1. Working Module topic

Cerebellar and spinal neuromodulation by transcutaneous current stimulation: from basic science to technical progress and clinical applications

2. Working Module description

Transcranial cerebellar direct current stimulation (tDCS) and transcutaneous spinal DCS (tSDCS) are two innovative neuromodulatory techniques based on applying direct current (DC) non-invasively through the skin. Previous experimental works showed that weak DC delivered transcutaneously in humans over the cerebellum and over the spinal cord for minutes could elicit prolonged changes in neurophysiological and behavioural responses related to cerebellar and spinal functions.
This WM aims to booster the advance of these two neuromodulatory techniques by generating fora to discuss specific issues on experimental and clinical research and modeling, hence facilitating the translation from basic neuroscience, scientific developments and technical progresses into clinical and therapeutic applications. It will prioritize involvement of early-stage researchers at all levels of this process, and encourage cross modal interaction between groups by shared doctoral and postdoctoral research projects.

3. Comprehensive review (state-of-the-art)

The idea of using transcutaneous DC for modulating functions in the cerebellum and spinal cord arose from the observation that DC delivered through the scalp is able to modulate cortical excitability [1] and hence DC could also modulate other central nervous system (CNS) structures. As happens for cerebral transcranial direct current stimulation (tDCS), these two approaches using DC applied transcutaneously on the cerebellum or spinal cord presumably act by polarising the neuronal membrane and inducing neuroplasticity [2].
Because no drugs can yet primarily influence cerebellar dysfunction in pathological conditions, cerebellar stimulation offers a promising therapeutic opportunity. Since the cerebellum intervenes in several brain activities, cerebellar stimulation might help to improve deficits arising from brain lesions. The cerebellum could therefore be a unique ‘window’ through which cerebellar tDCS could modulate functions residing elsewhere in the brain.
Already in their classic experiments conducted in cats in the 1950s Moruzzi and co-workers recognised cerebellar sensitivity to polarising DC [3-9]. This sensitivity might well underlie the DC-induced changes in human cerebellar functions that were recently found in the literature. Indeed, starting from the pioneering paper by Ferrucci and colleagues [10] that first proposed cerebellar tDCS as a simpler techniques than Transcranial Magnetic Stimulation (TMS) for non-invasive cerebellar neuromodulation, it has been shown that cerebellar tDCS could modulate cerebellar motor cortical inhibition, gait adaptation, motor behaviour, and cognition (learning, language, memory, attention). Moreover preliminary clinical studies in patients with cerebellar disorders have reported beneficial effects (for a review see 2 and 11).
The effects of transcranial DC stimulation depend on the electric field distributions produced in the nervous tissue. Their knowledge is therefore important to predict the location and extent of the stimulated region as well as the stimulation intensity in a specific region of the CNS. At present, this knowledge is quite limited since only two modelling studies has been specifically designed for cerebellar tDCS. Mimicking the electrode montage used by Ferrucci and co-workers [10], a modelling study [12] characterized the relationship between stimulation dose and the resulting current flow, showing also the effect that the individual anatomical variability can have on the electrical field distributions. Using a different electrode montages, another preliminary modelling study [13] confirmed the conclusion by Parazzini and co-workers [12]. Because the electrode montages used by Rahman and colleagues [13] have never been experimentally tested in humans, their results remains questionable. Anyway, due to the limited number of studies, future modeling studies are needed.

Since studies on cerebellar tDCS began only recently few data are available about its mechanisms of action. Current experimental knowledge provides no precise information on where cerebellar tDCS-induced changes take place (cerebellar cortex, deep nuclei, white matter). Nor does it specify whether they involve one cerebellar area alone or the whole cerebellum. Cerebellar tDCS could interfere with membrane polarisation in Purkinje cells and in other neurons, fibres (mossy fibres and climbing fibres) and glial cells [2]. Overall, current knowledge therefore shows that the human cerebellum responds to cerebellar tDCS in a complex manner, possibly depending on the function studied, the task used, the electric field geometry and orientation, and its strength or duration.

Another fascinating target for novel neuromodulatory approaches is the spinal cord. The spinal cord, besides the reflex centres, contains sensory, motor and associative propriospinal pathways. Increasing evidence implies that because the spinal cord stores some functions that the brain controls under normal conditions, these could be rescued if the cord is diseased or injured and detached from the rest of the CNS [14]. Hence spinal neuromodulation could enhance this rescue and facilitate functional recovery in patients. An innovative view comes also from envisaging the spinal cord as a 'highway' to the brain: stimulating or modulating the spinal cord might induce diffuse functional changes other than purely motor or sensory functions elsewhere in the CNS, such as for example synchronizing the activity in different cortical areas and inducing neuroplasticity.

That the spinal cord, like the cerebellum, is sensitive to polarising DC is again hardly surprising given that research conducted more than 50 years ago showed that even low-intensity DC, <0.5–1 mA, can modulate spinal cord function in the cat [15]. The first evidence that the application of direct current stimulation over the spinal cord can modulate conduction along the spinal somatosensory pathways in humans was provided by the first study of Cogiamanian and colleagues [16]. Afterwards, further studies in healthy subjects supported the possibility that tsDCS can alter spinal cord functions. More specifically, literature data suggest that spinal tDCS can influence the ascending and descending spinal pathways and spinal reflex excitability. In the anaesthetized mouse, DC stimulation applied under the skin along the entire spinal cord may affect intrinsic properties of the motoneurons and that effect could be mediated by changes in the glutamatergic neurotransmission. Moreover, preliminary clinical studies in animals and patients with spinal cord injuries have reported beneficial effects [for a review see 2 and 17]. This suggests the possibility that tsDCS could be an innovative noninvasive neuromodulatory tool to prevent neuronal dysfunction developing after spinal cord injury. However, this possibility needs further investigations. Despite that, the knowledge of the electric field distribution due to tsDCS in the spine is quite limited. Indeed, up till now only one modelling study [18] provide determinant information on the relationship between stimulation dose, electrode montages and the resulting current flow underlying spinal tDCS, therefore future modeling studies are needed.

As for cerebellum, the underlying mechanisms remain speculative. The physiological effects elicited by both techniques arise from functional changes in the stimulated structure (cerebellum or spinal cord) though no evidence yet rules out possible (trans-synaptic or antidromic) effects in other brain or brainstem structures triggered by changes in the primary target structure. Several effects probably underlie DC-induced neuroplasticity and possibly neurotransmitter changes could be important.

4. Gaps, challenges and objectives to be achieved

These two neuromodulation techniques are becoming day after day highly diffuse and promise to be increasingly used in the near future. They represent two novel and exciting tools for neuroscientists. However, much work remains to be done:

- Confirm the previous data and the preliminary clinical applications.
- Better understand the mechanisms of action underlying these two techniques
- Finalize a common protocol among different centers and optimize how to apply them in daily practice

- Investigate the possible effects of alternative type of electric stimulation, such as use of random noise or alternating current in place of direct current.
- Better characterize and validate the spatial and temporal characteristics of the electric field produced in the neural targets, by modeling techniques based not only on computational electromagnetics but also on other modeling techniques
- Facilitate dose design by appropriate metrics
- Evaluate safety aspect (i.e. epilepsy, heart defibrillation, heart rate variability, use in children)

The above topics represent the primary objectives of this WM.

5. Proposed research activities

Research activities are planned to be boosted and performed in the course of this WM. They are substantially based on the list of gaps and objectives discussed above. On a preliminary basis, there is an urgent need to investigate changes induced by repeated stimulation sessions, compare stimulating electrode montages, examine how body size and age could influence results, study possible interactions with ongoing drug treatments, the possible effects of random noise or alternating current stimulation, and the combined effects of multiple stimulation targets.

This WM will provide the needed platform for coordinating and boosting common activities among different groups participating to this COST Action, organizing at first meetings to discuss the main needs and to define a priority list for research.

Moreover, research activities will be also performed through the involvement of early-stage researchers by activation of a significant number of STSM.

6. References

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