Letter to the Editor

Title: critical considerations on tDCS-mediated changes in corticospinal response to fatiguing exercise.

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Word count: 1005

Running head: neuromodulation and exercise induced fatigue

Keywords: central fatigue, perception of effort, exercise, non-invasive brain stimulation

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This is an Accepted Article that has been peer-reviewed and approved for publication in The Journal of Physiology, but has yet to undergo copy-editing and proof correction. Please cite this article as an 'Accepted Article'; doi: 10.1113/JP284152.

The neurophysiological mechanisms leading to fatigue during exercise have been investigated since the early 19th century, and since the introduction of stimulation techniques, used either at the cortical or spinal level, the understanding of such mechanisms has been improved. I read with great interest the recent topical review by Amann and colleagues (2022), where they well described and summarised some of the most relevant findings regarding the contribution of the corticomotoneuronal pathway during fatiguing exercise, thus providing an updated overview on this complex and debated topic. The authors should also be congratulated for their excellent contribution to this field of study.

Amann and colleagues (2022) highlighted the potential for transcranial direct current stimulation (tDCS) to alter central fatigue and motoneuronal output. Their conclusion and interpretation can be further extended in some experimental works investigating the effect of tDCS prior to, or during fatiguing exercise. Non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) and tDCS provide researchers a safe way to temporarily alter brain function in a controlled manner, thus providing advanced and exciting opportunities to study the relationship between the altered neural network and different aspects of behaviour and human performance (Polania *et al.*, 2018). Having performed experiments for almost ten years in the field of neuromodulation and physical exercise, I would like to provide specific comments on the following two points for the author's and reader's consideration: 1) the cause-effect relationship between tDCS mediated changes in corticospinal-motoneuronal excitability and neuromuscular function; 2) the potential relationship between cortical excitability and the perception of effort. I hope that both points will provide a detailed overview on the effect of tDCS on the corticospinal-motoneuronal pathway and central fatigue related to exercise.

Cause-effect relationship between tDCS mediated changes in corticospinal-motoneuronal excitability and neuromuscular function

To date, two experimental studies that monitored the corticospinal-motoneuronal response and neuromuscular function following tDCS over the primary motor cortex (M1) have reported improvement in a submaximal isometric knee extension task (Angius *et al.*, 2016) and a submaximal cycling task to exhaustion (Angius *et al.*, 2018a). No changes in maximal voluntary force or voluntary activation were reported following tDCS despite an increase in corticospinal-motoneuronal excitability (Angius *et al.*, 2018a). During exercise, muscle electrical activity measured via surface EMG and cardiorespiratory response were not

affected by tDCS (Angius *et al.*, 2016). Likewise, no changes in neuromuscular function were observed at task failure (Angius *et al.*, 2016). Similarly, improvement in isometric task duration of the bicep brachii were found with (Cogiamanian *et al.*, 2007), and without changes in corticospinal-motoneuronal excitability (Abdelmoula *et al.*, 2016) and no changes in EMG activity (Cogiamanian *et al.*, 2007; Abdelmoula *et al.*, 2016). The authors speculated that tDCS may have influenced sensorimotor integration and the associated cognitive demand during sustained activity, but unfortunately these studies did not provide any information on such possible mechanisms.

The findings described above showed that following tDCS, the neuromuscular function and voluntary activation are independent of changes in corticospinal-motoneuronal excitability. That is, the improvement in exercise performance can be achieved without changes in corticospinal-motoneuronal excitability and central fatigue. Collectively, these experiments suggest that the relationship between corticospinal-motoneuronal excitability, central fatigue and exercise performance is complex. As proposed by Amann and colleagues (2022), the assessment of cortical inhibitory mechanisms such as short interval intracortical inhibition (SICI) might help to elucidate some mechanisms following tDCS. Nevertheless, other physiological factors acting the brainstem or spinal level, together with neural processes upstream of the motor cortex, could contribute to the development of central fatigue and changes in corticospinal-motoneuronal excitability (Gandevia, 2001).

Potential relationship between corticospinal-motoneuronal excitability and perception of effort following tDCS

A common feature following anodal tDCS is the reduced perception of effort during submaximal tasks with participants reaching a similar level of effort at task failure (Vitor-Costa *et al.*, 2015; Angius *et al.*, 2016; Angius *et al.*, 2018a). These findings might provide interesting experimental evidence regarding the relationship between cortical excitability and perception of effort. Perception of effort seems to originate from processing of corollary discharges from areas upstream of the M1 such as the supplementary motor area (SMA) (McCloskey, 2011). The SMA provides excitatory inputs into M1 that ultimately lead to a discharge and recruitment of the required locomotor muscles. Based on this mechanism, it is plausible that because of the increased excitability induced by anodal tDCS, less input to M1 is required to produce the same level of locomotor muscle recruitment. Therefore, the activity of SMA and other premotor areas involved in the corollary discharges to generate perception

of effort is lower. This seems to be also confirmed in previous works involving post-stroke individuals who experienced high level of effort and reduced cortical excitability (Kuppuswamy *et al.*, 2015) and in healthy individuals following repeated TMS over the SMA (Zenon *et al.*, 2015) which allows a more focal stimulation.

Current limitations and future directions

As suggested by Amman and colleagues (2022), a true cause-and-effect relationship between brain responsiveness following tDCS and exercise performance is difficult to establish, and many doubts on the ability of tDCS to affect corticospinal-motoneuronal excitability and exercise performance are present. In regard to this, only a few experimental works have systematically included the assessment of neuromuscular or corticospinal motoneuronal function for studying the effect of tDCS on different aspects of physical exercise and therefore many mechanisms remain unknown. These important methodological limitations should be considered with extreme concern among the scientific community as many experiments and commercial off-the-shelf tDCS devices, claim tDCS induces some neurophysiological mechanisms that have never been demonstrated or measured (Angius *et al.*, 2018b). As a logical next step, experimental studies must systematically include, when possible, the assessment of the corticospinal-motoneuronal or neuromuscular function together with the measurement of perception of effort to firmly establish and understand the cause effect relationship between tDCS mediated alterations and fatigue related symptoms commonly experienced during exercise. Lastly, these findings are of importance for clinical populations where the functionality of the corticospinal-motoneuronal function is impaired and the high level of fatiguability or perceived effort, are key limiting factors for many daily activities.

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