised (Hu, Salmeron, Gu, Stein & Yang, 2015; Zhang et al., 2015).

Looking at it in this way, addiction can be thought of as a psychiatric condition associated with an imbalance in brain networks, in particular a perturbation of two central circuits that play opposite roles in behaviour regulation. While the NS makes it possible to exercise control over decision-making processes, the VMN has the potential to generate craving. To simplify the treatment perspective, it can be said that psychosocial interventions seek to enhance the NS and avoid the stimuli that trigger the VMN, while pharmacological interventions seek to inhibit the VMN to make control of craving more viable.

In this framework, neuromodulation techniques have emerged as a promising therapeutic alternative given their ability to restore the homeostatic functioning of brain networks by modulating their main nodes (e.g., Antonenko et al., 2018; Meinzer et al., 2015; Orlov et al., 2017; for a review of this aspect in cognitive aging, see Abellana-Pérez, Vaqué-Alcázar, Solé-Padullés & Bartrés-Faz, 2022b). Most of the research involving non-invasive brain stimulation (NIBS) procedures in the field of addictive disorders has focused on the use of transcranial magnetic stimulation (TMS) and on transcranial direct current stimulation (tDCS). These techniques, particularly TMS, have also emerged with great translational potential, and protocols approved by the *Food and Drug Administration* (FDA; <https://www.fda.gov/>), to treat other psychiatric disorders, for example treatment-resistant depression and obsessive-compulsive disorder.

Before moving on to the application of these techniques to brain networks, let us take a look at how they work. Firstly, TMS is a technique that allows non-invasive stimulation of the cerebral cortex by generating brief and powerful magnetic pulses to produce a secondary electrical current in the brain, modifying its excitability (e.g., Ridding & Rothwell, 2007; Rossini et al., 2015). TMS can be applied in single, paired and repetitive pulses. In

clinical practice, single and paired pulses have been used mainly for diagnostic purposes (for example, in multiple sclerosis: Conte et al., 2009; or in pathological aging: Benussi et al., 2017; 2020), while repetitive pulse trains (repetitive TMS, rTMS) have been applied for therapeutic purposes (Burke, Fried & Pascual-Leone, 2019). There are two main types of rTMS protocols: classic and patterned. In classical, depending on the stimulation parameters, rTMS can increase or decrease cortical excitability (Hallett, 2007). Procedures that use specific patterns of rTMS, such as 'theta-burst stimulation' (TBS), also allow mechanisms associated with neuronal plasticity to be induced (Huang, Edwards, Rounis, Bhatia & Rothwell, 2005). Secondly, tDCS is characterized by producing weak direct and tonic currents in the brain (Nitsche & Paulus, 2000). Similarly, new-generation electrical stimulation procedures called multifocal stimulation protocols have recently been developed which allow different brain regions to be stimulated simultaneously (Abellana-Pérez et al., 2021; Ruffini, Fox, Ripolles, Miranda & Pascual-Leone, 2014).

The studies performed to explore the clinical efficacy of neuromodulation techniques in addictions have followed two complementary approaches (e.g., Dunlop et al., 2017; Hanlon et al., 2015). The first focuses on boosting different nodes of the salience network through excitatory stimulation techniques. In line with the above, this should increase the cognitive control of the patients involved. One example is the classic study by Eichhammer et al. (2003), in which excitatory stimulation of the DLPFC was associated with significant reductions in cigarette smoking. Other studies have gone further by simultaneously stimulating different nodes of the SN, such as the DLPFC and the anterior insulae, with a special rTMS method which allows deep regions to be reached (e.g., by using H7-type coils); this also produced a reduction in drug use (Dinur-Klein et al., 2014). It is important to mention that research in this area, with exceptions where more refined procedures have been applied with the help of neuronavigation (e.g., Li et al., 2020), have primarily been able to control the behavioural spectrum of addiction, with only a minor impact on craving. This suggests that these protocols would mainly allow the cognitive control network (i.e., SN) to be modulated, but not so clearly its anti-network, the reward network (i.e., VMN).

The alternative approach, focusing on attenuating craving by reducing the activity of the ventromedial network, began development later. Initially, Hanlon et al. (2013) demonstrated, in a healthy sample, that by using TMS combined with neuroimaging it was possible to modulate the neural pathways governing executive control differentially from those associated with reward by stimulating dissimilar brain nodes. The DLPFC was stimulated in one way and the VMPFC in another. Once confirmed that was possible to modulate the VMPFC and the ventral striatum in a specific

way, the authors replicated the study with cocaine users. In this case, they applied inhibitory rTMS while the patients performed a craving induction task. Results showed that, as hypothesized, inhibitory rTMS significantly reduced brain activity in these ventromedial and striatal regions in study subjects (Hanlon et al., 2015). Nevertheless, subsequent studies have shown that the effect of these protocols is not the same in all subjects, and the observed effects may depend on various baseline neurobiological aspects (Kearney-Ramos et al., 2019). At a generic level, this is because neuromodulation techniques, both in their basic and clinical application, show notable inter- and intra-individual variability (Hamada, Murase, Hasan, Balaratnam & Rothwell, 2013; Martín-Trias et al., 2018).

To date, several biological factors contributing to such individual variability have been identified. Among them, we have found differences in the activation of intracortical networks (Hamada et al., 2013), in the basal functional connectivity of the modulated network (Nettekoven et al., 2015), in cortical excitability (Jannati, Block, Oberman, Rotenberg & Pascual-Leone, 2017), in the induced current in the brain (Abellana-Pérez et al., 2021; Saturnino, Thielscher, Madsen, Knösche & Weise, 2019) and even in genetic endowment (Abellana-Pérez et al., 2021; Pérez et al., 2022a; Di Lazzaro et al., 2015). In the context of the clinical application of these techniques, the studies reveal two crucial elements: on the one hand, the importance of offering applied interventions with the highest possible level of personalization, and, on the other, the possible existence of individual predictors of treatment efficacy. Taking these elements into consideration when applying neuromodulation protocols would presumably maximize treatment success, allowing subjects in whom a high probability of therapeutic response is estimated to receive the most personalized interventions possible.

With reference to the personalization of interventions, it is important to consider that rTMS can be applied with different levels of precision. At this point, it should be noted how crucial the combined use of brain stimulation with neuroimaging has been, since it has made it possible to reveal the neurobiological pathways mediating the therapeutic effects of this type of intervention in different psychiatric disorders. One of the disorders which has seen more research in this regard is depression, where the location of the stimulation point has been perfected in recent years. Specifically, this has changed from determining the stimulation target with simple calculations on the scalp based on the motor cortex or following the 10-20 international system to the use of neuroimaging, first structural, and then functional, to determine the optimal stimulation point in the DLPFC according to its level of connectivity (anti-correlation) with the subgenual nucleus (Cash et al., 2021; Fox, Buckner, White, Greicius & Pascual-Leone, 2012; Weigan et al., 2018). This optimization in

target location, which has led to a substantial improvement in the response to treatment in depression, could also be effective in addictions, given the shared pathophysiology at the level of macroscopic networks between both conditions (Dunlop et al., 2017). A second element of personalization that has gradually become more important is related to the possibility of determining the exact stimulation dose that needs to be applied to each patient in order to suitably modulate the selected region, going beyond what is related to the threshold of the motor cortex. In this sense, in the future, the application of finite element calculation methods applied to structural images will probably be a relevant element to take into account in increasing the individualization of these interventions (Abellana-Pérez et al., 2021; Saturnino et al., 2019). Finally, it is worth mentioning the possibility of using neuromodulatory procedures that require fewer pulses and shorter treatment sessions, such as those using patterned rTMS (i.e., TBS). Being equally effective (e.g., Blumberger et al., 2018), these may be tolerated much better and can thus increase treatment adherence, essential in addictive disorders. Furthermore, given that TBS induces brain plasticity mechanisms, it could reverse the lasting neural effects due to psychiatric pathology on the one hand and, on the other, produce beneficial long-term effects, an essential aspect in the treatment of addictions.

Moving on to the second line of action, this focuses on carefully characterizing patients so that they can receive the most effective treatment option in each case. Here, we may consider that initial patient assessment, aimed at collecting as much data as possible on the predictive variables of treatment response, can be essential in guiding clinical decisions based on the markers identified. In this sense, structural examination of brain atrophy (Wagner et al., 2008), exploration of the basal functional state of brain networks (Nettekoven et al., 2015), together with the plasticity or malleability shown by them (Abellana-Pérez et al., 2019; Perellón-Alfonso et al., 2022), the specific ability to affect deep areas of interest (Vink et al., 2018), and even the genetic profile associated with synaptic plasticity (i.e., Abellana-Pérez et al., 2022a) would be key factors in estimating the chances of success of a specific neuromodulation protocol in a specific patient. This characterization should not be aimed solely at determining which patients are candidates for stimulation or not. That is, rather than being a go/no-go decision, it would make it possible to determine which patients would be candidates for which particular type of intervention. This line of action could lead to a radical change in the clinical use of neuromodulation, allowing the principles of personalized medicine to be applied to the field of psychiatry. However, these approaches are currently in the process of neuroscientific development, pending the identification of markers that are scalable to daily clinical practice.

All of the above suggests an approach involving a new perspective in the clinical implementation of neuromodulation. This new paradigm arises from the need to leave behind the notion that the heterogeneity associated with neuromodulation techniques are a limiting factor in clinical application, instead beginning to see it as an opportunity. It is an element that we can take use to our own ends in optimizing, and thus maximizing, treatment success in each patient. The fundamental idea behind this perspective is that the variability observed through stimulation techniques does not, of course, inform us of the differences in the techniques per se, but of the different ways in how each brain responds to them. And knowing how each brain responds is essential in determining how to apply the best therapy. Future research should thus focus not only on the clinical efficacy of this type of intervention, but also on the customization capacity that these protocols present and on the identification of their treatment efficacy markers. All this is key for making effective progress in the application of such interventions. In this way, we will be able to integrate advances in precision neuroscience into the clinical context of addictive disorders, with the ultimate goal of promoting treatment success in these patients.

In conclusion, it is reasonable today to imagine that in the near future it will be possible to study the addicted patient using neuroimaging techniques to establish exactly which brain networks to stimulate in order to reduce craving and increase cognitive abilities to deal with drugs. Undoubtedly, clinical work focusing on the patient and tackling the complex comorbidities and social situations that accompany addictive processes will continue to be essential, but it is clear that, if this new scenario is realized, it will not only constitute an important scientific advance, but will also contribute greatly to reducing the stigma associated with addictive behaviours.

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