



## Development of an experimental paradigm to investigate the effect of TMS and cognitive training on executive function in athletes with traumatic brain injury (TBI) using a closed-loop approach

Executive functions are high-level cognitive processes that enable individuals to plan, focus attention, remember instructions, and juggle multiple tasks successfully. These functions, which include working memory, cognitive flexibility, and inhibitory control, are crucial for decision-making and goal-directed behavior (Diamond, 2013). In athletes who have sustained traumatic brain injuries (TBI), particularly through repetitive concussions, executive functions are frequently impaired. Such impairments can affect daily life, manifesting as difficulties in concentration, problem-solving, and dishinibition (Ozga et al., 2018). Recovery of executive functions is critical not only for improving cognitive health but also for the overall well-being of athletes (Pettemeridou et al., 2020).

Transcranial magnetic stimulation (TMS), a non-invasive brain stimulation (NIBS; Klomjai) technique, has shown potential in enhancing executive functions by modulating neural activity in key brain areas, for example the dorsolateral prefrontal cortex (DLPFC) (Tik et al., 2017). The DLPFC is a hub for executive function, supporting working memory, inhibitory control, and cognitive flexibility (Miller & Cohen, 2001).

Combining TMS with cognitive training (CT) may improve executive functions, but more evidence is required (Nousia et al., 2021). Cognitive training involves engaging in structured tasks designed to enhance specific cognitive domains, fostering neuroplasticity and functional recovery through repetition and adaptation (Cicerone et al., 2019). The effect of CT may be enhanced by TMS application. Moreover, by implementing a closed-loop system, in which real-time brain activity guides delivery of stimulation, the intervention accounts for brain state (Zrenner & Ziemann, 2023) and may therefore be more effective. This project seeks to explore the benefits of closed-loop TMS combined with cognitive training to improve executive functions in athletes with TBI.

## **Assignment**

Your task is to develop an experimental paradigm that integrates closed-loop TMS and cognitive training to improve executive functions in athletes with TBI. The intervention should target a relevant brain area, using brain-derived measures for real-time feedback to adjust TMS. The behavioral tasks should be chosen to challenge and improve executive functions (you can choose specific ones). So overall your goal is to enhance executive functions through TMS and cognitive training, with stimulation parameters dynamically adjusted based on neurophysiological signals.

## Challenges

• Combining TMS and cognitive training: Identify optimal TMS parameters (e.g., frequency and intensity) that can complement cognitive training to enhance executive function. You will need to

determine how the type (excitatory, inhibitory), timing and intensity of stimulation might interact with cognitive tasks to produce the best outcomes.

- Choosing cognitive tasks: Selecting appropriate cognitive training tasks is crucial for improving specific executive functions. The tasks should be adaptable to the participant's performance, becoming more challenging as their cognitive abilities improve (Zini et al., 2022).
- Designing the closed-loop system: A closed-loop system relies on real-time, subject-level data to adjust TMS parameters dynamically. You will need to select neurophysiological markers, that influence the effect of TMS on the brain and at behavioural level. Ensuring that the system can process these signals in real time is a key challenge.

## **References**

Cicerone, K. D., Goldin, Y., Ganci, K., Rosenbaum, A., Wethe, J. V., Langenbahn, D. M., Malec, J. F., Bergquist, T. F., Kingsley, K., Nagele, D., Trexler, L., Fraas, M., Bogdanova, Y., & Harley, J. P. (2019). Evidence-Based Cognitive Rehabilitation: Systematic Review of the Literature From 2009 Through 2014. *Archives of physical medicine and rehabilitation*, 100(8), 1515–1533. https://doi.org/10.1016/j.apmr.2019.02.011

Diamond, A. (2013). Executive functions. *Annual Review of Psychology*, 64, 135-168. https://doi.org/10.1146/annurev-psych-113011-143750

Klomjai, W., Katz, R., & Lackmy-Vallée, A. (2015). Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Annals of physical and rehabilitation medicine*, *58*(4), 208–213. https://doi.org/10.1016/j.rehab.2015.05.005

Nousia, A., Martzoukou, M., Liampas, I., Siokas, V., Bakirtzis, C., Nasios, G., & Dardiotis, E. (2022). The effectiveness of non-invasive brain stimulation alone or combined with cognitive training on the cognitive performance of patients with traumatic brain injury:  $\alpha$  systematic review. *Archives of Clinical Neuropsychology*, 37(2), 497-512.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual review of neuroscience*, 24, 167–202. https://doi.org/10.1146/annurev.neuro.24.1.167

Pettemeridou, E., Kennedy, M. R. T., & Constantinidou, F. (2020). Executive functions, self-awareness and quality of life in chronic moderate-to-severe TBI. *NeuroRehabilitation*, *46*(1), 109–118. <a href="https://doi.org/10.3233/NRE-192963">https://doi.org/10.3233/NRE-192963</a>

Tik, M., Hoffmann, A., Sladky, R., Tomova, L., Hummer, A., Navarro de Lara, L., Bukowski, H., Pripfl, J., Biswal, B., Lamm, C., & Windischberger, C. (2017). Towards understanding rTMS mechanism of action: Stimulation of the DLPFC causes network-specific increase in functional connectivity. *NeuroImage*, *162*, 289–296. https://doi.org/10.1016/j.neuroimage.2017.09.022

Zini, F., Le Piane, F., & Gaspari, M. (2022). Adaptive cognitive training with reinforcement learning. *ACM Transactions on Interactive Intelligent Systems*, *12*(1), 1–29. https://doi.org/10.1145/3476777

Zrenner, C., & Ziemann, U. (2024). Closed-Loop Brain Stimulation. *Biological psychiatry*, *95*(6), 545–552. https://doi.org/10.1016/j.biopsych.2023.09.014