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RESEARCH ARTICLE

REVISED Transcranial direct current stimulation and attention skills in burnout patients: a randomized blinded sham-controlled pilot study [version 2; peer review: 2 approved]

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Abstract

Background: Burnout is characterized by deficiencies in attention and several components of the working memory. It has been shown that cognitive behavioral therapy can have a positive effect on burnout and depressive symptoms, however, the lingering effects of impaired attention and executive functions are the most frustrating. We hypothesized that anodal transcranial direct current stimulation (atDCS) over the left dorsolateral prefrontal cortex (DLPFC) can improve the executive control of attention and possibly several other components of working memory in patients with burnout.

Methods: This was a randomized double-blind sham-controlled pilot study with two groups. Patients with burnout received three weeks of daily sessions (15 sessions in total) of atDCS or sham stimulation in addition to three weekly sessions of standard behavioral therapy. The primary outcome measure was attention and the central executive of the working memory. Secondary, the effect of atDCS was measured on other components of working memory, on burnout and depression scores, and on quality of life (QoL).

Results: We enrolled and randomly assigned 16 patients to a sham or real stimulation group, 15 (7 sham, 8 real) were included in the analysis. atDCS had a significant impact on attention. Post-hoc comparisons also revealed a trend towards more improvement after real tDCS for inhibition and shifting, updating and control, and encoding. Both groups improved on burnout and depression scores.

Open Peer Review

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	Invited Reviewers	
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Any reports and responses or comments on the article can be found at the end of the article.

Conclusion: These data provide preliminary evidence for the value of atDCS over the left DLPFC in rehabilitating attention deficits, and possibly also central executive and encoding deficits, in burnout. However, the current study has some limitations, including the sample size and heterogeneous patient population. More elaborate studies are needed to elucidate the specific impact of atDCS over the left DLPFC on burnout.

Trial registration: ISRCTN.com (ISRCTN94275121) 17/11/19

Keywords
burnout, direct current stimulation, attention, working memory, prefrontal cortex

This article is included in the All trials matter collection.

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Author roles: Van Noppen P: Conceptualization, Investigation, Resources, Writing – Review & Editing; **van Dun K**: Conceptualization, Formal Analysis, Methodology, Supervision, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Depestele S**: Formal Analysis, Writing – Review & Editing; **Verstraelen S**: Formal Analysis, Writing – Review & Editing; **Meesen R**: Writing – Review & Editing; **Manto M**: Conceptualization, Funding Acquisition, Methodology, Resources

REVISED **Amendments from Version 1**

All changes made are in response to the comments of reviewer 1. The introduction has been extended with a brief paragraph on the necessity of multiple sessions and the possible neurophysiological mechanism in burnout. In addition, it has been stressed that this is, to our knowledge, the first study investigating the effect of tDCS in burnout patients. The methodology has been clarified on how tDCS was administered to ensure effective stimulation. In the results section, Table 2 has been extended to provide more information about the participants (concerning medication, education level, etc.). The limitations section has also been extended to point out some weaknesses of our study that should be addressed in future studies (recruitment issues, impact of medication, efficacy of blinding, electrode placement, relation with the dopaminergic system). The discussion was also updated to clarify which results were expected and which were unexpected due to the left DLPFC stimulation. Some paragraphs have also been added about the effect of the behavioral therapy since this could also have played a role in the improvement of the patients' scores.

Any further responses from the reviewers can be found at the end of the article

Abbreviations

atDCS anodal transcranial Direct Current Stimulation

BDI Beck's Depression Inventory

BNT Boston Naming Test

DSM-V 5th edition of the Diagnostic and Statistical Manual for Mental Disorders

ICD-10 10th edition of the International Statistical Classification of Diseases and Related Health Problems

MBS Maslach Burnout Scale

NMDA N-Methyl-D-Aspartate

RBANS Repeatable Battery for the Assessment of Neuropsychological Status

SD Standard Deviation

tDCS transcranial Direct Current Stimulation

TMT Trail Making Test

WCST Wisconsin Card Sorting Test

QoL McGill Quality of Life Questionnaire

Introduction

The percentage of employees experiencing burnout is dramatically increasing in Europe (Eurofound, 2018), which has a significant socio-economic impact. Burnout consists of three components: (1) exhaustion at the physical level (energy loss, fatigue, weakness, physical and psychosomatic complaints), the mental level (negative behavior towards oneself, work, or life in general), or the emotional level (feelings of being trapped in a situation, helplessness, or hopelessness); (2) depersonalization or alienation towards the actual work, towards patients or pupils, etc. (Demerouti *et al.*, 2001; Schaufeli & Enzmann, 1998); (3) and reduced professional performance, which can

be attributed to depersonalization and alienation (Demerouti *et al.*, 2001). Since the beginning of 2011, burnout has been added to the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD-10: Z73.0: Word Health Organization, 2011), which describes burnout as a 'state of vital exhaustion'. The 5th edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-V: American Psychiatric Association, 2013), on the other hand, categorizes burnout under 'somatic symptoms and related disorders'.

Patients with burnout are impaired in one or more of the four components of working memory, i.e. the central executive, the phonological loop, the visuospatial sketchpad and/or the episodic buffer (see Figure 1) (Baddeley, 2000; Deligkaris *et al.*, 2014). The working memory, or the short-term memory, refers to a limited-capacity cognitive system that allows the temporary storage and manipulation of information from different modalities, provided by the sensory memory, that are necessary for complex tasks. (1) The phonological loop is responsible for encoding language in the long-term memory and for short-term retention of phonological information through repetition (Baddeley *et al.*, 1998). (2) The visuospatial sketchpad temporarily stores visual and spatial information. (3) The episodic buffer temporarily stores and integrates information from the other components, and links information to time and space to make storage and invocation easier (Baddeley, 2000). These three components are controlled by the fourth component, i.e. (4) the central executive, which ensures that targeted actions can be taken by guiding attention towards relevant information in the sensory memory (Baddeley, 1996). The central executive operates by (1) inhibition, i.e. the suppression of dominant, automatic answers, and the resistance to interference caused by distractors; (2) shifting, which refers to the possibility to switch cognitively between various tasks, mental states, or operations; and (3) updating of the working memory (Miyake *et al.*, 2000).

The working memory does not only monitor and direct attention, it is also responsible for the storage of information in the long-term memory (encoding) and recall of information from that same memory (retrieval) (Baddeley, 1996; Baddeley & Sala, 1996).

Based on this model, deficits of executive functions and attention could be attributed to dysfunction of the central executive component (Baddeley, 1996). Accordingly, impairment of nonverbal memory deficits could be associated with the visuospatial sketchpad (Papagno, 2002), verbal memory deficits could be connected to the phonological loop (Vallar & Baddeley, 1984), and episodic (long-term) memory disruption could be attributed to dysfunction of the episodic buffer (Quinette *et al.*, 2006). However, not all components of the working memory model are equally affected in burnout. A recent meta-analysis stated that burnout primarily affects attention, vigilance (i.e. sustained attention), and the central executive, more specifically memory updating and monitoring (Riedrich *et al.*, 2017).
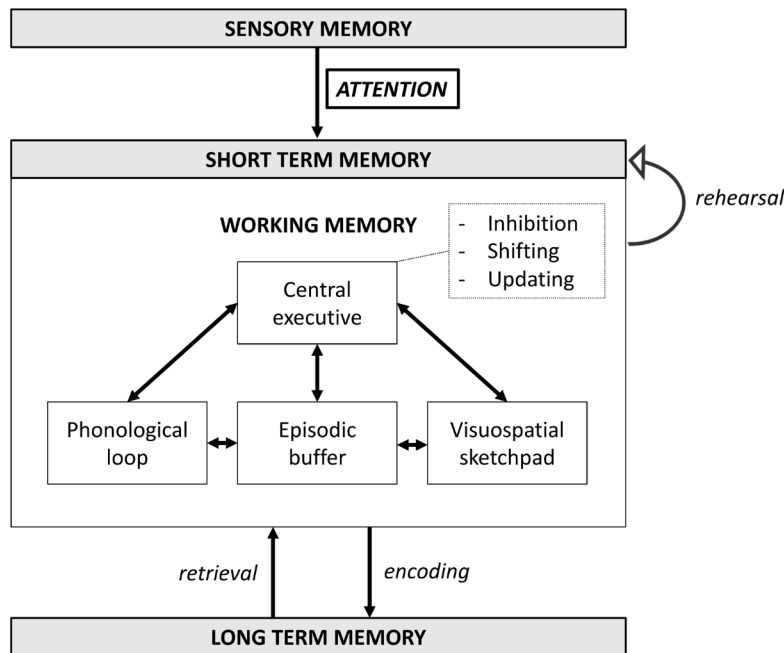
Figure 1. Memory model with the different components of the working memory and the interactions between the short-term and the long-term memory, based on (Baddeley, 2003).

Transcranial direct current stimulation (tDCS) is a non-invasive neurostimulation technique that modulates cortical excitability to enhance brain function by means of a low electrical current applied over the skull (Brunoni *et al.*, 2012; Nitsche & Paulus, 2011). tDCS is increasingly used in the treatment of motor, cognitive, and affective symptoms in different patient populations, both in neurological (e.g. Alzheimer's disease; Flöel, 2014), and psychiatric disorders; (e.g. major depressive disorder Nitsche *et al.,* 2009) (Brunoni *et al.*, 2012). The therapeutic potential of tDCS is gaining interest. In a double-blind sham-controlled trial consisting of three weeks (15 sessions) of active or sham anodal tDCS (atDCS) (2mA) over the left dorsolateral prefrontal cortex (DLPFC), Loo *et al.* confirmed the antidepressant efficacy of atDCS in patients with depression. In addition, mood, attention skills, and working memory also significantly improved after active tDCS treatment (Loo *et al.*, 2012). Moreover, a recent study by Miler, Meron, Baldwin, and Garner showed that a single session of DLPFC stimulation can improve executive control of attention in healthy adults (Miler *et al.*, 2018). However, to induce a longer-lasting effect, repeated sessions are advised and it has already been shown that this can have a cumulative effect which is associated with greater magnitude and longer duration of the behavioral effects (Brunoni *et al.,* 2012).

One of the mechanisms that might be responsible for the cognitive problems in burnout patients is a dopaminergic dysfunction in the prefrontal cortex. It has been shown that dopamine in the prefrontal cortex plays a critical role in working memory and cognitive control (Polizzotto *et al.,* 2020; Cools & D'Esposito, 2011) and that (chronic) stress can have a deteriorating effect on the dopaminergic system in this area (Mizoguchi *et al.*, 2000). tDCS has been known to interact with dopaminergic systems (Polizzotto *et al.*, 2020) and therefore tDCS over the DLPFC might be able to restore dopaminergic prefrontal cortex function.

The effects of tDCS have not yet been extensively evaluated in burnout patients. Some studies have used tDCS in stress-related patient populations, such as professional nurses (Stanton *et al.*, 2015) or post-traumatic stress disorder (Saunders *et al.*, 2015), however, to our knowledge, our study is the first to use tDCS in a burnout population.

Studies have shown that burnout patients are primarily impaired in attention and the central executive (Riedrich *et al.*, 2017). We tested the hypothesis that multiple sessions of atDCS over the left DLPFC could improve the general well-being of recovering burnout patients by boosting the recovery of the executive control of attention. Since this is the first study using tDCS in the rehabilitation of burnout patients, other components of the working memory were also measured to monitor the impact of burnout and the effect of atDCS on these components.

Methods
Patients
Patients were recruited between January 2015 and December 2017 via a treatment center in Belgium specialized in the diagnosis and treatment of burnout (DIADIS NV, Oud-Turnhout). The definition of (Brenninkmeijer *et al.*, 2001) was used to identify burnout patients, and a score of > 4 on the Dutch version of

the Maslach Burnout Scale (MBS: Maslach-Pines, 2005) was considered an inclusion criterium. Patients with 1) excessive drug or alcohol use, 2) epilepsy, 3) depression, 4) bipolar syndrome, 5) chronic fatigue syndrome or any other history of psychiatric or neurological disorders, 6) implanted neurostimulator or pace-maker, 7) drugs interacting directly with the NMDA receptors, or 8) pregnancy were excluded. When new patients were diagnosed with burnout in the treatment center, they were asked whether they wanted to participate in the study. Included patients were pseudo-randomly assigned to a real atDCS or sham tDCS group using a pre-defined allocation code file in excel (to make sure that both groups were of equal size). Initially, 20 participants were targeted (10 per tDCS group) as a pilot study. This number was primarily based on practical issues, such as the average number of burnout patients that were treated every year at the treatment center, and the time the treating psychologist could devote to the study. All assessments were performed by the sole psychologist of the treatment center (PVN).

This study was approved by the ethical committee CME of the Vrije Universiteit Brussels (VUB) (B.U.N. 143201422009). All patients signed an informed consent. The trial was retrospectively registered at ISRCTN.com on 17/11/19 (ISRCTN94275121), since clinical trial registration was not explicitly required by the advising ethical committee for trials with an experimental device at the start of the trial. All protocol and trial details are available from the registration page.

Pretesting
After inclusion, baseline measures were taken to evaluate burnout, depression, quality of life, attention, and different components of the working memory. Burnout, depression, and overall quality of life were assessed by the MBS, the Beck's Depression Inventory (BDI: Van der Does, 2002), and Question A of the Dutch version of the McGill Quality of Life Questionnaire (QoL: Cohen et al., 1997); translated by Kenniscentra Palliatieve Zorg) respectively.

Attention was measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS: Randolph, 1998) Attention Index, and vigilance by the s-score of the D2 test (variability in processing speed).

The central executive of the working memory was evaluated with the following tests. Inhibition and shifting were assessed with Card III of the Stroop Color-Word test (Golden, 1978), the Trail Making Test part B (TMT: Reitan, 1958) and the Wisconsin Card sorting test (WCST: Heaton et al., 1993). Processing speed, i.e., updating and control, was assessed by the TMT part A, Cards I and II of the Stroop Color-Word test, and the D2 test (G_z: total number of tokens scanned; F%: error percentage relative to G_z; G_z – F: number of correctly identified tokens) (Brickenkamp, 1962).

As regards to the other components of the working memory: the phonological loop was tested by the Language Index of

the RBANS, the Boston naming test (BNT: Kaplan et al., 1983; Flemish version BNT: Mariën et al., 1998) and semantic fluency tasks (naming as many animals, vegetables, means of transportation and clothes as possible within one minute). To determine the percentile of semantic fluency, Dutch non-published age-, gender-, and education-related norms were used (These data were obtained by master students in Linguistics at the VUB of 200 healthy participants in Belgium of varying age, gender, education, and geographic location and are available as extended data (van Dun, 2020)). These data were used to calculate the z-scores that were then converted to percentiles. The visuospatial sketchpad was assessed using the Raven's progressive matrices (Raven, 1965), and the Visuospatial Index of the RBANS. Encoding was evaluated with the Immediate Memory Index and retrieval with the Recent Memory Index of the RBANS.

A categorized overview of the different tests is presented in Table 1.

After treatment, all tests were repeated to evaluate the impact of atDCS. Therapy always started on a Monday, and re-evaluation was completed the first Monday after the final atDCS session.

Primary and secondary outcome measures
The primary outcome measure was attention. Secondary outcome measures were general measures (burnout, depression, and quality of life), and other components of the working memory (central executive, phonological loop, visuospatial sketchpad, encoding and retrieval).

Treatment
All patients received the standard behavioral therapy consisting of one session a week (for 3 weeks) focusing on 1) psycho-education and relaxation, 2) reducing mental over-load, 3) defining and working to personal goals, 4) relapse prevention. 1) In the first session, the stress mechanism was explained, together with the characteristics that belong to it. Breathing exercises were taught to the patient through heart rhythm coherence, using EmWave2 software to visually guide the patients. 2) To reduce the mental overload, 'don't worry'-techniques were explained. Patients were advised to write down their worries and not get distracted by them continuously. Via cognitive behavioral therapy, using the ABCDE model (Ellis et al., 1997), they were taught to translate negative into positive thoughts. 3) During therapy, the patient's life goals in different domains (e.g. work, personal relations, education, parenthood, friends, physical well-being, …) were established together with the therapist. In dialogue, priorities were established and possible (mental) barriers were discussed. This discussion primarily focused on rebalancing the different domains in the patient's life. 4) Lastly, the therapy focused on reintegration on the work floor. Bad habits were identified and strategies were discussed to prevent the patients from falling back into these habits.

None of the patients had received psychotherapy before inclusion in this study.

Table 1. Overview of the different tests for measuring relevant impaired functions accompanying burnout.

Category		Test	Mean (SD) or Maximum score or Type of score
Burnout		MBS	Max 7
Depression		BDI	Max 63
Quality of Life		QoL	Max 10
Attention		RBANS Attention Index	100 (15)
Vigilance		D2 (s-score)	Pct.
Working memory			
Central executive	*Inhibition and shifting*	Stroop III TMT B WCST	Pct. Pct. #Categories
	Processing speed (updating and control)	TMT A Stroop I and II D2 (G_z, F%, $G_z - F$)	Pct. Pct. Pct.
Phonological loop		RBANS Language Index	100 (15)
		BNT	SS
		Semantic fluency tasks	Pct.
Visuospatial sketchpad		Raven	100 (15)
		RBANS Visuospatial Index	100 (15)
Encoding		RBANS Immediate Memory Index	100 (15)
Retrieval		RBANS Recent Memory Index	100 (15)

[i] **Legend**: MBS = Maslach Burnout Scale; BDI = Beck's Depression Inventory; QoL = McGill Quality of Life Questionnaire; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; Stroop = Stroop Color-Word test; TMT = TrailMaking Test; WCST = Wisconsin Card Sorting Test; BNT = Boston Naming Test; Raven = Raven's progressive matrices; SS = Standard Score; Pct. = Percentile.

In addition, patients received daily sessions of 2mA atDCS (TCT Research Limited, Hong Kong) over the left DLPFC (AF3 on the international 10/20 EEG system) (electrode size: 5x5cm²) and the reference electrode (5x7cm²) over the lateral aspect of the contralateral orbit (F8), as described in (Loo *et al.*, 2012). The carbon electrodes were covered in sponges soaked in saline solution (0.9% NaCl) to improve conductivity. These were placed over the scalp using neoprene straps. Since these can absorb the saline solution, two different straps were used for both electrodes to avoid creating bridges, and throughout the sessions the absorption was monitored so that it would not spread beyond the surface of the electrodes. In the real tDCS group, stimulation lasted for 20min with a gradual ramp up over 30s. This resulted in a maximal current density of 0.08mA/cm² and a total charge of 0.096C/cm² per session. Impedance was continuously monitored during stimulation to stay below 10kOhm and was automatically disrupted for safety when it went above 15kOhm. During sham stimulation, the current was ramped up over 30s to 2mA after which it was immediately ramped down to simulate the cutaneous sensation of tDCS in the sham group.

No therapy was given during stimulation. This resulted in 15 sessions in total (3 weeks, 5x / week). One group received real tDCS, the other received sham tDCS. The tDCS device was programmed by the therapist, but the patients did not know which type of tDCS they received. All test results were coded to blind the researcher who performed the analyses and data was unblinded only after the analyses were done. The protocol and electrode placement are illustrated in Figure 2.

All therapy and tDCS sessions were performed at the treatment center DIADIS NV in Oud-Turnhout, where the patients were recruited, by the same psychologist and co-author Pia Van Noppen.

Statistical analyses
Means and standard deviations (SDs) were reported to give a general overview of the results. An independent samples t-test was used to compare mean age between groups.

A full-factorial 2 (tDCS: sham, real) x 2 (time: pre, post) fixed effects linear mixed model with subject as a random effect was
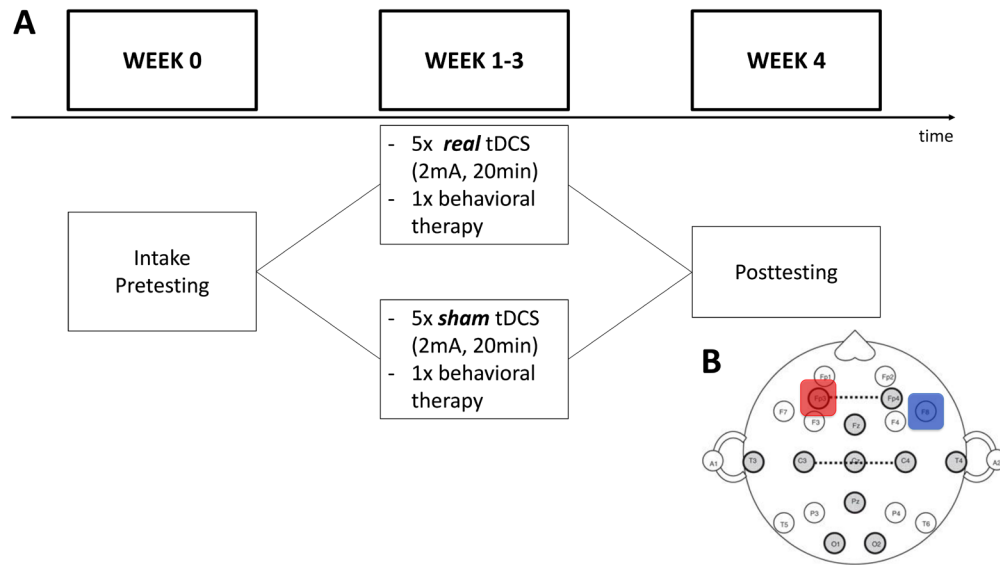
Figure 2. A. Visualization of the protocol, and **B**. electrode placement of the tDCS protocol.

used to compare the results on all test measures between the sham and real tDCS groups before and after treatment. Normality and homoscedasticity of the residual data were checked via a normal quantile plot and residual plot, respectively. If model assumptions were violated, the outcome variable was transformed using the Box-Cox procedure (Box & Cox, 1964), as implemented in the MASS package in R version 7.3-51.4. Tukey HSD post-hoc pairwise comparisons were used to compare baseline scores between groups and to explore possible interaction effects. The level of significance was set at $\alpha = 0.05$. All statistical analyses and figures were generated using the statistical software R version 3.6.0.

Results
Demographics
In total, 16 patients (11F, 5M) were recruited and received either real (n = 8) or sham (n = 8) treatment. Of these, 15 (10F, 5M) were included in the analysis. One participant (pp01, F, sham) was excluded after analysis because she was diagnosed with sensory processing sensitivity (SPS). Mean age of our final sample (n = 15) was 44.8y ± 5.8y, with no significant difference between the real (42.5y ± 5.5y) and sham group (47.4y ± 5.3y) (t(12.86) = 1.76, p = 0.103). No participants reported serious adverse events. Only one complained about dizziness at the end of the stimulation.

An overview of the demographic characteristics and the initial scores on the MBS, the Dutch version of the BDI, and question A of the Dutch version of the QoL are given in Table 2A (see underlying data (van Dun, 2020)). Table 2B contains additional demographic characteristics and working-related information. A flow chart is provided in Figure 3.

Impact of tDCS on burnout, depressive symptoms, and quality of life
The linear mixed model revealed a significant effect of Time for the MBS (F(1, 13) = 15.10, p = 0.002), but no effect of tDCS (F(1, 13) = 0.00, p = 0.971) or an interaction (F(1, 13) = 0.73, p = 0.408) (see Figure 4A). Tukey HSD post-hoc multiple comparisons indicated that only the real tDCS group improved significantly on the MBS (real: t(13) = 3.886, p = 0.009; sham: t(13) = 2.465, p = 0.113).

For the BDI, only an effect of Time was found ((F(1, 13) = 7.93, p = 0.015) (see Figure 4B). Post-hoc analyses revealed that only the sham group improved significantly after the intervention (t(13) = 3.58, p = 0.016) and the real group demonstrated a tendency towards improvement (t(13) = 2.82, p = 0.062).

The linear mixed model revealed no significant effects or interaction for the McGill Quality of Life (QoL) questionnaire. However, post-hoc analysis did reveal a significant improvement for the real group (t(13) = -3.21, p = 0.031) (see Figure 4C).

No significant differences were found at baseline for these three measures (MBS: t(13) = 0.04, p = 1.000; BDI: t(13) = -0.73, p = 0.883; QoL: t(13) = 0.00, p = 1.000). All means, SDs, and p-values of the post-hoc analyses are listed in Table 3. The results of the linear mixed model can be found in Table 7.

Impact of tDCS on attention and vigilance
Means, standard deviations, and p-values of the post-hoc analyses are shown in Table 4. The linear mixed model revealed a significant interaction between Time and tDCS for the RBANS Attention Index (F(1,13) = 14.80, p = 0.048), where

Table 2A. Demographic characteristics of the patients.

Participant	Gender	atDCS	Age	MBS	BDI	QoL
pp02	F	Real	40	5.8	35	6
pp03	F	Real	52	4.5	21	3
pp04	F	Sham	49	4.0	26	9
pp05	F	Sham	42	4.2	35	5
pp06	F	Real	44	4.4	32	4
pp07	F	Real	36	4.0	17	4
pp08	F	Real	38	4.1	19	4
pp09	F	Real	38	4.5	31	5
pp10	M	Sham	38	4.4	24	5
pp11	F	Real	48	4.0	24	8
pp12	F	Real	44	4.6	20	6
pp13	M	Sham	51	6.0	46	1
pp14	M	Sham	51	4.0	28	4
pp15	M	Sham	52	4.5	19	5
pp16	M	Sham	49	4.2	20	6
# or Average ± SD	10F / 5M	8 Real / 7 Sham	*44.8 ± 5.8*	*4.5 ± 1.0*	*26.5 ± 8.1*	*5.0 ± 1.9*

[i] **Legend**: F = Female; M = Male; MBS = Maslach Burnout Scale; BDI = Beck's Depression Inventory; tDCS = transcranial Direct Current Stimulation; QoL = McGill Quality of Life Questionnaire; SD = Standard Deviation.

Table 2B. Demographic characteristics and working-related information.

Participant	Employment	Education	#working hours at intake	Smokers	Living together/ Children	Antidepressant medication
pp02	Fulltime	>12y	70	No	Yes/Yes	OFF
pp03	Parttime	12y	0	Yes	Yes/Yes	OFF
pp04	Parttime	>12y	14	No	Yes/Yes	OFF
pp05	Fulltime	>12y	19	No	Yes/Yes	ON (SNRI)
pp06	Parttime	>12y	0	No	Yes/Yes	OFF
pp07	Parttime	12y	32	No	Yes/No	OFF
pp08	Fulltime	>12y	28	No	Yes/Yes	OFF
pp09	Fulltime	>12y	0	No	Yes/Yes	OFF
pp10	Fulltime	12y	36	No	No/No	OFF
pp11	Parttime	>12y	2	No	Yes/No	OFF
pp12	Parttime	>12y	0	No	Yes/Yes	ON (SSRI)
pp13	Fulltime	12y	37	No	Yes/Yes	ON (SARI)
pp14	fulltime	>12y	45	No	Yes/Yes	OFF
pp15	Fulltime	12y	30	No	**Yes/Yes**	OFF
pp16	Fulltime	>12y	60	No	**Yes/Yes**	OFF

[i] **Legend**: SARI = Serotonin Antagonist Reuptake Inhibitor; SNRI = Selective Serotonin and Noradrenalin Reuptake Inhibitor;SSRI = Selective Serotonin Reuptake Inhibitor; y = years.
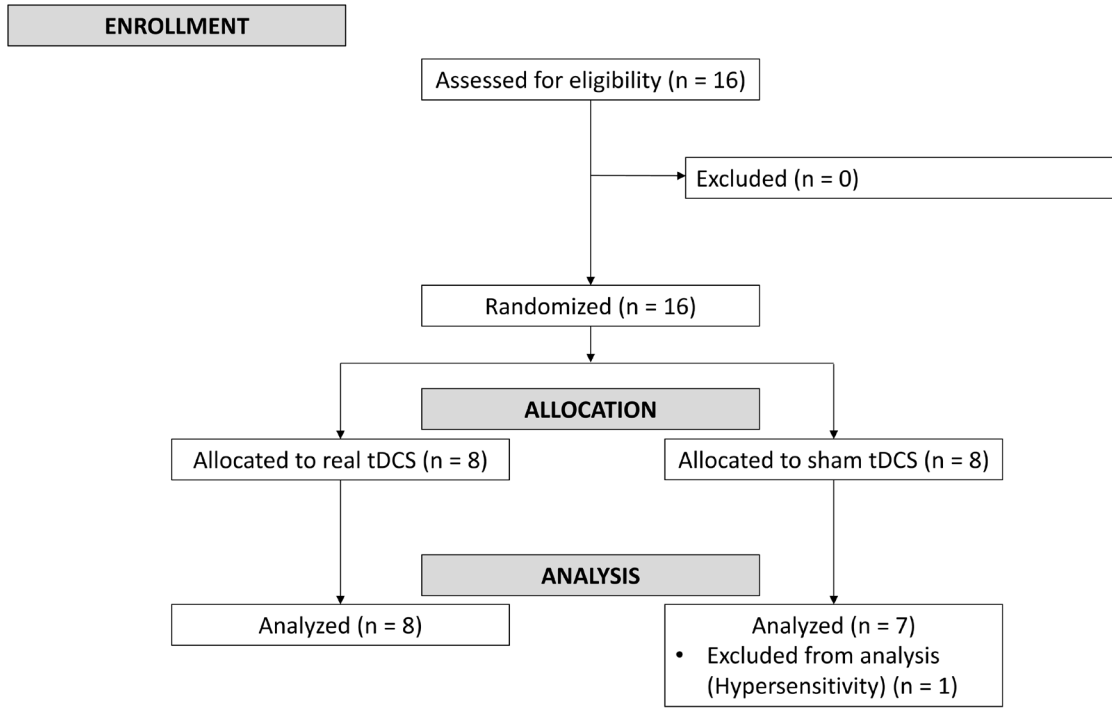
Figure 3. Flow chart of the enrollment procedure (CONSORT 2010 Flow Diagram).
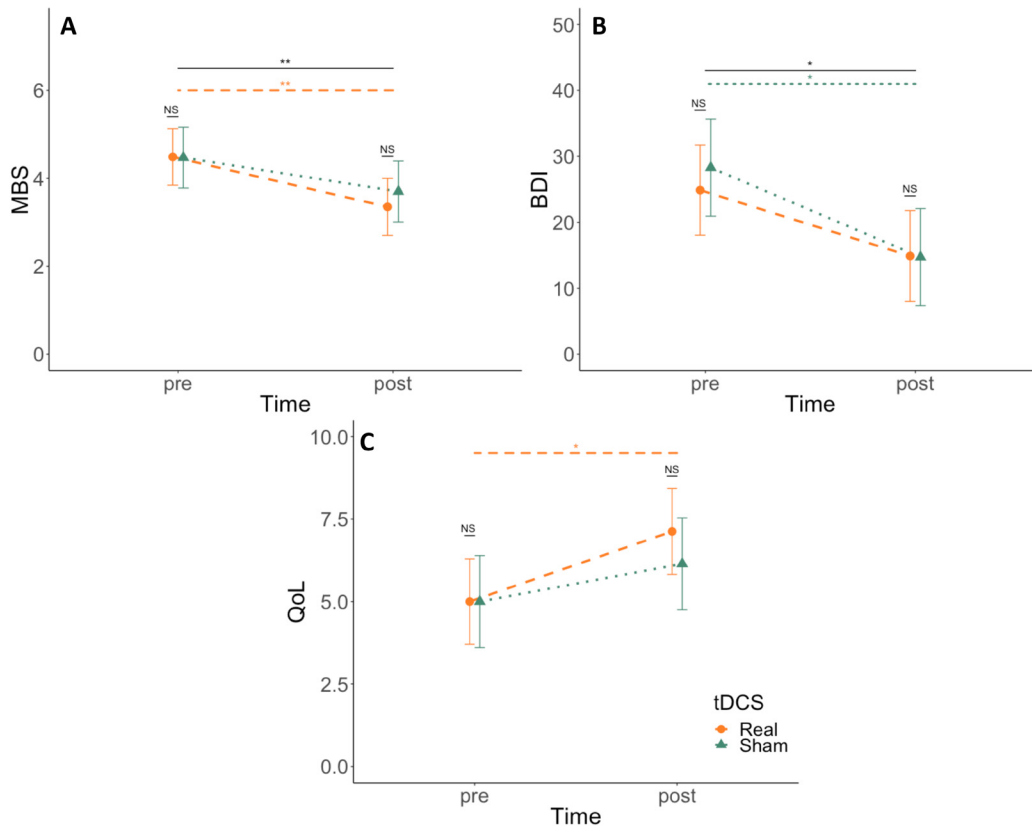
Figure 4. Mean pre- and postscores on **A**. the Maslach Burnout Scale (MBS), **B**. Beck's Depression Inventory (BDI), and C. McGill Quality of Life (QoL) questionnaire for the sham (dotted, triangles) and real (dashed, circles) group with 95% confidence intervals. Continuous lines indicate main effects, dashed and dotted lines indicate a significant difference between the pre- and postscores of the separate group (real: dashed; sham: dotted) as found by the post-hoc analyses. NS = non-significant; * = p≤0.05; ** = p≤0.01.

Table 3. Pre- and postscores and p-values of the burnout and depression assessments and the Quality of Life questionnaire per group.

General	tDCS	pre	p (real vs sham)	post	p (pre vs post)
MBS	real	4.49 ± 0.58	1.000	3.35 ± 0.93	0.009**
	sham	4.47 ± 0.70		3.70 ± 1.11	0.113
BDI	real	24.88 ± 6.83	0.883	14.88 ± 10.72	0.062
	sham	28.29 ± 9.46		14.71 (8.60	0.016*
QoL	real	5.00 ± 1.60	1.000	7.13 ± 1.13	0.031*
	sham	5.00 ± 2.38		6.14 ± 1.57	0.406

* : p≤0.05
** : p≤0.01
Legend: tDCS = transcranial Direct Current Stimulation; MBS = Maslach Burnout Scale, BDI = Beck's Depression Inventory; QoL = Quality of Life questionnaire.

Table 4. Pre- and postscores and p-values of the attention and vigilance assessments per group.

Attention	tDCS	pre	p (real vs sham)	post	p (pre vs post)
RBANS Attention	real	106.25 ± 15.28	0.984	123.25 ± 10.15	0.010**
	sham	103.29 ± 16.10		106.14 ± 21.57	0.929
D2 s#	real	80.75 ± 13.58	0.061	72.00 ± 23.27	0.660
	sham	54.43 ± 17.41		84.14 ± 16.09	0.013*

* p≤0.05
** p≤0.01
Legend: tDCS = transcranial Direct Current Stimulation; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; # = assumptions of the linear mixed model are violated.

the real group improved significantly more than the sham group (real: t(13) = -3.85, p = 0.010; sham: t(13) = -0.61, p = 0.929) (see Figure 5A). No significant difference was detected in the baseline scores (t(13) = 0.36, p = 0.984).

A significant interaction effect was also found for vigilance (F(1,13) = 12.15, p = 0.004), as measured by the s-score of the D2 test, with the sham group improving significantly. However, the assumptions of homoscedasticity and normality of the residuals of the model were doubtful, but did not improve using the Box-Cox transformation, which makes it difficult to interpret the results. In addition, the real and sham tDCS group tended to differ significantly at baseline (t(13) = 2.82, p = 0.061), with the sham group performing worse than the real tDCS group.

Impact of tDCS on the central executive
All means, standard deviations, and p-values of the post-hoc analyses are shown in Table 5.

The linear mixed model demonstrated a significant effect of Time for inhibition and shifting on the Stroop Color-Word test (card III) (F(1,13) = 5.96, p = 0.030) (Figure 6A) and the WCST (F(1,13) = 9.20, p = 0.010) (Figure 6B). Post-hoc

comparisons only revealed a significant improvement in the real tDCS group on the WCST (real: t(13) = -3.03, p = 0.042; sham: t(13) = -0.54, p = 0.948). For the Stroop (card III) no significant improvements were found for either group post-hoc (real: t(13) = -2.44, p = 0.118; sham: t(13) = -0.53, p = 0.951). For the TMT B, the assumption of homoscedasticity of the residuals was violated and did not improve using the Box-Cox transformation, making interpretation of the model difficult. No significant effects or interaction were found with the non-transformed data.

No significant differences were found in the baseline measures (Stroop card III: t(13) = -1.78, p = 0.327; WCST: t(13) = -1.79, p = 0.323; TMT B: t(13) = 0.54, p = 0.947).

For updating and control, a significant effect of Time was found for the TMT A (F(1,13) = 7.69, p = 0.016) (Figure 7A), the Stroop Color-Word test (card I) (F(1,13) = 6.30, p = 0.026) (Figure 7B) and the D2 (G_z: F(1,13) = 7.38, p = 0.018; and G_z − F: F(1,13) = 8.10, p = 0.014) (Figure 7C and 7D). The post-hoc tests only revealed trends towards improvement in the real group for the TMT A (real: t(13) = -2.77, p = 0.067; sham: t(13) = -2.00, p = 0.238), the Stroop Color-Word test (card I) (real: t(13) = -2.51, p = 0.105; sham: t(13) = -0.24,
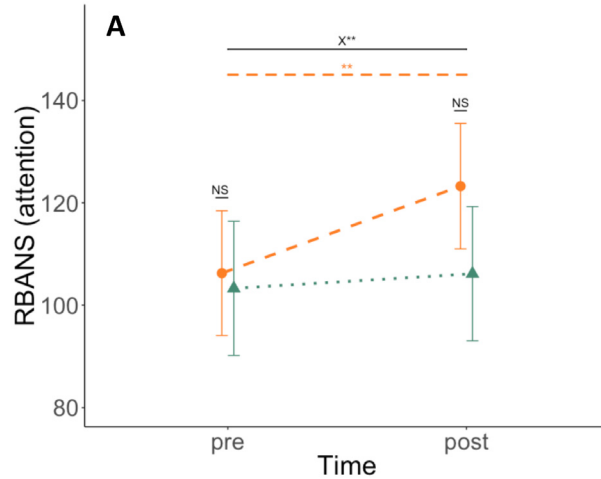
Figure 5. Mean pre- and postscores on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Attention index for the sham (dotted, triangles) and real (dashed, circles) group with 95% confidence intervals. Continuous lines with X indicate interaction effects, dashed and dotted lines indicate a significant difference between the pre- and postscores of the separate group (real: dashed; sham: dotted) as found by the post-hoc analyses. X = interaction effect; NS = non-significant; * = p≤0.05; ** = p≤0.01.

Table 5. Pre- and postscores and p-values of the executive function assessments per group.

Central executive	tDCS	pre	p (real vs sham)	post	p (pre vs post)
Inhibition & Shifting					
Stroop Card III	real	47.94 ± 33.90	0.327	64.63 ± 26.67	0.118
	sham	73.57 ± 25.45		77.43 ± 23.44	0.951
WCST	real	2.25 ± 1.49	0.323	3.00 ± 1.20	0.042*
	sham	3.29 ± 0.76		3.43 ± 0.79	0.948
TMT B#	real	72.25 ± 30.84	0.947	80.63 ± 15.26	0.546
	sham	65.86 ± 25.12		76.14 ± 15.73	0.433
Updating & Control					
TMT A	real	52.88 ± 39.08	0.925	70.88 ± 22.77	0.066
	sham	61.86 ± 24.95		75.71 ± 20.61	0.238
Stroop Card I	real	41.00 ± 35.29	0.689	67.75 ± 26.89	0.105
	sham	59.43 ± 29.71		62.14 ± 35.62	0.995
Stroop Card II#	real	49.38 ± 37.65	0.585	55.13 ± 30.77	0.935
	sham	71.29 ± 31.42		69.86 ± 30.43	0.999
D2 G_z	real	39.81 ± 31.52	0.771	63.64 ± 23.82	0.074
	sham	54.00 ± 30.36		63.57 ± 27.42	0.741
D2 G_z – F	real	45.26 ± 33.96	0.596	72.33 ± 20.48	0.059
	sham	62.86 ± 27.30		71.86 ± 22.87	0.812
D2 F%	real	83.13 ± 13.70	0.952	75.00 ± 24.20	0.699
	sham	87.29 ± 9.25		93.29 ± 5.65	0.872

* p≤0.05

** p≤0.01

Legend: tDCS = transcranial Direct Current Stimulation; TMT = Trail Making Test; WCST = Wisconsin Card Sorting Test; # = assumptions of the linear mixed model are violated.
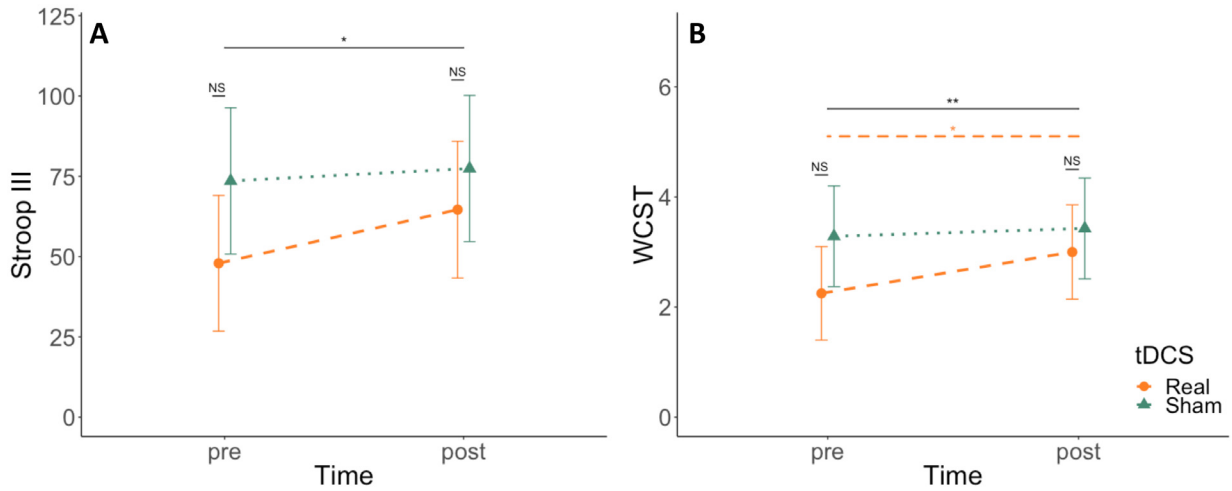
Figure 6. Mean pre- and postscores for inhibition and shifting on **A.** the Stroop Color-Word test Card III, and **B.** the Wisconsin Card Sorting Test (WCST), for the sham (dotted, triangles) and real (dashed, circles) group with 95% confidence intervals. Continuous lines indicate main effects, dashed and dotted lines indicate a significant difference between the pre- and postscores of the separate group (real: dashed; sham: dotted) as found by the post-hoc analyses. NS = non-significant; * = p≤0.05; ** = p≤0.01.
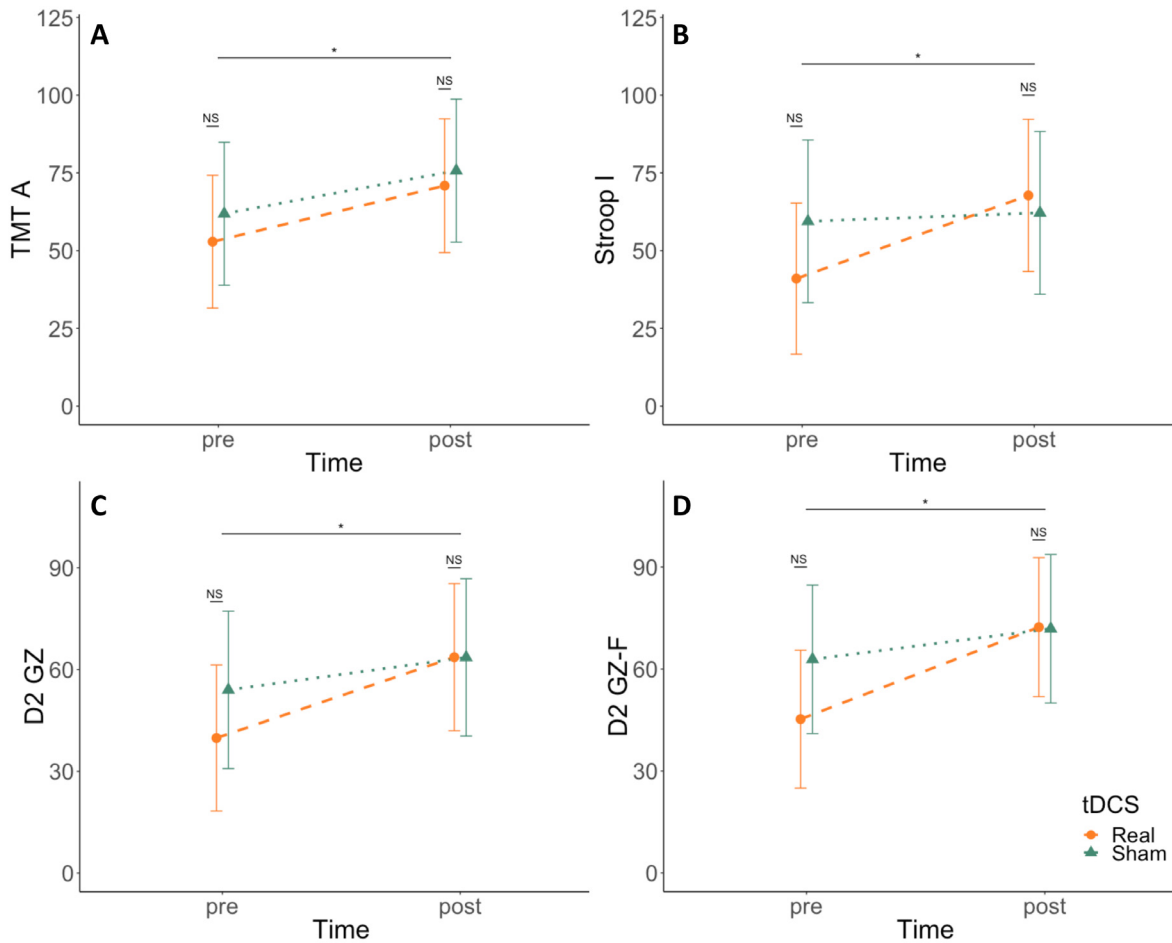
Figure 7. Mean pre- and postscores for updating and control on the **A.** Trail Making Test (TMT) part **A, B.** Stroop-Color Word test Card I, **C.** D2 G_z score, and D. D2 G_z – F score for the sham (dotted, triangles) and real (dashed, circles) group with 95% confidence intervals. Continuous lines indicate main effects, dashed and dotted lines indicate a significant difference between the pre- and postscores of the separate group (real: dashed; sham: dotted) as found by the post-hoc analyses. NS = non-significant; * = p≤0.05; ** = p≤0.01.

p = 0.995), D2 G_z (real: t(13) = -2.72, p = 0.074; sham: t(13) = -1.02, p = 0.741), nd D2 G_z – F (real: t(13) = -2.85, p = 0.059; sham: t(13) = -0.89, p = 0.812). No significant effects or interaction was found for the Stroop Color-Word test (card II) or F% of the D2 test. However, the assumption of homoscedasticity of the residuals was violated in the Stroop Color-Word test (card II), which might have resulted in unreliable p-values.

No significant differences were found in the baseline measures (TMT A: t(13) = 0.62, p = 0.925; Stroop card I: t(13) = -1.11, p = 0.689; Stroop card II: ; D2 G_z: t(13) = -0.97, p = 0.771; D2 G_z – F: t(13) = -1.27, p = 0.596; D2 F%: t(13) = -0.52, p = 0.952).

Impact of tDCS on other working memory components
All mean scores, standard deviations, and p-values of the post-hoc analyses are listed in Table 6.

For the phonological loop, the linear mixed model revealed a main effect of Time for the BNT (F(1,13) = 12.92, p = 0.003) (Figure 8A) and the Language index of the RBANS (F(1,13) = 4.76, p = 0.048) (Figure 8B). Tukey HSD post-hoc comparisons revealed that only the real tDCS group improved significantly

on the BNT (t(13) = -3.60, p = 0.015), a trend towards improvement was observed in the sham group (t(13) = -2.83, p = 0.060). No significant improvements were found for the groups separately for the RBANS Language Index (real: t(13) = -2.18, p = 0.180; sham: t(13) = 0.78, p = 0.863). No significant effects or interactions were seen for semantic fluency. Baseline scores did not differ significantly for these measures (BNT: t(13) = 0.23, p = 0.995; RBANS Language Index: t(13) = 1.72, p = 0.352; Semantic fluency: t(13) = 0.63, p = 0.921).

No significant effects or interaction were observed for the visuospatial sketchpad (RBANS Visuospatial index and Raven). However, the assumptions for the linear mixed model of the Raven were violated, which could have affected the p-values. The Box-Cox transformation did not improve the data. Baseline scores did not differ significantly (RBANS Visuospatial Index: t(13) = 1.72, p = 0.452; Raven: t(13) = -0.16, p = 0.999).

A main effect of Time was observed for encoding, evaluated by the Immediate Memory index of the RBANS (F(1,13) = 11.93, p = 0.004) (Figure 9A). Post hoc analysis showed that this was mainly driven by a significant improvement of the real

Table 6. Pre- and postscores and p-values of the post-hoc analyses of the other working memory components per group.

Working memory	tDCS	pre (Standard Scores)	p (real vs sham)	post (Standard Scores)	p (pre vs post)
Phonological loop					
RBANS Language	real	110.00 ± 6.82	0.352	116.00 ± 6.59	0.180
	sham	102.29 ± 9.43		104.57 ± 11.43	0.863
BNT	real	0.34 ± 0.55	0.995	1.30 ± 0.67	0.015*
	sham	0.27 ± 0.79		1.08 ± 0.30	0.060
Semantic fluency	real	82.50 ± 7.45	0.921	89.50 ± 11.01	0.416
	sham	77.86 ± 18.21		88.43 ± 18.58	0.162
Visuospatial sketchpad					
Raven[#]	real	123.00 ± 4.21	0.999	124.50 ± 3.96	0.915
	sham	123.43 ± 6.48		125.00 ± 6.14	0.920
RBANS Visuospatial Memory	real	115.88 ± 8.31	0.355	121.25 ± 6.11	0.452
	sham	107.43 ± 12.78		110.86 ± 10.22	0.800
Encoding					
RBANS Immediate Memory	real	109.00 ± 8.98	0.986	124.25 ± 14.34	0.020*
	sham	106.29 ± 17.31		113.00 ± 20.15	0.508
Retrieval					
RBANS Recent Memory	real	103.88 ± 11.19	0.943	113.75 ± 9.51	0.051
	sham	106.71 ± 8.52		116.00 ± 9.87	0.094

* : p≤0.05
** : p≤0.01
Legend: tDCS = transcranial Direct Current Stimulation; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; BNT = Boston Naming Test; # = assumptions of the linear mixed model are violated.
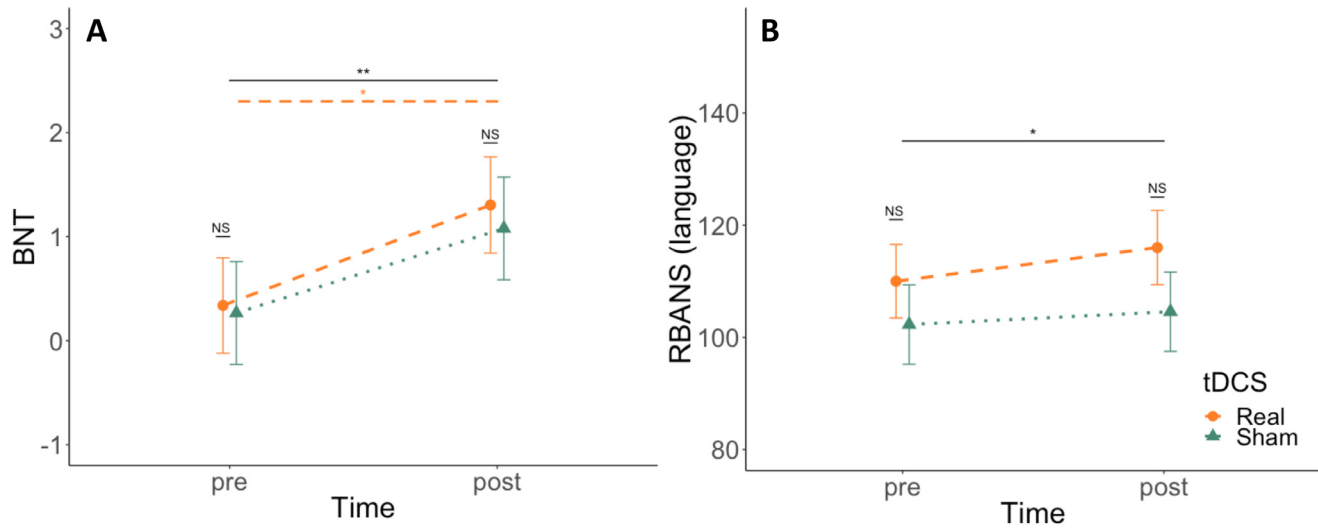
Figure 8. Mean pre- and postscores for the phonological loop on the **A**. Boston Naming Test (BNT), and **B**. RBANS Language index for the sham (dotted, triangles) and real (dashed, circles) group with 95% confidence intervals. Continuous lines indicate main effects, dashed and dotted lines indicate a significant difference between the pre- and postscores of the separate group (real: dashed; sham: dotted) as found by the post-hoc analyses. NS = non-significant; * = p≤0.05; ** = p≤0.01.
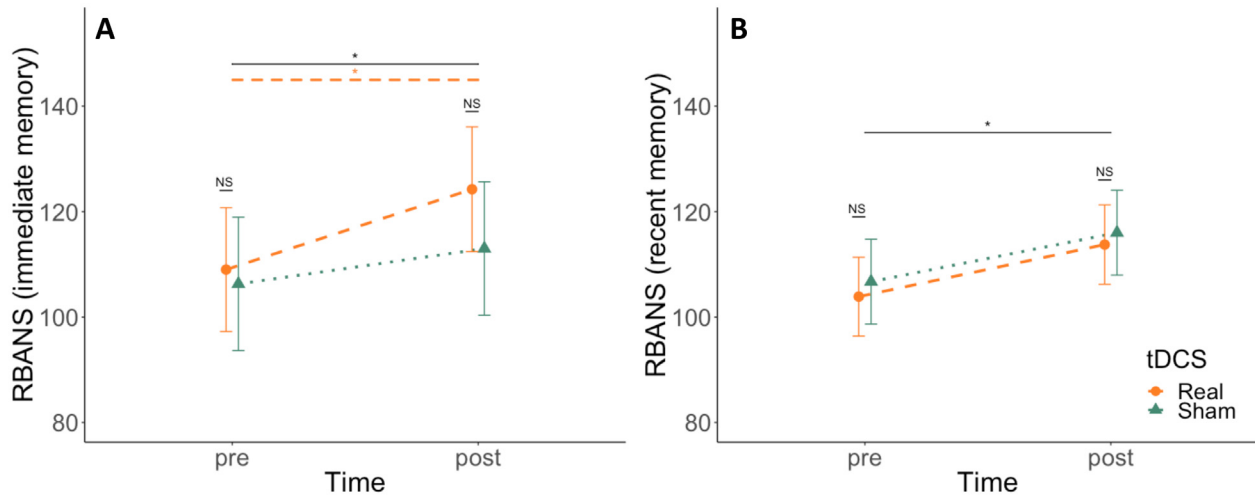

Figure 9. Mean pre- and postscores for encoding on the **A**. Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Immediate Memory, and retrieval on the **B**. RBANS Recent Memory for the sham (dotted, triangles) and real (dashed, circles) group with 95% confidence intervals. Continuous lines indicate main effects, dashed and dotted lines indicate a significant difference between the pre- and postscores of the separate group (real: dashed; sham: dotted) as found by the post-hoc analyses. NS = non-significant; * = p≤0.05; ** = p≤0.01.

tDCS group (real: t(13) = -3.45, p = 0.020; sham: t(13) = -1.42, p = 0.508). Retrieval (RBANS Recent Memory index) also showed a significant effect of Time (F(1,13) = 8.58, p = 0.012) (Figure 9B). For retrieval, both groups trended towards significance (real: t(13) = -2.93, p = 0.051; sham: t(13) = -2.58, p = 0.094). No differences in baseline scores were observed for Immediate or Recent Memory (RBANS Immediate Memory

Index: t(13) = 0.34, p = 0.986; RBANS Recent Memory Index: t(13) = -0.56, p = 0.943).

Discussion

This randomized blinded sham-controlled study investigated the impact of daily atDCS sessions (2mA, 20min) over the left DLPFC (AF3) with the reference over the contralateral

Table 7. F- and p-values for the linear mixed models.

Test	Effect	F(1, 13)	p
GENERAL			
MBS	Time	15.10	0.002**
	tDCS	0.00	0.971
	Time x tDCS	0.73	0.408
BDI	Time	7.93	0.015*
	tDCS	0.53	0.478
	Time x tDCS	0.47	0.504
QoL	Time	2.60	0.131
	tDCS	0.00	1.000
	Time x tDCS	1.02	0.330
ATTENTION			
RBANS Attention	Time	14.80	0.002**
	tDCS	0.13	0.727
	Time x tDCS	4.78	0.048*
D2 s[#]	Time	1.35	0.267
	tDCS	7.96	0.014*
	Time x tDCS	12.15	0.004*
CENTRAL EXECUTIVE *Inhibition & Shifting*			
Stroop Card III	Time	5.96	0.030*
	tDCS	3.16	0.099
	Time x tDCS	1.64	0.222
WCST	Time	9.20	0.010**
	tDCS	3.19	0.097
	Time x tDCS	2.81	0.117
TMT B[#]	Time	1.84	0.198
	tDCS	0.29	0.598
	Time x tDCS	0.04	0.836
Updating & Control			
TMT A	Time	7.69	0.016*
	tDCS	0.38	0.548
	Time x tDCS	0.19	0.670
Stroop Card I	Time	6.30	0.026*
	tDCS	1.24	0.287
	Time x tDCS	2.37	0.147
Stroop Card II[#]	Time	0.34	0.568
	tDCS	1.66	0.220
	Time x tDCS	0.25	0.626
D2 G_z	Time	7.38	0.018*
	tDCS	0.93	0.352
	Time x tDCS	1.23	0.287
D2 G_z – F	Time	8.10	0.014*
	tDCS	1.61	0.226
	Time x tDCS	1.68	0.217
D2 F%	Time	1.20	0.294
	tDCS	0.28	0.609
	Time x tDCS	1.69	0.216

Test	Effect	F(1, 13)	p
WORKING MEMORY *Phonological loop*			
RBANS Language	Time	4.76	0.048*
	tDCS	2.97	0.109
	Time x tDCS	0.85	0.373
BNT	Time	12.92	0.003**
	tDCS	0.05	0.819
	Time x tDCS	0.15	0.705
Semantic fluency	Time	2.53	0.136
	tDCS	0.40	0.541
	Time x tDCS	0.31	0.589
Visuospatial sketchpad			
Raven#	Time	0.42	0.530
	tDCS	0.03	0.877
	Time x tDCS	0.00	0.984
RBANS Visuospatial Memory	Time	2.32	0.151
	tDCS	2.95	0.110
	Time x tDCS	0.14	0.712
ENCODING			
RBANS Immediate Memory	Time	11.93	0.004**
	tDCS	0.11	0.740
	Time x tDCS	1.75	0.209
RETRIEVAL			
RBANS Recent Memory	Time	8.58	0.012*
	tDCS	0.31	0.588
	Time x tDCS	0.01	0.907

* : p≤0.05
** : p≤0.01

Legend: tDCS = transcranial Direct Current Stimulation; MBS = Maslach Burnout Scale; BDI = Beck's Depression Inventory; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; TMT = Trail Making Test; WCST = Wisconsin Card Sorting Test; BNT = Boston Naming Test; # = assumptions of the linear mixed model are violated.

orbit (F8) on attention and the central executive, as well as other components of the working memory in patients with burnout. This electrode montage has been shown to be effective in patients with depression, showing not only an antidepressant effect but also a positive effect on mood, attention skills, and working memory (Loo *et al.*, 2012). We included 15 patients (7 sham, 8 tDCS) in a 3-week protocol and investigated their cognitive and attention skills, as well as their burnout severity, depression, and overall quality of life before and after treatment. Both groups improved on all these measures, which can be expected due to the behavioral therapy both groups received, but the improvement of burnout and overall quality of life was only significant after real tDCS. Surprisingly, however, only the sham group significantly improved on the depression scale. This might be due to the fact that depression scores were moderate, while in the study of Loo *et al.* only patients with a DSM IV major depression episode were included (Loo *et al.*, 2012). Moreover, in the study of Loo *et al.* depression was rated by an experienced psychia-

trist/psychologist using the Montgomery Asberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979), while in our study a self-assessment scale (BDI) was used (Loo *et al.*, 2012).

For the main variable of interest (**Attention** index of the RBANS), a significant interaction between tDCS and Time was found, showing that real anodal tDCS over the left DLPFC can have an added value to conventional therapy in the rehabilitation of attention in burnout patients.

It is known that burnout primarily impairs functions of the **central executive**, whereas brain areas that regulate other components of the working memory are affected to a lesser degree. The central executive -mainly located in the prefrontal brain regions- could be the component that is most vulnerable to chronic stress because its higher order attention control functions are more demanding and complex than those performed by the other subcomponents (Deligkaris *et al.*, 2014). Several

studies investigating the impact of burnout on cognitive functions have confirmed that the most pronounced differences between patients and controls were seen on tests that are highly dependent upon the executive functions, e.g. prospective memory, processing speed, complex working memory, sustained attention, and letter fluency (Eskildsen *et al.*, 2015; Jonsdottir *et al.*, 2013; Öhman *et al.*, 2007; Orena *et al.*, 2013)(35–38)(Eskildsen *et al.*, 2015; Jonsdottir *et al.*, 2013; Öhman *et al.*, 2007; Orena *et al.*, 2013). This study showed that three weeks of therapy, combined with real or sham stimulation, significantly improved several components of the central executive. However, analyses revealed that improvement was driven by a significant improvement after real tDCS for inhibition and shifting (WCST), and was also primarily seen after real tDCS for updating and control (TMT A, D2 G_z, D2 G_z – F). These results are in line with the study of Miler *et al.* who found that atDCS over the left DLPFC significantly improves the executive control of attention (Miler *et al.*, 2018). As in the study of Miler *et al.*, no effect was seen on the percentage of mistakes, but the processing speed did improve more on the D2 test of attention after real tDCS than after sham tDCS (Miler *et al.*, 2018). However, the improvement on inhibition and shifting after tDCS was somewhat unexpected, since this is primarily associated with the right DLPFC and the right inferior frontal gyrus (Lie *et al.*, 2006; Hampshire *et al.*, 2010). Since this effect was only observed for the WCST, this might be related to this specific task. Indeed, studies have shown that, although the right DLPFC seems to be the most prominent in handling complex/manipulative working memory operations in the WCST (Lie *et al.*, 2006), the left DLPFC is also involved during this task (Lie *et al.,* 2006; Nagahama *et al.*, 2005).

atDCS also seemed to have a positive impact on other components of the working memory. The phonological loop might also be positively influenced by real tDCS as shown by a significant improvement of the real tDCS group on the BNT, although the sham group also trended towards a significant improvement. No effect was seen on the visuospatial sketchpad, which might not be surprising because this is believed to be situated primarily in the right prefrontal cortex (Suchan, 2008), but encoding clearly improved more after real atDCS than after sham tDCS (RBANS Immediate Memory Index). Transcranial magnetic stimulation (TMS) studies have shown a prominent role for the left DLPFC during encoding, observing shorter reaction times using a paired-pulse paradigm over this area (Gagnon *et al.*, 2011). Though de Lara *et al.* (2017) did not find any effect of anodal tDCS over the left DLPFC on encoding, this might be due to the lesser intensity (1mA vs 2mA) they used in their study.

These data provide preliminary evidence for the value of tDCS over the left DLPFC in rehabilitating attention deficits, and possibly also central executive and encoding deficits, in burnout patients.

Limitations and conclusion

Our study has several important limitations. First, our group of patients was relatively small. This is an important limitation given the positive trends of the effect of real tDCS on several outcome measures. Studies with more power will have to show whether these trends failed to reach significance due to a lack of power. In addition, some variables of interest (D2 s-score, TMT B, Stroop Card II, Raven) could not be interpreted correctly with the linear mixed model analysis because of a violation of assumptions. More data points could help to resolve this issue. Setting up multi-site cooperations to recruit participants and maintaining close relationships with primary care providers making them aware of the safety of tDCS when applied in the correct manner, could also help to convince patients to participate in tDCS studies. Larger groups to validate the efficacy of tDCS are crucial to investigate the clinical usability of this therapeutic aid.

Second, patients were randomized over both groups, which led to an overrepresentation of men in the sham group. At the moment, it is not clear whether gender can have a significant impact on the effect of tDCS (Antal *et al.*, 2017), or whether there are gender-related differences in the symptoms of burnout (Purvanova & Muros, 2010), but this imbalance of gender between both groups might have affected the results.

Third, our group of patients was very heterogeneous. For example, the moment of participation in the study was variable during the burnout process. Some participants were still at work, others were not yet able to start working, others were already re-integrated in their jobs. Due to the sample size, it was not possible to investigate the effects of different factors, such as living circumstances, age, gender, education, etc. on the progress of burnout. In addition, three of the patients were taking antidepressant medication during the study, of whom one received real stimulation. It has been shown that this type of medication (selective serotonin reuptake inhibitors or SSRIs) might enhance the LTP-like plasticity induced by anodal tDCS (Kuo *et al.*, 2016). Future studies should focus on these parameters to elucidate the influence of these factors on burnout recovery and on tDCS outcome. In addition, it is recommended to test for the efficiency of blinding the type of stimulation by asking the participants afterwards whether they think they were actively stimulated or not. Gathering information about the amount of discomfort could also be of importance for future studies using tDCS.

Fourth, the placement of the electrodes might not have been optimal to target attention deficits. Our study was based on the outcome of Loo *et al.* (2012) who aimed to investigate the anti-depressant effect in patients with depression, but found an improvement of attention and working memory instead (Loo *et al.,* 2012). By copying this electrode placement, we hoped to replicate these results in patients with burnout. However, by placing the cathode on F8, we might have unwantedly inhibited the right inferior frontal gyrus, which has been linked to inhibition and attentional control (Hampshire *et al.*, 2010). Although cathodal tDCS over the right inferior frontal gyrus did not appear to have a significant effect on response stopping or reaction times in a stop-signal task (Stramaccia *et al.,* 2015), another choice for the cathodal

reference electrode might be warranted. In addition, AF3 targets primarily the more frontal site of the left DLPFC, while a more common placement to target DLPFC in attention studies is F3 (Coffman *et al.*, 2014).

Lastly, research has shown that the effect of tDCS on working memory might be dependent on, amongst others, the initial dopaminergic level that can impact the excitation/inhibition balance (i.e. homeostasis between relative contributions of excitatory and inhibitory synaptic inputs) (Polizzotti *et al.*, 2020). More insight into the exact working mechanisms underlying the cognitive and attention deficits in burnout patients might be beneficial for future research.

Despite these shortcomings, these data provide preliminary evidence for the value of atDCS over the left DLPFC in rehabilitating attention deficits in burnout. tDCS might prove to be a useful, affordable, and easy-to-use addition to conventional therapy to speed up reintegration of burnout patients.

Consent
Written informed consent for publication of the patients' details was obtained from the patients.

Data availability
Underlying data
Harvard Dataverse: Transcranial direct current stimulation and attention skills in burnout patients: a randomized blinded sham-controlled pilot study. https://doi.org/10.7910/DVN/4VG2XS (van Dun, 2020)

This project contains the following underlying data:
- Data_burnout.txt (Data used for statistical analyses)

- Raw Data Burnout.tab (Raw data for the Burnout study (Raw Scores (RS) and Standard Scores (SS)))

Extended data
Harvard Dataverse: Transcranial direct current stimulation and attention skills in burnout patients: a randomized blinded sham-controlled pilot study. https://doi.org/10.7910/DVN/4VG2XS (van Dun, 2020)

This project contains the following extended data:
- Verbal_fluency.pdf (Means and standard deviations per age, gender, and educational level of 200 Dutch-speaking participants for the verbal (semantic) fluency task)

Reporting guidelines
CONSORT checklist and flow chart for "Transcranial direct current stimulation and attention skills in burnout patients: a randomized blinded sham-controlled pilot study". https://doi.org/10.7910/DVN/4VG2XS (van Dun, 2020)

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 14 December 2020

✔ **Hongxing Wang** [iD]

Division of Neuropsychiatry and Psychosomatics, Department of Neurology of Xuanwu Hospital, Capital Medical University, Beijing, China

It is an interesting piece of work; however, I have some concerns:

1. The manuscript does not include the current literature, such as:
   Wang HX, Wang L, Zhang WR, et al. Effect of Transcranial Alternating Current Stimulation for the Treatment of Chronic Insomnia: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Clinical Trial. Psychother Psychosom. 2020;89(1):38-47. doi: 10.1159/000504609. Epub 2019 Dec 17. PMID: 31846980.[1]

2. Sample is the main limitation, therefore, the title is recommended to change into the following:
   "Transcranial direct current stimulation and attention skills in burnout patients: a proof of concept study using a randomly blinded design"

3. Limitations section of Discussion should be further summarized and merged for a more concise and clear style, from reader's view.

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: psychiatry, neuroscience, neuropsychoneurology. psychosomatics, neuromodulation, transcranial alterative current stimulation in different patients affected with brain disorders and psychitrical disorders.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 17 August 2020

https://doi.org/10.5256/f1000research.28282.r68460

✅ **Choi Deblieck**

UPC KU Leuven, Gasthuisberg, Belgium

I read through the revised version of the paper, and conclude that the authors have addressed my comments in a satisfactory way.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: non-invasive neuromodulation (TMS/tDCS), fMRI

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 03 June 2020

https://doi.org/10.5256/f1000research.24067.r63825

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Choi Deblieck
UPC KU Leuven, Gasthuisberg, Belgium

"Transcranial direct current stimulation and attention skills in burnout patients: a randomized blinded sham-controlled pilot study" is addressing an important research and clinical question regarding executive memory, attention, and clinical symptoms in burnout. Data from 15 patients, randomized to 3 weeks of active anodal tDCS over left DLPFC or sham combined with standard behavioral therapy revealed that anodal tDCS significantly improved attention in patients with burnout.

Major Comments:

Major problems with neuromodulation studies are the small sample sizes and heterogeneous patient populations. The authors already mentioned those pitfalls as their biggest shortcomings. Nonetheless, it remains a major point of criticism for me. In order to get significance in TMS (and tDCS studies), Sack *et al.*, (2009)[1] demonstrated that power analyses showed 5 participants are sufficient to reveal a significant behavioral effect on cognition in TMS studies using fMRI-guided neuronavigation. However, the number of necessary participants increases to n = 9 in studies using MRI-guided neuronavigation, to n = 13 when using group Talairach coordinates, and to n = 47 when using EEG positions, like F3 or AF3.

As for the limitation of using heterogeneous patient groups, the demographic characteristics revealed are limited to age, gender, and burnout severity expressed by MBS. Reporting other relevant characteristics, such as duration, employment, ON/OFF medication, etiology, level of education, hospitalization, etc,... would give us a better understanding of how representative the groups were. Also, some of these variables could be explored for significance or even predictivity in future studies.

Also, since a trend towards inhibition and shifting was reported, and the right inferior frontal gyrus has been associated with inhibition, the choice of placing the cathode on F8 was not optimal. rIFG is only about 2 to 2.5 cm posterior to F8. Since the reference sponge used had a size of 5x7, rIFG could have been affected by the current.

Only continuous outcome measures were reported. Since it better reflects better clinical practice, I would add a categorical outcome measure, i.e., percentage of responders/remitters.

A TCT device was used. The strap it comes with is made of a neoprene strap which could absorb the saline solution potentially increasing the surface area of the target area. Also, is this device EC approved?

It was unclear whether all the patients in both conditions had been undergoing psychotherapy prior to the add-on tDCS therapy. If psychotherapy was new to all, it is a major confound. It could also be the reason why both groups improved burnout and depression-wise.

In the tDCS protocol section, Fp3 is mentioned as the target site, "left DLPFC". Since the 10-20 system of electrode placement is used, defining the target site as AF3 is probably better than Fp3. Also, the vast majority of TMS/tDCS studies targeting left DLPFC to stimulate F3. Why was Fp3/AF3 selected? DLPFC is indeed a large area. But an elaboration on the reason why a more anterior part of DLPFC was chosen should be explained.

Minor Comments:

In the background section of the abstract/methods, only one objective (attention and executive control) is mainly elaborated upon. I would also add the clinical objective, i.e., burnout, depression amelioration. Only QoL was briefly mention.

The tDCS section of the introduction is not well structured. It's better to subdivide the use of tDCS into neurological and psychiatric conditions. Now a distinction is made between "motor, cognitive, affective disorders" and "Alzheimer's and MDD".

Two papers on depression are mentioned: one submitting patients to 1 session and the other to 15 sessions. I would talk about the importance of the number of sessions as a potential variable that could increase tDCS effect (Brunoni)[2] to explain why you submitted the patients to 15 sessions. Also, there are maybe one or two articles on stress in professionals, indirectly referring to burnout with no tDCS effect on burnout. One of the contributions of this article is that it may be the first looking at burnout. I would highlight this.

I would also go more into details of other potential brain regions that could have been targeted, especially for those tasks that did not show a tDCS effect. Only DLPFC is mentioned. E.g. as

mentioned above, inhibition has not been linked to DLPFC. Or why you included those tasks while targeting DLPFC. It could be the reason why no significance was observed in inhibition.

A paragraph on neurotransmitters could also be added. Specifically, alterations in dopamine and noradrenaline levels in DLPFC have been associated with impaired working memory performance. TMS and tDCS over DLPFC have also been shown to release dopamine in various brain regions, including the right ventral striatum. Further, tDCS to DLPFC has shown to improve participants' memory accuracy, an effect that has been correlated significantly with dopamine release.

I would also mention briefly why it took 3 years to recruit 15 patients. It could be helpful for future studies recruiting patients with burnout.

Were the patients asked at the end of the treatment whether they knew they had received sham or real? (chi-squared test to test the integrity of masking).

Were patients asked to evaluate their level of discomfort? The level of discomfort/pain has been associated with a TMS/tDCS effect.

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Partly

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: non-invasive neuromodulation (TMS/tDCS), fMRI

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 22 Jul 2020

Kim van Dun, UHasselt, Diepenbeek, Belgium

"Transcranial direct current stimulation and attention skills in burnout patients: a randomized blinded sham-controlled pilot study" is addressing an important research and clinical question regarding executive memory, attention, and clinical symptoms in burnout. Data from 15 patients, randomized to 3 weeks of active anodal tDCS over left DLPFC or sham combined with standard behavioral therapy revealed that anodal tDCS significantly improved attention in patients with burnout.

Major Comments:

Major problems with neuromodulation studies are the small sample sizes and heterogeneous patient populations. The authors already mentioned those pitfalls as their biggest shortcomings. Nonetheless, it remains a major point of criticism for me. In order to get significance in TMS (and tDCS studies), Sack *et al.*, (2009)[1] demonstrated that power analyses showed 5 participants are sufficient to reveal a significant behavioral effect on cognition in TMS studies using fMRI-guided neuronavigation. However, the number of necessary participants increases to n = 9 in studies using MRI-guided neuronavigation, to n = 13 when using group Talairach coordinates, and to n = 47 when using EEG positions, like F3 or AF3.

Response: This is indeed a major shortcoming of our study but unfortunately, as a private practice, we do not have the facilities to set up a big study. Nonetheless, we do think our results are noteworthy and we therefore referred to our study as a "pilot study" hoping to instigate more interest in burnout in the field of non-invasive stimulation. In addition, since tDCS is not as focal as TMS, we do not think the use of EEG positions instead of neuronavigation will impact the power of the study as much as for TMS.

As for the limitation of using heterogeneous patient groups, the demographic characteristics revealed are limited to age, gender, and burnout severity expressed by MBS. Reporting other relevant characteristics, such as duration, employment, ON/OFF medication, etiology, level of education, hospitalization, etc,... would give us a better understanding of how representative the groups were. Also, some of these variables could be explored for significance or even predictivity in future studies.

Response: We did collect other demographic characteristics and have added these to the article to help future studies unravel the significance of these characteristics. Table 2B: Demographic characteristics and working-related information shows Employment (parttime or fulltime), Education level (12y of >12y), #working hours at intake, Smokers (yes or no), Living together / Children (yes or no), and Medication. Since three patients were on antidepressants (SSRI, SNRI, or

SARI), of whom one (SSRI) received real stimulation, it has also been added to the limitations section that this might have impacted the outcome of this patient since it has been shown that chronic use of SSRIs can enhance the effect of tDCS.

"In addition, three of the patients were taking antidepressant medication during the study, of whom one received real stimulation. It has been shown that this type of medication (selective serotonin reuptake inhibitors or SSRIs) might enhance the LTP-like plasticity induced by anodal tDCS (Kuo et al., 2016)."

Also, since a trend towards inhibition and shifting was reported, and the right inferior frontal gyrus has been associated with inhibition, the choice of placing the cathode on F8 was not optimal. rIFG is only about 2 to 2.5 cm posterior to F8. Since the reference sponge used had a size of 5x7, rIFG could have been affected by the current.

Response: This is a very good point that we have now addressed in the discussion. We based the placement of the electrodes on the study of Loo et al. (2012), who initially wanted to study the anti-depressant effect of tDCS but found an improvement of attention and working memory. Therefore, the electrode placement might not be optimal for working memory and attention. We have added this to the limitations section of the discussion.

"Fourth, the placement of the electrodes might not have been optimal to target attention deficits. Our study was based on the outcome of Loo et al. (2012) who aimed to investigate the anti-depressant effect in patients with depression, but found an improvement of attention and working memory instead (Loo et al., 2012). By copying this electrode placement, we hoped to replicate these results in patients with burnout. However, by placing the cathode on F8, we might have unwantedly inhibited the right inferior frontal gyrus, which has been linked to inhibition and attentional control (Hampshire et al., 2010). Although cathodal tDCS over the right inferior frontal gyrus did not appear to have a significant effect on response stopping or reaction times in a stop-signal task (Stramaccia et al., 2015), another choice for the cathodal reference electrode might be warranted. In addition, AF3 targets primarily the more frontal site of the left DLPFC, while a more common placement to target DLPFC in attention studies is F3 (Coffman et al., 2014)."

Only continuous outcome measures were reported. Since it better reflects better clinical practice, I would add a categorical outcome measure, i.e., percentage of responders/remitters.

Response: Although we agree that, clinically, this would have added value, we do not really have a theoretical base for categorizing our participants into responders/remitters based on the outcome measures we used. Therefor we prefer to use the continuous scores for these outcome measures.

A TCT device was used. The strap it comes with is made of a neoprene strap which could absorb the saline solution potentially increasing the surface area of the target area. Also, is this device EC approved?

Response: The TCT device is not EC approved but it was thoroughly tested in the lab of prof. dr. Mario Manto and approved by our ethical committee. The neoprene strap indeed can absorb the saline solution but during stimulation it was checked whether this absorption spread beyond the electrode surface. In addition, both electrodes were attached to the scalp using different straps to avoid bridges between the electrodes through the straps. This has now been added to the methodology:

"These were placed over the scalp using neoprene straps. Since these can absorb the saline solution, two different straps were used for both electrodes to avoid creating bridges and throughout the sessions the absorption was monitored so that it would not spread beyond the surface of the electrodes."

It was unclear whether all the patients in both conditions had been undergoing psychotherapy prior to the add-on tDCS therapy. If psychotherapy was new to all, it is a major confound. It could also be the reason why both groups improved burnout and depression-wise.

Response: Psychotherapy was new to all, therefore we did expect a significant improvement, burnout- and depression-wise, in both groups. We have added this also to the text. However, our main focus for the effect of tDCS was on the attention component, since personal experience learned that attention deficits are the most resilient symptom of burnout.

Methodology: "None of the patients had received psychotherapy before inclusion in this study." Discussion: *"Both groups improved on all these measures,* **which can be expected due to the behavioral therapy both groups received,** *but the improvement of burnout and overall quality of life was only significant after real tDCS."*

In the tDCS protocol section, Fp3 is mentioned as the target site, "left DLPFC". Since the 10-20 system of electrode placement is used, defining the target site as AF3 is probably better than Fp3. Also, the vast majority of TMS/tDCS studies targeting left DLPFC to stimulate F3. Why was Fp3/AF3 selected? DLPFC is indeed a large area. But an elaboration on the reason why a more anterior part of DLPFC was chosen should be explained.

Response: As mentioned above, we based the placement of the electrodes on the study of Loo et al. (2012), who initially wanted to study the anti-depressant effect of tDCS. Therefore, this might indeed not be the ideal stimulation site for our purposes, but it has been proven to be effective in Loo et al. (2012). This has been added in the limitations section. We also changed Fp3 to AF3 as suggested.

"In addition, AF3 targets primarily the more frontal site of the left DLPFC, while a more common placement to target DLPFC in attention studies is F3 (Coffman et al., 2014)."

Minor Comments:

In the background section of the abstract/methods, only one objective (attention and executive control) is mainly elaborated upon. I would also add the clinical objective, i.e., burnout, depression amelioration. Only QoL was briefly mentioned.

Response: Since we did expect a good outcome on burnout and depression scores with the behavioral therapy, the main focus of the study was on the added value of tDCS in improving the more resilient attention deficits. Therefore, we primarily elaborated on that objective. We hope that we have made this clearer as follows in the abstract:

*Abstract: "Background: Burnout is characterized by deficiencies in attention and several components of the working memory**. It has been shown that cognitive behavioral therapy can have a positive effect on burnout and depressive symptoms, however,** the lingering effects of impaired attention and executive functions are the most frustrating."*

The tDCS section of the introduction is not well structured. It's better to subdivide the use of tDCS into neurological and psychiatric conditions. Now a distinction is made between "motor, cognitive, affective disorders" and "Alzheimer's and MDD".

Response: Thank you for the thorough reading of the manuscript, this was indeed badly phrased. We have now changed it into the following, hopefully better, sentence:

*"tDCS is increasingly used in the treatment of motor, cognitive, and affective symptoms in different patient populations, **both in neurological (e.g. Alzheimer's disease; Flöel, 2014), and psychiatric disorders (e.g. major depressive disorder; Nitsche et al., 2009) (Brunoni et al., 2012)**."*

Two papers on depression are mentioned: one submitting patients to 1 session and the other to 15 sessions. I would talk about the importance of the number of sessions as a potential variable that could increase tDCS effect (Brunoni)[2] to explain why you submitted the patients to 15 sessions. Also, there are maybe one or two articles on stress in professionals, indirectly referring to burnout with no tDCS effect on burnout. One of the contributions of this article is that it may be the first looking at burnout. I would highlight this.

Response: In the introduction, we have added an explanation for using repeated sessions instead of a single session in our study and we have pointed out that our study is probably the first to study the effects of tDCS in a burnout population. Thank you for this suggestion!

"However, to induce a longer-lasting effect, repeated sessions are advised and it has already been shown that this can have a cumulative effect which is associated with greater magnitude and longer duration of the behavioral effects (Brunoni et al., 2012).
The effects of tDCS have not yet been extensively evaluated in burnout patients. Some studies have used tDCS in stress-related patient populations, such as professional nurses (Stanton et al., 2015) or post-traumatic stress disorder (Saunders et al., 2015), however, to our knowledge, our

study is the first to use tDCS in a burnout population."

I would also go more into details of other potential brain regions that could have been targeted, especially for those tasks that did not show a tDCS effect. Only DLPFC is mentioned. E.g. as mentioned above, inhibition has not been linked to DLPFC. Or why you included those tasks while targeting DLPFC. It could be the reason why no significance was observed in inhibition.

Response: *We have added several sentences to the discussion to clarify when we expected a result of left DLPFC stimulation and when it was rather unexpected. The discussion now reads as follows:*

"This study showed that three weeks of therapy, combined with real or sham stimulation, significantly improved several components of the central executive. However, analyses revealed that improvement was driven by a significant improvement after real tDCS for inhibition and shifting (WCST), and was also primarily seen after real tDCS for updating and control (TMT A, D2 G z, D2 G z – F). These results are in line with the study of Miler et al. who found that atDCS over the left DLPFC significantly improves the executive control of attention (Miler et al., 2018). As in the study of Miler et al., no effect was seen on the percentage of mistakes, but the processing speed did improve more on the D2 test of attention after real tDCS than after sham tDCS (Miler et al., 2018). ***However, the improvement on inhibition and shifting after tDCS was somewhat unexpected, since this is primarily associated with the right DLPFC and the right inferior frontal gyrus (Lie et al., 2006; Hampshire et al., 2010). Since this effect was only observed for the WCST, this might be related to this specific task. Indeed, studies have shown that, although the right DLPFC seems to be the most prominent in handling complex/manipulative working memory operations in the WCST (Lie et al., 2006), the left DLPFC is also involved during this task (Lie et al., 2006; Nagahama et al., 2005).*** *atDCS also seemed to have a positive impact on other components of the working memory. The phonological loop might also be positively influenced by real tDCS as shown by a significant improvement of the real tDCS group on the BNT, although the sham group also trended towards a significant improvement. No effect was seen on the visuospatial sketchpad,* ***which might not be surprising because this is believed to be situated primarily in the right prefrontal cortex (Suchan, 2008),*** *but encoding clearly improved more after real atDCS than after sham tDCS (RBANS Immediate Memory Index).* ***Transcranial magnetic stimulation (TMS) studies have shown a prominent role for the left DLPFC during encoding, observing shorter reaction times using a paired-pulse paradigm over this area (Gagnon et al., 2011). Though de Lara et al. (2017) did not find any effect of anodal tDCS over the left DLPFC on encoding, this might be due to the lesser intensity (1mA vs 2mA) they used in their study.****"*

A paragraph on neurotransmitters could also be added. Specifically, alterations in dopamine and noradrenaline levels in DLPFC have been associated with impaired working memory performance. TMS and tDCS over DLPFC have also been shown to release dopamine in various brain regions, including the right ventral striatum. Further, tDCS to DLPFC has shown to improve participants' memory accuracy, an effect that has been correlated significantly with dopamine release.

Response: This might indeed be relevant information for the interested reader. We have added the following paragraph in the introduction:

"One of the mechanisms that might be responsible for the cognitive problems in burnout patients is a dopaminergic dysfunction in the prefrontal cortex. It has been shown that dopamine in the prefrontal cortex plays a critical role in working memory and cognitive control (Polizzotto et al., 2020; Cools & D'Esposito, 2011) and that (chronic) stress can have a deteriorating effect on the dopaminergic system in this area (Mizoguchi et al., 2000). tDCS has been known to interact with dopaminergic systems (Polizzotto et al., 2020) and therefore tDCS over the DLPFC might be able to restore dopaminergic prefrontal cortex function."

In addition, a paragraph was added to the limitations section with the findings of a very recent paper on DLPFC stimulation and working memory:

"Lastly, research has shown that the effect of tDCS on working memory might be dependent on, amongst others, the initial dopaminergic level that can impact the excitation/inhibition balance (i.e. homeostasis between relative contributions of excitatory and inhibitory synaptic inputs) (Polizzotti et al, 2020). More insight into the exact working mechanisms underlying the cognitive and attention deficits in burnout patients might be beneficial for future research."

I would also mention briefly why it took 3 years to recruit 15 patients. It could be helpful for future studies recruiting patients with burnout.

Response: We have added some suggestions in the Limitations section to help with recruiting larger patient groups. As a single site with one therapist, it was very difficult to recruit several patients at the same time due to time constraints and a limited number of new intakes. In addition, several patients were discouraged by their primary physicians to participate in the experiment, since the primary physicians did not have enough information to judge the safety of tDCS.

*"Our study has several important limitations. First, our group of patients was relatively small. This is an important limitation given the positive trends of the effect of real tDCS on several outcome measures. Studies with more power will have to show whether these trends failed to reach significance due to a lack of power. In addition, some variables of interest (D2 s-score, TMT B, Stroop Card II, Raven) could not be interpreted correctly with the linear mixed model analysis because of a violation of assumptions. More data points could help to resolve this issue. **Setting up multi-site cooperations to recruit participants and maintaining close relationships with primary care providers making them aware of the safety of tDCS when applied in the correct manner, could also help to convince patients to participate in tDCS studies. Larger groups to validate the efficacy of tDCS are crucial to investigate the clinical usability of this therapeutic aid**."*

Were the patients asked at the end of the treatment whether they knew they had received sham or real? (chi-squared test to test the integrity of masking).

Were patients asked to evaluate their level of discomfort? The level of discomfort/pain has been associated with a TMS/tDCS effect.

Response: *Unfortunately, we did not systematically address these issues. We have added this to the limitations section and recommended it for future studies.*

"In addition, it is recommended to test for the efficiency of blinding the type of stimulation by asking the participants afterwards whether they think they were actively stimulated or not. Gathering information about the amount of discomfort could also be of importance for future studies using tDCS."

Competing Interests: No competing interests were disclosed.

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