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Can a single session of noninvasive brain stimulation applied over the prefrontal cortex prevent stress-induced cortisol release?

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1 **TITLE:**

2 Can a single session of noninvasive brain stimulation applied over the prefrontal cortex
3 prevent stress-induced cortisol release?

4

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37 **KEY WORDS:**

38 Repetitive transcranial magnetic stimulation; rTMS; transcranial direct current stimulation;

39 tDCS; cortisol; HPA axis; stress

40 **ABSTRACT**

41 Introduction A better understanding of how the hypothalamic-pituitary-adrenal (HPA) axis
42 can be externally regulated is of major importance, especially because hyperreactivity to
43 stress has been proposed as a key factor in the onset and maintenance of many psychiatric
44 conditions. Over the past decades, numerous studies have investigated whether non-invasive
45 brain stimulation (NIBS) can regulate HPA axis reactivity in acute stress situation. As the
46 current results did not allow us to draw clear conclusions, we decided to conduct a systematic
47 review of the literature investigating the effect of a single NIBS session on stress-induced
48 cortisol release.

49 Methods: We searched MEDLINE and Web Of Science for articles indexed through
50 December 2021. Among the 1,246 articles identified, 15 fulfilled our inclusion criteria with a
51 quality estimated between 52 and 93%.

52 Results: Of the different NIBS used and targeted brain regions, stimulating the left
53 dorsolateral prefrontal cortex, with either high frequency repetitive transcranial magnetic
54 stimulation or anodal transcranial direct current stimulation, seems to be the most appropriate
55 for reducing cortisol release in acute stress situations.

56 Conclusions: Despite the heterogeneity of the stimulation parameters, the characteristics of
57 participants, the modalities of cortisol collection, the timing of the NIBS session in relation to
58 the stressor exposure, and methodological considerations, stimulating the left dorsolateral
59 prefrontal cortex can be efficient to modulate stress-induced cortisol release.

60 1. INTRODUCTION

61 Stress is an ubiquitous experience in human beings that alters homeostasis. Acute stress induces
62 physiological and psychological changes enabling individuals to face a novel challenging
63 situation. Thereafter, the stress reaction progressively decreases as soon as the threat has been
64 overcome. Although including feelings of distress and negative emotions, stress is generally a
65 positive phenomenon leading to an adaptive reaction to the environment. However, the adaptive
66 function of stress may get impaired when it arises too frequently (because of stress factors
67 occurring very repeatedly) or too intensively (for example after a potential traumatic event
68 occurred). In both cases, the stress response may become either inappropriate or not turn off
69 although the stress trigger is over (McEwen, 1998). An abnormal and exacerbated response to
70 stress has been associated with the onset and relapse of psychiatric symptoms and recurrency
71 in many psychiatric conditions such as major depressive disorder, anxiety disorders, and
72 psychosis (Tafet and Nemerof, 2016; Wingenfeld and Wolfe, 2015; Zorn et al., 2017).

73 At the physiological level, the sympathetic nervous system and the hypothalamus-pituitary-
74 adrenal (HPA) axis are core elements in the response to stress. The activation of the sympathetic
75 nervous system leads to the release of catecholamines, which are especially responsible for
76 increased heart rate and vasoconstriction, thus allowing the “flight-or-fight response” (Ulrich-
77 Lai and Herman, 2009). The activation of the HPA axis leads to the final secretion of
78 glucocorticoids, cortisol in human, by the adrenal gland. The HPA axis is a dense network of
79 interactions and bilateral loops of negative feedback between the frontal cortex, the
80 hypothalamus, the pituitary gland, and the adrenal gland. The HPA axis is also influenced by
81 specific neurohormones, neuromediators, and neurotransmitters (e.g., glutamate, gamma-
82 aminobutyric acid, dopamine, serotonin, noradrenaline). In addition, the cortisol can affect its
83 own secretion through a negative feedback system and can influence cerebral activity,

84 particularly in regions with a dense presence of glucocorticoid receptors such as the frontal
85 cortex (De Kloet et al., 2005; Lupien et al., 2009).

86 Moreover, an acute stress will also induce the shift from a state of cognitive control to a state
87 of alertness. Thus, it influences major executive functions, such as working memory, flexibility,
88 and inhibition (Taverniers et al., 2010; Plessow et al., 2012; Duan et al., 2019). Notably, it is
89 well known that the prefrontal cortex (PFC) plays a key role in these executive functions. On
90 the one hand, the executive functions are affected by stress, and on the other hand their
91 regulation is necessary to provide an appropriate response to stress. Thus, the PFC was reported
92 to play a crucial role in the initiation and the regulation of the response to stress (Arnsten, 2015;
93 Radley et al., 2015). When stress occurs in an inappropriate way, i.e., too frequently or too
94 intensively, the ability of the PFC to regulate stress may get depleted and PFC structures and
95 functions can get altered (McEwen and Morrison, 2013; Arnsten, 2015; Shields et al., 2016).
96 In addition, a modulatory role of the PFC on the HPA axis was reported, either stimulating or
97 inhibiting, depending on which part of the PFC is involved (Radley et al., 2006; Ulrich-Lai and
98 Herman, 2009). Specifically, different subparts of the PFC have been involved in the stress
99 response. Animal studies have highlighted a causal role of the median PFC in inhibiting the
100 HPA axis reactivity (Diorio et al., 1993; Radley et al., 2006), which exhibits dorso-ventral
101 distinctions regarding chronic stress-induced damages (Lee et al., 2011). In addition, the median
102 PFC and the DLPFC project to a different part of the striatum (Haber and Knutson, 2010), partly
103 responsible for the catecholamines release observed during stressful situation. The modulatory
104 role of the PFC on the HPA axis may also be supported by connections with the amygdala (Ray
105 and Zald, 2012), which play a central role in stress response initiation notably through its
106 noradrenergic afferences, as well as connections with the hippocampus (Godsil et al., 2013), an
107 inhibitory structure of the HPA axis (Ulrich-Lai and Herman, 2009). Abnormal reactivity of the
108 pathway including the PFC, the amygdala and the hippocampus has been involved in the

109 physiopathology and the treatment of several psychiatry condition including acute stress
110 disorder and post-traumatic stress disorder (Yabuki and Fukunaga, 2019). Therefore, improving
111 the regulatory function of the PFC may be a relevant way to regulate the stress reaction more
112 appropriately, leading to decreases in cortisol secretion in acute stress situations (Brunelin and
113 Fecteau, 2015).

114 Non-invasive brain stimulation (NIBS) methods can modulate the activity of the targeted and
115 interconnected cortical brain areas non-invasively (Dayan et al., 2013; Keeser et al., 2011).
116 Currently, two main NIBS techniques are widely used for both research and clinical purposes:
117 transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).
118 With TMS, a coil of stimulation is applied over the scalp of a participant, delivering a magnetic
119 pulse that can induce action potentials in the neurons of the stimulated area by increasing
120 membrane potential beyond the action potential threshold. Using it repeatedly, (r)TMS results
121 in either an increase or a decrease of the cortical excitability of the stimulated region depending
122 on the stimulation frequency. High-frequency rTMS (HF-rTMS; frequency ≥ 5 Hz) classically
123 increases the cortical excitability whereas low-frequency rTMS (LF-rTMS; frequency ≤ 1 Hz)
124 classically decreases the cortical excitability (Fitzgerald et al., 2006). A variant of rTMS, called
125 theta burst stimulation (TBS), used a specific form of trains with three 50 Hz pulses repeated
126 every 200 ms, corresponding to the theta frequency (5Hz). When the pulses are delivered in an
127 intermittent way, classically with 8s pauses between the trains, namely intermittent theta burst
128 stimulation (iTBS), cortical excitability generally increases. In contrast, when the pulses are
129 delivered continuously, most often for 40s, namely continuous theta burst stimulation (cTBS),
130 cortical excitability generally decreases (Huang et al., 2005). With tDCS, a weak electrical
131 current (up to 4 mA) is delivered between two electrodes, one anode and one cathode, which
132 are applied over the scalp. tDCS may work by altering the neuronal resting membrane potential.
133 Anodal tDCS generally increases resting membrane potential and thus increases cortical

134 excitability and plasticity whereas cathodal tDCS generally decreases it (Nitsche and Paulus,
135 2000). For both techniques, the effect is not limited to the stimulated area but can spread to
136 other brain regions that are interconnected with the stimulated area along the cortico-cortical
137 networks dynamics (Dayan et al., 2013). Moreover, as observed with HF-rTMS (Strafella et al.,
138 2001), anodal stimulation of the DLPFC can also impact cortico-subcortical loops by inducing
139 dopamine release in the striatum (Fonteneau et al., 2018), a catecholamine involved in the acute
140 stress-induced modulation of the PFC activity (Arnsten, 2015). Both tDCS and rTMS devices
141 allow setting up sham conditions. Because of the key role of the PFC in the response to stress
142 regulation and its privileged accessibility for NIBS, numerous studies have investigated the
143 effects of NIBS applied over the PFC on the biological and cognitive consequences of stress.
144 Although a recent meta-analysis reported a significant beneficial effect of NIBS on stress-
145 related emotional reactivity in healthy volunteers (Smits et al., 2020), little is known about the
146 effects of NIBS on the reactivity of the HPA axis to stress.

147 Overall, it can be assumed that NIBS applied to the PFC could influence the reactivity of the
148 HPA axis in acute stress situations. However, the optimal parameters to be delivered remain
149 unclear regarding the type of NIBS, the timing of the NIBS session in relation to the stressor
150 exposure, and the stimulation parameters (for rTMS: stimulation frequency, total number of
151 pulses; for tDCS: stimulation intensity, polarity of electrodes, number and spacing of
152 stimulations).

153 Consequently, here, we conducted a systematic review of randomized sham-controlled studies
154 investigating the effect of a single NIBS session on the HPA cortisol reactivity to a stress
155 measured by cortisol release. The objective of this review is therefore to perform a systematic
156 inventory of studies investigating whether the cortisol release is affected by a single application
157 of NIBS and to determine which experimental parameters are the most appropriate to expect
158 the NIBS to modulate the reactivity to induced acute stress.

159

160 2. MATERIAL AND METHODS

161 We performed a systematic review following the recommendations of the *Preferred Reporting*
162 *Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines (Page et al., 2021). The
163 protocol was preregistered with PROSPERO (CRD42021258756) on 2021, July, 11th.

164

165 2.1. Eligibility

166 The inclusion criteria were as follows: i) full-length original articles published in English
167 language in peer-reviewed journals; ii) randomized sham-controlled trials; iii) use of an
168 experimental acute stress procedure; iv) use of a single session of NIBS; v) measure of cortisol
169 (either in saliva or blood) at least once before and after the stress task and the NIBS session.

170 There were no age restrictions to inclusion; healthy participants and those with a psychiatric
171 condition could be included.

172 Studies were excluded from the qualitative synthesis when the following criteria were
173 identified: i) comments, index, protocol designs, open-label, case-reports, review, meta-
174 analysis, letter to editors; ii) full-text not available; iii) studies delivering more than one NIBS
175 session.

176

177 2.2. Research strategy

178 We conducted a systematic search in the PubMed and Web of science databases until December
179 2021 using the following MESH words with no limitation of date: cortisol AND (("transcranial
180 direct current stimulation") OR "iTBS" OR "tDCS" OR ("transcranial magnetic stimulation")
181 OR "TMS" OR ("non invasive brain stimulation") OR "tACS "OR "neuromodulation" or "TBS"
182 or ("theta burst stimulation")). We also examined the citation lists of the identified publications
183 for additional studies and used the related articles function of the PubMed database for other

184 relevant sources of data. Two investigators (PV and OA) independently screened the title,
185 abstract and key words of each reference identified by the search and applied the inclusion and
186 exclusion criteria. For each potentially eligible reference, the same procedure was applied to
187 the full-text articles. Discrepancies between the reviewers were resolved through discussion
188 with a third investigator (JB).

189

190 2.3. Data extraction

191 Two investigators (PV and OA) independently extracted the following data: i) demographic
192 data (number of participants, age, sex, level of education, handedness); ii) clinical
193 characteristics of participants (healthy participants or patients with a psychiatric condition, and
194 if applicable illness duration); iii) experimental design (cross-over or parallel arms); iv)
195 characteristics of the stress task (type of stressor, duration); v) type of NIBS applied (rTMS or
196 tDCS) and stimulation parameters; vi) timing of the NIBS session in relation with the stress
197 exposure (before, during or after the stress task); vii) time of day when the experimental design
198 was executed (mornings, evenings) to control for circadian cortisol variations.

199 In studies that used rTMS, the following stimulation parameters were extracted: targeted
200 cortical area, stimulation intensity, stimulation duration, total number of pulses. When tDCS
201 was delivered, the following stimulation parameters were extracted: position of both electrodes,
202 size of electrodes, current intensity, and stimulation duration.

203

204 2.4. Quality assessment

205 The quality of each study was assessed with the QualSyst checklist for assessing the quality of
206 quantitative studies. The QualSyst checklist has proven to have high reliability (Kmet et al.,
207 2004). The checklist consists of 14 questions investigating the study design, the blinding, the
208 analytic methods, and the report of methodological information and results. Each question can

209 result in a score of 2 when the study meets the criterion, a score of 1 for a partial response, and
210 0 if the criterion is not met. A not applicable (NA) response to some criterion is also possible
211 when the study design of the original publication does not allow for the criterion to be met. A
212 summary score is calculated for each study by summing the obtained total score and dividing it
213 by the total possible score taking into account the number of NA responses. Two investigators
214 (PV, OA) independently assessed and calculated a score for each included study. Scores of both
215 investigators were then averaged. In case of discrepancies (i.e., if the difference between the
216 QualSyst scores of both investigators was larger than 10% of the max score), these were solved
217 with the intervention of a third party (JB). A QualSyst score > 0.80 was interpreted as strong
218 quality, $0.65\text{--}0.79$ as good quality, $0.55\text{--}0.64$ as adequate quality, and < 0.55 as poor
219 methodological quality (Kmet et al., 2004).

220

221 3. RESULTS

222 3.1. Search results and eligibility

223 As shown in Figure 1, 246 articles were identified on the databases and 23 full-text articles
224 were assessed after exclusion of duplicates and exclusion based on the abstract. Among the 23
225 full-text articles read, 8 articles were excluded. Finally, 15 articles that met all our inclusion
226 criteria were retained.

227

228 **PLEASE INSERT FIGURE 1 ABOUT HERE**

229

230 3.2. Quality Assessment

231 The overall methodological quality of the 15 retrieved articles was estimated between 0.52 and
232 0.93 (on possible scores ranging from 0.0 to 1.0). The mean and the median methodological
233 quality score were 0.75. The study of Schulreich and Schwabe (2021) had the highest
234 methodological quality (0.93), while the study of Zwanzger and colleagues (2007) got the
235 weakest score (0.52). Among all the included studies, only 2 reach a QualSyst score lower than
236 0.65 (Table 1).

237

238

239 **PLEASE INSERT TABLE 1 ABOUT HERE**

240

241 3.3. Qualitative synthesis

242 A large heterogeneity regarding the type of NIBS was observed between the 15 included
243 studies. Despite considerable heterogeneity in stimulation parameters, all studies stimulated the
244 PFC. Therefore, we sorted studies into 2 groups depending on the NIBS method: i) a group of
245 8 studies where the participants received rTMS. This group was then separated into two
246 subgroups based on rTMS parameters, a subgroup of 5 studies using conventional rTMS
247 parameters and a subgroup of 3 studies using theta burst stimulation (TBS); ii) a group of 7
248 studies where the participants received tDCS. Studies from this group were then divided into 2
249 subgroups depending on the montage of the electrodes (anode over the left DLPFC coupled
250 with cathode over the right DLPFC versus other montages). We also observed a large
251 heterogeneity regarding the type of stress task.

252

253 3.3.1 Studies where the participants received rTMS

254 All the retrieved studies targeted the left DLPFC except one that targeted the right DLPFC. Five
255 studies used conventional rTMS parameters: four used HF-rTMS over the left DLPFC (Baeken
256 et al., 2014; Pulpulos et al., 2020; Claudino et al., 2011; McClelland et al., 2016), and one
257 used LF-rTMS over the right DLPFC (Zwanzger et al., 2007). All the HF-rTMS studies
258 delivered stimulation at 110% of the intensity of the resting motor threshold (RMT) of each
259 participant, 2 of them with a frequency of 10 Hz (Claudino et al., 2011; McClelland et al., 2016)
260 and the 2 others with a 20 Hz frequency (Baeken et al., 2014; Pulpulos et al., 2020). The study
261 using LF-1 Hz-rTMS delivered the stimulation at 120% RMT (Zwanzger et al., 2007). Three
262 studies used TBS parameters, either iTBS (Pulpulos et al., 2019; De Witte et al., 2020)
263 delivered at 110% RMT with a total number of pulses of 1620 pulses, or cTBS (Era et al., 2021)
264 delivered at 40% of the maximal stimulator device power (300 pulses/session). The stimulation
265 parameters are summarized in the Table 2.

266

267 ****PLEASE INSERT TABLE 2 ABOUT HERE****

268

269 **3.3.1.1 Studies where the participants received conventional rTMS**

270 In a first study (Baeken et al., 2014), healthy volunteers received a single session of either active
271 or sham HF-rTMS over the left DLPFC just before being stressed using a psychological stress
272 task (the Critical Feedback Test, CFT). The authors did not find any significant difference
273 between the sham and the active rTMS condition regarding the whole cortisol secretion
274 (measured by area under curve (AUC) with respect to ground - AUCg). However, they reported
275 a lower reactivity of the HPA axis in the active group as compared to sham (measured by AUC
276 with respect to increase - AUCi). In another study, the same group of authors proposed to
277 deliver a single HF-rTMS session over the left DLPFC before another stress task (Pulpulos et

278 al., 2020). They used a modified version of the Trier Social Stress Test (TSST), a stress task
279 combining psychological and cognitive stress (Kirschbaum et al., 1993). In this study, the
280 authors also reported a lower reactivity of the HPA axis (measured by AUC_i) in the active group
281 as compared to the sham group.

282 The 2 other studies that used HF-rTMS over the left DLPFC involved participants diagnosed
283 with an eating disorder (Claudino et al., 2011; McClelland et al., 2016). In a first study
284 (Claudino et al., 2011), a group of participants with bulimic disorder received a single session
285 of either active or sham HF-rTMS after being exposed to the Food Challenge Task (FCT), a
286 stress task where patients were exposed to highly palatable food. The stress-induced salivary
287 cortisol release was significantly lower in patients who received the active stimulation as
288 compared to sham. Finally, no difference between active and sham rTMS was observed on
289 stress-induced salivary cortisol release in patients with anorexia nervosa who received HF-
290 rTMS after they were being exposed to the FCT (McClelland et al., 2016).

291 A last, rTMS study investigated the effect of a single LF-rTMS session over the right DLPFC
292 delivered just before healthy volunteers were exposed to a panic attack, induced by
293 cholecystokinin-tetrapeptide challenge. No difference between active and sham groups were
294 observed on stress-induced cortisol release (Zwanzger et al., 2007).

295

296 3.3.1.2. Studies where the participants received TBS

297 In a first study, the authors evaluated the effect of a single iTBS session over the left DLPFC
298 delivered after healthy participants (females only) completed a modified version of the TSST
299 (Pulopulos et al., 2019). They found no differences between active and sham groups in neither
300 total cortisol secretion (i.e., AUC_g) nor cortisol response to stress (i.e., AUC_i). However, in this
301 study, the authors observed that participants who received active stimulation during the first

302 visit displayed a greater AUC_i than sham during the second visit as compared with participants
303 who received sham at the first visit. The lack of effect of iTBS on cortisol secretion was
304 corroborated by a second study, also applying iTBS over the left DLPFC in healthy females
305 after they completed the TSST (De Witte et al., 2020).

306 In the study of Era and colleagues, cTBS was applied over the left DLPFC, between the 2 parts
307 of the stress task consisting in a non-standardized rumination task. In this cross-over study, the
308 healthy participants undergo 2 control conditions: active cTBS over the left ventral-premotor
309 cortex (vPM, active control) and sham stimulation. The stress-induced cortisol release was
310 higher when cTBS was applied over the left DLPFC as compared to vPM and sham (Era et al.,
311 2021). These results are summarized in Table 3.

312

313 **PLEASE INSERT TABLE 3 ABOUT HERE**

314

315 3.3.2 Studies where the participants received a tDCS session

316 Among the 7 studies that delivered a single tDCS session, an electrode montage with the anode
317 over the left DLPFC coupled with the cathode over the right DLPFC was applied in 4 studies
318 (Sarkar et al., 2014; Mehrosfar et al., 2020; Brunelin and Fecteau, 2021; Carnevali et al., 2020).
319 One of them delivered a 1 mA stimulation for 30 min (Sarkar et al., 2014) while the 3 others
320 delivered a 2 mA stimulation for 15 (Carnevali et al., 2020), 20 (Mehrosfar et al., 2020) or 30
321 min (Brunelin and Fecteau, 2021). The 3 remaining studies proposed to deliver tDCS with other
322 electrode montages described below (Antal et al., 2014; Bogdanov and Schwabe, 2016;
323 Schulreich and Schwabe, 2021). One study targeted the right median PFC with the anode for
324 20 min at 1 mA (Antal et al., 2014). The others placed the anode over the right DLPFC and the
325 cathode over the vertex, delivering a stimulation at 1 mA (Bogdanov and Schwabe, 2016;

326 Schulreich and Schwabe, 2021). Stimulation parameters of tDCS studies are summarized in the
327 Table 4.

328

329 ***PLEASE INSERT TABLE 4 ABOUT HERE***

330

331 3.3.2.1 Studies where the participants received bifrontal tDCS

332 In a first study stimulating bilaterally the DLPFC with the anode over the left one, Sarkar and
333 colleagues reported that the effect of tDCS delivered during a stressful arithmetic decision task
334 depends on the level of mathematical anxiety at baseline (Sarkar et al., 2014). Indeed, in
335 participants with higher anxiety at baseline, there was a significant decrease of cortisol secretion
336 in the active tDCS group as compared to the sham group whereas the opposite effect was
337 reported in participants with lower anxiety (i.e., a significant larger decrease in cortisol
338 secretion in the sham group than in the active group).

339 In another study with the same electrode montage, a significantly lower stress induced-cortisol
340 release was observed with active tDCS as compared to sham when tDCS was delivered during
341 the stress task in healthy volunteers (Brunelin and Fecteau, 2021). In this study, the stress task
342 was the Maastricht Acute Stress Test (MAST, Smeets et al., 2012), a task combining a physical
343 stress (hand immersion trials in 8°C water) and cognitive task (arithmetic calculation under
344 social pressure). Mehrsifar and colleagues (2020) also reported a significant effect of tDCS on
345 the cortisol reactivity in elite athletes stimulated before an official competition. Here, salivary
346 cortisol was significantly decreased after the competition, as compared to sham. However, they
347 observed no difference between active and sham tDCS with the reverse electrode montage (i.e.,
348 anode over the right DLPFC – cathode over the left DLPFC).

349 Finally, Carnevali and colleagues (2020) did not find any significant difference between active
350 and sham tDCS on the stress-induced cortisol release by a modified version of the TSST when
351 tDCS was delivered during the stress task.

352

353 3.3.2.2 Studies involving other tDCS montages

354 First, Schulreich and Schwabe (2021) tested the effect of tDCS with the anode over the right
355 DLPFC coupled with the cathode over the vertex. tDCS was delivered after participants faced
356 the Social Evaluated Cold Pressor Test (SECPT). In the SECPT, participants immerse a hand
357 up to the wrist into ice water (0-2 °C) for 3 min (or until they get out of tolerance) while they
358 are video-recorded and continuously monitored by a cold and non-reinforcing experimenter
359 (Schwabe et al., 2008). They did not find any significant difference between active and sham
360 conditions. Second, Bogdanov and Schwabe (2016) tested 2 different electrode montages
361 (anode or cathode over the right DLPFC, respectively, with return electrode over the vertex)
362 compared to a sham group. The tDCS session was delivered after the stress task (TSST). The
363 authors did not report any difference between groups on cortisol release. In a last study
364 developed by Antal and colleagues (2014) using a 3-arm parallel design (anodal, cathodal or
365 sham stimulation of the right medial PFC with return electrode over the occipital region (O2-
366 P4)), tDCS was delivered before the TSST in healthy participants. Cortisol secretion was found
367 significantly lower in the anodal group than in the sham group and significantly lower in the
368 anodal group than in the cathodal group. These results are summarized in table 5.

369

370 ****PLEASE INSERT TABLE 5 ABOUT HERE****

371

372 4. DISCUSSION

373 We systematically reviewed studies investigating the effect of a single NIBS session on the
374 cortisol reactivity to an acute stress challenge. The systematic search yielded 15 articles that
375 met our inclusion criteria with various design and methodological quality, leading to
376 heterogeneous results regarding NIBS effect on stress-induced cortisol reactivity in acute stress
377 conditions. However, all of them applied the stimulation over the PFC. Because the PFC has
378 been implicated in stress regulatory mechanisms (Ulrich-Lai and Herman, 2009), modulating
379 its activity when a person is faced with an acute stress situation may alter the stress response.
380 As NIBS can modulate the excitability and activity of targeted brain regions and functionally
381 connected structures, they are therefore of particular interest for investigating the impact of
382 modulating PFC activity in acute stress situation. Indeed, changes in connectivity between the
383 PFC and other brain regions, such as the anterior cingulate cortex, the hippocampus or the
384 amygdala, have been involved in the acute stress response and recovery phase (Quaedflieg et
385 al., 2015).

386

387 4.1 Influence of the target location

388 4.1.1. Effect of rTMS on the cortisol reactivity to stress

389 Among the eight studies investigating the effect of rTMS over the PFC on cortisol reactivity,
390 four studies observed convergent effects. Among them, three studies reported that HF-rTMS
391 over the left DLPFC, supposed to exert excitatory effects on the cortical excitability (Maeda et
392 al., 2000), can prevent stress-induced cortisol release both in healthy volunteers (Baeken et al.,
393 2014; Pulpulos et al., 2020) and in patients with eating disorder (Claudino et al., 2011).
394 Conversely, one study highlighted that cTBS, supposed to exert inhibitory effects on cortical
395 excitability (Huang et al., 2009), can increase stress-induced cortisol release when applied over
396 the left DLPFC (Era et al., 2021). These four studies suggest that the left DLPFC plays a
397 regulatory role on HPA axis reactivity in acute stress situations. Activation of the DLPFC

398 induced by HF-rTMS may exert a top-down control of the HPA axis leading to the decrease in
399 cortisol secretion. Conversely, inhibition of the DLPFC top-down control induced by cTBS led
400 to exacerbated cortisol release. One may note that HF-rTMS over the left DLPFC can modulate
401 the arterial perfusion of the hippocampus (Shang et al., 2018), which can also contribute to the
402 increased top-down control over the HPA axis.

403 Four studies did not observe significant differences between active and sham rTMS on cortisol
404 release in acute stress situations. It was the case in the two studies that evaluated the stress-
405 induced cortisol release after the participants received an iTBS session over the left DLPFC
406 (Pulopulos et al., 2019; De Witte et al., 2020), supposed to exert excitatory effects on the
407 cortical excitability, in a study with patients with eating disorder who received HF-rTMS over
408 the left DLPFC (McClelland et al., 2016), and in healthy volunteers who received LF-rTMS
409 over the right DLPFC (Zwanzger et al., 2007).

410 These studies suggested that iTBS over the left DLPFC and LF-rTMS over the right DLPFC
411 are not able to affect cortisol reactivity while HF-rTMS in healthy controls appears to promote
412 this top-down regulation of the HPA axis in acute stress situations. Although HF-rTMS may
413 lead to top-down control on HPA axis reactivity in patients with bulimic disorder (Claudino et
414 al., 2011), no difference was observed between active and sham stimulation in patients with
415 anorexia nervosa (McClelland et al., 2016), supporting the hypothesis of dissociable
416 pathophysiology related to stress regulation in these two distinct disorders (Westwater et al.,
417 2020). One may note that eating disorders have been associated with altered cortisol secretion,
418 possibly related to traumatic events (Lo Sauro et al., 2008). Importantly, traumatic events and
419 chronic stress alter the mechanisms of stress regulation (Ulrich-Lai and Herman, 2009).
420 However, the presence of chronic stress has not been controlled in healthy participants, thus
421 limiting the comparability of results with those from participants with eating disorders.

422

423 4.1.2 Effect of tDCS on the cortisol reactivity to stress

424 The major role of the left DLPFC is also supported by the findings in tDCS studies. Indeed,
425 among the 4 tDCS studies that reported an effect of tDCS on cortisol reactivity, all but one
426 study used an electrode montage with the anode over the left DLPFC coupled with the cathode
427 over the right DLPFC (Sarkar et al., 2014; Mehrafar et al., 2020; Brunelin and Fecteau, 2021).
428 The other study that observed an effect of tDCS on cortisol proposed an electrode montage with
429 the anode over the right medial frontal gyrus and the cathode over the occipital region (Antal
430 et al., 2014). Interestingly, except the study of Carnevali and colleagues (2020), the anodal
431 stimulation of the left DLPFC was found to decrease the cortisol reactivity (Sarkar et al., 2014;
432 Mehrafar et al., 2020; Brunelin and Fecteau, 2021), as observed in HF rTMS studies. This is
433 of major interest since anodal stimulation is supposed to exert a similar excitatory
434 neurophysiological effect as compared with HF-rTMS when applied over the motor cortex
435 (Nitsche and Paulus, 2000). When using cathodal stimulation, supposed to decrease cortical
436 excitability, the effects were contrasted between studies. One study reported that the cathodal
437 stimulation of the left mPFC (coupled with anodal occipital), lead to an increased cortisol
438 reactivity (Antal et al., 2014), as observed with cTBS, supposed to exert similar inhibitory
439 effect. However, these results were not corroborated by two other studies that reported that the
440 cathodal stimulation of the left DLPFC, either coupled with anodal stimulation of the right
441 DLPFC (Mehrafar et al., 2020) or of the vertex (Bodganov and Schwabe, 2016), did not impair
442 the cortisol reactivity.

443 A lacking effect of anodal stimulation of the right DLPFC was observed in other studies.
444 Indeed, among the 3 studies where no effect on the cortisol reactivity was reported, 2 studies
445 delivered the tDCS session with the active electrode over the right DLPFC and the reference
446 electrode over the vertex (Schulreich and Schwabe, 2021; Bogdanov and Schwabe, 2016).
447 Results from these two studies are in line with results from the study of Zwanzger and

448 colleagues (2007) where no effect of LF-rTMS over the right DLPFC was observed on cortisol
449 reactivity before the stress induction. These results suggest that the right DLPFC displays a less
450 important role than the left DLPFC in modulating cortisol reactivity.

451 In sum, to prevent stress-induced cortisol release in acute stress situations, stimulating the left
452 DLPFC with either HF-rTMS (and not iTBS) or anodal tDCS seems to be the most efficient.
453 However, the target location is probably not the only parameter to determine a significant
454 biological effect of NIBS on HPA axis reactivity since some contradictory results persist.

455

456 4.2 Influence of the timing to apply the NIBS session

457 Among the eight studies where NIBS was found to affect the cortisol reactivity, the stimulation
458 session was delivered before the stress task in four studies (two with rTMS: Baeken et al., 2014;
459 Pulpulos et al., 2020; two with tDCS: Antal et al., 2014; Mehrsafari et al., 2020), during the
460 stress task in three studies (one with rTMS: Era et al., 2021; two with tDCS: Mehrsafari et al.,
461 2020; Brunelin and Fecteau, 2021) and after the stress task in one rTMS study (Claudino et al.,
462 2011).

463 Interestingly, in the 3 included studies reporting no effect of rTMS on the cortisol reactivity,
464 the NIBS session was systematically delivered after the stress task (McClelland et al., 2016;
465 Pulpulos et al., 2019; De Witte et al., 2020). The session was delivered before the stress-
466 induction in the study that used LF-rTMS (Zwanzger et al., 2007). In the 3 included studies
467 reporting no effect of tDCS on the cortisol reactivity, the tDCS session was delivered after the
468 stress task in 2 studies (Schulreich and Schwabe, 2021; Bogdanov and Schwabe, 2016), before
469 and during the stress task in one study (Carnevali et al., 2020).

470 In sum, to observe an influence of NIBS on HPA reactivity in acute stress situations, delivering
471 the NIBS session before or during the stress induction seems to be the most adapted timing.

472 When the stimulation is delivered after the stress task, there is less evidence of a biological
473 effect of the NIBS session on stress-induced cortisol release. If further investigations confirm
474 these results, this will support the role of the DLPFC in the early initiation phase of the stress
475 response (Herman et al., 2005). Moreover, the influence of a NIBS session strongly depends on
476 the brain state at the moment the NIBS session is being delivered. This was displayed in a time
477 scale of minutes to hours and reported for both tDCS and rTMS (Silvanto and Pascual-Leone,
478 2008; Bergmann, 2018; Li et al., 2019). One can therefore assume that the effect of a NIBS
479 session varies depending on whether the brain is still at rest or already stressed. In line with it,
480 not only the timing but also the specific type of stress task (cognitive or physical stress) may
481 play a role in the brain state-dependency. In addition, since NIBS applied over the DLPFC can
482 influence subcortical dopamine release (Strafella et al., 2001, Fonteneau et al., 2018), their
483 effect on stress reactivity may be also depend on dopaminergic tone at the time of the
484 stimulation (also reflecting the level of stress of the participant).

485

486 4.3. Other parameters that may modulate the influence of the NIBS on the cortisol reactivity

487 Some other parameters may have influenced NIBS effects on cortisol reactivity. First, the
488 choice of the stress task and the heterogeneity among the selected studies should be discussed.
489 The proposed stress tasks used either social, cognitive, emotional, and/or physical stressors or
490 a combination of different stressors leading to different effects on cortisol reactivity. More
491 critically, in some studies, the authors did not report any effect of the used stress task on cortisol
492 release (Claudino et al., 2011; McClelland et al., 2016; Schulreich and Schwabe, 2021). This is
493 of major importance because to be able to observe an effect of NIBS on cortisol release in acute
494 stress situations, it is mandatory to use a stress task that effectively induces a cortisol release.

495 Second, the type of participants should also be considered since the HPA axis reactivity can be
496 impaired in several conditions. In all but 3 studies, the participants were healthy volunteers.
497 Two studies included participants with an eating disorder (Claudino et al., 2011; McClelland et
498 al., 2016) and one study included elite athletes (Mehrsafar et al., 2020). In eating disorders, the
499 HPA axis may be impaired and the cortisol reactivity was reported to be blunted in patients
500 with bulimic disorders (Culbert et al., 2016; Lawson et al., 2013; Vaz-Leal et al., 2018). As
501 compared to sedentary healthy controls (Duclos et al., 2001), the HPA axis may be altered in
502 elite athletes and the cortisol reactivity was found to be increased in that subgroup (Minetto et
503 al., 2007). Moreover, the PFC plays a significant role in the sport performance as it increases
504 neuronal activation to reinforce the muscle force during a physical activity (Thomas and
505 Stephane, 2008) and supports motivation as well (Pageaux, 2014; Robertson and Marino, 2016).
506 The specific features of the included population have to be taken into consideration when the
507 effects of NIBS on the HPA axis are investigated.

508 Third, tDCS is a kind of NIBS where many parameters vary, such as stimulation intensity or
509 duration of stimulation. Among the studies where tDCS was delivered with the montage anode
510 left DLPFC/cathode right DLPFC, which seems more efficient to affect the cortisol reactivity,
511 only one study reported no effect of tDCS. Interestingly, the stimulation duration was shorter
512 in that study (15 min in Carnevali et al., 2020) as compared to the other studies where an effect
513 of tDCS with the same montage was reported (20 min in Sarkar et al., 2014 and in Mehrsafar
514 et al., 2020; 30 min in Brunelin and Fecteau, 2021). This aspect is in line with other studies
515 highlighting the variability in the effect of tDCS according to the stimulation duration (Vignaud
516 et al., 2018; Monte Silva et al., 2013). This probable dosage-effect relation should be taken into
517 consideration for future studies, although there is no linearity between dosage and cognitive
518 performance in neuropsychological studies.

519

520 4.4. Methodological considerations

521 Among the 15 selected studies included, the methodological quality as assessed with the
522 QualSyst tool was quite satisfactory in 14 of them with a mean score 0.75 (range 0.0 – 1.0);
523 four studies were ranked with strong quality. Nevertheless, some methodological limitations
524 must be highlighted. First, in all but three studies (Claudino et al., 2011; Baeken et al., 2014;
525 Pulpulos et al., 2020), the cortisol reactivity was not the primary outcome of the included
526 studies, and thus no a priori sample size calculation was performed regarding this highly
527 variable outcome. Moreover, in several studies, cortisol was assessed only at baseline and at
528 the end of the experimental design, without any repeated cortisol assessment during and/or after
529 the stress task that could allow to measure the peak of cortisol release that varies across
530 individuals. Second, the outcome measure to assess the cortisol reactivity was quite
531 heterogeneous: the area under the curve (AUC_i or AUC_g), the value of the peak, etc. The AUC_i
532 seems the more appropriate outcome to assess stress-induced cortisol release since it reflects
533 the time course of the cortisol secretion (Fekedulgen et al., 2007). Nevertheless, this measure
534 was used in only 3 of the included studies (Baeken et al., 2014; Pulpulos et al., 2019; 2020).
535 Third, it is well-known that the physiological cortisol level varies largely over the circadian
536 rhythm, with a secretion peak in the early morning and a progressive decrease in the cortisol
537 level over a 24h period. However, the time of day the experiments took place was very
538 heterogeneous between the included studies. Indeed, the participants completed the
539 experimental session in the morning in 1 study (Brunelin and Fecteau, 2021), in the afternoon
540 in 8 studies, at any time of the day in 2 studies (Sarkar et al., 2014; Carnevali et al., 2020) and
541 this parameter was not reported in 3 studies. Alternatively, one study used the previous day's
542 cortisol as a baseline measure (Bogdanov and Schwabe, 2016). The time of day when the
543 experimental sessions are executed needs to be controlled to increase the comparability between
544 the studies. Fourth, although we only included randomized sham-controlled studies, the study

545 design was also heterogeneous among studies. Only 8 studies proposed a parallel-arm design.
546 A cross-over procedure was used in almost half of the included studies, although this may alter
547 the quality of the double blind (regarding both the NIBS or the stress procedure) and thus may
548 influence the expecting results from these studies. Fifth, some basic demographic
549 characteristics may have influenced the effect of a NIBS session on the cortisol reactivity. There
550 may be associations between the sexual hormones and the cortisol secretion. The female
551 menstrual cycle may affect the cortisol reactivity, which was reported to be higher in the luteal
552 phase (Montero-Lopez et al., 2018). In addition, the cortisol reactivity as well as the ACTH
553 secretion after a stress task was found to be higher in healthy men than in healthy women
554 (Stephens et al., 2016). Nevertheless, 6 of the studies considered in this review included only
555 female participants, so a sampling bias cannot be excluded and potentially limits the
556 extrapolation of the results. Then, the smoking status was not reported in 6 of the included
557 studies. This is a notable methodological weakness as nicotine affects the cortico-spinal
558 excitability and is a factor of variability in the response to a NIBS session (Grundey et al., 2012;
559 Lücke et al., 2014; Guerra et al., 2020). Furthermore, the cortisol secretion may be also
560 influenced by the nicotine consumption: the basal cortisol and the cortisol awakening were
561 found higher in smokers than in non-smokers (Steptoe and Ussher, 2006). Moreover, it is well
562 documented that age affects the response to a NIBS session as the plasticity induced by the
563 stimulation declines with age in both healthy subjects and subjects with a neurologic disorders
564 (Ridding and Ziemann, 2010). Age also strongly impacts the HPA axis at both central and
565 peripheral levels (Velduis et al., 2013). In all studies included in our review, the participants'
566 age approximately ranged from 20 to 30: this potential bias was therefore controlled but on the
567 other hand the extrapolation of the results gets limited.

568

569 4.5. Recommendations and Perspectives

570 Existing literature suggests that NIBS may prevent the stress-induced cortisol elevation in acute
571 stress situations. HF-rTMS and anodal tDCS over the left DLPFC (with the cathode over the
572 right DLPFC) appear to be the most efficient configurations. When comparing tDCS with
573 rTMS, none of the two NIBS seems clearly more reliable to affect cortisol reactivity. To achieve
574 a significant beneficial effect by decreasing acute stress reactivity, the NIBS session should be
575 delivered before and/or during the stress task. This is of major importance in pathological
576 conditions where hyperreactivity of the HPA axis has been repeatedly reported, especially
577 psychiatric conditions such as major depression, anxiety disorders or psychosis. To expand the
578 knowledge concerning the effect of NIBS on the cortisol reactivity, supplementary studies are
579 needed and the following methodological guidelines should be considered i) using an
580 experimental stress task that actually increases cortisol secretion ; ii) measuring the kinetic of
581 cortisol release by assessing the cortisol level at repeated occurrences through the experimental
582 session; iii) controlling for daytime of the experimental procedure to account for nycthemeral
583 cortisol variability ; iv) controlling for the influence of sex, smoking status, and age ; v)
584 controlling for the influence of previous exposure to traumatic events including childhood
585 trauma, in both healthy and pathological participants.

586

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588 No potential competing interest was reported by the authors.

589

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851 **FIGURE CAPTION**

852

853 **Figure 1. PRISMA 2020 flow diagram.**

854

855 **Table 1. Quality assessment of the included studies with the QualSyst method**

Authors	QualSyst Score (from 0.0 to 1.0)	Methodology Quality
Zwanzger et al., 2007	0.52	Poor
Claudino et al., 2011	0.61	Adequate
Antal et al., 2014	0.70	Good
Baeken et al., 2014	0.71	Good
Sarkar et al., 2014	0.68	Good
Bogdanov & Schwabe, 2016	0.88	Strong
Mc Clelland et al., 2016	0.75	Good
Pulopulos et al., 2019	0.75	Good
Carnevali et al., 2020	0.86	Strong
De Witte et al., 2020	0.70	Good
Mehrsafar et al., 2020	0.73	Good
Pulopulos et al., 2020	0.79	Good
Brunelin & Fecteau, 2021	0.89	Strong
Era et al., 2021	0.77	Good
Schulreich & Schwabe, 2021	0.93	Strong

856

857 Methodological quality: strong > 80%; good 65–79%; adequate 55–64%; poor < 55%.

Table 2. Stimulation parameters of rTMS studies

Authors	NIBS	Target area	Session duration (min)	Total number of pulses	Condition	Intensity	Frequency (Hz)
Zwanzger et al., 2007	LF-rTMS	right DLPFC	30	1800	active	120% RMT	1
				NA	sham	20% RMT	1
Baeken et al., 2014	HF-rTMS	left DLPFC	7.66	1560	active	110% RMT	20
				NA	sham	NA	NA
Claudino et al., 2011	HF-rTMS	left DLPFC	20	1000	active	110% RMT	10
				NA	sham		
McClelland et al., 2016	HF-rTMS	left DLPFC	20	1000	active	110% RMT	10
				NA	sham		
Pulopulos et al., 2020	HF-rTMS	left DLPFC	9.13	1600	active	110%RMT	20
				NA	sham		
Pulopulos et al., 2019	iTBS	left DLPFC	7.1	1620	active	110%RMT	50Hz. Burst
				NA	sham		frequency 5Hz

NIBS Stress

De Witte et al., 2020	iTBS	left DLPFC	7.1	1620	active	110% RMT	50Hz. Burst frequency 5Hz
				NA	sham		
Era et al., 2021	cTBS	left DLPFC	0.33	300	active	40% of the maximal	50Hz. Burst frequency 5Hz
		left vPM		300	active control	stimulator power	

cTBS, continuous Theta Burst Stimulation; DLPFC, Dorso-Lateral Pre-Frontal Cortex; HF-rTMS, High-Frequency repeated Transcranial Magnetic Stimulation; iTBS, intermittent Theta Burst Stimulation; LF-rTMS, Low-Frequency repeated Transcranial Magnetic Stimulation; RMT, Rest Motor Threshold; vPM, ventral Pre-Motor cortex.

Table 3. Main results of rTMS studies

Authors	Design	Stress protocol (duration)	NIBS timing	Time of day	N subjects	Age (SD)	N female	N smoker	Main Results
Zwanzger et al., 2007	Cross Over	CCK4 (NA)	before stress	NR	11 HC	26.0 (1.0)	6	NR	No difference between active and sham AUCi: significant cortisol decrease with HF rTMS compared to sham
Baeken et al., 2014	Cross Over	CFT (NR)	before stress	NR	30 HC	21.0 (2.8)	30	NR	AUCg: no difference between active and sham
Claudino et al., 2011	Parallel Arms	FCT (NR)	after stress	p.m.	11 patients with bulimic disorder (active)	28,2 (9.2)	11	3	Significant cortisol decrease with HF rTMS compared to sham

					11 patients with bulimic disorder (sham)	28.9 (8.5)	11	3	
McClelland et al., 2016	Parallel Arms	FCT (2 min)	after stress	p.m.	21 patients with anorexia nervosa (active)	25.3 (6.9)	21	6	No difference between active and sham
					28 patients with anorexia nervosa (sham)	27.7 (9.9)	28	9	
Pulopulos et al., 2020	Parallel Arms	TSST (25 min)	before stress	p.m.	35 HC (active)	20.9 (2.9)	37	NA	AUCi: significant cortisol decrease with HF rTMS compared to sham
					38 HC (sham)	21.2 (2.3)	38		
Pulopulos et al., 2019	Cross Over	TSST (13 min)	after stress	p.m.	35 HC	23.6 (2.9)	35	NR	AUCg, AUCi No effect of iTBS on cortisol

NIBS Stress

De Witte et al., 2020	Cross Over	TSST (10 min)	after stress	p.m.	38 HC	23.5 (3.0)	38	NR	No significant effect of iTBS on salivary cortisol
Era et al., 2021	Cross Over	Rumination task (3x2 min)	between the 2 stress	NR	32 HC	22.2 (3.2)	16	14	Higher cortisol secretion in the active group

AUCg, Area Under the Curve with respect to the ground; AUCi, Area Under the Curve with respect to the increase; CCK4, CholeCystoKinin tetrapeptide; CFT, Critical Feedback Test; FCT, Challenge Food Task; HC, Healthy Controls; HF-rTMS, High-Frequency repeated Transcranial Magnetic Stimulation; iTBS, intermittent Theta Burst Stimulation; LF-rTMS, Low-Frequency repeated Transcranial Magnetic Stimulation; NIBS, Non Invasive Brain Stimulation; TSST, Trier Social Stress Test

Table 4. Stimulation parameters of tDCS studies

Authors	Target areas (anode/cathode)	Electrode size (cm)	Session duration (min)	Intensity (mA)
Antal et al., 2014	F2-Fpz/O2-P4 or O2-P4/F2-Fpz	7X5	20	1
Sarkar et al., 2014	F3/F4	5X5	30	1
Bogdanov & Schwabe, 2016	F4/Cz or Cz/F4	F4 electrode, 5X5; Cz electrode, 10X10	NR	1.075
Carnevali et al., 2020	F3/F4	7X5	15	2
Mehrsafar et al., 2020	F3/F4 or F4/F3	5X5	20	2
Brunelin & Fecteau, 2021	F3/F4	25cm ² *	30	2

NIBS Stress

Schulreich & Schwabe, 2021	F4/Cz	Anode, 5X5; Cathode, 10X10	During the whole Belief- Updating task	1.075
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The positions of the electrodes were reported according to the 10-20 EEG system.

*Circular electrodes

Table 5. Main results of tDCS studies

Authors	Design	Stress protocol (duration)	NIBS timing	Time of day	N subjects	Age (SD)	N female	N smoker	Main Results
Antal et al., 2014	Parallel Arms	TSST (10 min)	before stress	NR	60 HC (20 anodal, 20 cathodal, 20 sham)	25.0 (6.0)	0	NR	Polarity-dependent effect: cathodal tDCS increased cortisol response, anodal tDCS decreased it
Sarkar et al., 2014	Cross Over	Affective and arithmetic (NR)	During stress	All day	45 HC	NR	27	NR	Significant decrease of stress-induced cortisol secretion in the active but not sham tDCS group in the high anxiety group. An opposite effect was reported in the low anxiety group
Bogdanov &	Parallel Arms	TSST (10 min)	After stress	p.m.	20 HC (anodal)	25.5 (0.3)	10 10	0	No significant differences between tDCS groups

Schwabe,					20 HC		10			
2016					(cathodal)					
					20 HC					
					(sham)					
Carnevali		Before			15 HC					
et al.,	Parallel	TSST	and	All	(active)	23.4 (0.6)	0	6	No significant differences between	
	Arms	(10 min)	during	day	15 HC	23.7 (0.9)		8		tDCS groups
2020		stress			(sham)					
Mehrsafar		Official	45min					Significant decrease of stress-induced		
et al.,	Cross	competition	before	p.m.	12 elite	26.5 (2.3)	0	0	cortisol secretion in the active tDCS	
	Over	(60-75 min)	stress		athletes					(compared to cathode and sham)
2020					15 HC					
Brunelin		Parallel	MAST	During		(active)	24.2 (2.6)	8	2	Significant decrease of stress-induced
& Fecteau,	Arms	(10 min)	stress	a.m.	15 HC				cortisol secretion in the active tDCS as	
	2021					(sham)	28.2 (5.4)	7		3

Schulreich										
&	Parallel	SECPT	After			26.1				No significant differences between tDCS groups
Schwabe,	Arms	(3 min max)	stress	p.m.	46 HC	(5.1)*	23	0		
2021										

HC, Healthy Controls; MAST, Maastricht Acute Stress Test; SECPT, Social Evaluated Cold-Pressor Test; tDCS, transcranial Direct Current Stimulation; TSST, Trier Social Stress Test

*Mean age corresponds to the whole sample of the study, including participants that did not underwent stress protocol.