

Modulation of brainstem reflexes induced by non-invasive brain stimulation: is there a future?

Hatice Kumru*, Markus Kofler, Josep Valls-Sole

Kumru et al. (2019) have recently reported significant reduction of the R2 component of the trigeminal blink reflex following high-frequency (20 Hz) repetitive transcranial magnetic stimulation (rTMS) over the vertex in both, healthy subjects and in patients with spinal cord injury (SCI) (Figure 1). The modulatory influence of non-invasive brain stimulation (NIBS) on brainstem reflexes has been only scarcely studied.

NIBS is currently used as an add-on treatment in various neurological disorders, based on stimulation-induced neuroplasticity. In a broad sense, neural plasticity can be understood as the mechanisms enabling the nervous system to adapt to environment- or lesion-induced changes. rTMS and transcranial direct current stimulation (tDCS) are the two most commonly used NIBS methods. rTMS acts by discharging intense electrical currents into an insulated coil (magnetic coil), which generates a magnetic field that in turn induces electrical currents in electrically excitable structures. Depending on stimulation parameters, rTMS can upregulate or downregulate to different extents the excitability of the neural structures beneath the stimulating coil, inducing long-lasting trans-synaptic changes in the descending corticospinal tract and spinal cord circuits. High-frequency rTMS (≥ 5 Hz) increases cortical excitability, whereas low-frequency rTMS (≤ 1 Hz) decreases cortical excitability. A faster modulation of motor cortex excitability can be reached with a form of rTMS, theta burst stimulation (TBS), in which bursts of 3 pulses are repeated at 50 Hz every 200 ms. This is known to lead to an increase of excitability when administered intermittently (iTBS) and to a decrease in excitability when administered continuously (cTBS). tDCS delivers a continuous current (1–2 mA) over the scalp, through anodal and cathodal contacts, which does not produce action potentials in cortical neurons but modifies the discharge rate of already active neurons. The anodal contact increases firing by hyperpolarizing the dendrites and depolarizing the cell body, whereas the cathode induces the opposite effect. The stimulation-induced neuroplasticity is the basis for the therapy-oriented use of NIBS, as it leads to neural changes akin to those known as long-term potentiation and long-term depression, observed in laboratory preparations.

Studies on brainstem reflexes have provided important information on the functional integrity of suprasegmental structures influencing reflex excitability. The blink reflex is doubtless the most extensively studied brainstem reflex. When elicited by electrical stimulation of the supraorbital nerve, the blink reflex recorded in the orbicularis oculi muscles is composed of two components: an ipsilateral R1 and a bilateral R2. These

responses are conveyed through a complex chain of interneurons at the pontomedullary level, whose excitability is under the control of supranuclear structures, including the basal ganglia and the cerebral cortex. Blink reflex excitability is known to be altered in disorders such as Parkinson's disease, stroke, spinal cord injury, and others, in which therapy-oriented NIBS has shown some symptomatic improvement. Therefore, an eventual correlation with therapeutic benefits would enable using data on brainstem reflex excitability as a quantifiable surrogate measure of clinical change. Unfortunately, though, various NIBS methods have been used in the few studies reported so far on that topic, but their consistency remains unclear. We considered appropriate to review what is known at present about NIBS-induced modulation of brainstem reflex excitability and put forward a challenge in further research in this area.

Effects of NIBS on brainstem reflexes in healthy subjects and in patients: The effects of single pulse TMS on blink reflexes has been scarcely studied. Leis et al. (1993) studied the relationship between trigeminal blink reflex and cortical silent period. They observed suppression of the R2 component but no change in R1 (or a trend toward potentiation) when TMS preceded supraorbital nerve stimulus by 90–100 ms with subjects at rest. A clear R1 facilitation was observed when the supraorbital nerve stimulus was applied in the middle of the silent period induced by TMS in the volitionally activated orbicularis oculi muscle while the R2 component was inhibited. These findings imply that the blink reflex circuit mediating R1 remains excitable during the cortical silent period which originates mostly in the cerebral cortex. Suppression of the R2 component and concomitant facilitation of R1 with preceding single pulse TMS may at least in part be explained by mechanisms related to prepulse modulation. Two possible sensory modalities may contribute to such a prepulse effect: the auditory click, unavoidably linked with TMS, and the possible TMS-induced activation of corticobulbar pathways leading to engagement of prepulse circuits at the subcortical level.

In another study, focal TMS was used to condition masseter stretch reflexes at different conditioning–testing intervals (Sowman et al., 2008). Masseter reflexes were elicited by a servo-controlled electromagnetic device that imposed a controlled displacement of the lower jaw in healthy subjects at rest. Masseter stretch reflexes were suppressed when TMS was applied between 75 ms before the stretch and 2 ms afterwards. TMS of the same intensity did not evoke a motor evoked potential in masseter muscle at rest but induced a silent period in

volitionally activated masseter muscle at 10% of maximum force. This silent period was shorter than the duration of significant stretch reflex suppression. The authors concluded that TMS-induced corticobulbar activity acts on brainstem interneurons that either inhibit masseter motoneurons or increase pre-synaptic inhibition of Ia-afferents.

In healthy subjects, slow (1 Hz) sub-threshold rTMS over the hand motor cortex suppressed the excitability recovery of the R2 component of the blink reflex. Significant inhibition occurred as early as 30 s following rTMS (De Vito et al., 2009). Possibly, long-lasting reduction of blink reflex excitability might be a consequence of reduced cortical excitability and of subsequently reduced descending cortico-nuclear facilitation of the blink reflex-mediating interneuronal network (De Vito et al., 2009). In another study in healthy subjects, Cabib et al. (2016) reported enhanced excitability of trigemino-facial reflex circuits induced by bi-hemispheric tDCS, the opposite of what was reported with rTMS. The finding by these authors of larger ipsilateral than contralateral effects of tDCS with unilateral stimulation suggested that sensitization through cutaneous trigeminal afferents added to other possible mechanisms such as activation of cortico-nuclear or cortico-reticular connections. The possibility of peripheral mechanisms contributing to changes in brainstem reflexes after NIBS may also be present with rTMS. No effects of high frequency (20 Hz) vertex rTMS on the blink reflex excitability recovery curve to paired stimuli were reported in a sham-controlled study by Kumru et al. (2019). However, using TBS of the motor cortex, Suppa et al. (2014) showed modulation of the R2 component of the blink reflex, which increased with facilitatory iTBS and decreased with inhibitory cTBS. Nardone et al. (2019) found also a bimodal effect of prefrontal TBS on the acquisition of the classical conditioned eyeblink responses, i.e., enhanced acquisition with iTBS and reduced acquisition with cTBS. The effects on conditioned eyeblink responses have also been examined with cerebellar TBS by Hoffland et al. (2012) and with tDCS by Zuchowski et al. (2014), who both found reduction in the acquisition of conditioned responses, concurring with the known inhibitory effect of the cerebellum on the motor cortex. Finally, Bocci et al. (2018) reported on modulatory effects of cerebellar tDCS on the hand-blink reflex, suggesting a role of the cerebellum in the control of protective reflexes within the defensive peripersonal space in humans.

Only a few studies have been carried out in patients: Kumru et al. (2019) found a significant decrease of the R2 component in patients with SCI using high frequency vertex rTMS. Interestingly, patients with SCI had enhanced blink reflexes to supraorbital nerve stimulation, which was rapidly normalized after intrathecal baclofen, in parallel to the clinical effect (Kumru et al., 2011). Suppa et al. (2014) found absence of a modulatory effect of TBS on the R2 component of the blink reflex in patients with Tourette's syndrome, which the authors interpreted as a sign of reduced plasticity in relation to the pathophysiology of Tourette's syndrome. In patients with blepharospasm, low frequency rTMS induced an immediate decrease of the enhanced blink

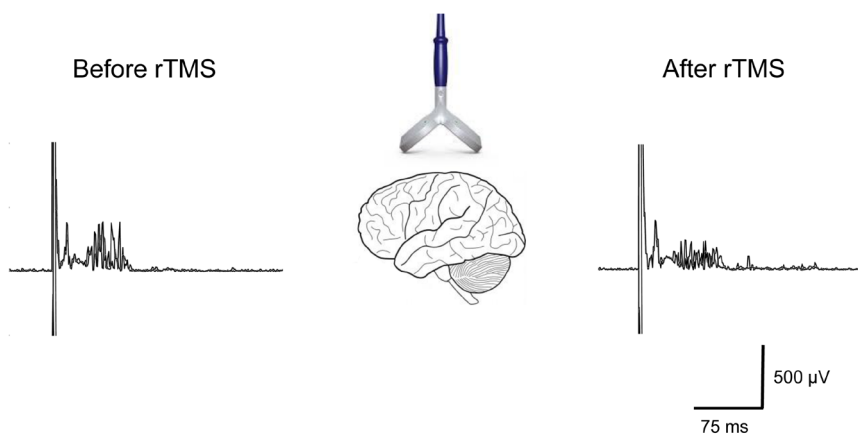


Figure 1 | Representative example of blink reflex recordings in a male patient with spinal cord injury before and after real repetitive transcranial magnetic stimulation (rTMS) at 20 Hz over the vertex.

reflex excitability recovery characteristic for this condition, in parallel with clinical improvement (Kranz et al., 2010).

Future research: The topic of modulating brainstem reflexes with NIBS is one of the least explored in neurophysiology. There are many gaps in our knowledge of how therapy-oriented NIBS works, but neurophysiological recording of the effects in brainstem and spinal cord circuits is certainly feasible. Various questions may direct future research in this area:

Clinical correlation of the effects of NIBS on brainstem reflexes. It is always challenging to seek a clinical correlation in neurophysiological findings. They are usually better correlated with the pathophysiological mechanisms leading to clinical expressions. This is not different for the abnormalities reported in brainstem reflexes in patients with various disorders. Interestingly, however, the changes induced in brainstem reflexes by NIBS parallel in most instances the changes in the clinical context (Kranz et al., 2010; Kumru et al., 2019). This raises the question whether changes in the blink reflex may have clinical relevance as a consequence, or *vice versa*, whether clinical changes may serve to explain subsequent changes in the blink reflex.

Other brainstem reflexes and functions apart of the blink reflex may be relevant for clinical correlation of NIBS benefit but have not been studied so far. One such example is the startle reaction, which reveals activation of the bulbopontine reticular formation and the reticulospinal tract. Since excitability of the startle circuits is abnormal in many neurological conditions, it would be worth knowing if NIBS can cause any modulation of the startle reflex. The same could be said of other functions with a strong link to the brainstem such as the control of pain, sleep, respiration, etc.

Targeting brainstem reflex excitability with therapy-oriented NIBS. With the increasingly recognized role of plasticity in spinal and supraspinal neuronal networks, the current challenge is to effectively integrate neurophysiological techniques that modulate intrinsic sensorimotor processing in the neurorehabilitation setting in order to regain functional recovery following neurological injury or to maintain the residual function in

neurodegenerative diseases. The brainstem is the main hub of many important functions. Likely, the supranuclear control of those functions entails a fine regulation of interneuronal excitability, which is often altered in neurological disorders. Most reported effects of rTMS on the excitability of the blink reflex are inhibitory (save those induced by iTBS on the size of the R2 component or on the acquisition of conditioned eyeblink responses). In contrast, most of the effects reported for tDCS are facilitatory.

The results obtained so far with NIBS modulation of the blink reflex should be expanded using different stimulation techniques and different stimulation frequencies. The studies should cover also blink reflexes elicited with other stimulus modalities, e.g., the acoustic blink reflex, which would avoid interference from peripheral trigeminal stimulation. Comparison of the effects of rTMS and tDCS applied over different cortical regions, such as the facial and supplementary motor areas, cingulate cortex, and brainstem would be useful. It would be also adequate to compare the effects of rTMS and tDCS on blink reflex excitability in the same subjects.

In conclusion, we need to better understand the mechanisms of reorganization of neural pathways at different levels of the central nervous system following injury. Based on such knowledge, we may be able to apply different types of NIBS in order to promote controlled and thoughtful neuromodulation in preserved and undamaged neural pathways. Ultimately, we should strive to develop better neurophysiological strategies aiming at implementing neuronal reorganization into carefully planned therapy.

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Date of submission: September 20, 2020

Date of decision: November 30, 2020

Date of acceptance: December 22, 2020

Date of web publication: February 19, 2021

<https://doi.org/10.4103/1673-5374.308083>

How to cite this article: Kumru H, Kofler M, Valls-Sole J (2021) Modulation of brainstem reflexes induced by non-invasive brain stimulation: is there a future? *Neural Regen Res* 16(10):2004-2005.

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C-Editors: Zhao M, Wang L; T-Editor: Jia Y