Perspectives on Promises and Challenges of Electrical Brain Stimulation to Improve Stress Regulation in the Military

Fenne Smits
Centraal Militair Hospitaal, MGGZ Expertisecentrum
THE NETHERLANDS

F.M.Smits-2@umcutrecht.nl

Dennis Schutter
Martinus J. Langeveldgebouw, Psychologische Functieleer
THE NETHERLANDS

D.J.L.G.Schutter@uu.nl

Elbert Geuze
Centraal Militair Hospitaal, MGGZ Expertisecentrum
THE NETHERLANDS

S.G.Geuze@umcutrecht.nl

ABSTRACT

Electrical stimulation of the brain could provide a relatively easy and non-invasive way to improve cognitive and motor functions. The potential benefits of non-invasive brain stimulation for military operational performance and wellbeing have not remained unnoticed. One of the most widely used techniques is transcranial direct current stimulation (tDCS). Here, we review some potential effects of tDCS on cognitive functioning and mental health in military personnel, in particular with respect to the adverse effects of stress exposure. The assumed working mechanisms of tDCS on cognitive functions and present challenges are briefly addressed. Increasing evidence suggests that stimulating the prefrontal cortex with tDCS improves the ability to regulate stress responses. However, effect sizes of current tDCS protocols are still small and variable. Moreover, major knowledge gaps remain regarding tDCS use in the military context and in relation to stress-related functioning. Altogether, tDCS could be a promising tool to support stress-related cognitive performance and wellbeing, but the technique is in its initial phase and requires much more research to establish applications in military settings.

1.0 STIMULATING MILITARY BRAINS

Stimulating the brain with electrical currents from outside the head is becoming more and more popular in neuroscientific research and clinical applications. Could non-invasive brain stimulation also provide a valuable tool in the military context? Several researchers including Davis and Smith (2019) and Levasseur-Moreau et al. (2013) [1,2] put forward that the enhancing effects of non-invasive brain stimulation on motor and cognitive performance may help to improve important aspects of military operational performance and wellbeing. However, others argue against such use of brain stimulation; worries have been raised regarding the safety, autonomy and responsibility of actions in military personnel undergoing brain stimulation [3].

Whether non-invasive brain stimulation should be used in the military is a discussion beyond the scope of this paper. In our opinion, the first and foremost question is: Can non-invasive brain stimulation, and in particular transcranial direct current stimulation (tDCS), provide practically relevant effects on the individual level, in the complex, stressful, or even life-threatening military contexts?

Here, we will address several aspects of this question by reviewing the scientific literature from recent tDCS studies.

2.0 MILITARY OPERATIONS AND STRESS REGULATION

2.1 Adverse consequences of stress

Exposure to stressful situations is inherent to military operations. There is a wide variety of military operational stressors, including working under constant threat, extreme environments (e.g., heat, high altitude, time pressure), witnessing severe suffering, and risking physical injury or death [4–6]. These stressors cause a cascade of physiological and psychological effects, including increases in activity of the central and peripheral nervous system, and increased alertness to stay attentive to the developing situation [7]. Stress responses serve to adequately respond to the highly stressful situation. However, severe or chronic stress can have a maladaptive impact; it narrows perception and attention (i.e., tunnel vision), reduces cognitive flexibility and increases automatic (stereotypical) behaviours, resulting in declined situational awareness, less adequate decision-making and worse task performance in military operations, and increased risk of physical health issues and mental health issues like anxiety and post-traumatic stress disorder (PTSD) [4,6,8–10]. One way to prevent or effectively mitigate these adverse consequences of stress exposure is to strengthen the ability to regulate reactions to stress, in order to diminish its impact on cognitive and emotional functioning [11].

2.2 Stress regulation and cognitive functions

Effectively guiding or managing your own stress-related and emotional reactions in context-appropriate ways is called emotion regulation or stress regulation. Effective stress regulation depends on several cognitive functions, and working memory in particular plays a critical role. Working memory comprises the active process of holding and updating information in mind. Controlling emotional information in working memory is an essential aspect of reappraisal, the regulation strategy of reinterpreting the meaning of a situation to change its emotional impact [12]. Accordingly, people with greater working memory capacity show better regulation of emotional reactions to threat or aversive inputs [12–16]. Another line of studies showed that training *emotional* working memory, that is, working memory with pieces of emotionally negative information, enhances the ability to regulate responses to stress-related stimuli [17].

Besides supporting stress regulation, working memory and related executive functions such as cognitive inhibition and attentional control, are more broadly implicated in military operational skills. For example, improving these functions could also support the ability to rapidly evaluate the situation (i.e., achieving situational awareness) and to formulate judgements and decisions based on the available information to coordinate action (i.e., formulation of intent) [1]. Therefore, executive functions may play an important role in stress-related wellbeing as well as stress-related operational performance.

2.3 Stress regulation in the brain

In the brain, stress regulation has a strong link with the frontoparietal cognitive control network. The dorsolateral prefrontal cortex (DLPFC) is an important hub in this neural network that facilitates top-down regulation of attention, thoughts and emotions [18,19]. Not surprisingly, the DLPFC also plays a major role in executive functions including working memory [20]. Importantly, DLPFC-dependent functions are particularly vulnerable to acute and chronic stress [21]. As Arnsten (2015) [21] put it: High stress levels flip the balance in the brain from a reflective to a reflexive way of controlling behaviour. Stress weakens higher cognitive functions that depend on prefrontal regions, including working memory [22], and strengthens emotional and habitual responses that depend on more primitive brain circuits including the amygdala and basal ganglia. These effects of stress in the brain can impair operational performance and stress regulation abilities, also in extensively trained soldiers [8,23].

The impact of stress exposure can, at least to a certain extent, be controlled. One way to lower stress levels is by modulating DLPFC activity. A growing body of research shows that increasing DLPFC activity with non-invasive brain stimulation attenuates the intensity of physiological stress responses [24–35]. Several studies suggest that this effect is established through enhanced stress regulation capacity. For example, Feeser et al. (2014) [36] showed that stimulating the lateral PFC only helps to reduce the intensity of stress responses when participants actively attempted to downregulate their reactions to the stress exposure. These findings were replicated in subsequent studies by He et al (2018) and Marques et al. (2019) [37,38]. Furthermore, Schweizer et al. (2013) [17] found that extensive working memory training resulted in improved stress regulation success that was accompanied by increased DLPFC activity. Hence, enhancing DLPFC function is able to improve stress regulation abilities, providing a possible means to improve resilience against adverse effects of stress.

3.0 TRANSCRANIAL DIRECT CURRENT STIMULATION

3.1 Working mechanism of transcranial direct current stimulation (tDCS)

TDCS works by applying weak electrical currents (typically 1-2.5 mA) to two or more electrodes placed on the scalp, an anodal and cathodal electrode [39–41]. The resulting electrical field in the brain modulates neural excitability and enhances ongoing synaptic plasticity by facilitating long term potentiation (LTP) – the basic process allowing learning and memory [42,43]. Although effects on neural excitability depend on several factors including neural orientation with respect to the electric field, anodal stimulation is often assumed to facilitate neural excitability in the targeted brain area, while cathodal stimulation inhibits excitability [43,44]. In general, anodal stimulation seems to have stronger effects than cathodal stimulation on both neural and cognitive outcomes [42,44,45].

TDCS provides a way to improve stress regulation by enhancing PFC activity and associated cognitive functions; in addition to evidence of PFC stimulation effects on stress responses reviewed above, anodal tDCS to the DLPFC has also been shown to enhance functional connectivity within the cognitive control network [46] and improve cognitive functions like working memory [47,48].

3.2 Theoretical frameworks of tDCS-induced cognitive enhancement

Ongoing research efforts are dedicated to unravel how exactly brain stimulation techniques like tDCS lead to cognitive enhancement. The entrainment model, the stochastic resonance model, and the zero-sum model are three main theoretical frameworks [49]. The entrainment model poses that ‘imitating’ neural patterns via non-invasive brain stimulation can drive a natural brain state. When that brain state is linked to a specific cognitive function, performance in this function is facilitated. Stochastic resonance refers to increasing the fidelity of a neuron or circuit by introducing small amounts of random noise (variability). A little bit of noise can drive low-level signals to a threshold. The stochastic resonance model therefore poses that techniques like tDCS inject low-level noise into a targeted brain area, increase the responsiveness of the system, and thereby facilitate neural functioning [50]. The zero-sum model poses that there is a finite amount of neural processing power [51]. As a consequence, every gain in neural processing power in one place means a loss of neural processing power elsewhere.

Depending on which model or combination of models is most accurate, enhancing cognitive processes by tDCS may turn out to be either a specific functional improvement, an overall increase in neural processing, coming at the cost of some other neural process, or a mixture of these outcomes. Evidence can be found for all three models, and to date there is no consensus on which model best accounts for the observed tDCS effects or how to conceive their complementary effects. Yet, keeping these possible mechanisms in mind is important. For instance, from a zero-sum model perspective, maintaining more information in working memory may come at the cost of, for example, reaction speed, which in a military operation could ultimately mean the difference between life and death. Hence, the different consequences following from these frameworks imply that special caution is warranted for tDCS or other cognitive enhancement methods for military use.

3.3 TDCS and cognitive enhancement

The functional range of tDCS effectivity is still to be determined. Some studies suggest that tDCS can only improve performance until arriving at some “natural” maximum level. This is in line with evidence showing that only low performers benefit from tDCS. For example, the study by Tseng et al. (2012) [53] showed that tDCS in low performers improved working memory performance and modulated associated waveforms in EEG brain activity recordings, whereas tDCS in high performers had no effect on behavior or EEG waveforms. This suggests that tDCS would primarily be useful in clinical settings or supporting low-performers. There is also some evidence that is indicative of a dissociative effect in which low performers improve, but high performers become worse in response to tDCS [54]. By contrast, Schmicker et al. [55] showed that tDCS only improved working memory performance in high performers, but not in low performers. They speculated that high performers have a neural processing organization that more easily allows for the effects of tDCS. These latter findings may also imply that tDCS can improve cognitive performance above some expected maximum level; an interesting perspective for the field of cognitive enhancement.

4.0 KNOWLEDGE GAPS

Although the underlying mechanisms are yet to be determined, some tDCS protocols already yield encouraging results. However, to date, concrete non-clinical tDCS applications beyond scientific experiments are scarce. Significant gaps still exist in the understanding of tDCS efficacy and uncertainties in the cost-benefit ratio for healthy individuals.

Substantial knowledge gaps exist with respect to the duration of tDCS effects and potential long-term negative side effects. In addition, specific tDCS use in the military context may be problematic as long as knowledge gaps remain in (i) inter-individual differences in tDCS-response, (ii) generalizability of laboratory- and civilian-based research findings to military contexts and personnel, (iii) the effect size of tDCS on practically relevant outcomes of military capability and wellbeing, and (iv) the feasibility to implement tDCS in military training or operational contexts [1,2]. In addition, the consequences of using tDCS to interfere with the stress response in psychiatrically healthy individuals remain unclear.

4.1 Inter-individual differences

Significant inter-individual differences in tDCS response are present when stimulating the PFC [56]. Effects of tDCS depend on neuronal and synaptic function in the targeted networks. The outcome of prefrontal stimulation depends, for example, on genetic variations that affect neurotransmitter systems involved in PFC-related network communication and plasticity, such as the dopaminergic system [57,58]. Another widely-recognized source of variability is anatomy; factors like grey matter atrophy and brain-skull distance determine the influence of the electrical field in the brain [59,60]. An example of inter-individual variety in location and intensity of the electrical field in the brain is depicted in Figure 1. Such biological trait characteristics are an important determinant of the possibilities and limits of tDCS to modulate individual cognitive outcomes.

State factors also affect tDCS effectivity; the effects of stimulation depend on the moment-to-moment activational state of the brain [61]. For example, prefrontal tDCS was shown to have differential effects on brain network activity when applied during a cognitive task vs. during rest [62]. Brain state can to some extent be controlled by subjecting individuals to a specific task. For example, when aiming at enhancing cognitive functions like working memory, tDCS may have its optimal effect in combination with performing cognitive exercises, as the latter already probes the neurocognitive process of interest [63,64].

Increasing our understanding of individual variability will contribute to the development of new methods of personalized tDCS protocols. Two promising examples are individual current dosing [65] and adapting neurostimulation to real-time brain state in so-called closed-loop set-ups [66]. Although still in an early stage, such developments are crucial with regard to use in the military context where an average group improvement might be insufficient if some individuals worsen [1].

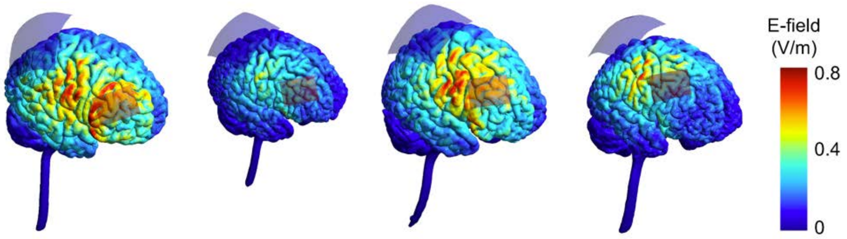

Figure 1: Example of electrical field distributions on four individual brains. The electrical fields are simulated in SimNIBS 3.2.3 [85] based on 2 mA direct current stimulation with a 3x3 cm anode over F4 and a 5x7 cm cathode over C2 (10-20 system scalp electrode positions). The brain models are obtained from a publicly available MRI dataset of neurologically healthy individuals [86] (here depicted: sub04, sub05, sub07 and sub11).

4.2 Generalizability to the military context

One aspect of the generalizability issue comprises the translation from standardized laboratory settings to the complex and stressful military operational environment. This is especially relevant regarding the impact of stress on cognitive functioning. The translation to the military environment seems difficult to scientifically assess when tDCS in such environments is obstructed by the very knowledge gap itself. Yet, we believe it is important to investigate tDCS effects in stress-like contexts. TDCS effects could, for example, be studied in contexts that include stress-inducing aspects like unpredictable occurrence of adverse stimuli, uncontrollability or social evaluative threat [67]. Still, typical laboratory stress manipulations like these may elicit relatively mild stress responses in military personnel. Where the methodological and ethical aspects of research allow, methods that more realistically mimic military stressors may provide better insight in tDCS effects on stress regulation in the actual operational environment.

Another aspect is the translation of findings from civilian research participants – often university students – to army service members, who may differ on important aspects like stressful or traumatic experiences, age and related brain characteristics, personality traits, and education. The translation of tDCS effects between these populations is easier to investigate, although it has to our knowledge never been systematically analyzed. Yet, taking into account sources of individual variability, research from us (in prep.) and others (e.g., [23,68]) suggest that the effects of stress and the effects of tDCS on cognitive functions are comparable across soldiers and civilian samples.

4.3 Effect size

On one hand, tDCS provides a useful tool for studying and assessing (pathological) brain function and plasticity, for example related to stress-induced brain alterations [21]. On the other hand, it is argued that tDCS may only be a useful tool in the military operational context if its effects induce a practically relevant impact on military capability and wellbeing that outweighs effects of other methods used in the military [2], such as breathing techniques and caffeine [69]. Recent estimations show that tDCS does not yet yield such effects; effect sizes of prefrontal tDCS for outcomes related to stress regulation are relatively low [70,71]. These meta-analytic studies considered tDCS effects on executive functions (including working memory) and on stress-related emotional reactivity. However, “the” effect size of tDCS is hard to determine since the effect depends not only on individual characteristics but also on stimulation settings and the outcome variable. At present, standardized tDCS study protocols are lacking and the optimal tDCS parameters are still subject to investigation. Moreover, many studies apply tDCS in a single session and only look at the immediate effect that typically lasts for no more than one hour. For military applications, prolonged effects may be required for sufficiently long-lasting improvements in operational performance and mental health.

4.4 Feasibility in the military context

The tDCS technique fits well into the military operational context due to its easy use, portability, and low costs [72,73]. Yet, the feasibility of implementing effective tDCS protocols depends on the circumstances. Considering the low effect sizes of currently used tDCS protocols with few sessions, tDCS may not be suitable for ad hoc applications during operations. Instead, a much higher tDCS dose may be required for relevant effects on cognitive functioning (e.g., 20-30 repeated tDCS sessions, in line with non-invasive brain stimulation procedures for clinical treatment [74]). The integration of such extended tDCS protocols could be more feasible in military training programs. Yet, this requires further insights in possible decreases in effectivity due to sensitization and habituation effects after repeated or chronic tDCS use, in analogy to other neuromodulators like drugs (see e.g. [52]).

4.5 Interfering in healthy stress systems

Our research follows from the objective to better treat and prevent adverse stress-related impact on mental health. Diminishing stress responses could be one way to do so. However, in its core, the stress response is an adaptive system. When in balance, the stress system promotes adaptation and homeostasis in response to challenges [7]. Before reaching extreme levels, stress can actually improve learning and cognitive performance and is thus essential for enhancing adaptation [75,76]. Also, in severely threatening situations, weakening the relatively slow and complex PFC-dependent functions in favour of fast and reflexive behaviour is crucial for survival. In combination with the uncertainties of tDCS effects, this raises questions about the consequences of using tDCS or other enhancement methods to interfere with healthy stress systems.

5.0 TOWARDS TDCS-IMPROVED STRESS REGULATION

The overarching question in our field of study is: Can tDCS become a useful tool to improve stress regulation in a way that effectively protects mental health and operational performance under stress? Current evidence largely depends on single session tDCS applications that only induce short-duration temporary effects. One of the first steps is therefore to determine if favourable effects of tDCS on stress-related cognitive functioning can last, i.e., will remain after the stimulation period. Also, tDCS effects that are induced on a very specific function, like a particular aspect of working memory, must generalize to related but untrained functions, like stress regulation.

5.1 How can tDCS become useful?

Promising evidence of lasting, transferrable tDCS effects come from studies on cognitive training and psychiatric treatment. In these studies, tDCS is applied during multiple sessions in attempts to establish lasting effects. TDCS can affect synaptic strength through LTP-like processes [40,42]. The idea behind applying tDCS over multiple sessions is to repeatedly activate this process in order to generate lasting changes in synaptic strength that will facilitate neural processing in the targeted brain area or network. In addition, tDCS effects seem to be strongest in neural networks and cognitive functions that are activated or trained during stimulation [63,64,77–79]. Cognitive training studies showed that the benefits of repeated tDCS combined with cognitive training can last for months and can even transfer to non-trained cognitive skills [80,81].

5.2 Developments for effective protocols

Linking these lines of evidence, applying TDCS in multiple sessions in combination with cognitive training could be beneficial. Importantly, repeated tDCS with cognitive training was also shown to have beneficial effects on emotion regulation; in patients with depression it resulted in decreased rumination and reduced symptoms [82,83]. Yet, replication of these findings is needed and further research should determine to what extent these findings translate to practical skills in emotion regulation during stress. The rationale to test and improve stress regulation with a tDCS-cognitive training intervention forms the basis of a recently initiated study in active service members. Details can be found in the study pre-registration (www.trialregister.nl, Trail ID; NL8698).

When investigating in this direction, future research should additionally focus on the translation to the military context. If tDCS research progresses along these lines, tDCS may ultimately provide a relatively easy technique to support the resilience of military personnel.

5.3 Outstanding issues

The currently limited effectiveness of tDCS tempers high expectations regarding the potential neuromodulatory effects on the stress system. Moreover, tDCS may not achieve a direct influence on the stress system; the weak and diffuse electric currents are unlikely to directly reach deeper brain structures that are driving stress responses, albeit indirect (transsynaptic) effects have been demonstrated via network connectivity with the stimulated area [84]. Stimulating the PFC with the aim to boost someone’s stress regulation capacity might therefore not immediately modulate the stress response itself, and is insufficient to completely turn it off, see e.g. [36]. In fact, by this way of applying tDCS, the tDCS-user presumably keeps control of the outcome; tDCS will affect the intensity of stress responses only if and when he or she chooses to put effort in regulating those responses.

Yet, the balance in healthy and adaptive behaviour is a prominent issue when it comes to potential cognitive enhancement methods like tDCS. Therefore, together with future developments in tDCS effectiveness, the health-related and ethical impact of brain stimulation will determine whether or not tDCS can provide a useful and acceptable tool to improve military capability and wellbeing. Altogether, tDCS is a promising technique, but the application in its current form is still hampered by many unknowns as discussed in this review. These outstanding issues need to be clarified in order to establish the potential of tDCS in military, stress-related contexts.

REFERENCES

[1] Davis SE, Smith GA. Transcranial Direct Current Stimulation Use in Warfighting: Benefits, Risks, and Future Prospects. Front Hum Neurosci 2019;13:114. https://doi.org/10.3389/fnhum.2019.00114.

[2] Levasseur-Moreau J, Brunelin J, Fecteau S. Non-invasive brain stimulation can induce paradoxical facilitation. Are these neuroenhancements transferable and meaningful to security services? Front Hum Neurosci 2013;0:449. https://doi.org/10.3389/FNHUM.2013.00449.

[3] Sehm B, Ragert P. Why non-invasive brain stimulation should not be used in military and security

services. Front Hum Neurosci 2013;7:553. https://doi.org/10.3389/fnhum.2013.00553.

[4] Reijnen A, Rademaker AR, Vermetten E, Geuze E. Prevalence of mental health symptoms in Dutch military personnel returning from deployment to Afghanistan: a 2-year longitudinal analysis. Eur Psychiatry 2015;30:341–6. https://doi.org/10.1016/j.eurpsy.2014.05.003.

[5] Bartone PT, Adler AB, Vaitkus MA. Dimensions of Psychological Stress in Peacekeeping Operations. Mil Med 1998;163:587–93. https://doi.org/10.1093/milmed/163.9.587.

[6] Kavanagh J. Stress and Performance A Review of the Literature and Its Applicability to the Military 2005.

[7] McEwen BS. Stress, Adaptation, and Disease: Allostasis and Allostatic Load. Ann N Y Acad Sci 1998;840:33–44. https://doi.org/10.1111/j.1749-6632.1998.tb09546.x.

[8] Martin K, McLeod E, Périard J, Rattray B, Keegan R, Pyne DB. The Impact of Environmental Stress on Cognitive Performance: A Systematic Review: Https://DoiOrg/101177/0018720819839817 2019;61:1205–46. https://doi.org/10.1177/0018720819839817.

[9] Sareen J, Cox BJ, Afifi TO, Stein MB, Belik S-L, Meadows G, et al. Combat and peacekeeping operations in relation to prevalence of mental disorders and perceived need for mental health care: findings from a large representative sample of military personnel. Arch Gen Psychiatry 2007;64:843–52. https://doi.org/10.1001/archpsyc.64.7.843.

[10] van der Wal SJ, Vermetten E, Elbert G. Long-term development of post-traumatic stress symptoms and associated risk factors in military service members deployed to Afghanistan: Results from the PRISMO 10-year follow-up. Eur Psychiatry 2021;64. https://doi.org/10.1192/j.eurpsy.2020.113.

[11] GROSS JJ. Emotion regulation: Affective, cognitive, and social consequences. Psychophysiology 2002;39:S0048577201393198. https://doi.org/10.1017/S0048577201393198.

[12] Pe ML, Raes F, Kuppens P. The Cognitive Building Blocks of Emotion Regulation: Ability to Update Working Memory Moderates the Efficacy of Rumination and Reappraisal on Emotion. PLoS One 2013;8:69071. https://doi.org/10.1371/JOURNAL.PONE.0069071.

[13] Schmeichel BJ, Demaree HA. Working Memory Capacity and Spontaneous Emotion Regulation: High Capacity Predicts Self-Enhancement in Response to Negative Feedback. Emotion 2010;10:739–44. https://doi.org/10.1037/a0019355.

[14] Schmeichel BJ, Volokhov RN, Demaree HA. Working Memory Capacity and the Self-Regulation of Emotional Expression and Experience. J Pers Soc Psychol 2008;95:1526–40. https://doi.org/10.1037/a0013345.

[15] Xiu L, Zhou R, Jiang Y. Working memory training improves emotion regulation ability: Evidence from HRV. Physiol Behav 2016;155:25–9. https://doi.org/10.1016/j.physbeh.2015.12.004.

[16] Xiu L, Wu J, Chang L, Zhou R. Working Memory Training Improves Emotion Regulation Ability. Sci Rep 2018;8. https://doi.org/10.1038/s41598-018-31495-2.

[17] Schweizer S, Grahn J, Hampshire A, Mobbs D, Dalgleish T. Training the Emotional Brain: Improving Affective Control through Emotional Working Memory Training. J Neurosci 2013;33:5301–11. https://doi.org/10.1523/JNEUROSCI.2593-12.2013.

[18] Kohn N, Eickhoff SB, Scheller M, Laird AR, Fox PT, Habel U. Neural network of cognitive emotion regulation — An ALE meta-analysis and MACM analysis. Neuroimage 2014;87:345–55. https://doi.org/10.1016/j.neuroimage.2013.11.001.

[19] Moodie CA, Suri G, Goerlitz DS, Mateen MA, Sheppes G, McRae K, et al. The neural bases of cognitive emotion regulation: The roles of strategy and intensity. Cogn Affect Behav Neurosci 2020 202 2020;20:387–407. https://doi.org/10.3758/S13415-020-00775-8.

[20] Niendam TA, Laird AR, Ray KL, Dean YM, Glahn DC, Carter CS. Meta-analytic evidence for a superordinate cognitive control network subserving diverse executive functions. Cogn Affect Behav Neurosci 2012;12:241–68. https://doi.org/10.3758/s13415-011-0083-5.

[21] Arnsten AFT. Stress weakens prefrontal networks: molecular insults to higher cognition. Nat Neurosci 2015;18:1376–85. https://doi.org/10.1038/nn.4087.

[22] Shields GS, Sazma MA, Yonelinas AP. The effects of acute stress on core executive functions: A meta-analysis and comparison with cortisol. Neurosci Biobehav Rev 2016;68:651–68.

https://doi.org/10.1016/j.neubiorev.2016.06.038.

[23] Morgan CA, Doran A, Steffian G, Hazlett G, Southwick SM. Stress-Induced Deficits in Working Memory and Visuo-Constructive Abilities in Special Operations Soldiers. Biol Psychiatry 2006;60:722–9. https://doi.org/10.1016/J.BIOPSYCH.2006.04.021.

[24] Remue J, Vanderhasselt MA, Baeken C, Rossi V, Tullo J, De Raedt R. The effect of a single HF-rTMS session over the left DLPFC on the physiological stress response as measured by heart rate variability. Neuropsychology 2016;30:756–66. https://doi.org/10.1037/neu0000255.

[25] Brunoni AR, Vanderhasselt M-A, Boggio PS, Fregni F, Dantas EM, Mill JG, et al. Polarity- and valence-dependent effects of prefrontal transcranial direct current stimulation on heart rate variability and salivary cortisol. Psychoneuroendocrinology 2013;38:58–66. https://doi.org/10.1016/j.psyneuen.2012.04.020.

[26] Herrmann MJ, Beier JS, Simons B, Polak T. Transcranial Direct Current Stimulation (tDCS) of the Right Inferior Frontal Gyrus Attenuates Skin Conductance Responses to Unpredictable Threat Conditions. Front Hum Neurosci 2016;10:1–6. https://doi.org/10.3389/fnhum.2016.00352.

[27] Herrmann MJ, Simons BSE, Horst AK, Boehme S, Straube T, Polak T. Modulation of sustained fear by transcranial direct current stimulation (tDCS) of the right inferior frontal cortex (rIFC). Biol Psychol 2018;139:173–7. https://doi.org/10.1016/j.biopsycho.2018.10.013.

[28] Pulopulos MM, Schmausser M, De Smet S, Vanderhasselt MA, Baliyan S, Venero C, et al. The effect of HF-rTMS over the left DLPFC on stress regulation as measured by cortisol and heart rate variability. Horm Behav 2020;124:104803. https://doi.org/10.1016/J.YHBEH.2020.104803.

[29] Antal A, Fischer T, Saiote C, Miller R, Chaieb L, Wang DJJ, et al. Transcranial electrical stimulation modifies the neuronal response to psychosocial stress exposure. Hum Brain Mapp 2014;35:3750–9. https://doi.org/10.1002/hbm.22434.

[30] Carnevali L, Pattini E, Sgoifo A, Ottaviani C. Effects of prefrontal transcranial direct current stimulation on autonomic and neuroendocrine responses to psychosocial stress in healthy humans. Stress 2019:1–11. https://doi.org/10.1080/10253890.2019.1625884.

[31] Baeken C, Vanderhasselt MA, Remue J, Rossi V, Schiettecatte J, Anckaert E, et al. One left dorsolateral prefrontal cortical HF-rTMS session attenuates HPA-system sensitivity to critical feedback in healthy females. Neuropsychologia 2014;57:112–21. https://doi.org/10.1016/j.neuropsychologia.2014.02.019.

[32] Peña-Gómez C, Vidal-Piñeiro D, Clemente IC, Pascual-Leone Á, Bartrés-Faz D. Down-regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics. PLoS One 2011;6:e22812. https://doi.org/10.1371/journal.pone.0022812.

[33] Maeoka H, Matsuo A, Hiyamizu M, Morioka S, Ando H. Influence of transcranial direct current stimulation of the dorsolateral prefrontal cortex on pain related emotions: A study using electroencephalographic power spectrum analysis. Neurosci Lett 2012;512:12–6. https://doi.org/10.1016/j.neulet.2012.01.037.

[34] Chen NTM, Basanovic J, Notebaert L, MacLeod C, Clarke PJF. Attentional bias mediates the effect of neurostimulation on emotional vulnerability. J Psychiatr Res 2017;93:12–9. https://doi.org/10.1016/j.jpsychires.2017.05.008.

[35] Vergallito A, Riva P, Pisoni A, Romero Lauro LJ. Modulation of negative emotions through anodal tDCS over the right ventrolateral prefrontal cortex. Neuropsychologia 2018;119:128–35. https://doi.org/10.1016/j.neuropsychologia.2018.07.037.

[36] Feeser M, Prehn K, Kazzer P, Mungee A, Bajbouj M. Transcranial Direct Current Stimulation Enhances Cognitive Control During Emotion Regulation. Brain Stimul 2014;7:105–12. https://doi.org/10.1016/j.brs.2013.08.006.

[37] He Z, Lin Y, Xia L, Liu Z, Zhang D, Elliott R. Critical role of the right VLPFC in emotional regulation of social exclusion: A tDCS study. Soc Cogn Affect Neurosci 2018;13:357–66. https://doi.org/10.1093/scan/nsy026.

[38] Marques LM, Morello LYN, Boggio PS. Ventrolateral but not Dorsolateral Prefrontal Cortex tDCS effectively impact emotion reappraisal – effects on Emotional Experience and Interbeat Interval. Sci Rep 2018;8:15295. https://doi.org/10.1038/s41598-018-33711-5.

[39] Cirillo G, Di Pino G, Capone F, Ranieri F, Florio L, Todisco V, et al. Neurobiological after-effects of non-invasive brain stimulation. Brain Stimul 2017;10:1–18. https://doi.org/10.1016/j.brs.2016.11.009.

[40] Liebetanz D. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain 2002;125:2238–47. https://doi.org/10.1093/brain/awf238.

[41] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol 2000;527:633–9. https://doi.org/10.1111/j.1469-7793.2000.t01-1-00633.x.

[42] Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct Current Stimulation Modulates LTP and LTD: Activity Dependence and Dendritic Effects. Brain Stimul 2017;10:51–8. https://doi.org/10.1016/j.brs.2016.10.001.

[43] Filmer HL, Dux PE, Mattingley JB. Applications of transcranial direct current stimulation for understanding brain function. Trends Neurosci 2014;37:1–12. https://doi.org/10.1016/j.tins.2014.08.003.

[44] Lafon B, Rahman A, Bikson M, Parra LC. Direct Current Stimulation Alters Neuronal Input/Output Function. Brain Stimul 2017;10:36–45. https://doi.org/10.1016/j.brs.2016.08.014.

[45] Jacobson L, Koslowsky M, Lavidor M. tDCS polarity effects in motor and cognitive domains: a meta-analytical review. Exp Brain Res 2012;216:1–10. https://doi.org/10.1007/s00221-011-2891-9.

[46] Keeser D, Meindl T, Bor J, Palm U, Pogarell O, Mulert C, et al. Prefrontal Transcranial Direct Current Stimulation Changes Connectivity of Resting-State Networks during fMRI. J Neurosci 2011. https://doi.org/10.1523/JNEUROSCI.0542-11.2011.

[47] Brunoni AR, Vanderhasselt M-A. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. Brain Cogn 2014;86:1–9. https://doi.org/10.1016/j.bandc.2014.01.008.

[48] Imburgio MJ, Orr JM. Effects of prefrontal tDCS on executive function: Methodological considerations revealed by meta-analysis. Neuropsychologia 2018. https://doi.org/10.1016/j.neuropsychologia.2018.04.022.

[49] Pascual-Leone A, Horvath JC, Robertson EM. Enhancement of Normal Cognitive Abilities Through Noninvasive Brain Stimulation. Cortical Connect., Berlin, Heidelberg: Springer Berlin Heidelberg; 2012, p. 207–49. https://doi.org/10.1007/978-3-642-32767-4_11.

[50] Fertonani A, Miniussi C. Transcranial Electrical Stimulation. Neurosci 2017;23:109–23. https://doi.org/10.1177/1073858416631966.

[51] Brem AK, Fried PJ, Horvath JC, Robertson EM, Pascual-Leone A. Is neuroenhancement by noninvasive brain stimulation a net zero-sum proposition? Neuroimage 2014;85:1058–68. https://doi.org/10.1016/J.NEUROIMAGE.2013.07.038.

[52] McSweeney FK, Murphy ES, Kowal BP. Regulation of Drug Taking by Sensitization and Habituation. Exp Clin Psychopharmacol 2005;13:163–84. https://doi.org/10.1037/1064-1297.13.3.163.

[53] Tseng P, Hsu T-Y, Chang C-F, Tzeng OJL, Hung DL, Muggleton NG, et al. Unleashing Potential: Transcranial Direct Current Stimulation over the Right Posterior Parietal Cortex Improves Change Detection in Low-Performing Individuals. J Neurosci 2012;32:10554–61. https://doi.org/10.1523/JNEUROSCI.0362-12.2012.

[54] Splittgerber M, Salvador R, Brauer H, Breitling-Ziegler C, Prehn-Kristensen A, Krauel K, et al. Individual Baseline Performance and Electrode Montage Impact on the Effects of Anodal tDCS Over the Left Dorsolateral Prefrontal Cortex. Front Hum Neurosci 2020;14. https://doi.org/10.3389/FNHUM.2020.00349.

[55] Schmicker M, Menze I, Schneider C, Taubert M, Zaehle T, Mueller NG. Making the rich richer: Frontoparietal tDCS enhances transfer effects of a single-session distractor inhibition training on working memory in high capacity individuals but reduces them in low capacity individuals. Neuroimage 2021;242:118438. https://doi.org/10.1016/J.NEUROIMAGE.2021.118438.

[56] Tremblay S, Lepage JF, Latulipe-Loiselle A, Fregni F, Pascual-Leone A, Théoret H. The uncertain

outcome of prefrontal tDCS. Brain Stimul 2014. https://doi.org/10.1016/j.brs.2014.10.003.

[57] Plewnia C, Zwissler B, Längst I, Maurer B, Giel K, Krüger R. Effects of transcranial direct current stimulation (tDCS) on executive functions: Influence of COMT Val/Met polymorphism. Cortex 2013;49:1801–7. https://doi.org/10.1016/J.CORTEX.2012.11.002.

[58] Stephens JA, Jones KT, Berryhill ME. Task demands, tDCS intensity, and the COMT val158met polymorphism impact tDCS-linked working memory training gains. Sci Reports 2017 71 2017;7:1–11. https://doi.org/10.1038/s41598-017-14030-7.

[59] Antonenko D, Nierhaus T, Meinzer M, Prehn K, Thielscher A, Ittermann B, et al. Age-dependent effects of brain stimulation on network centrality. Neuroimage 2018;176:71–82. https://doi.org/10.1016/j.neuroimage.2018.04.038.

[60] Opitz A, Paulus W, Will S, Antunes A, Thielscher A. Determinants of the electric field during transcranial direct current stimulation. Neuroimage 2015;109:140–50. https://doi.org/10.1016/j.neuroimage.2015.01.033.

[61] Krause B, Cohen Kadosh R. Not all brains are created equal: the relevance of individual differences in responsiveness to transcranial electrical stimulation. Front Syst Neurosci 2014;0:25. https://doi.org/10.3389/FNSYS.2014.00025.

[62] Li LM, Violante IR, Leech R, Ross E, Hampshire A, Opitz A, et al. Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. Hum Brain Mapp 2019;40:904–15. https://doi.org/10.1002/hbm.24420.

[63] Simonsmeier BA, Grabner RH, Hein J, Krenz U, Schneider M. Electrical brain stimulation (tES) improves learning more than performance: A meta-analysis. Neurosci Biobehav Rev 2018;84:171–81. https://doi.org/10.1016/j.neubiorev.2017.11.001.

[64] Gill J, Shah-basak PP, Hamilton R. It's the Thought That Counts: Examining the Task-dependent Effects of Transcranial Direct Current Stimulation on Executive Function. Brain Stimul 2015;8:253–9. https://doi.org/10.1016/j.brs.2014.10.018.

[65] Evans C, Bachmann C, Lee JSA, Gregoriou E, Ward N, Bestmann S. Dose-controlled tDCS reduces electric field intensity variability at a cortical target site. Brain Stimul 2020;13:125–36. https://doi.org/10.1016/J.BRS.2019.10.004.

[66] Guerrero Moreno J, Biazoli CE, Baptista AF, Trambaiolli LR. Closed-loop neurostimulation for affective symptoms and disorders: An overview. Biol Psychol 2021;161:108081. https://doi.org/10.1016/J.BIOPSYCHO.2021.108081.

[67] Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: A theoretical integration and synthesis of laboratory research. Psychol Bull 2004;130:355. https://doi.org/10.1037/0033-2909.130.3.355.

[68] Goodarzi N, Nosratabadi M, Ahmadi H. The Effects of Transcranial Direct Current Stimulation (tDCS) on Attention and Shooting Performance in Shooters. J Biochem Tech 2019:140–4.

[69] Lieberman HR, Tharion WJ, Shukitt-Hale B, Speckman KL, Tulley R. Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U.S. Navy SEAL training. Psychopharmacol 2002 1643 2002;164:250–61. https://doi.org/10.1007/S00213-002-1217-9.

[70] Smits FM, Schutter DJLG, van Honk J, Geuze E. Does non-invasive brain stimulation modulate emotional stress reactivity? Soc Cogn Affect Neurosci 2020;15:23–51. https://doi.org/10.1093/scan/nsaa011.

[71] Feltman KA, Hayes AM, Bernhardt KA, Nwala E, Kelley AM. Viability of tDCS in Military Environments for Performance Enhancement: A Systematic Review. Mil Med 2020. https://doi.org/10.1093/milmed/usz189.

[72] Priori A, Hallett M, Rothwell JC. Repetitive transcranial magnetic stimulation or transcranial direct current stimulation? Brain Stimul 2009;2:241–5. https://doi.org/10.1016/j.brs.2009.02.004.

[73] Valero-Cabré A, Amengual JL, Stengel C, Pascual-Leone A, Coubard OA. Transcranial magnetic stimulation in basic and clinical neuroscience: A comprehensive review of fundamental principles and novel insights. Neurosci Biobehav Rev 2017;83:381–404. https://doi.org/10.1016/j.neubiorev.2017.10.006.

[74] McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, et al. Consensus

Recommendations for the Clinical Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in the Treatment of Depression. J Clin Psychiatry 2018;79:35–48. https://doi.org/10.4088/JCP.16cs10905.

[75] Hadar R, Edemann-Callesen H, Hlusicka EB, Wieske F, Vogel M, Günther L, et al. Recurrent stress across life may improve cognitive performance in individual rats, suggesting the induction of resilience. Transl Psychiatry 2019;9. https://doi.org/10.1038/S41398-019-0523-5.

[76] Plieger T, Reuter M. Stress & executive functioning: A review considering moderating factors. Neurobiol Learn Mem 2020;173:107254. https://doi.org/10.1016/J.NLM.2020.107254.

[77] Pisoni A, Mattavelli G, Papagno C, Rosanova M, Casali AG, Romero Lauro LJ. Cognitive Enhancement Induced by Anodal tDCS Drives Circuit-Specific Cortical Plasticity. Cereb Cortex 2018;28:1132–40. https://doi.org/10.1093/cercor/bhx021.

[78] Martin DM, Liu R, Alonzo A, Green M, Loo CK. Use of transcranial direct current stimulation (tDCS) to enhance cognitive training: effect of timing of stimulation. Exp Brain Res 2014;232:3345–51. https://doi.org/10.1007/s00221-014-4022-x.

[79] Mancuso LE, Ilieva IP, Hamilton RH, Farah MJ. Does Transcranial Direct Current Stimulation Improve Healthy Working Memory?: A Meta-analytic Review. J Cogn Neurosci 2016;28:1063–89. https://doi.org/10.1162/jocn_a_00956.

[80] Elmasry J, Loo C, Martin D. A systematic review of transcranial electrical stimulation combined with cognitive training. Restor Neurol Neurosci 2015;33:263–78. https://doi.org/10.3233/RNN-140473.

[81] Berryhill ME, Martin D. Cognitive Effects of Transcranial Direct Current Stimulation in Healthy and Clinical Populations: An Overview. J ECT 2018;34:e25–35. https://doi.org/10.1097/YCT.0000000000000534.

[82] Vanderhasselt M-A, De Raedt R, Namur V, Lotufo PA, Bensenor IM, Boggio PS, et al. Transcranial electric stimulation and neurocognitive training in clinically depressed patients: A pilot study of the effects on rumination. Prog Neuropsychopharmacol Biol Psychiatry 2015;57:93–9. https://doi.org/10.1016/j.pnpbp.2014.09.015.

[83] Brunoni AR, Boggio PS, De Raedt R, Bensenor IM, Lotufo PA, Namur V, et al. Cognitive control therapy and transcranial direct current stimulation for depression: A randomized, double-blinded, controlled trial. J Affect Disord 2014;162:43–9. https://doi.org/10.1016/j.jad.2014.03.026.

[84] Ironside M, Browning M, Ansari TL, Harvey CJ, Sekyi-Djan MN, Bishop SJ, et al. Effect of Prefrontal Cortex Stimulation on Regulation of Amygdala Response to Threat in Individuals With Trait Anxiety: A Randomized Clinical Trial. JAMA Psychiatry 2019;76:71–8. https://doi.org/10.1001/JAMAPSYCHIATRY.2018.2172.

[85] Thielscher A, Antunes A, Saturnino GB. Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? 2015 37th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc., IEEE; 2015, p. 222–5. https://doi.org/10.1109/EMBC.2015.7318340.

[86] Hanke M, Baumgartner FJ, Ibe P, Kaule FR, Pollmann S, Speck O, et al. A high-resolution 7-Tesla fMRI dataset from complex natural stimulation with an audio movie. Sci Data 2014 11 2014;1:1–18. https://doi.org/10.1038/sdata.2014.3.