Don't Hurt Me No More: State-dependent Transcranial Magnetic Stimulation for the treatment of specific phobia

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Sara Borgomaneri[1,2]*, Simone Battaglia[1], Alessio Avenanti[1,2], Giuseppe di Pellegrino[1]

[1] Centro studi e ricerche in Neuroscienze Cognitive, Dipartimento di Psicologia, Università di Bologna, Campus di Cesena, 47521, Cesena, Italy;
[2] IRCCS Fondazione Santa Lucia, 00179 Rome, Italy;

*Correspondence should be addressed to: Sara Borgomaneri. Department of Psychology, University of Bologna. Viale Berti Pichat 5, Bologna, 40127, Italy. mailto: sara.borgomaneri@unibo.it

Dear Editor,

Specific phobia (SP) is the most prevalent anxiety disorder, with especially high prevalence in women (6-12%). SP is characterized by an excessive, irrational fear of a specific object or situation, which is either avoided at all cost, or endured with great distress, interfering with work and quality of life. The combination of psychotherapy and pharmacotherapy are generally regarded as first-line treatment. However, about 25% of patients respond poorly to treatment and show a high risk of chronicity, or experience a return of fear. Estimates of direct and indirect annual costs for SP are high (Bajbouj and Padberg, 2014). Therefore, developing and implementing new effective treatments for such a highly debilitating disorder is urgently needed. Increasing evidence suggests that targeted modulation of neural networks by non-invasive brain stimulation (NIBS) might represent a further treatment option (Bajbouj and Padberg, 2014). However, very few studies have tested the efficacy of NIBS in the treatment of SP. Among the few, Notzon et al. (2015) evaluated the effects of intermittent theta burst stimulation (iTBS) on virtual reality–provoked anxiety in SP patients. They showed no significant improvements following a single session of iTBS over the dorsolateral prefrontal cortex (dlPFC). Yet, a potential issue in NIBS is the limited efficacy and specificity of neurostimulation when NIBS protocols are not associated with specific behavior or cognitive process. Following this idea, Marin et al. (2014) proposed to use NIBS to specifically target fear-relevant processes in order to deepen our understanding of the pathophysiology of anxiety disorders. Indeed, one influential model of the etiology of SP proposes that phobias emerges as a result of misguided fear conditioning processes (Herrmann et al., 2017), which might render originally innocuous stimuli fear-inducing and threatening. In support of this notion, it has been reported that exposure to phobia-specific stimuli elicits brain activation that is consistent with current understandings of the neuroanatomy of fear conditioning (Ipser et al., 2013), supporting the model of SP as originating from learnt fear responses. In particular, phobic individuals show enhanced brain activations to phobia-relevant stimuli in the fear network, including the amygdala and the prefrontal cortex (Ipser et al., 2013). Therefore, in order to modulate extinction learning, Herrmann et al. (2017) administered rTMS over the ventromedial prefrontal

cortex (vmPFC) immediately before a virtual reality exposure to heights in two groups of individuals diagnosed with acrophobia. The protocol consisted of two active sessions of rTMS with 10 Hz, and the sessions were 1 week apart. Anxiety and avoidance ratings decreased in the active group at the end of the treatment, but the beneficial effect was no longer observed at the 3-months follow-up, where both groups showed similar improvements, suggesting that rTMS tended to ameliorate the immediate efficacy of exposure treatment of acrophobia. Although promising, these results are based on the increase of extinction learning which is potentially problematic, as several studies have shown that exposure to aversive stimuli following extinction may reinstate the expression of the original fear memory (Kindt et al., 2009). In contrast, recent findings have suggested that persistent reduction of fear may be achieved by targeting the memory reconsolidation process, during which reactivated memories enter into a labile state and can be modified (Kindt et al., 2009).

In a recent study (Borgomaneri et al., 2020), we have reduced the expression of fear in healthy humans by administering repetitive transcranial magnetic stimulation (rTMS) during the reconsolidation window of fear memory. We applied rTMS over dlPFC in a state-dependent manner, i.e., following presentation of a fear reminder that reactivated a fear memory acquired one day before using a fear conditioning paradigm. After rTMS, participants exhibited decreased physiological expression of fear, as shown by their skin conductance response (SCR). Moreover, dlPFC-rTMS prevented subsequent return of fear after extinction training, highlighting the key role of the dlPFC in reconsolidation of fear memory, and suggesting that rTMS can be safely used to prevent the return of fear. These findings pave the way to the potential therapeutic use of rTMS delivered in a state-dependent manner during the reconsolidation window. The concept of state-dependency relies on the idea that the effects of TMS are dependent on the current state of excitation of the brain tissue being stimulated (Silvanto and Pascual-Leone, 2008). The presentation of the reminder should reactivate the patient's traumatic memory and thus activating the fear-related network. Thus, time-locked inhibitory rTMS (i.e., within the reconsolidation window) delivered on crucial part of such network (i.e., the prefrontal cortex) should disrupt the reconsolidation of the traumatic memory. Finally, previous studies lacked neurophysiological markers supporting the rTMS treatment efficacy, which was selectively based on self-report questionnaires. It is possible to speculate the rTMS treatment to modulate brain connectivity and specific neurophysiological electroencephalographic (EEG) markers, such as the P300 components, which is affected in phobic individuals (Sachs et al., 2004). The P300 represents a general measure of 'cognitive efficiency' and its reduction in SP may reflect reduced cognitive resources for the evaluation of relevant information. Importantly, TMS studies have demonstrated that differences in brain connectivity might contribute to inter-individual differences in the rTMS treatment outcome (Gießing et al., 2020). Therefore, assessing individual brain connectivity may promote the development of personalized treatment strategies, opening new possibilities of combining TMS with pharmacotherapies to obtain supraordinal effects on neuroplasticity in the treatment of abnormally persistent memories. The rTMS treatment is expected to decrease symptomatology in SP, such as anxiety and hypervigilance, by affecting brain connectivity and restoring the P300 component elicited by the oddball task, either at the end of treatment and at subsequent follow up, since disrupting the reconsolidation of fear memory has been found to prevent the return of fear (Kindt et al., 2009). This would

refine and improve the therapeutic potential of rTMS, which may represent a valid alternative for those patients not responding to psychotherapy and/or drug treatments.

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