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Review Article

Transcranial Direct Current Stimulation as a Therapeutic Approach for Anxiety and Related Markers: Comprehensive Systematic Review

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Transcranial Direct Current Stimulation as a Therapeutic Approach for Anxiety and Related Markers: Comprehensive Systematic Review"

Short Title: tDCS Stimulation as a Therapeutic for Anxiety

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Abstract

Objective: This systematic review aims to assess the effects of transcranial electrical stimulation (tES) on adults with anxiety. It focuses on evaluating physiological markers like heart rate variability (HRV), electroencephalogram (EEG), cortisol, and Interleukin-6 (IL-6) levels alongside various rating scales. *Methods:* The review process, adhering to PRISMA guidelines, involved a thorough literature search

across databases such as Embase, Scopus, PsycINFO, PubMed, and Web of Science. The risk of bias and quality of studies was evaluated using the JADAD scale. In total, 34 articles were meticulously chosen and analyzed by independent reviewer pairs. *Results:* The review included 34 studies, encompassing 1567 participants aged between 18 to 65. The findings were mixed: while 19 studies reported a reduction in anxiety symptoms, 10 found no significant differences, and 4 did not report changes in anxiety. Two studies were inconclusive. *Conclusions:* The review highlights a lack of standardized protocols for using tDCS in treating anxiety. The methodological quality of most studies was critically low, per PRISMA guidelines. There was considerable variation in methodological approaches across the studies, indicating a need for standardization in the research of anxiety treatment using tES.

Keywords: Systematic Review, Anxiety, tDCS, Non-Invasive.

Introduction

Anxiety is one of the most prevalent psychological conditions worldwide, affecting millions of people across different age groups. It is the sixth leading cause of disability worldwide and the second most debilitating in most countries in the Americas[1,2]. According to WHO`s survey, Brazil has the highest prevalence of anxiety disorders worldwide. Brazil exhibits the highest prevalence in primary care settings[1,3,4]. Its negative impact on individuals' quality of life and mental and physical health makes searches for effective therapeutic interventions imperative. In this context, transcranial direct current stimulation (tDCS) has emerged as a promising approach for the treatment of anxiety[5–7].

tDCS is a non-invasive neuromodulatory technique that involves the application of low-intensity electrical current through electrodes placed on the scalp. This electrical stimulation aims to modulate neuronal excitability and has been investigated in various neuropsychiatric conditions, including anxiety. Scientific literature has reported evidence that tDCS can influence not only brain activity, but also biological and physiological markers related to anxiety. Additionally, tDCS

intervention may have effects on psychological aspects closely associated with anxiety, such as mood, cognition, and emotional regulation [8–13].

However, despite preliminary research indicating promising results, there is still no clear consensus on the efficacy of tDCS as a treatment for anxiety, as well as on the underlying mechanisms of its biological, physiological, and psychological effects [14–17]. However, the efficacy of tDCS for anxiety treatment is still under debate, as highlighted by the need for further research. Despite numerous studies, the mechanisms and effects of tDCS on anxiety remain unclear and require further investigation, as discussed by Shin[18].

Therefore, a systematic review is necessary to gather, synthesize, and critically evaluate the available evidence in the scientific literature to provide a comprehensive and up-to-date understanding of the topic. We aim to examine and analyze studies that have investigated biological, physiological, and psychological markers associated with tDCS intervention, where anxiety is one of the markers. The goal is to identify the main findings of these studies, assess their methodological quality, and discuss the clinical and theoretical implications of this evidence.

By providing a critical synthesis of the current state of research in this field, it is hoped that this systematic review will contribute to advancing knowledge about the role of tDCS as an intervention for anxiety and stimulate future investigations that can clarify the neurobiological mechanisms involved and enhance available therapeutic approaches for individuals dealing with this challenging psychological condition.

Materials and Methods

A systematic literature review followed PRISMA guidelines[19,20]. Bibliographic and cross-sectional research was carried out through publications of scientific articles obtained in electronic media that answered what changes occur in people with anxiety after intervention with transcranial direct current stimulation (tDCS).
Data from the included studies were summarized descriptively in Table 1 containing authors, year of publication, country, sample, aims, assessment, results and conclusions of each study and a narrative synthesis was conducted. The

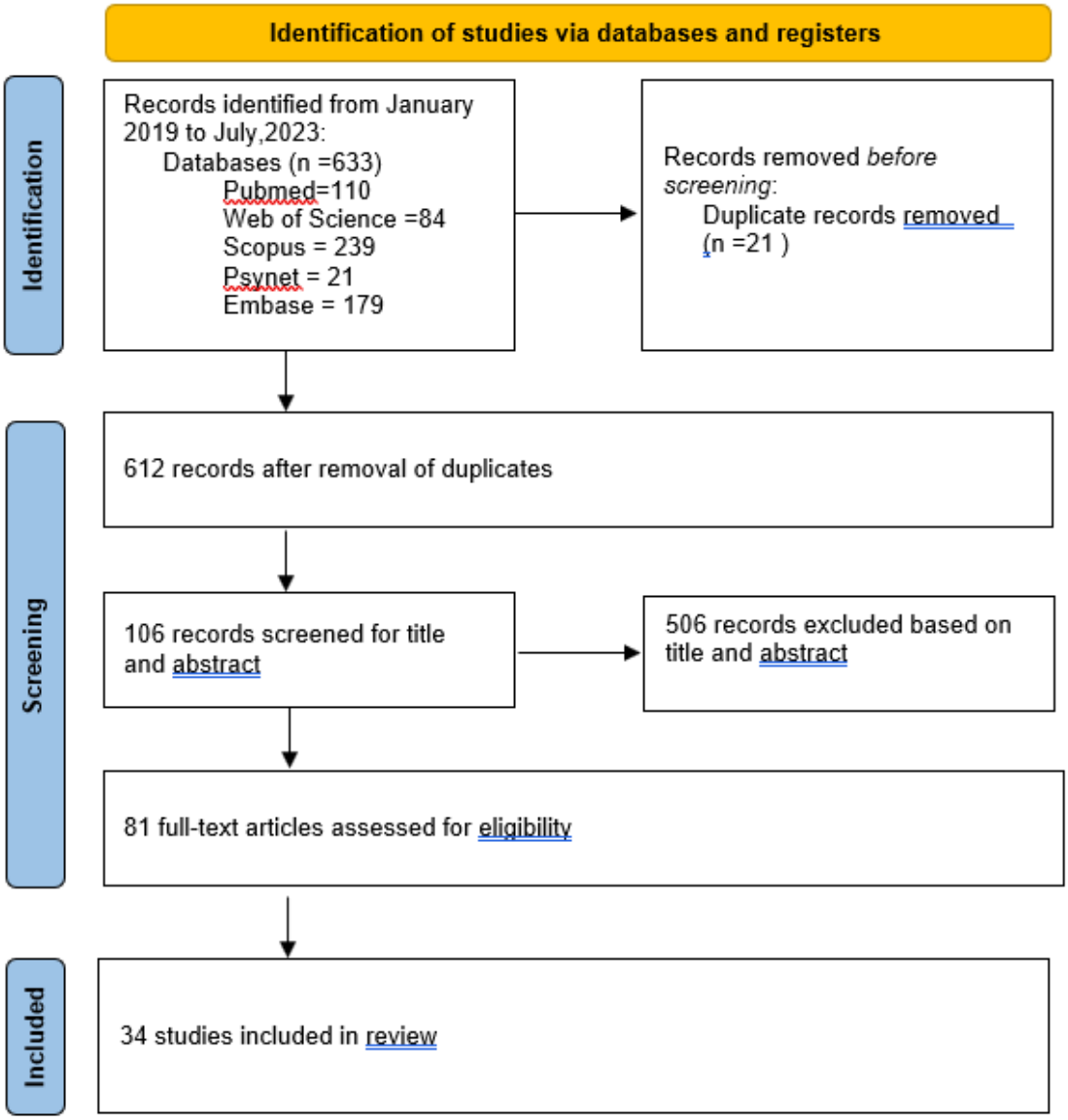
Supplementary Material of Table 1 is presented in Appendix A - Supplementary material- Table 1.

We adhered to the PICO framework guidelines for search strategies, and the research question addressed the following components: Are there changes in cortisol and Interleukin-6 levels, Heart Rate Variability, Electroencephalogram (EEG) records, and anxiety assessment scales after Transcranial Direct Current Stimulation (tDCS) in adults with anxiety?

To identify studies with relevant information, literature searches were conducted using five online databases: Embase, Scopus, PsycINFO, PubMed, and Web of Science. We searched for studies in any language between 2017 and July 2023 that referred to the assessment of anxiety levels after the intervention of transcranial electrical stimulation. MeSH terms were as follows: (("Transcranial Direct Current Stimulation" OR "Transcranial Direct Current Stimulation" OR tDCS OR "Cathodal Stimulation tDCS" OR "Transcranial Random Noise Stimulation" OR "Transcranial Alternating Current Stimulation" OR "Transcranial Electrical Stimulation" OR "Transcranial Electrical Stimulations" OR "Anodal Stimulation Transcranial Direct Current Stimulation" OR "Anodal Stimulation tDCS" OR "Repetitive Transcranial Electrical Stimulation" AND ((Anxiety OR Anxiet* OR Angst] OR Nervousness OR Hypervigilance OR Anxiousness OR "Social Anxiety" OR "Social Anxieties") OR ("Anxiety Disorders" OR "Anxiety Disorders" OR "Anxiety Disorder" OR "Anxiety Neuroses" OR "Neurotic Anxiety States" OR "Generalized anxiety disorder" OR "generalized anxiety"). Details of the protocol for this review were registered on the International Prospective Register of Systematic Reviews (PROSPERO) - under the CRD473699 registration number.

Figure 1 contains a flowchart illustrating the analysis, and the PRISMA Checklist is presented in Appendix B - Supplementary material- PRISMA 2020 Checklist.

Figure 1- PRISMA 2020 flow diagram for new systematic reviews



Inclusion/exclusion criteria

Articles eligible for this systematic review investigated whether the occurrence of January 2017 to July 2023. The studies had to meet specific criteria: articles published in peer-reviewed journals, involving only human participants, reporting original research, case-control, cohort, cross-sectional study, clinical trial, pilot study,

individuals over 18 years of age, and reporting outcome measures on changes in anxiety symptoms.

We excluded studies that included repeated articles, book chapters, doctoral thesis, master's dissertation, summary (only), articles without summary, letters to the editor, conference publications, literature reviews/Meta-analysis, animal models under 18 years old, and associated pathologies.

Charting methods

Two independent reviewers, supervised by a third person, systematically extracted information following a predefined format. The extracted study characteristics included qualitative summaries of (1) the aims of the review, (2) the type of study, (3) treatment and control/comparison groups, (4) inclusion and exclusion criteria, (5) sample characteristics (e.g., age, gender), and (6) main findings. The extracted quantitative variables included (1) the date range of databases searched, (2) the number of included studies, and (3) the effect size results (e.g., Hedges's g). If articles included Supplemental Materials, those were also examined along with the review article. Any discrepancies in data extraction were resolved through discussion with the judge author.

Data extraction and quality assessment

Once an article was selected for review, fulfilling the exclusion and inclusion criteria, the following data were extracted: authors, country, description of objectives, study design, sample characteristics, number of sessions, session time, number of weeks, device used, assessment instruments used, recording of heart rate variability (HRV), collection of interleukin-6 and cortisol, measured by EEG and reduction of anxiety and conclusion of the study.

Quality of evidence

Based on the GRADE system downgrading factors, the quality was classified as high, moderate, low, and very low[21]. Two independent judges assessed each study's limitations, inconsistency, imprecision, and publication bias. The

methodological quality of the studies was evaluated by two reviewers (FM and FRTA); the evaluation was based on the quality of both the RCTs and the moderation analyses to obtain a combined quality score. The differences between the two reviewers were resolved by discussion until a consensus was reached.

Quality assessment

The methodological quality of the studies was assessed using the Jadad scale ("Appendix: Jadad Scale for Reporting Randomized Controlled Trials," 2005). This scale comprises a set of five questions evaluating three aspects of clinical trials – randomization, blinding, and reporting of follow-up losses. The questions offer a binary response option (yes=1/no=0), with a scoring range of 0 to 5. Studies scoring below three possess low methodological quality, and their findings are deemed unsuitable for clinical practice.

Study characteristics

This search strategy yielded 663 articles. After removing duplicates and screening articles based on their titles and abstracts, 106 articles were selected for full-text evaluation. Following abstract and full-text screening, 25 were excluded and did not meet our inclusion criteria.

As a result, 34 [22–55]studies were analyzed, a sample of 1567 individuals, mean age ranged from 18 to 65 years old.

This data was summarized using a table (Table 1).

Table 1- Articles analyzed in the study

Author (year)	Country	Method	Sample	Aims	Instruments	HRV	EEG	Initial interleukin-6	final Interleukin-6	Cortisol	Decrease in anxiety	Conclusion
Dutra, L. R. D. V. et al. (2020)[22]	Brazil	double-blind, placebo-controlled trial	26 women with the diagnosisof primary dysmenorrhea	To determine whether tDCS could offer clinical benefits on pain, anxiety, affectivity, and functionality in women with primary dysmenorrhea.	Hamilton Anxiety Scale (HAS), Positive and Negative AffectSchedule, The Six-Minute Walk Test (6MWT), Numeric Rating Scale for Pain	No	No	No	No	No	Yes	Anodal tDCS over the left DLPFC seems to be an effective therapeutic approach for improving anxiety and functional capacity in patients with primary dysmenorrhea. Although painful symptomatology decreased, no significant effects were seen between groups.
Garcia, S. et al. (2020)[23]	United States Of America	double-blind, placebo-controlled trial	143 undergraduate students with and without a history of anxiety disorder diagnoses were recruited for this study.	To investigate the use of transcranial direct current stimulation (tDCS) on both common anxiety symptoms and executive function abilities in a college aged sample.	State Trait Anxiety Inventory (STAI) ; GAD-7; Rey-Osterreith Complex Figure Task; Wisconsin Card Sorting Task	NI	NI	NI	NI	NI	No	Overall, results suggest that while anodal stimulation of the lDLPFC may benefit cognitive abilities for this population, targeting psychological symptoms of anxiety likely requires stimulation over other cortex, possibly right DLPFC. Further, the use of tDCS, whether active or sham, may be distressing to patients.
Gibson, B. C. et al. (2021)[24]	United States Of America	double-blind, placebo-controlled trial	54 healthy individuals	To explore the extent to which differences in state anxiety and related measures affect visual attention and category learning, both with and without the influence of tDCS.	short form of the Profile of Mood States (POMS), Remote Associates Test (RAT), Remote Associates Test (RAT)	NI	NI	NI	NI	NI	It cannot be ruled out, and may even be likely, that trepidation about tDCS itself was the driving force behind individual differences	These results indicate that anxiety can influence the quality of subjects' attention at the onset of the task and that these attentional differences can influence tDCS-mediated category learning during the rapid assessment of visual scenes. These findings have implications for understanding the complex interactions that give rise to the variability in response to tDCS.
Clarke, P. J. F. et al. (2020)[25]	Australia	double-blind, placebo-controlled trial	75 (female) healthy participants	To assess the impact of tDCS on worry in terms of its immediate effects on negative intrusive thoughts and worry-related emotional reactivity. Secondly, to examine whether concurrent engagement in a mindful task during tDCS delivery would further augment any observed effects.	DASS e STAI-S	NI	NI	NI	NI	NI	No	Active tDCS was associated with significantly greater elevation in anxiety in response to the worry induction. No effects were observed on the frequency of negative thought intrusions, and the combined delivery of tDCS with the concurrent mindful task did not alter the pattern of observed effects. While inviting replication in a high anxious sample, the present results highlight the possibility that tDCS may interact with motivated engagement in negative patterns of cognition, such as worry, to produce greater emotional reactivity.
Cobb, A. R. et al. (2021)[26]	United States Of America	double-blind, placebo-controlled trial	49 healthy participants with marked fear of snakes, spiders, and/or contamination-related threats	To preliminarily test whether excitatory tDCS of left mPFC and inhibitory tDCS of right dlPFC accelerates responding and improves outcomes from a single session of in vivo exposure in a transdiagnostic sample with marked arachnophobic, ophidophobic, and contamination-related fear. Also, to test the prediction that the effects of facilitating therapeutic learning should depend on qualities of that learning, in terms of emotional, cognitive, and behavioral reactions to feared targets and to test whether several negative prognostic indicators moderate tDCS augmentation effects.	DMQ = Demographics and Medical Questionnaire; MINI-5= Mini International Neuropsychiatric Interview, Version 5; ADIS-5 = Anxiety and Related Disorders Interview Schedule for DSM-5 Disorders; C-SSRS = Columbia Suicide Severity Rating Scale; CLQ = Claustrophobia Questionnaire; FSQ = Fear of Snakes and Spiders ; Questionnaire; OCI-R = ; experiential avoidance (EA; BEAQ), generalanxiety (BAI), and depression (BDI-II).	NI	NI	NI	NI	NI	Yes	This investigation provides novel preliminary support for the use of tDCS to enhance in vivo exposure. Along with other emerging neuromodulation approaches to enhance extinction learning, the present results are encouraging. The most remarkable pattern across study findings suggests tDCS may promote good clinical outcomes despite the presence of several negative prognostic indicators. In sum, active tDCS was found to especially benefit individuals with more severe phobic symptoms and elevated fearful reactivity to anxiety, as well as individuals who exhibited persistent

												emotional distress and threat-related beliefs about feared targets at the last exposure trial. These results should be interpreted cautiously due to the preliminary nature of this investigation. However, replication with larger and more severe clinical samples, and parallel efforts to optimize dosing parameters appear warranted. tDCS and other neuromodulation technologies have clear therapeutic potential for patients who are otherwise refractory to standard exposure-based interventions.
Ney, L. J. et al. (2021)[27]	Australia and Italy	single-blinded	30 healthy participants	To investigate whether tDCS immediately following extinction learning improves efficacy of extinction memory retention.	Depression, Anxiety and Stress Scales (DASS-21), Alcohol Use Disorder Identification Test (AUDIT), Skin Condutance Response (SCR)	No	No	No	No	No	No	Participants in the tDCS group showed impaired fear extinction retention on day 2, marked by significant generalisation of fear to the safety stimulus. This contrasts with earlier studies showing improved extinction retention when stimulation occurred during encoding of extinction learning, compared to immediate consolidation as in our study. These findings may have important implications for the use of tDCS during exposure therapy for anxiety and trauma disorders.
Movahed, F. S. et al. (2018)[28]	Iran	single-blind, placebo-controlled trial	18 Adults with GAD !! (46% female; 64%male= +100%)	To conduct an experimental design using tDCS on reduction of depressive and anxiety symptoms, and worry in patients with generalized anxiety disorder (GAD).	GAD-7; Hamilton anxiety rating scale (HARS); Hamilton depression rating scale (HDRS); Penn state worry questionnaire (PSWQ)avaliação de depressão de Hamilton (HDRS)	NI	NI	NI	NI	NI	No	The tDCS is a promising treatment for generalized anxiety disorder, especially in depressive and worry symptoms.
Ahmadizadeh, M. J., Rezaei, M., & Fitzgerald, P. B. (2019)[29]	Iran	double-blind, placebo-controlled trial	40 Adults with PTSD (26 female; 14 males)	To examine the efficacy of tDCS for PTSD and its sub-symptoms.	Posttraumatic stress disorder checklist for DSM-5 (PCL-5); Beck Depression Inventory-II (BDI-II); Beck Anxiety Inventory (BAI)	NI	NI	NI	NI	NI	yes	This study supported the efficacy of 10 sessions of bilateral DLPFC tCDS delivered at 2 mA for the treatment of PTSD symptoms. Taken together, these findings suggest that although tDCS can reduce PTSD symptoms, researchers should consider the different types of PTSD and use strategies to ensure sufficient power to detect a potential effect of tDCS on various types of PTSD.
Author (year)	Country	Method	Sample	Aims	Instruments	HRV	EEG	Initial interleukin-6	final Interleukin-6	Cortisol	Decrease in anxiety	Conclusion
Azmoodeh, S., Soleimani, E., & Issazadegan, A. (2021)[30]	Iran	randomized clinical trial	30 pacientes with epilepsy	To examine the effects of transcranial direct current stimulation (tDCS) on the psychological profile of patients with epilepsy.	DASS-21	NI	NI	NI	NI	NI	Yes	The results showed that tDCS could reduce depression, anxiety, and stress with the changes caused in the brain system.
Bornheim, E. et al. (2020)[31]	Belgium	double-blind, placebo-controlled trial	50 acute stroke patients aged between 18 and 80 years old, presenting their first ever symptomatic ischemic stroke confirmed by CT or MRI were eligible for the study (33 female; 17 male)	To measure the effects of tDCS on functional and sensory outcomes throughout the first year post onset of stroke.	Wolf Motor Function Test, Semmes Weinstein Monofilament Test, Upper Extremity Section (UEFM), Lower Extremity section (LEFM), Somatosensory section do Fugl Meyer Test, Tardieu Spasticity Scale, Stroke Impact Scale (SIS), Hospital Anxiety and Depression Scale (HADS) e Barthel Index.	NI	NI	NI	NI	NI	yes	tDCS seems to be an effective adjuvant to conventional rehabilitation techniques. If applied in the acute stages of stroke, functional recovery is not only accelerated, but improved, and results are maintained up to one-year post stroke
De Doncker, W., Ondobaka, S., & Kuppuswamy, A. (2021)[32]	United Kingdom	double-blind, placebo-controlled trial	30 Adults - Post-stroke after 3 months	To assess whether fatigue symptoms can be reduced by increasing cortical excitability using anodal transcranial direct current stimulation (tDCS).	FSS-7, VAS, EMG, The Hospital Anxiety and Depression Scale	NI	NI	NI	NI	NI	Unclear	A single session of anodal tDCS improves fatigue symptoms with the effect lasting up to a week post stimulation. tDCS may therefore be a useful tool for managing fatigue symptoms post-stroke.
de Lima, A. L. et al. (2019)[33]	Brazil	double-blind, placebo-controlled trial	30 adults with GAD	To evaluate the effect of anodal tDCS over DLPFC	Hamilton Anxiety Rating Scale and the Beck	NI	NI	NI	NI	NI	No	Five sessions of anodal tDCS along the DLPFC

				on anxiety and on the level of stress, depression and positive/negative affectivity.	Anxiety Inventory, the Lipp Inventory of Stress Symptoms for Adults, Positive and Negative Affect Schedule, and the Beck Depression Inventory (BDI).							did not improve key outcomes for patients with GAD, although physical stress symptoms improved. The role of tDCS in GAD should be explored in larger patient samples using different parameters.
Jafari, E. et al. (2021)34	Iran	double-blind, placebo-controlled trial	45 patients with SAD	To determine whether modulation of the dorsolateral and medial PFC activity with a novel intensified stimulation protocol reduces SAD core symptoms, improves treatment-related variables, and reduces attention bias to threatening stimuli.	Liebowitz Social Anxiety Scale (LSAS), Penn State Worry Questionnaire (PSWQ), Beck Depression Inventory-II (BDI-II),Difficulties in Emotion Regulation Scale (DERS) ,WHOQUL questionnaire,paradigma dot-probe	NI	NI	NI	NI	NI	Yes	Modulation of lateral-medial PFC activity with intensified stimulation can improve cognitive control, motivation and emotion networks in SAD and might thereby result in therapeutic effects. These effects can be larger with 2-mA vs 1-mA intensities, though a linear relationship between intensity and efficacy should not be concluded. Our results need replication in larger trials.
Kumari, B. et al. (2023)35	India	simple-blind, placebo-controlled trial	50 adults with depression	To compare the change in Hamilton Depression Rating Scale (HAM-D) scores with an early, add-on tDCS versus sham tDCS in patients with major depressive disorder. Also, to compare the rates of tDCS related side effects between the active and sham tDCS group.	Hamilton Depression Rating Scale (HAM-D), Beck's Depression Inventory (BDI), and Hamilton Anxiety Rating Scale (HAM-A)	NI	NI	NI	NI	NI	No	The study revealed a significant reduction in symptom severity with tDCS augmentation implying beneficial aspects of tDCS as an early augmentation strategy in drug-free patients of moderately severe depression. The tDCS application hastens the process of reduction in depressive and anxiety symptoms. The side effects associated with tDCS were usually of mild to moderate intensity, and tDCS was well tolerated. The findings from our study support the use of tDCS along with medications as an augmentation strategy early in the intervention process for moderate to severe depressive episode. However, the beneficial effects of tDCS may be time-limited. Increasing the number of tDCS sessions or incorporating the strategy of booster sessions may prolong the benefits; further studies are warranted to analyze this.
Marcolin, K. A. S. et al. (2023)36	Brazil	clinical trial	8 Patients over 18 years of age diagnosed with PTSD without complete remission of symptoms	To present a clinical trial study conducted in patients with PTSD caused by the KISS nightclub fire disaster who, being unresponsive to pharmacological therapy, underwent tDCS treatment.	The Post-Traumatic Stress Disorder Checklist, Civilianversion (PCL-C), The Montreal Cognitive Assessment (MoCA), The Hamilton Depression Rating Scale (HAM-D) and The Hamilton Anxiety Rating Scale (HAM-A)	No	No	No	No	No	Yes	Despite decrease over time, improvement in post-traumatic stress disorder, depression and anxiety symptoms was maintained throughout the first month after treatment. Transcranial direct current stimulation adjuvant can be analternative treatment to refractory post-traumatic stress disorder, either as monotherapy or as treatment enhancementstrategy. They can also be an option for patients who do not want or do not tolerate pharmacological management.
McAleer, J. et al. (2023)37	United States Of America	double-blind, pseudo-counterbalanced design; pilot study	29 volunteers with depression and/or anxiety, confirmed via psychiatric evaluation by a board-certified psychiatrist (>23 on the Depression Anxiety Stress Scale, DASS-21)	To analyze the effects of dlPFC-targeting tDCS and offset (180-degree phase difference in stimulating electrodes) theta-tACS on emotion regulation in individuals with internalizing psychopathologies (IPs), measured by analyzing changes in their heart rate variability (HRV) in the context of repeated emotion regulation tasks.	DASS-21	Yes	Yes	no	no	no	NI	tACS appears to increase ER capacity as reflected in increased HRV in individuals with internalizing psychopathologies, particularly after two sessions of stimulation. This study adds validity to the use of tACS as a neuromodulatory technique in cognitive and clinical research. Additional research is required to better

Naeim, M., Rezaeisharif, A., & Moghadam, S. A. (2021)38	Iran	double-blind, placebo-controlled trial	60 methadone users who had severe depression and anxiety.	To evaluate the effectiveness of transcranial direct current stimulation (tDCS) on depression and anxiety in methadone users.	Beck's depression inventory, Berger's test	NI	NI	NI	NI	NI	Yes	understand potential carry-over effects of multiple sessions of stimulation. It seems that the method of tDCS can reduce the severity of symptoms of depression and anxiety. Therefore, it can be claimed that this intervention can be considered by experts as a complementary intervention along with other psychological and pharmacological treatments.
Author (year)	Country	Method	Sample	Aims	Instruments	HRV	EEG	Initial interleukin-6	final Interleukin-6	Cortisol	Decrease in anxiety	Conclusion
Nejati, V. et al. (2021)39	Iran	randomized, single-blinded, and complete crossover design	34 adults with GAD, with an age range between 20 and 45 years ;19 females,	To explore the causal contribution of the dorsolateral and ventromedial prefrontal cortices (dlPFC, vmPFC) on cognitive bias via non-invasive brain stimulation.	The state-trait anxiety inventory (STAI), Dot probe task, Reading mind from eyes test (RMET)	NI	NI	NI	NI	NI	NI	As suggested by the results of this study, both dlPFC and vmPFC are involved in cognitive bias in GAD, but with partially different roles. Anodal stimulation over the right vmPFC and the left dlPFC reduced attention bias, supporting the relevance of these areas for attention bias. For interpretation bias, the significant effect of anodal dlPFC/cathodal vmPFC stimulation, but only trendwise effect of anodal tDCS over the dlPFC combined with an extracephalic return electrode is in accordance with a predominant effect of the dlPFC on interpretation bias, but does not rule out an additional minor involvement of the vmPFC. Based on these results, a new model is suggested for the neural underpinnings of anxiety symptoms.
Nikakhlagh, S. et al. (2023)40	Iran	double-blind, placebo-controlled trial	42 right-handed participants with normal hearing sensitivity, who reported a chronic tinnitus lasting for at least 12 months	To evaluate the therapeutic effects of repeated sessions of anodal bifrontal tDCS on tinnitus symptoms. Furthermore, the tDCS impacts on the comorbid depression and anxiety of the patients were investigated.	Tinnitus Handicap Inventory (THI), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI)	No	No	No	No	No	Yes	Our findings indicated that THI score, depression and anxiety level has been gradually diminished across subsequent measurement intervals. We also find significant reduction of distress-related tinnitus in the real-tDCS group after treatment. We conclude that application of tDCS to the bilateral DLPFC region alleviates chronic tinnitus and it should be considered in patients with refractory tinnitus.
Nishida, K. et al. (2021)41	Japan/Germany	randomized clinical trial	58 healthy participants (n=28-active; 30 sham)	To augment the effects of mindfulness, suggested for reducing anxiety, with concurrent use of tDCS.	STAI, the Positive and Negative Affect Schedule (PANAS)25, the Schedule for the Evaluation of Individual QoLDirect Weighting (SEIQoL-DW)26, and the Five Facet Mindfulness Questionnaire (FFMQ)	No	Yes	NI	NI	NI	Yes	The results of this study revealed an interaction effect between tDCS and time, and that SA-STAI scores were significantly decreased at 1 week after active tDCS. Furthermore, we found that the actual density of alpha activity in the rACC was significantly decreased only in the active tDCS group, and this reduction was significantly greater in the active group than in the sham tDCS group.
Paula, T. M. H. et al. (2023)42	Brazil	double-blind, placebo-controlled trial	86 women with fibromyalgia (18-65)	To investigate the analgesic and neuromodulatory effects of previous treatment with LDN combined with anodal tDCS in women with fibromyalgia.	sociodemographic, Visual Analog Pain Scale (VAS), Pain Catastrophizing Scale (PCS), State-Trait Anxiety Inventory (STAI), Fibromyalgia Impact Questionnaire (FIQ), Beck Depression Inventory (BDI-II), Profile of Chronic Pain Scale (PCP:S), Pain Pressure Threshold (PPT), and Conditioned Pain Modulation (CPM).	No	No	No	No	No	Yes	Combined LDN+tDCS has possible benefits in reducing pain frequency and intensity;

Pinto, A. C. P. N. et al. (2021)43	Brazil	Randomized Controlled Trial (piloto)	36 Women aged 18–65 years with pSS, on stable pharmacological therapy for least threemonths, with complaints of fatigue for at least three months.	To evaluate the effect of a tDCS protocol on fatigue in patients with primary Sjögren's Syndrome (pSS)	Fatigue Severity Scale (FSS), Profile of Fatigue and Discomfort -Sicca Symptoms Inventory (PROFAD-SSI), EULAR Sjogren € ’s Syndrome Patient Reported Index (ESSPRI), ShortForm 12 Health Survey (SF-12), Pittsburgh Sleep Quality Index, Beck Depression Inventory (BDI), Elecsys Cortisol II assay kit.	No	No	No	No	Yes	No	tDCS seems to be safe and reduce fatigue in pSS. A differential effect on pain and sleep may underlie its effects. Further studies are needed to optimise tDCS treatment strategies in pSS
Singh, S. et al. (2021)44	India	Pilot Study - prospective interventional study	35 patients diagnosed with depressive disorder (based on CID-10) who showed inadequate improvement on antidepressant selective serotonin reuptake inhibitors	To study the effect of tDCS as an augmentation strategy in depression and its various symptom domains.	Hamilton Rating Scale for Depression-17 items (HAM-D)	No	No	No	No	No	Yes	tDCS increase improves depressive symptoms in the short term. Almost all domains or variables of depressive symptomatology responded to tDCS in our sample. In clinical practice, this may help reduce sequential trials of multiple antidepressants or adjuvant drugs and avoid their costly side effects, thereby providing a safer alternative modality for treating depression. However, the open-label nature, absence of a control group, modest sample size, lack of uniform doses of antidepressant treatment, and lack of long-term evaluation of outcome measures are limitations that restrict the generalizability of this study.
Smits, F. M. et al. (2022)45	Netherlands	double-blind, placebo-controlled trial	100 active-duty mili-tary personnel and post-active veterans with PTSD, anxiety, or impulsive aggression symp-toms	To replicate tDCS-enhanced inhibitory control training in a clinical sample and test whether this reduces stress-related mental health symptoms.	Stop-signal response time (SSRT), Bochum Emotional Stimulus Set (BESST), Implicit association task (IAT), PTSD Checklist for DSM-5, the trait version of thepositive and negative affect schedule (PANAS), STAXI-2, Beck Depression Inventory 2nd edition (BDI-II), Outcome Questionnaire 45 (OQ45), Dutch version of the childhood trauma questionnaire shortform (CTQ-SF) and Barrett’s ImpulsivityScale (BIS-11)	No	No	No	No	No	No	The current RCT in military patients with stress-related symptoms provides no evidence for short-term or long-term benefits of 5 sessions of 20-min tDCS targeting the right IFG at an intensity of 1.25 mA combined with response inhibition training, on inhibitory control or PTSD, anxiety, and impulsive aggression symptoms. For these patients, tDCS may be more effective in higher doses (e.g. higher current density, more sessions) or when combined with emotionally challenging tasks or psychotherapy. Gaining insight in determinants of tDCS efficacy and convenient brain targets for neuromodulation in stress-related disorders will allow the tailoring of future tDCS interventions.
Szeremeta, E. M. et al. (2023)46	Australia	double-blind, placebo-controlled trial	101	To examine the effects of tDCS to the left DLPFC on attentional bias towards both negative and positive information, as well as its effects on both negative and positive emotional reactivity in response to emotional content.	Positive and Negative Affect Schedule (PANAS); STAI-S; DASS-21; IDATE-S	Yes	no	no	no	no	Yes	We found no evidence of tDCS-induced effects on attentional bias towards either negative or positive information, with Bayesian analyses suggesting more evidence in favour of the absence of such effects in the present study. However, though results should be treated as preliminary, we found some evidence that tDCS may enhance emotional regulation that is aligned with intent, and may increase positive mood. These findings provide some support for effects of left frontal tDCS stimulation on emotional regulation and positive effects on overall mood.
Wang, Y. et. al (2022)47	China	double-blind, placebo-controlled trial	70 healthy female students	To investigate whether one single session of tDCS could reduce creativity	Stai-T ; BDI-II; PANAS ;Stai-S ; Trier Social Stress Test(TSST)	Yes	Yes	Yes	NI	Yes	Yes	Results showed that R+L□ stimulation facilitated the recovery of

				impairments induced by acute stress, and whether the effect of tDCS on creativity performance is partially mediated by the recovery of the stress response.								anxious state compared to sham stimulation. We also found that the decreased value of AUT scores after stress in the R+L□ group was significantly lower than that in the sham group. Moreover, further analysis revealed state anxiety mediated the effect of tDCS on the flexibility component of the AUT. We concluded that bilateral tDCS over the DLPFC is efficient in alleviating stress-induced creativity impairment, which may correlate with greater recovery of state anxiety. Our findings provide causal evidence for the neurophysiological mechanisms by which stress affects creativity, as well as clinical suggestions for stress-related psychiatric disorders prevention and intervention.
Author (year)	Country	Method	Sample	Aims	Instruments	HRV	EEG	Initial interleukin-6	final Interleukin-6	Cortisol	Decrease in anxiety	Conclusion
Loreti, E. H. et al. (2023)48	Brazil	randomized clinical trial	35 women with FM	To analyze the effects of ten sessions of active transcranial direct current stimulation transcranial direct current stimulation (tDCS) (2 mA) with 13:20:13 stimulation at M1 in women with fibromyalgia (FM).	Fibromyalgia Impact Questionnaire, Hamilton Anxiety Rating Scale, Hamilton Depression Rating Scale, World Health Organization's Quality of Life Questionnaire, and Fatigue Assessment Scale	No	No	No	No	No	No	The active tDCS group showed improvement in pain after ten sessions ($p < 0.001$), after 30 days ($p < 0.01$), and after 90 days ($p < 0.001$) compared with sham tDCS. In addition, improvement in quality of life (QoL) and fatigue was observed in the active tDCS group. The results of this study suggest that active tDCS with an intensity of 2 mA for ten sessions was effective in decreasing pain and fatigue and improving QoL in patients with FM.
Brooks, H. et al. (2021)49	Canada/ United States Of America	double-blind, placebo-controlled trial	36 individuals with subjective cognitive complaints and symptoms of depression and/or anxiety were randomized to active (n = 12) or sham tDCS (n = 14).	To assess the feasibility of combining Mindfulness-Based Stress Reduction (MBSR) with transcranial direct current stimulation (tDCS) to increase putative benefits of MBSR for cognitive function and everyday mindfulness in depressed or anxious older adults with subjective cognitive decline.	Fluid Cognition Composite do National Institutes of Health (NIH) Toolbox Cognition Battery, The Cognitive Affective Mindfulness Scale (CAMS-R) e the 8-item short form v2.9 PROMIS Scale for Satisfaction with Social Roles and Activities and the 8-item short form v2.0 PROMIS Ability to Participate in Social Roles and Activities	NI	NI	NI	NI	NI	Yes	Our findings suggest that it is feasible and safe to combine tDCS with MBSR in older depressed and anxious adults, including during remote, at-home use. Furthermore, tDCS may enhance MBSR via transferring its meditative learning and practice into increases in everyday mindfulness. Future studies need to improve adherence to MBSR with tDCS.
Quinn, D. K. et al. (2020)50	United States Of America	double-blind, placebo-controlled trial	24 subjects with chronic mild-moderate TB	To identify whether anodal tDCS applied to the left dorsolateral prefrontal cortex paired with a cognitive training protocol in mild traumatic brain injury (mTBI) patients results in changes in cerebral blood flow (CBF) on pCASL sequences.	The Neurobehavioral Symptom Inventory (NSI); the Hamilton Depression Rating Scale (HAM-D); the Beck Depression Inventory-II (BDI); the Posttraumatic Stress Disorder Checklist-Civilian version (PCL-C); the Patient-Reported Outcomes Measurement Information System-29 (PROMIS); the Glasgow Outcome Scale-Extended (GOS-E); the Frontal Systems Behavior Scale (FrSBe); Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV): Digit Span and Coding subtests; the Test of Premorbid Functioning (TOPF); the Hopkins Verbal Learning Test-Revised (HVLT-R) (54); and Test of Memory Malingering (TOMM) (55).	NI	NI	NI	NI	NI	yes	The current study suggests a complex picture between mmTBI, cerebral perfusion, and recovery. Changes in CBF may result from physiologic effect of the intervention, compensatory neural mechanisms, or confounding factors. Limitations include a small sample size and heterogenous injury sample, but these findings suggest promising directions for future studies of cognitive training paradigms in mmTBI.
Suen, P. J. C. et al. (2021)51	Brazil	double-blind, placebo-controlled trial	16 patients who were diagnosed with major depressive disorder during an acute depressive episode per DSM-5 criteria	To investigate whether electric field (EF) strength is correlated with behavioral changes in depressed patients using simulated electric fields in	Magnetic resonance imaging, HDRS - Hamilton depression rating scale, STAI state–trait anxiety inventory,	No	No	No	No	No	No	We found no correlation between trait or state anxiety and EF strength over the DLPFC and ACC. Although some studies suggested that tDCS can

				real patient data from a controlled clinical trial.	Positive and Negative Affect Scale (PANAS)							downregulate anxiety, negative findings have been also reported. For instance, recent trials showed modest or null effects of prefrontal tDCS in ameliorating anxiety symptoms. In this context, other tDCS protocols that could be more effective in improving anxiety symptoms should be investigated. In addition, tDCS effects on anxiety might be more effective when down-regulating stress-induced tasks.
Nasiri, F. et al. (2020)52	Iran	double-blind, placebo-controlled trial	43 (32 female) individuals diagnosed with GAD and comorbid depression	To compare the unified protocol for transdiagnostic treatment of emotional disorders (UP) with and without transcranial direct current stimulation (tDCS) for the treatment of emotion regulation and executive control dysfunction in individuals diagnosed with generalized anxiety disorder (GAD) and comorbid major depressive disorder (MDD).	Anxiety disorders interview schedule for DSM-IV (ADIS-IV), Anxiety sensitivity index (ASI), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Generalized anxiety disorder questionnaire-IV (GAD-Q-IV), Intolerance of uncertainty scale, Penn state worry questionnaire (PSWQ).	No	No	No	No	No	Yes	In the current study, combined UP+tDCS resulted in significantly greater reductions in anxiety, anxiety sensitivity, and worry relative to UP alone both post-treatment and at a three-month follow-up. Thus, a combined UP+tDCS approach may result in better and longer treatment improvement in treatment-resistant GAD patients with comorbid depression.
Dechantsreiter, E. et al. (2023)53	Israel/ Latvia/ Germany	two-arm, double-blind, randomized and placebo-controlled multi-center trial	14 patients with a primary diagnosis of MDD	To examine the synergistic effects of a self-administered home-treatment, encompassing transcranial direct current stimulation (tDCS) along with a video game based training of attentional control.	Hamilton Depression Rating Scale (HAM-D), Mini-International Neuropsychiatric Interview (M.I.N.I.), Montgomery and Åsberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder 7-item (GAD-7), Rumination Response Scale, Clinical Global Impression-Severity, Clinical Global Impression-Improvement, WHO-5 well-being index, Global Assessment of Functioning Scale, Adaptive Cognitive Evaluation (ACE) battery.	No	No	No	No	No	NI	Refers to anxiety scales, but shows no results
Mariano, T. Y. et al. (2019)54	United States Of America	double-blind, placebo-controlled trial	30 (23 male; 7 female) patients with chronic low back pain	To test whether 10 daily tDCS sessions aimed to inhibit the left dorsal anterior cingulate cortex (dACC), a region strongly implicated in the affective component of pain, would produce selective reduction in pain-related symptoms.	11 point DVPRS, West Haven-Yale Multidimensional Pain Inventory (WHY-MPI-C), Roland Morris Disability Questionnaire (RMDQ) , Chronic Pain Acceptance Questionnaire (CPAQ-8), Sintomas de Ansiedade da Dor (PASS-20) , Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder scale (GAD-7), Credibility/Expectancy Questionnaire (CEQ) and Client Satisfaction Questionnaire-8 (CSQ-8)	NI	NI	NI	NI	NI	yes	To our knowledge, this is the first double-blinded RCT of multiple tDCS sessions targeting the left dACC to modulate CLBP's affective symptoms. Results are encouraging, including several possible tDCS-associated improvements. Better-powered RCTs are needed to confirm these effects. Future studies should also consider different stimulation schedules, additional cortical targets, high-density multi-electrode tDCS arrays, and multimodal approaches.
Liu, Y. et al. (2023)55	China	double-blind, placebo-controlled trial	40 students from Southwest University who were about to take the postgraduate entrance examination in China (20 males;20 females)	To investigate the effects of repeated DLPFC tDCS on attentional control in chronically stressed individuals.	Student Life Stress Inventory (SLSI), State-Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI), Positive and Negative Affect Schedule, Perceived stress scale (PSS), Positive and Negative Affect Schedule (PANAS)	No	Yes	No	No	No	yes	All in all, our study exhibited supporting evidence for potential benefits of anodal tDCS for attention control in chronically stressed individuals. Specifically, the anodal tDCS targeting the left DLPFC brain region modulated participants' moods, as shown by the reductions in perceived stress, state anxiety, and trait anxiety. In addition, the reduction in reaction time indicated an enhanced attentional control, which is also supported by the decrease in the N2 amplitudes and

the increase in the P3 amplitudes

The PRISMA flow diagrams depict the screening and article selection process (Fig. 1). Studies originated from Iran (n=9), Brazil (n=7), The United States Of America (n=7), Australia (n=3), China (n=2), India (n=2), and Australia (n=1), Belgium (n=1), Canada (n=1), Italy (n=1), Germany (n=1), Israel (n=1), Japan (n=1), Latvia (n=1), Netherlands (n=1), Turkey (n=1), and United Kingdom (n=1).

According to the Jadad scale, 34 RCTs included (77,1%) were high-quality studies. Table 2 shows the score of each subitem of the Jadad scale for the RCTs included.

Table 2: Jadad Scale

	Author (year)	randomization		blinding		Withdrawals and dropouts		
		Was the study described as randomized?	Was the method of randomization appropriate?	Was the study described as blinding? a	Was the method of blinding appropriate?	Was there a description of withdrawals and dropouts?	**Total Score**	Decrease in anxiety
22	Dutra, L. R. D. V. *et al.* (2020)	1	1	1	1	1	**5**	Yes
23	Garcia, S. *et al.* (2020)	1	1	1	1	1	**5**	No
24	Gibson, B. C. *et al.* (2021)	1	1	1	1	1	**5**	**y**
25	Clarke, P. J. F. *et al.* (2020)	0	0	1	1	1	**3**	No
26	Cobb, A. R. *et al*. (2021)	1	1	1	1	1	**5**	y
27	Ney, L. J. *et al.* (2021)	1	1	0,5	0	1	**3,5**	y
28	Movahed, F. S. *et al.* (2018)	1	1	0,5	0	0	**2,5**	Yes
29	Ahmadizadeh, M. J. et al. (2019)	1	1	1	1	1	**5**	Yes
30	Azmoodeh, S. et al. (2021)	1	1	0	0	1	**3**	y
31	Bornheim, E. *et al*. (2020)	1	1	1	1	1	**5**	Yes
32	De Doncker, W.et al. (2021)	1	1	1	1	1	**5**	unclear
33	de Lima, A. L. *et al.* (2019)	1	1	1	1	1	**5**	No
34	Jafari, E. *et al*. (2021)	1	1	1	0	1	**4**	Yes
35	Kumari, B. et al. (2023)	1	1	0,5	1	1	**4,5**	Yes
36	Marcolin, K. A. S. *et al.* (2020)	1	0	1	0	1	**3**	Yes
37	McAleer, J. *et al.* (2023)	1	1	1	0	0	**3**	Not infomed
38	Naeim, M.et al. (2021)	1	0	0	0	0	**1**	Not infomed
39	Nejati, V. *et al.* (2021)	1	1	0,5	1	1	**4,5**	uncler
40	Nikakhlagh, S. *et al.* (2023)	1	1	1	0	0	**3**	Yes
41	Nishida, K. *et al.* (2021)	1	0	1	0	1	**3**	y
42	Paula, T. M. H. *et al.* (2023)	1	1	1	1	1	**5**	Yes
43	Pinto, A. C. P. N. *et al.* (2021)	1	1	1	1	1	**5**	Not infomed
44	Singh, S. *et al.* (2021)	Pilot study	0	0	0	0	**0**	y

45	Smits, F. M. *et al.* (2021)	1	1	1	1	1	**5**	no
46	Szeremeta, E. M. *et al.* (2023)	1	1	1	1	0	**4**	Yes
47	Wang, Y. *et. al* (2022)	1	1	1	1	0	**4**	Yes
48	Loreti, E. H. *et al.* (2023)	1	1	1	1	1	**5**	Not infomed
49	Brooks, H. *et al.* (2021)	1	1	1	1	1	**5**	y
50	Quinn, D. K. *et al.* (2020)	1	1	1	1	1	**5**	Yes
51	Suen, P. J. C. *et al.* (2020)	1	1	1	1	1	**5**	no
52	Nasiri, F. *et al.* (2020)	1	1	1	1	0	**4**	Yes
53	Dechantsreiter, E. *et al.* (2023)	1	1	1	1	0	**4**	No
54	Mariano, T. Y. *et al.* (2019)	1	1	1	0	1	**4**	No
55	Liu, Y. *et al.* (2023)	1	1	0	0	0	**2**	Yes

Discussion

This systematic literature review synthesized studies that evaluated markers of anxiety in adults who used tDCS. To our knowledge, this is the first systematic review that analyzes neurobiological, physiological, and psychological markers in tDCS intervention for anxiety together. The sample characterization of each study included in this review has been summarized in detail in Table 1.

Based on the Jadad Scale (table 2), studies with scores greater than 3, only 1, despite being classified, did not mention whether randomization occurred. The study also reported no change in anxiety.

Among the four studies that scored 0.5, it was because they were single-blind studies; only one did not score above 3[27]. The main issue with single-blind studies is the potential for assessment bias by the researchers, which can influence the study outcomes. This occurs because researchers may inadvertently influence participant responses or interpret results in a biased manner due to their knowledge of the treatment group to which participants were assigned. Therefore, double-blind studies (where participants and researchers are unaware of the treatment allocation) are more robust as they help minimize assessment bias. Out of all the studies with a score greater than 3, only one did not mention whether randomization occurred despite being classified. Additionally, a study was reported that showed no change in anxiety. However, this result can be questioned since it needed to follow essential steps.

Of the four studies that scored 0.5, because they were single-blind, only one[28] did not obtain a score above 3. The main issue with single-blind studies is the potential for researchers to assess bias, which can influence the study outcomes. This occurs because researchers may inadvertently influence participant responses or interpret results in a biased manner due to their knowledge of the treatment group to which participants were assigned. Therefore, double-blind studies (where participants and researchers are unaware of the treatment allocation) are more robust as they help minimize assessment bias.

Three studies were considered low-quality (scores ≤ 3.0). One study described a fitting randomization process, with an investigator informed about participant randomization and responsible for configuring the stimulator based on

the prescribed protocols for the sham and anodal-tDCS groups. This points towards a controlled and systematic randomization approach, ensuring an unbiased distribution of participants across the different stimulation groups. However, in Liu's study[55], the issue of blinding was not explicitly addressed. Although the investigator setting up the stimulator was aware of participant randomization, there was no explicit mention of blinding for participants or data collectors.

Consequently, the study's blinding status remains unclear, lacking information to determine whether blinding measures were implemented definitively.

In the second study, a pilot study based on the provided paper, there needs to be a specific mention of the appropriateness of randomization and blinding. Without detailed information on how randomization and blinding were implemented in the specific study described in the text, it is difficult to make a direct reference to the appropriateness of these methods, and the third study excluded, the article does not provide detailed information on the randomization process and does not explicitly mention whether blinding (also known as masking) was used in the study.

As known, randomization is a crucial step in clinical trials to ensure that participants are assigned to treatment groups in an unbiased manner. Appropriate randomization methods include computer-generated randomization, block randomization, and stratified randomization. Moreover, is also essential to know who was blinded (e.g., participants, researchers, outcome assessors) and how the blinding was carried out. With specific information, it is easier to determine what measures were implemented.

Regarding the reported outcomes, tree studies did not specify whether there was a change in anxiety[37,52,53], two concluded as unclear[24,65], ten articles reported no differences in anxiety symptoms [23,25,27,28,33,35,43,45,48,51], and nineteen articles showed a decrease in signs of anxiety [22,26,29–31,36,38,40,42,44–47,49,50,52,54,55].

Out of the 34 studies analyzed, 24 showed that a sample of 1633 individuals had a session intervention time of 20 minutes. However, there is no consensus on the number of sessions [22,23,25,26,28–46]. The others were distributed between 10 minutes[27], 21 minutes[47], 26 minutes[48], and 30 minutes[24,49–51]. Therefore, it is difficult to determine the correct number of sessions for the correct treatment protocol and frequency.

It was observed that a small number of these studies had the main objective of evaluating anxiety markers in a population with anxiety disorders[28,33,39,52]. Most studies analyzed anxiety as comorbidity, and other comorbidities such as depression[35,51,53], pain[54] or fibromyalgia[48,42,54], dysmenorrhea[22], Sjögren's Syndrome[43], tinnitus symptoms[40], psychopathologies[37], stroke[31], epilepsy[30], mild traumatic brain injury[50], methadone users[38].

There was also an analysis of anxiety markers in executive and cognitive functions[23,24,27,50,53] , situations of fatigue[32], stress [45,47] and PTSD[29,36,45] , emotions[25,34,46] or phobias[26] , as well as the effects of mindfulness[41,49].

There was no uniformity in the use of scales to assess anxiety. The main tools for measuring outcomes were the State-Trait Anxiety Inventory (STAI) in eight studies, the Negative Affect Scale (PANAS) in six studies, the Beck Anxiety Inventory (BAI) in five studies, the Hamilton Anxiety Rating Scale (HAM-A) in five studies, Anxiety and Stress Scales (DASS-21) in four studies, and Anxiety and Stress Scales (DASS-21) in four studies and Positive and.

Previous studies have explored the use of HRV as a biomarker of depression and anxiety in patients was lower than that of healthy controls[56–58] and some standard waves in electroencephalography (EEG) are localized in some brain areas. However, in this review, only two studies were included to analyze HRV[37,46].

Although HRV has been examined in the context of anxious symptomatology and attentional bias, some research has found that tDCS targeting prefrontal areas can affect HRV. However, no such effects were found in Szeremeta's study[46]. Inspection of the HRV data revealed significant noise, which may have contributed to the lack of results. In the McAleer study[37], participants receiving tDCS displayed few significant changes in HF-HRV and no significant changes in RMSSD-HRV.

Studies refer to the identification of signs of depression and anxiety through EEG[59,60]. Two studies used EEG as a marker[55,61] . One study[55] shows that anodal tDCS stimulation enhances cognitive processing efficiency, selective attention, and possible improvement in response capability. The study also revealed a correlation between variations in P3 component amplitudes in EEG were negatively associated with scores on the Perceived Stress Scale (PSS), suggesting that improvements in stress were linked to a more efficient allocation of attention resources, as reflected

by the negative changes in P3 component amplitudes. In another study[41] , the association between anxiety and neurophysiological was examined, and a correlation was observed between the ratios of change in STAI scores. These results suggest a complex relationship between anxiety and neurophysiological activity measured by EEG.

As known, individuals suffering from anxiety disorders can exhibit elevated circulating levels of inflammatory markers, such as cortisol[62,63] and Interleukin-6[63,64]. In this review, one study has referred to IL-6(IL-6) studies [47], and two studies linked cortisol to anxiety[43,47].

Conclusions

The international scientific community acknowledges the importance of generating high-quality evidence on clinical neuromodulation techniques, including transcranial Direct Current Stimulation (tDCS). In this systematic review, our main findings suggest that while some studies point to a potential positive effect of tDCS in reducing anxiety in adults and improving conditions such as subjective pain, depression, cognitive processes, and Post-Traumatic Stress Disorder (PTSD), this potential is currently limited by the quality and heterogeneity of the available evidence.

Despite promising results in some studies, the presence of bias and methodological concerns in other works underscore the urgent need for more specific and standardized investigations. The lack of uniformity in intervention parameters (such as the number and duration of sessions) and the scarcity of robust sample sizes hinder the consolidation of clear evidence regarding the effects of tDCS. This is particularly evident in the relationship between neurobiological markers like cortisol and Interleukin-6 and anxiety reduction through tDCS.

Markers such as Electroencephalography (EEG) and Heart Rate Variability (HRV) are believed to be applicable as anxiety markers. However, our review highlights the need for further studies to consistently establish the relationship between these markers and the use of tDCS in anxiety interventions**.**

Therefore, developing a specific and standardized protocol for tDCS intervention would be highly beneficial, ensuring uniformity in all evaluation and comparison parameters. This, in turn, would lead to more robust and conclusive results.

The existing evidence is not sufficient to indicate the efficacy of tDCS in medium to long-term follow-up, and future research is crucial to alter this situation. Consequently, customization of the research model for anxiety investigations is a possibility to be explored. We hope these results provide valuable information for clinicians and contribute to thoughtful reflections for establishing a protocol of parameters for comparison.

As suggested by Valiengo and colleagues[66], more studies are needed to show evidence of the benefits of tDCS in GAD patients.

Limitations

The findings from this research should be interpreted considering its limitations. We did not search for unpublished manuscripts and/or grey literature, which may increase publication bias in our review.

Several limitations are acknowledged in the present review. First, the level of heterogeneity was high; this was attributed to the use of different adjustment factors across the studies, such as a varying study methodology, sample sizes, and markers.

Future directions

The results obtained in this synthesis highlight the need for methodologically more robust studies to identify biological, physiological, cognitive, and psychological measurement methods in interventions with tDCS.

This review confirmed the idea of carrying out a project including several measurement measures in the same study. That reinforces the study being carried out with a group of researchers, where the authors are included.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki.

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Appendix A. Supplementary material- Table 1

The Supplementary Material for this article can be found online at: https://docs.google.com/spreadsheets/d/1-zb0g7I-aReFcV3Z1ZQUINJ3KzRxKXZg/edit?usp=sharing&ouid=108746755103962240531&rtpof=true&sd=true

Appendix B. Supplementary material- PRISMA 2020 Checklist

The Supplementary Material for this article can be found online at:

https://docs.google.com/document/d/10DgX0fcXgyjtxQ0lYUfkH2ZVUeA-dDpT/edit?usp=sharing&ouid=108746755103962240531&rtpof=true&sd=true

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Appendix B. Supplementary material- PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1-2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	1
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	2-3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Appendix A
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	4-6

PRISMA 2020 Checklist			
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4 ; Appendix A
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	3-4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	3-4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	3-4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	2-4

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16 a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	4-5
	16 b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	4-5
Study characteristics	17	Cite each included study and present its characteristics.	4-5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	5
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20 a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20 b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20 c	Present results of all investigations of possible causes of heterogeneity among study results.	

	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	5
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	4-5
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	6
	23b	Discuss any limitations of the evidence included in the review.	6-7
	23c	Discuss any limitations of the review processes used.	7
	23d	Discuss implications of the results for practice, policy, and future research.	6
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	2
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	8

Competing interests	26	Declare any competing interests of review authors.	8
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	8

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Apendix_A-Suplementary Material Table 1- Articles analyzed in the study

Author (year)	Country	Method	Clinical Trials	Aims	Sample	Age control / sham	Number of Sessions	Time for sessions (minutes)	Week days	Device	Instruments	HRV	EEG	Initial interleukin-6	final Interleukin-6	Cortisol	Decrease in anxiety	Conclusion
Dutra, L. R. D. V. et al. (2020)22	Brazil	double-blind, placebo-controlled trial	registered on Rebec (Brazilian platform of clinical trials) (identifier RBR-77Z6Q8)	To determine whether tDCS could offer clinical benefits on pain, anxiety, affectivity, and	26 women with the diagnosis of primary dysmenorrhea	Active = 26.1 ± 3.8 Sham = 21.0 ± 2.1	5	20	5	(DT832; WeiHua Electronic Co. Ltd, China)	Hamilton Anxiety Scale (HAS), Positive and Negative Affect Schedule, The Six-Minute Walk Test (6MWT),	No	No	No	No	No	Yes	Anodal tDCS over the left DLPFC seems to be an effective therapeutic approach

				functionality in women with primary dysmenorrhea.							Numeric Rating Scale for Pain							for improving anxiety and functional capacity in patients with primary dysmenorrhea. Although painful symptomatology decreased, no significant effects were

																		seen between groups.
Garcia, S. et al. (2020)23	United States Of America	double-blind, placebo-controlled trial	NI	To investigate the use of transcranial direct current stimulation (tDCS) on both common anxiety symptoms	143 undergraduate students with and without a history of anxiety disorder diagnoses were recruited for	(mean age = 19.45, SD = 1.76; 69% female) Anodal = 19.38 (1.16) Active = 19.74 (2.62) Sham = 19.25 (1.10)	1	20	1	Soterix Medical Inc.	State Trait Anxiety Inventory (STAI); GAD-7; Rey-Osterreith Complex Figure Task; Wisconsin Card Sorting Task	NI	NI	NI	NI	NI	No	Overall, results suggest that while anodal stimulation of the lDLPFC may benefit cognitive abilities for this

				and executive function abilities in a college aged sample.	this study.													population, targeting psychological symptoms of anxiety likely requires stimulation over other cortex, possibly right DLPFC. Further, the use of tDCS, wheth

																		er active or sham, may be distressing to patients.
Gibson, B. C. et al. (2021)24	United States Of America	double-blind, placebo-controlled trial	NI	To explore the extent to which differences in state anxiety and related measures affect visual attention	54 healthy individuals	23,20 (8,34)	1	30	1	ActivaDoseII	short form of the Profile of Mood States (POMS), Remote Associates Test (RAT), Remote Associates Test (RAT)	NI	NI	NI	NI	NI	It cannot be ruled out, and may even be likely, that trepidation abo	These results indicate that anxiety can influence the quality of subjects' attention at the onset of the task

				and category learning, both with and without the influence of tDCS.													ut tDCS itself was the driving force behind individual differences in state anxiety and not pre existing	and that these attentional differences can influence tDCS-mediated category learning during the rapid assessment of visual scenes. These findings have implic

																	differences.	ations for understanding the complex interactions that give rise to the variability in response to tDCS.
Clarke, P. J. F. et al. (2020)[25]	Australia	double-blind, placebo-controlled trial	NI	To assess the impact of tDCS on worry in terms of its imme	75 (female) healthy participants	Active Mindful-focus = 21.72 Active Mind-wandering = 22.64 Sham Mindful-focus	1	20	1	NI	DASS e STAI-S	NI	NI	NI	NI	NI	No	Active tDCS was associated with significantly greater elevat

				diate effects on negative intrusive thoughts and worry-related emotional reactivity. Secondly, to examine whether concurrent engagement in a mindf		= 23.74 Sham Mind-wandering = 36.8												ion in anxiety in response to the worry induction. No effects were observed on the frequency of negative thought intrusions, and the combined delivery of tDCS with

				ul task during tDCS delivery would further augment any observed effects.														the concurrent mindful task did not alter the pattern of observed effects. While inviting replication in a high anxious sample, the present results

																		highlight the possibility that tDCS may interact with motivated engagement in negative patterns of cognition, such as worry, to produce greater emoti

																		onal reactivity.
Cobb, A. R. et al. (2021)[26]	United States Of America	double-blind, placebo-controlled trial	NCT03095482	To preliminarily test whether excitatory tDCS of left mPFC and inhibitory tDCS of right dlPFC accelerates responding	49 healthy participants with marked fear of snakes, spiders, and/or contamination-related	mean age=21.41, SD=7.12	1	20	1	foc.us, Model V2	DMQ = Demographics and Medical Questionnaire; MINI-5= Mini International Neuropsychiatric Interview, Version 5; ADIS-5 =	NI	NI	NI	NI	NI	Yes	This investigation provides novel preliminary support for the use of tDCS to enhance in vivo exposure. Along with

				and improves outcomes from a single session of in vivo exposure in a transdiagnostic sample with marked arachnophobic, ophidophobic, and contaminati	threats						Anxiety and Related Disorders Interview Schedule for DSM-5 Disorders; C-SSRS = Columbia Suicide Severity Rating Scale; CLQ = Claustrophobia Questionnaire; FSQ = Fear of Snakes and							other emerging neuromodulation approaches to enhance extinction learning, the present results are encouraging. The most remarkable pattern across study findin

				on-related fear. Also, to test the prediction that the effects of facilitating therapeutic learning should depend on qualities of that learning, in terms of emotional,							Spiders; Questionnaire; OCI-R = ; experiential avoidance (EA; BEAQ), general anxiety (BAI), and depression (BDI-II).							gs suggests tDCS may promote good clinical outcomes despite the presence of several negative prognostic indicators. In sum, active tDCS was found to

				cognitive, and behavioral reactions to feared targets and to test whether several negative prognostic indicators moderate tDCS augmentation effects.														especially benefit individuals with more severe phobic symptoms and elevated fearful reactivity to anxiety, as well as individuals who exhibited persistent

																		emotional distress and threat-related beliefs about feared targets at the last exposure trial. These results should be interpreted cautiously due to the preli

																		minary nature of this investigation. However, replication with larger and more severe clinical samples, and parallel efforts to optimize dosing parameters

																		appear warranted. tDCS and other neuromodulation technologies have clear therapeutic potential for patients who are otherwise refractory to standard exposure-

																		based interventions.
Ney, L. J. et al. (2021)[27]	Australia and Italy	single-blinded	NI	To investigate whether tDCS immediately following extinction learning improves efficacy of extinction memo	30 healthy participants	Active = 24,1 (SD 5.5); Sham= 25,1 (SD 8.9)	1	10	1	DC-Stimulator Plus, NeuroConn, Ilmenau, Germany	Depression, Anxiety and Stress Scales (DASS-21), Alcohol Use Disorder Identification Test (AUDIT), Skin Conductance Respon	No	No	No	No	No	No	Participants in the tDCS group showed impaired fear extinction retention on day 2, marked by significant generalisation of

				ry retention.							se (SCR)							fear to the safety stimulus. This contrasts with earlier studies showing improved extinction retention when stimulation occurred during encoding of extinction

																		learning, compared to immediate consolidation as in our study. These findings may have important implications for the use of tDCS during exposure therapy for

																		anxiety and trauma disorders.
Movahed, F. S. et al. (2018)[28]	Iran	single-blind, placebo-controlled trial	No	To conduct an experimental design using tDCS on reduction of depressive and anxiety symptoms, and worry in	18 Adults with GAD!! (46% female; 64% male = +100%)	Mean = 28,7 (9,6)	10	20	NI	NI	GAD-7; Hamilton anxiety rating scale (HARS); Hamilton depression rating scale (HDRS); Penn state worry questionnaire (PSWQ)	NI	NI	NI	NI	NI	No	The tDCS is a promising treatment for generalized anxiety disorder, especially in depressive and worry symptoms.

				patients with generalized anxiety disorder (GAD).							avaliação de depressão de Hamilton (HDRS)							
Ahmadizadeh, M. J., Rezaei, M., & Fitzgerald, P. B. (2019)29	Iran	double-blind, placebo-controlled trial	NI	To examine the efficacy of tDCS for PTSD and its sub-sympt oms.	40 Adults with PTSD (26 female; 14 males)	Active = 44,5(2.34) Sham = 43 (2.42)	10	20	7	DC-Stimulator-Plus, NeuroConn	Posttraumatic stress disorder checklist for DSM-5 (PCL-5); Beck Depression Inventory-II (BDI-II); Beck Anxiety	NI	NI	NI	NI	NI	yes	This study supported the efficacy of 10 sessions of bilateral DLPFC tCDS delivered at 2 mA for the

											Inventory (BAI)							treatment of PTSD symptoms. Taken together, these findings suggest that although tDCS can reduce PTSD symptoms, researchers should consider the different

																		types of PTSD and use strategies to ensure sufficient power to detect a potential effect of tDCS on various types of PTSD.

Azmoodeh, S., Soleimani, E., & Issazadegan, A. (2021)30	Iran	randomized clinical trial	IRCT20190803044417N1	To examine the effects of transcranial direct current stimulation (tDCS) on the psychological profile of patients with epilepsy.	30 pacientes with epilepsy	38.13± 9.14- Intervention 34.73± 9.26 - control	10	20	5 after 3	NI	DASS-21	NI	NI	NI	NI	NI	NI	Yes	The results showed that tDCS could reduce depression, anxiety, and stress with the changes caused in the brain system.

Bornheim, E. et al. (2020) [31]	Belgium	double-blind, placebo-controlled trial	B707201629972	To measure the effects of tDCS on functional and sensory outcomes throughout the first year post onset of stroke.	50 acute stroke patients aged between 18 and 80 years old, presenting their first ever symptomatic ischemic stroke confirmed by CT or	Active = 62,48 (±11,86) Sham = 63,48 (±12,94)	20	20	5	NE STAR STIM tCS®	Wolf Motor Function Test, Semmes Weinstein Monofilament Test, Upper Extremity Section (UEFM), Lower Extremity section (LEFM), Somatosensory section do Fugl Meyer Test, Tardieu Spastic	NI	NI	NI	NI	NI	yes	tDCS seems to be an effective adjuvant to conventional rehabilitation techniques. If applied in the acute stages of stroke, functional recovery is not only

					MRI were eligible for the study (33 female; 17 male)						ity Scale, Stroke Impact Scale (SIS), Hospital Anxiety and Depression Scale (HADS) e Barthel Index.							accelerated, but improved, and results are maintained up to one-year post stroke
De Doncker, W., Ondobaka, S., & Kuppuswamy, A. (2021)[32]	United Kingdom	double-blind, placebo-controlled trial	NCT04634864	To assess whether fatigue symptoms can be reduced by increasing	30 Adults - Post-stroke after 3 months	56.95 (13.17) Active 59.83 (11.66) - Control	1	20' 1mA0 + 20' 2mA	1	DC-Stimulator Plus, NeuroConn, Alemanha	FSS-7, VAS, EMG, The Hospital Anxiety and Depression Scale	NI	NI	NI	NI	NI	Unclear	A single session of anodal tDCS improves fatigue symptoms with

				cortical excitability using anodal transcranial direct current stimulation (tDCS).														the effect lasting up to a week post stimulation. tDCS may therefore be a useful tool for managing fatigue symptoms post-stroke.

de Lima, A. L. et al. (2019)[33]	Brazil	double-blind, placebo-controlled trial	RBR-5QJG9T	**To evaluate the effect of anodal tDCS over DLPFC on anxiety and on the level of stress, depression and positive/negative affectivity.**	30 adults with GAD	Active = 32,07 (6,5) Sham = 29 (5,05)	5	20	5	NI	Hamilton Anxiety Rating Scale and the Beck Anxiety Inventory, the Lipp Inventory of Stress Symptoms for Adults, Positive and Negative Affect Schedule, and the Beck Depression Invento	NI	NI	NI	NI	NI	No	Five sessions of anodal tDCS along the DLPFC did not improve key outcomes for patients with GAD, although physical stress symptoms improved. The

											ry (BDI).							role of tDCS in GAD should be explored in larger patient samples using different parameters.
Jafari, E. et al. (2021)[34]	Iran	double-blind, placebo-controlled trial	IRCT20181013041327N2	To determine whether modulation of the dorsolateral and media	45 patients with SAD	18-50 mean age 32,36 +- 6,991ma = 32.83(7,46) 2ma = 33.66(6.19) sham =	14	20	7	Neuro Stim	Liebowitz Social Anxiety Scale (LSAS), Penn State Worry Questionnaire (PSWQ	NI	NI	NI	NI	NI	Yes	Modulation of lateral-medial PFC activity with intensified stimul

				l PFC activity with a novel intensified stimulation protocol reduces SAD core symptoms, improves treatment-related variables, and reduces attention bias		30.58(7.46)					), Beck Depression Inventory-II (BDI-II), Difficulties in Emotion Regulation Scale (DERS) , WHOQUL questionnaire, paradigma dot-probe							ation can improve cognitive control, motivation and emotion networks in SAD and might thereby result in therapeutic effects. These effects can be larger

				to threatening stimuli.														with 2-mA vs 1-mA intensities, though a linear relationship between intensity and efficacy should not be concluded. Our results need replication in larger trials.

Kumari, B. et al. (2023)[35]	India	simple-blind, placebo-controlled trial	CTRI/2022/01/039123	To compare the change in Hamilton Depression Rating Scale (HAM-D) scores with an early, add-on tDCS versus sham tDCS in patients with major depre	50 adults with depression	Active = 32.31 (11.57) SHAM = 29.08 (9.79)	10	20	5	Neurostim by Neurosoft)	Hamilton Depression Rating Scale (HAM-D), Beck's Depression Inventory (BDI), and Hamilton Anxiety Rating Scale (HAM-A)	NI	NI	NI	NI	NI	No	The study revealed a significant reduction in symptom severity with tDCS augmentation implying beneficial aspects of tDCS as an early augmentation strategy in

				ssive disorder. Also, to compare the rates of tDCS related side effects between the active and sham tDCS group.														drug-free patients of moderately severe depression. The tDCS application hastens the process of reduction in depressive and anxiety symptoms. The side effects associ

																		ated with tDCS were usually of mild to moderate intensity, and tDCS was well tolerated. The findings from our study support the use of tDCS along with medic

																		ations as an augmentation strategy early in the intervention process for moderate to severe depressive episode. However, the beneficial effects of tDCS may be time-

																			limited. Increasing the number of tDCS sessions or incorporating the strategy of booster sessions may prolong the benefits; further studies are warranted to

																		analyze this.
Marcolin, K. A. S. et al. (2023)[36]	Brazil	clinical trial	registered in The Brazilian Clinical Trials Registry (ReBEC) under number RBR-2qpv74b	To present a clinical trial study conducted in patients with PTSD caused by the KISS nightclub fire disaster	8 Patients over 18 years of age diagnosed with PTSD without complete remission of symptoms	30,88 ± 7,74	10	20	7	Striat; Ibramed, Amparo	The Post-Traumatic Stress Disorder Checklist, Civilian version (PCL-C), The Montreal Cognitive Assessment (MoCA), The Hamilt	No	No	No	No	No	Yes	Despite decrease over time, improvement in post-traumatic stress disorder, depression and anxiety symptoms

				who, being unresponsive to pharmacological therapy, underwent tDCS treatment.							on Depression Rating Scale (HAM-D) and The Hamilton Anxiety Rating Scale (HAM-A)							was maintained throughout the first month after treatment. Transcranial direct current stimulation adjuvant can be an alternative treatment to refractory post-traum

																		atic stress disorder, either as monotherapy or as treatment enhancement strategy. They can also be an option for patients who do not want or do not tolerat

																		e pharmacological management.
Mc Aleer, J. et al. (2023)[37]	United States Of America	double-blind, pseudo-counterbalanced design; pilot study	no	To analyze the effects of dlPFC-targeting tDCS and offset (180-degree phase difference in stimulating electr	29 volunteers with depression and/or anxiety, confirmed via psychiatric evaluation by a board-	29.85 ± 10.8	3	20	1	Pulvinar Neuro, LLC, Chapel Hill, NC	DASS-21	Yes	Yes	no	no	no	NI	tACS appears to increase ER capacity as reflected in increased HRV in individuals with internalizing psychopathologie

				odes) theta-tACS on emotion regulation in individuals with internalizing psychopathologies (IPs), measured by analyzing changes in their heart rate variability	certified psychiatrist (>23 on the Depression Anxiety Stress Scale, DASS-21)													s, particularly after two sessions of stimulation. This study adds validity to the use of tACS as a neuromodulatory technique in cognitive and clinical research. Additi

				(HRV) in the context of repeated emotion regulation tasks.														onal research is required to better understand potential carry-over effects of multiple sessions of stimulation.
Naeim, M., Rezaeisharif, A., & Moghadam,	Iran	double-blind, placebo-controlled trial	IR.ARUMS.REC.1398.558	To evaluate the effectiveness of transcranial direct curren	60 methadone users who had severe depression	age range of 20 to 50 years	10	20	3	Não informado	Beck's depression inventory, Berger's test	NI	NI	NI	NI	NI	Yes	It seems that the method of tDCS can reduce the severi

S. A. (2021)38				t stimulation (tDCS) on depression and anxiety in methadone users.	and anxiety.													ty of symptoms of depression and anxiety. Therefore, it can be claimed that this intervention can be considered by experts as a complementary intervention along

																		with other psychological and pharmacological treatments.
Nejati, V. et al. (2021)39	Iran	randomized, single-blinded, and complete crossover design	NI	To explore the causal contribution of the dorsolateral and ventromedial prefrontal cortices (dlPFC, vmPFC) on	34 adults with GAD, with an age range between 20 and 45 years;19 females,	26.26 (mean)	5	20	1	Activa Dose (ActivaTek Inc., EUA)	The state-trait anxiety inventory (STAI), Dot probe task, Reading mind from eyes test (RMET)	NI	NI	NI	NI	NI	NI	As suggested by the results of this study, both dlPFC and vmPFC are involved in cognitive bias in GAD, but

				cognitive bias via non-invasive brain stimulation.														with partially different roles. Anodal stimulation over the right vmPFC and the left dlPFC reduced attention bias, supporting the relevance of these areas for

																		attention bias. For interpretation bias, the significant effect of anodal dlPFC/cathodal vmPFC stimulation, but only trend wise effect of anodal tDCS

																		over the dlPFC combined with an extracephalic return electrode is in accordance with a predominant effect of the dlPFC on interpretation bias, but does not

																		rule out an additional minor involvement of the vmPFC. Based on these results, a new model is suggested for the neural underpinnings of anxiety symptoms.

Nikakhlagh, S. et al. (2023)[40]	Iran	double-blind, placebo-controlled trial	IRCT registration number: IRCT20210429051130N1	To evaluate the therapeutic effects of repeated sessions of anodal bifrontal tDCS on tinnitus symptoms. Furthermore, the tDCS impacts on the comorbid	42 right-handed participants with normal hearing sensitivity, who reported a chronic tinnitus lasting for at least 12 months	46.38 ± 7.16(active); 46.19 ± 9.23(sham)	24	20	6	OASIS Pro™ DC-Stimulator (Mind Alive Inc., Edmonton, Alberta, Canada).	Tinnitus Handicap Inventory (THI), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI)	No	No	No	No	No	Yes	Our findings indicated that THI score, depression and anxiety level has been gradually diminished across subsequent measurement intervals. We also find

				depression and anxiety of the patients were investigated.														significant reduction of distress-related tinnitus in the real-tDCS group after treatment. We conclude that application of tDCS to the bilateral DLPFC region

																		alleviates chronic tinnitus and it should be considered in patients with refractory tinnitus.
Nishida, K. et al. (2021)[41]	Japan/Germany	randomized clinical trial	NI	To augment the effects of mindfulness, suggested for	58 healthy participants (n=28-active; 30 sham)	38.29 (11.34) active 40.59 (9.27)control	1	20	1	DC Stimulator Plus; NeuroConn	STAI, the Positive and Negative Affect Schedule (PANAS)25, the	No	Yes	NI	NI	NI	Yes	The results of this study revealed an interaction effect betwe en

				reducing anxiety, with concurrent use of tDCS.							Schedule for the Evaluation of Individual QoLDirect Weighting (SEIQoL-DW)26, and the Five Facet Mindfulness Questionnaire (FFMQ)							tDCS and time, and that SA-STAI scores were significantly decreased at 1 week after active tDCS. Furthermore, we found that the actual density of alpha activity in the

																		rACC was significantly decreased only in the active tDCS group, and this reduction was significantly greater in the active group than in the sham tDCS group.

Paula, T. M. H. et al. (2023)[42]	Brazil	double-blind, placebo-controlled trial	NCT0450225	To investigate the analgesic and neuromodulatory effects of previous treatment with LDN combined with anodal tDCS in women with fibromyalgia.	86 women with fibromyalgia (18-65)	LDN+ETCC = 49,74 ± 1,97 LDN+SHAM = 48,09 ± 1,56 Placebo+ACTIVE = 50,57 ± 2,23 Placebo+SHAM = 48,95 ± 2,08	5	20	5	NI	sociodemographic, Visual Analog Pain Scale (VAS), Pain Catastrophizing Scale (PCS), State-Trait Anxiety Inventory (STAI), Fibromyalgia Impact Questionnaire (FIQ), Beck Depression Invento	No	No	No	No	No	Yes	Combined LDN+tDCS has possible benefits in reducing pain frequency and intensity;

											ry (BDI-II), Profile of Chronic Pain Scale (PCP:S), Pain Pressure Threshold (PPT), and Conditioned Pain Modulation (CPM).							
Pinto, A. C. P. N. et al. (2021)[43]	Brazil	Randomized Controlled Trial (piloto)	NCT04119128	To evaluate the effect of a tDCS protocol on	36 Women aged 18–65 years with pSS,	55,8 ± 8,5 (Active) 53,1 ± 10,3(Sham)	5	20	5	Neuroconn GmbH, Ilmenau, Germany	Fatigue Severity Scale (FSS), Profile of Fatigue and Discom	No	No	No	No	Yes	No	tDCS seems to be safe and reduce fatigue in

				fatigue in patients with primary Sjögren's Syndrome (pSS)	on stable pharmacological therapy for least three months, with complaints of fatigue for at least three months.						fort - Sicca Symptoms Inventory (PROFAD-SSI), EULAR Sjogren € ’s Syndrome Patient Reported Index (ESSPRI), ShortForm 12 Health Survey (SF-12), Pittsburgh Sleep Quality							pSS. A differential effect on pain and sleep may underlie its effects. Further studies are needed to optimise tDCS treatment strategies in pSS

											Index, Beck Depression Inventory (BDI), Elecsys Cortisol II assay kit.							
Singh, S. et al. (2021)[44]	India	Pilot Study - prospective interventional study	NI	To study the effect of tDCS as an augmentation strategy in depression and its various sympt	35 patients diagnosed with depressive disorder (based on CID-10) who showed inadequate	37.42 years, ranging 19–67 years	20	20	2 weeks	FOCUS V2	Hamilton Rating Scale for Depression-17 items (HAM-D)	No	No	No	No	No	Yes	tDCS increase improves depressive sympt oms in the short term. Almost all domains or variables of depre

				om domains.	improvement on antidepressant selective serotonin reuptake inhibitors													ssive symptomatology responded to tDCS in our sample. In clinical practice, this may help reduce sequential trials of multiple antidepressants or adjuvant

																		drugs and avoid their costly side effects, thereby providing a safer alternative modality for treating depression. However, the open-label nature, absence of a

																		control group, modest sample size, lack of uniform doses of antidepressant treatment, and lack of long-term evaluation of outcome measures are

																		limitations that restrict the generalizability of this study.
Smits, F. M. et al. (2022)[45]	Netherlands	double-blind, placebo-controlled trial	NL5709	To replicate tDCS-enhanced inhibitory control training in a clinical sample and test whether this reduc	100 active-duty military personnel and post-active veterans with PTSD, anxiety, or impulsive	Active = 40.5 (10.6) SHAM = 44.4 (9.4)	5	20	1-5 days between sessions	neuroConn DC-stimulator Plus	Stop-signal response time (SSRT), Bochum Emotional Stimulus Set (BESST), Implicit association task (IAT), PTSD	No	No	No	No	No	No	The current RCT in military patients with stress-related symptoms provides no evidence for short-term

				es stress-related mental health symptoms.	aggression symp-toms						Checklist for DSM-5, the trait version of the positive and negative affect schedule (PANAS), STAXI-2, Beck Depression Inventory 2nd edition (BDI-II), Outcome Questionnaire 45 (OQ45)							or long-term benefits of 5 sessions of 20-min tDCS targeting the right IFG at an intensity of 1.25 mA combined with response inhibition training, on inhibitory

											, Dutch version of the childhood trauma questionnaire short form (CTQ-SF) and Barrett's Impulsivity Scale (BIS-11)							control or PTSD, anxiety, and impulsive aggression symptoms. For these patients, tDCS may be more effective in higher doses (e.g. higher current density, more

																		sessions) or when combined with emotionally challenging tasks or psycho-therapy. Gaining insight in determinants of tDCS efficacy and convenient brain target

																		s for neuromodulation in stress-related disorders will allow the tailoring of future tDCS interventions.
Szeremeta, E. M. et al. (2023)46	Australia	double-blind, placebo-controlled trial	no	To examine the effects of tDCS to the left DLPFC on attenti	101	M*age* = 22.57, *SD* = 5.60; 66.33% female	1	20	1	Chattanooga dual channel iontophoresis system [	Positive and Negative Affect Schedule (PANAS); STAI-S;	Yes	no	no	no	no	Yes	We found no evidence of tDCS-induced effects on attenti

				onal bias towards both negative and positive information, as well as its effects on both negative and positive emotional reactivity in response to emoti							DASS-21; IDATE-S							onal bias towards either negative or positive information, with Bayesian analyses suggesting more evidence in favour of the absence of such effects in the

				onal content.														present study. However, though results should be treated as preliminary, we found some evidence that tDCS may enhance emotional regulation that is aligne

																		d with intent, and may increase positive mood. These findings provide some support for effects of left frontal tDCS stimulation on emotional regulation

																		and positive effects on overall mood.
Wang, Y. et. al (2022)47	China	double-blind, placebo-controlled trial	his study was supported by the National Natural Science Foundation of China grant (32071078), The Research Program Fund of the Collaborative Innovation Center of Assessment toward Basic Education Quality at Beijing Normal University (2018-05-009-BZPK01, 2020-05-009-BZPK01, 2021-05-009-BZPK01), Fundamental Research Funds for the Central Universities (GK201902011, 2019TS140, 2021CSWY022, 2021CSWY023), Innovation Capability Support Program of Shannxi Province (2020TD-037	To investigate whether one single session of tDCS could reduce creativity impairments induced by acute stress, and	70 healthy female students	19,6 (1,55)	1	21	1	DC-STIMULATOR MC	Stai-T ; BDI-II; PANAS ;Stai-S ; Trier Social Stress Test (TSST)	Yes	Yes	Yes	NI	Yes	Yes	Results showed that R+L □ stimulation facilitated the recovery of anxious state compared to sham stimulation.

				whether the effect of tDCS on creativity performance is partially mediated by the recovery of the stress response.														We also found that the decreased value of AUT scores after stress in the R+L group was significantly lower than that in the sham group. Moreover, further analys

																		is revealed state anxiety mediated the effect of tDCS on the flexibility component of the AUT. We concluded that bilateral tDCS over the DLPFC is efficie

																		nt in alleviating stress-induced creativity impairment, which may correlate with greater recovery of state anxiety. Our findings provide causal evidence for the

																		neurophysiological mechanisms by which stress affects creativity, as well as clinical suggestions for stress-related psychiatric disorders prevention and

																		intervention.
Loreti, E. H. et al. (2023)48	Brazil	randomized clinical trial	Brazilian Registry of Clinical Trials identifier: RBR-8wc8rjq	To analyze the effects of ten sessions of active transcranial direct current stimulation transcranial direct current stimulation	35 women with FM	41.17 ± 11.305	10	26	NI	conventional tDCS device	Fibromyalgia Impact Questionnaire, Hamilton Anxiety Rating Scale, Hamilton Depression Rating Scale, World Health Organization's Quality	No	No	No	No	No	No	The active tDCS group showed improvement in pain after ten sessions ($p < 0.001$), after 30 days ($p < 0.01$), and after

				(tDCS) (2 mA) with 13:20: 13 stimulation at M1 in women with fibromyalgia (FM).							of Life Questionnaire, and Fatigue Assessment Scale							90 days ($p < 0.001$) compared with sham tDCS. In addition, improvement in quality of life (QoL) and fatigue was observed in the active tDCS group. The results of

																		this study suggest that active tDCS with an intensity of 2 mA for ten sessions was effective in decreasing pain and fatigue and improving QoL in patients

																		with FM.
Brooks, H. et al. (2021)49	Canada/ United States Of America	double-blind, placebo-controlled trial	NCT03653351 and NCT03680664	To assess the feasibility of combining Mindfulness-Based Stress Reduction (MBSR) with transcranial direct curren	36 individuals with subjective cognitive complaints and symptoms of depression and/or anxiety were	Active = 68.3 (5.9) SHAM = 69.0 (5.0)	40	30	5	Magstim/Neuronika HDC-Kit	Fluid Cognition Composite do National Institutes of Health (NIH) Toolbox Cognition Battery, The Cognitive Affective Mindfu	NI	NI	NI	NI	NI	Yes	Our findings suggest that it is feasible and safe to combine tDCS with MBSR in older depressed and anxious

				t stimulation (tDCS) to increase putative benefits of MBSR for cognitive function and everyday mindfulness in depressed or anxious older adults with	randomized to active (*n* = 12) or sham tDCS (*n* = 14).						lness Scale (CAMS-R) e the 8-item short form v2.9 PROMIS Scale for Satisfaction with Social Roles and Activities and the 8-item short form v2.0 PROMIS Ability to Particip							adults, including during remote, at-home use. Furthermore, tDCS may enhance MBSR via transferring its meditative learning and practice into increa

				subjective cognitive decline.							ate in Social Roles and Activities							ses in everyday mindfulness. Future studies need to improve adherence to MBSR with tDCS.
Quinn, D. K. et al. (2020)50	United States Of America	double-blind, placebo-controlled trial	NI	To identify whether anodal tDCS applied to the	24 subjects with chronic mild-moderate TB	Active = 29.4 Sham = 36.8	10	30		NeuroConn (neuroCare Group GmbH, Munique, Alemanha)	the Neurobehavioral Symptom Inventory (NSI); the Hamilt	NI	NI	NI	NI	NI	yes	The current study suggests a complex picture betwe

				left dorsolateral prefrontal cortex paired with a cognitive training protocol in mild traumatic brain injury (mTBI) patients results in changes in cerebral blood flow							on Depression Rating Scale (HAM-D); the Beck Depression Inventory-II (BDI); the Posttraumatic Stress Disorder Checklist-Civilian version (PCL-C); the Patient-Reported Outcomes							en mmTBI, cerebral perfusion, and recovery. Changes in CBF may result from physiologic effect of the intervention, compensatory neural mechanisms, or confo

				(CBF) on pCASL sequences.							Measurement Information System-29 (PROMIS); the Glasgow Outcome Scale-Extended (GOS-E); the Frontal Systems Behavior Scale (FrSBe); Wechsler Adult Intelligence							unding factors. Limitations include a small sample size and heterogenous injury sample, but these findings suggest promising directions for future studies of

											Scale-Fourth Edition (WAIS-IV): Digit Span and Coding subtests; the Test of Premorbid Functioning (TOPF); the Hopkins Verbal Learning Test-Revised (HVLT-R) (54); and Test of Memor							cognitive training paradigms in mmTBI.

											y Maling ering (TOM M) (55).							
Suen , P. J. C. et al. (2021)[51]	Brazil	double-blind , placebo-controlled trial	NCT01894815	To investigate whether electric field (EF) strength is correlated with behavioral changes in depressed patients using	16 patients who were diagnosed with major depressive disorder during an acute depressive episode per	42.8 ± 10.9	22	30	10-week period	1 × 1 tDCS-CT, SoterixMedical, New York, NY	Magnetic resonance imaging, HDRS-Hamilton depression rating scale, STAI state–trait anxiety inventory, Positive and	No	No	No	No	No	No	We found no correlation between trait or state anxiety and EF strength over the DLPFC and ACC. Although

				simulated electric fields in real patient data from a controlled clinical trial.	DSM-5 criteria						Negative Affect Scale (PANAS)							some studies suggested that tDCS can downregulate anxiety, negative findings have been also reported. For instance, recent trials showed modest or

																			null effects of prefrontal tDCS in ameliorating anxiety symptoms. In this context, other tDCS protocols that could be more effective in improving anxiety

																		sympt oms shoul d be invest igated . In additi on, tDCS effect s on anxiet y might be more effecti ve when down-regula ting stress-induc ed tasks.

Nasiri, F. et al. (2020)[52]	Iran	double-blind, placebo-controlled trial	IRCT20140929019334N1 (see https://irct.ir/trial/27988).	To compare the unified protocol for transdiagnostic treatment of emotional disorders (UP) with and without transcranial direct current stimulation (tDCS) for	43 (32 female) individuals diagnosed with GAD and comorbid depression	UP+tDCS group = 20.23 (SD=2.89); UP group= 21.53 (SD=3.56).	10	20	5	NI	Anxiety disorders interview schedule for DSM-IV (ADIS-IV), Anxiety sensitivity index (ASI), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), Genera	No	No	No	No	No	Yes	In the current study, combined UP+tDCS resulted in significantly greater reductions in anxiety, anxiety sensitivity, and worry relative to UP alone both post-

				the treatment of emotion regulation and executive control dysfunction in individuals diagnosed with generalized anxiety disorder (GAD) and comorbid major							lized anxiety disorder questionnaire-IV (GAD-Q-IV), Intolerance of uncertainty scale, Penn state worry questionnaire (PSWQ).							treatment and at a three-month follow-up. Thus, a combined UP+tDCS approach may result in better and longer treatment improvement in treatment-resistant

				depressive disorder (MDD).														GAD patients with comorbid depression.
Dechantsreiter, E. et al. (2023)[53]	Israel/ Latvia/ Germany	two-arm, double-blind, randomized and placebo-controlled multi-center trial	NCT04953208	To examine the synergistic effects of a self-administered home-treatment, encompassing transcranial direct current	14 patients with a primary diagnosis of MDD	18-65	30	30	5	NI	Hamilton Depression Rating Scale (HAM-D), Mini-International Neuropsychiatric Interview (M.I.N.I.), Montgomery and Åsberg	No	No	No	No	No	NI	Refers to anxiety scales, but shows no results

				stimulation (tDCS) along with a video game based training of attentional control.							Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder 7-item (GAD-7), Rumination Response Scale,							

											Clinical Global Impression-Severity, Clinical Global Impression-Improvement, WHO-5 well-being index, Global Assessment of Functioning Scale, Adaptive Cognitive Evaluation							

											(ACE) battery.							
Mariano, T. Y. et al. (2019)[54]	United States Of America	double-blind, placebo-controlled trial	NCT02771990, NCT02768129	To test whether 10 daily tDCS sessions aimed to inhibit the left dorsal anterior cingulate cortex (dACC), a region strong	30 (23 male; 7 female) patients with chronic low back pain	ACTIVE = 65.1 ± 8.8 SHAM = 60.7 ± 11.8	10	20	7	DC-STIMULATOR PLUS, NeuroConn GmbH	11 point DVPRS, West Haven-Yale Multidimensional Pain Inventory (WHY-MPI-C), Roland Morris Disability Questionnaire (RMDQ) ,	NI	NI	NI	NI	NI	yes	To our knowledge, this is the first double-blinded RCT of multiple tDCS sessions targeting the left dACC to

				ly implicated in the affective component of pain, would produce selective reduction in pain-related symptoms.							Chronic Pain Acceptance Questionnaire (CPAQ-8), Sintomas de Ansiedade da Dor (PASS-20) , Patient Health Questionnaire (PHQ-9), Generalized Anxiety Disorder scale (GAD-7), Credibility/Ex							modulate CLBP's affective symptoms. Results are encouraging, including several possible tDCS-associated improvements. Better-powered RCTs are

											pectancy Questionnaire (CEQ) and Client Satisfaction Questionnaire-8 (CSQ-8)							needed to confirm these effects. Future studies should also consider different stimulation schedules, additional cortical targets, high-density multi-

																		electrode tDCS arrays, and multimodal approaches.
Liu, Y. et al. (2023)55	China	double-blind, placebo-controlled trial	no	To investigate the effects of repeated DLPFC tDCS on attentional control in chronically stressed individuals.	40 students from Southwest University who were about to take the postgraduate entrance examinati	18–26 years, Mage = 21.2 years, SD age = 1.65)	5	20	5	Soterix Medical, Woodbridge, NJ, EUA	Student Life Stress Inventory (SLSI), State-Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI), Positive and Negati	No	Yes	No	No	No	yes	All in all, our study exhibited supporting evidence for potential benefits of anodal tDCS for attention contro

					on in China (20 males;20 females)						ve Affect Schedule, Perceived stress scale (PSS), Positive and Negative Affect Schedule (PANAS)							l in chronically stressed individuals. Specifically, the anodal tDCS targeting the left DLPFC brain region modulated participants' moods, as shown by the reductions

																		in perceived stress, state anxiety, and trait anxiety. In addition, the reduction in reaction time indicated an enhanced attentional control, which is also supported by the

																		decrease in the N2 amplitudes and the increase in the P3 amplitudes