Umbrella review

Non-invasive brain stimulation in craving disorders: evidence-based umbrella review

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ABSTRACT | INTRODUCTION: The use of brain stimulation in the control of craving disorders is controversial, mainly in relation to the best target, technique, duration, frequency and parameters. Several meta-analyses have been published, and their data should be summarized to support the best evidence-based clinical practice. **OBJECTIVE:** To provide the best level of evidence for the use of non-invasive brain stimulation (NIBS) in the control of craving disorders. **METHODS:** Umbrella review registraded on Prospero (CRD42021239577), and conducted according to PRISMA recommendations. The methodological quality and evidence level were assessed through AMSTAR, AMSTAR rank and GRADE. **RESULTS:** A total of 81 meta-analyses were screened and the final analysis was made on 10 studies including 224 randomized clinical trials (RCTs) enrolling 5,555 patients. The main targets of stimulation were the right, left and bi-hemispheric dorsolateral prefrontal cortices. The studies used anodal tDCS, and high-frequency rTMS. The protocols with the larger effect sizes were anodal tDCS with 2mA, for 30 minutes over the right DLPFC (g=0.45; 95%CI 0.328-0.583; p<0.001), and high-frequency rTMS (10Hz), with 100% of the resting motor threshold, over the left DLPFC (g=1.116; 95%CI 0.597-1.634; p<0.001). The quality of evidence ranged from very low to moderate because of inconsistencies mainly due to sample heterogeneity. **CONCLUSION:** The results of 10 meta-analyses assessing the efficacy of NIBS in the control of craving disorders are robust regarding the effect sizes and provide evidence that bi-hemispheric tDCS and high-frequency rTMS over the DLPFC are effective in the control of craving disorders. However, the evidence level is from low to moderate.

KEYWORDS: Non-invasive Brain Stimulation. Neuromodulation. Craving. Transcranial Magnetic Stimulation. Transcranial Direct Current Stimulation.

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1. Introduction

The chronic use of psychoactive substances is a major public health problem in the contemporary world.[1] More than 12% of all deaths worldwide are attributed to alcohol, nicotine, and illegal drug use.[2] The World Drug Report showed that around 275 million people worldwide used psychoactive substances in 2019.[3] According to the DSM-5-TR, substance use disorder involves a cluster of behavioral, cognitive, and psychological consequences.[4] In addition to those psychoactive substances, many other emergent conditions can cause dependence such as screen dependence, game dependence, food craving, opioid dependence, shopping compulsion or vigorexia. The brain processes related to craving, uncontrolled consumption and dependence can be the same because it may involve the reward and pleasure circuits.[5] Because of this, all types of dependence have been studied together when the target of treatment is the brain as have been examined in several meta-analyses.[6-9]

Craving can be defined as "desire and urge of something" that may be unable to be recognized by those who feel it because of the overwhelming emotional experience during abstinence and withdrawal or not remember having experienced craving before the relapse occurred.[10] Pharmacological approaches combined with behavioral therapy are used to treat different kinds of craving. Unfortunately, no procedure has been approved for the treatment of dependence disorder, either in terms of managing, maintaining, or preventing withdrawal. Recent studies have found that non-invasive brain stimulation (NIBS) can reduce craving, improve anxiety and depression, and enhance cognitive function in drug-dependent subjects.[10,11] Furthermore, NIBS methods were non-inferior in comparison to guideline-recommended pharmacologic treatments in abstinence management.[12]

NIBS is a tool with good results and low risks in different psychiatric conditions.[13] Through the modification of cortical excitability, neurotransmitter release, signaling pathway, and gene expression, NIBS can help ascending dopaminergic tracts comprising the meso-cortico-limbic pathway or the brain reward circuit.[14] The dorsolateral prefrontal cortex (DLPFC) exerts inhibitory control over the reward circuit through the meso-fronto-limbic connections.[15] Stimulating DLPFC by NIBS may reduce craving by stimulating neuroplasticity and increasing dopamine excretion from ventral tegmental area to the ventral striatum, or by glutamate release in the ventral striatum, potentially increasing dopamine excretion. Furthermore, the insular cortex takes part of the reward system, and may also be stimulated by NIBS.[1,14] Hence, NIBS would be helpful in the treatment of craving disorders.

Several previous studies, including randomized clinical trials and systematic reviews with meta-analyses, have demonstrated the efficacy and security of NIBS uses in craving disorders or dependence consumption.[16,17] However, some of those studies have controversial results, mainly in relation to the target, resource, duration, frequency, and parameters of stimulation. Normally, the higher level of evidence is given by meta-analyses, however when there are many systematic reviews with meta-analyses with controversial results, readers have doubts about the best tool to recommend to their patients. Because of this, Umbrella Review (UR) can summarize the results of all meta-analyses in a single document and improve the evidence-based clinical practice. The aim of this umbrella review is to provide the major level of evidence on NIBS for craving disorders to suggest the best protocol.

2. Methods

2.1 Study design and registration

This umbrella review (UR) is part of a broad review produced by the Working Group on scientific evidence for the use of NIBS within the NIBS Brazilian Guidelines Development Group of the NAPeN Network. The protocol for this UR was registered on PROSPERO (CRD42021239577) and it is published on Brain Imaging and Stimulation (available on https://www5.bahiana.edu.br/index.php/brain/article/view/4400).

2.2 Eligibility criteria

Only meta-analyses with a minimum of two randomized controlled trials (RTCs) of NIBS technique vs. sham or other intervention for the treatment of different craving disorders were included. Furthermore, only studies published in English and with adult participants available in PubMed platform were included. Studies with duplicate data and surrogate outcomes as well as animal studies were excluded. If there were updates from a previous systematic review, the most recent update was included.

It was included the NIBS techniques: transcranial current stimulation (tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), high-definition transcranial direct current stimulation (HD-tDCS), repetitive transcranial magnetic stimulation (rTMS), theta burst repetitive transcranial magnetic stimulation (TBS), and cerebellar repetitive magnetic stimulation (crTMS).

The eligibility criteria were based on the PICO question: in patients with ***craving disorder***, how does noninvasive brain stimulation affect the symptoms when compared to sham/other intervention approaches?

2.3 Information sources

A systematic search was performed on the PubMed/MEDLINE electronic databases from 2 May 2023 to 3 May 2023 by two independent researchers (KNS and MNS).

Two independent reviewers (KNS and RFB) extracted data from the selected studies using a standardized extraction form. The extracted data were the name of the first author, year of publication, name of the article, number of included RCTs, number of participants in each group (active or sham), main outcome measure, number of sections, NIBS technique type, target of application, parameters of NIBS, main results, effect size, confidence interval, p value, and adverse events.

2.4 Search strategy

Medical Subject Headings (MeSH) were used for all included meta-analyses according to the selection process.

2.5 Selection process

Each one of the 13 PICO strategies was used separately to select articles: [1] (transcranial magnetic stimulation) AND (craving); [2] (rTMS) AND (craving); [3] (transcranial direct current stimulation) AND (craving); [4] (tDCS) AND (craving); [5] (transcranial alternating current stimulation) AND (craving); [6] (tACS) AND (craving); [7] (transcranial random noise stimulation) AND (craving); [8] (tRNS) AND (craving); [9] (transcranial cerebellar direct current stimulation) AND (craving); [10] (theta burst stimulation) AND (craving); [11] (TBS) AND (craving); [12] (cerebellar repetitive transcranial magnetic stimulation) AND (craving); and [13] (crTMS) AND (craving).

2.6 Data collection process

For each article, two independent authors (KNS and MNS) screened the titles and abstracts of retrieved articles. The full texts of all potential studies were then screened by two other authors (RFB and LS) based on predefined eligibility criteria. Any discrepancies were resolved through consensus. Manual source completed data collection.

2.7 Data items

The extracted data were input into the GRADE system tool (available on www.gradepro.org), according to their recommendation.

2.8 Study risk of bias assessment

The quality of all studies was assessed using A Measurement Tool to Assess Systematic Reviews (AMSTAR-2, available online on http://amstar.ca/Amstar-2.php) according to the recommendations of Shea et al.[18]. This tool uses a checklist of 16 domains to evaluate the quality of RCTs included in systematic reviews.

2.9 Certainty assessment

The quality of each included meta-analysis was assessed considering critical items (2, 4, 7, 9, 11, 13, and 15) and non-critical flaws of the AMSTAR-2 by three researchers (KNS, RFB, and LS). The meta-analyses were classified as 'high quality' (none or one non-critical weakness), 'moderate quality' (more than one non-critical weakness), 'low quality' (one critical flaw with or without non-critical weaknesses), and 'critically low' (more than one critical flaw with or without non-critical weaknesses). Any discrepancy between authors was resolved through consensus.

The GRADE tool provides a rating of high, moderate, low, or critically low quality, and a weak or strong recommendation for each outcome. High evidence indicates that future studies are unlikely to change the effect size estimate, moderate means that future RCTs may have an impact on the effect size estimate, low implies high probability that future studies will change the effect size estimate, and critically low implies a lack of certainty about the effect size estimate. The GRADEPRO assessments for all the conditions are shown in Table 1.

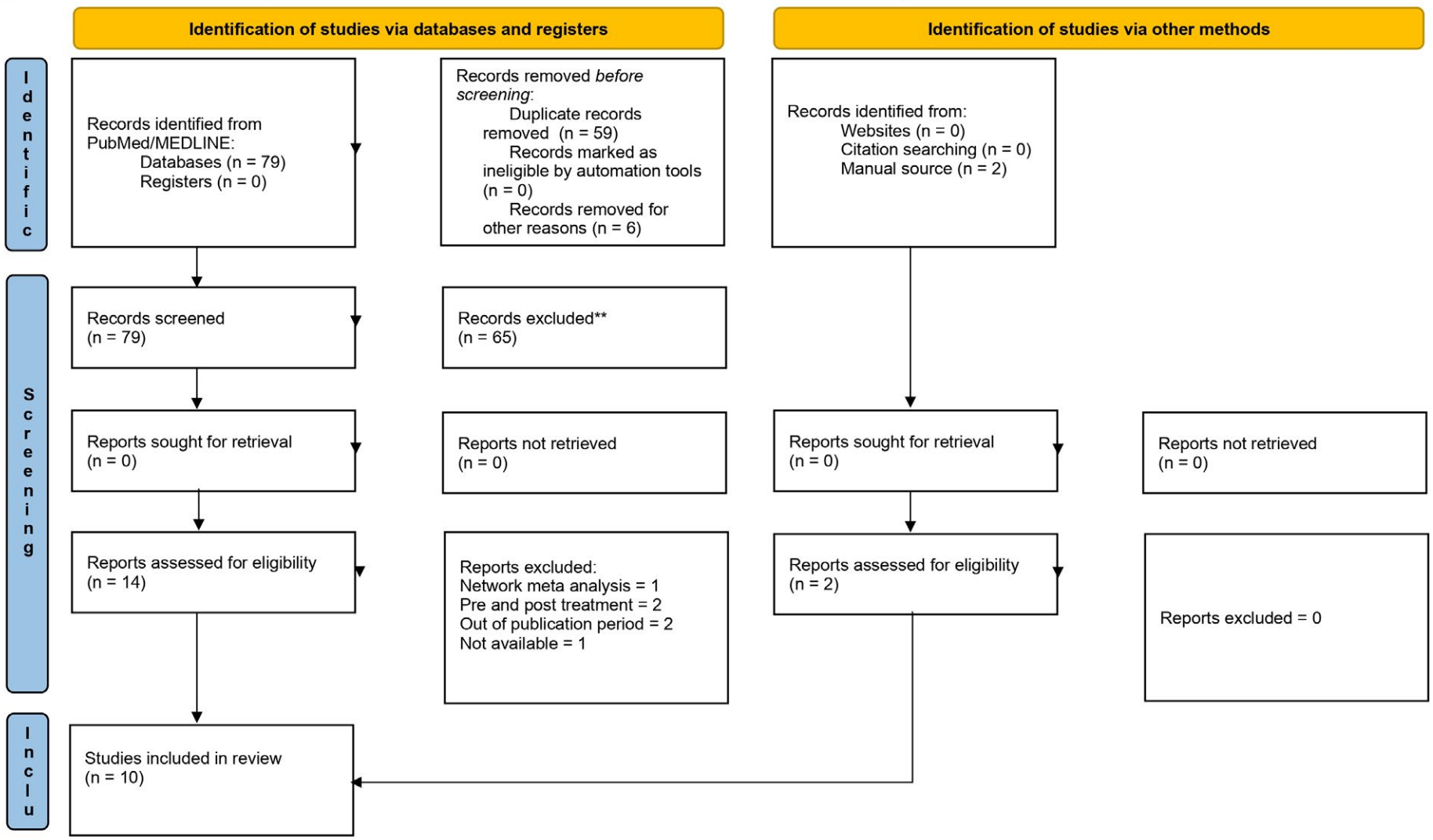
2.10 Synthesis of results

A qualitative analysis was performed to synthesize the best effect size for the use of NIBS in craving disorders.

3. Results

A total of 81 systematic reviews with meta-analyses were screened, and after title and abstract reading, 14 were selected to analyze the full text. Four studies were excluded, remaining 10 to the final analyses. The number of the screened, excluded with rationale, and included studies are reported in PRISMA Flowchart (Figure 1).

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Source: 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/.

A total of 224 RCTs enrolling 5,555 patients were included in the present analysis. The types of craving included were licit (alcohol and nicotine), illicit drugs (cocaine, marijuana or methamphetamine), and different conditions linked to dysfunctional consumption of food like food craving/eating addictions/food consumption/overeating. Most of the NIBS protocols applied were excitatory. The main target was the DLPFC, applying over the right or left side or the bi-hemispheric approach. It was tested using tDCS or rTMS modalities and the main outcome was the Visual Analog Scale (VAS). The major size effects were observed by high frequency of rTMS followed by anodal tDCS. Detailed information about the selected meta-analyses can be found in Table 1.

The effect size varied from 0.13 to 1.53 in the Hedge value. The more effective protocol was applying excitatory modalities of rTMS as soon as tDCS. Major difference observed between studies was in relation to the target of NIBS, mainly in the hemisphere side using tDCS (Table 1).

The methodological quality of the studies ranged from 23 to 28 on the AMSTAR-2 scale. On the AMSTAR rank analysis, most selected studies received moderate classification and only three studies were classified as low quality (Table 1). The main limitations in the selected meta-analyses were the absence of systematic review registration (5/8 studies), absence of bias discussion (4/8 studies), fund information about RCT (0/8 studies), and analyses of adverse effects (6/8 studies).

The evidence level assessed according to GRADE-pro was from very low to moderate. The main limitations were different populations, interventions, and outcomes that impact on the inconsistency and on the width of the confidence interval.

Table 1. Characteristics of the systematic reviews included in the umbrella analyses (to be continued)

Systematic Review	AMSTAR Total	AMSTAR Rank	GRADE	RCTs Number	Participants Number	Stimulation Target	Stimulation Type	Outcome Measure	Summary of findings	Effect size, confidence intervals and p-values
Maiti et al., 2017	26	Moderate	⊕⊕⊕ Moderate	10	293 patients Alcohol and nicotine use disorder	Excitatory DLPFC Stimulation	rTMS (l-DLPFC, r-DLPFC, or bi-PFC, 10-20Hz, 90-120% MT)	VAS Consumption	Excitatory rTMS reduce craving associated with nicotine but not alcohol use disorder.	g = 0.750 CI = 0.29-1.21 p = 0.010
Lowe et al., 2017	24	Moderate	⊕⊕ Low	11	189 patients Food craving and food consumption	Excitatory or Inhibitory Protocol	Anodal-tDCS* Cathodal-tDCS rTMS cTBS l-DLPFC r-DLPFC bi-DLPFC	VAS FCQ-S	rTMS was effective for craving (g = 0.834; p = 0.008) but not tDCS (g = 0.252; p = 0.37)	g = 0.516 CI = 0.031-1.008 p = 0.037

Table 1. Characteristics of the systematic reviews included in the umbrella analyses (continuation)

Systematic Review	AMSTAR Total	AMSTAR Rank	GRADE	RCTs Number	Participants Number	Stimulation Target	Stimulation Type	Outcome Measure	Summary of findings	Effect size, confidence intervals and p-values
Kang et al., 2019	23	Low	⊕⊕ Low	12	392 smokers Nicotine dependence	Excitatory or Inhibitory Protocol	Anodal-tDCS* l-PFDLC r-PFDLC bi-PFDLC	VAS QSU LSQ UTS	tDCS was effective in decreasing individual's smoking dependence symptoms.	g = 0.422 CI = 0.13-0.71 p = 0.004
Zhang et al., 2019	23	Low	⊕ Very Low	26	264 patients Alcohol, nicotine, and illicit drug disorder	Excitatory DLPFC Stimulation	rTMS (l-DLPFC, 10-20Hz, 90-120% MT)	VAS QSU SJQ sTCQ ACQ OCDS MCQ	Excitatory rTMS targeting the left DLPFC reduces craving and consumption (mainly) behavior.	g = 0.620 CI = 0.35-0.89 p < 0.001
Song et al., 2019	26	Moderate	⊕⊕⊕ Moderate	48	392 patients Alcohol, nicotine, illicit drugs, eating addictions	Excitatory Protocol	tDCS rTMS l-DLPFC r-DLPFC	VAS FCQ-S	NIBS targeted at DLPFC reducing craving and consumption in eating and drug addiction.	g = 0.456 CI = 0.328-0.583 p < 0.001

Table 1. Characteristics of the systematic reviews included in the umbrella analyses (continuation)

Systematic Review	AMSTAR Total	AMSTAR Rank	GRADE	RCTs Number	Participants Number	Stimulation Target	Stimulation Type	Outcome Measure	Summary of findings	Effect size, confidence intervals and p-values
Ma et al., 2019	24	Low	⊕⊕ Low	16	261 patients Cocaine, Amphetamine or Methamphetamine	Excitatory or Inhibitory Protocol	rTMS tDCS l-DLPFC	VAS	Persuasive evidence for the feasibility of using excitatory NIBS	g = 1.116 CI = 0.597-1.634 p<0.001
Mostafavi et al., 2020	26	Moderate	⊕⊕⊕ Moderate	34	tDCS = 238 patients rTMS = 379 patients Alcohol dependent	No evidence available	rTMS (l-PFDLC, 10Hz, 90-120% MT) tDCS (anode l-DLPFC, 2mA, 20min)	VAS QSU SJQ sTCQ ACQ OCDS MCQ	There is no evidence for the effect of tDCS/rTMS on various dimensions of alcohol dependence.	tDCS g = 0.13 CI = 0.08-0.34 p = 0.01 rTMS g = 0.43 CI = 0.17-1.02 p = 0.01
Chen et al., 2020	28	Moderate	⊕⊕⊕ Moderate	32	937 patients Substance and Food Craving	Excitatory Protocol	tDCS	VAS QSU UTS FCQ-S OCCS DDQ	tDCS can be effective way to reduce craving of substance or food	g = 0.416 CI = 0.262-0.570 p<0.001

Table 1. Characteristics of the systematic reviews included in the umbrella analyses (conclusion)

Systematic Review	AMSTAR Total	AMSTAR Rank	GRADE	RCTs Number	Participants Number	Stimulation Target	Stimulation Type	Outcome Measure	Summary of findings	Effect size, confidence intervals and p-values
Song et al., 2022	28	Moderate	⊕⊕ Low	22	720 patients Alcohol, drug, nicotine, and overeating disorder	Excitatory DLPFC Stimulation	rTMS (l-PFDLC, 10Hz, 90-120% MT) tDCS (anode l-DLPFC, 2mA, 20min)	Self-Report of Acute Effect on craving and consumption	Excitatory NIBS targeting the left DLPFC reduce craving and consumption in addiction or overeating behavior.	g = 0.734 CI = 0.447-1.021 p < 0.001
Tang et al., 2023	28	Moderate	⊕⊕ Low	13	327 patients MUD	Excitatory Protocol	rTMS (10-50Hz, l-PFDLC, 90-120% MT)	BSCS TWOB	rTMS was effective in reducing Methamphetamine Use Disorder	g = 1.53 CI = 0.98-2.08 p < 0.0001

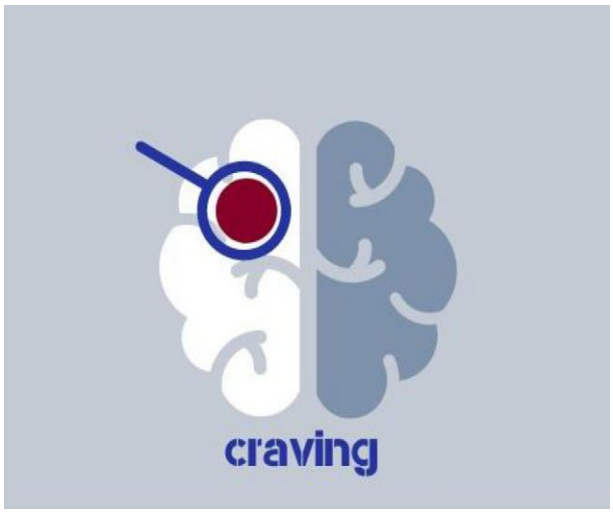
Legend (alphabetic order): ACQ-SF-R = alcohol craving questionnaire-short form-revised; AMSTAR = Oxford tool to analyze methodological quality; BSCS = Brief substance craving scale; cTBS = continuous theta burst stimulation; CAS = craving automated scale; CI = confidence interval; DDQ = drug questionnaire; DLPFC = dorsolateral prefrontal cortex; bi-DLPFC = bi-hemispheric DLPFC; l-DLPFC = left DLPFC; r-DLPFC = right DLPFC; g = Hedge value for effect size; FCQs = food craving questionnaire; GRADE = Cochrane tool to assess evidence level and recommendation force; Hz = Hertz; MT = motor threshold; MCQ = marijuana craving questionnaire; MUD = Methanphetamine use disorder; NIBS = non-invasive brain stimulation; OC-VAS = Opioid craving visual analog scale; OCCS = Obsessive-compulsive cocaine scale; PACS = Penn alcohol craving scale; PFC = prefrontal cortex; QSU = questionnaire smoking urge; RCT = randomized clinical trials;; rTMS = repetitive transcranial magnetic stimulation; SJQ = substance craving scale; sTCQ = stimulant craving questionnaire; tDCS = transcranial direct current stimulation; TCQ = tobacco craving questionnaire; TWOB = two back task; UTS = urge to smoke; VAS = visual analogical scale.
Source: the authors (2023).

About tDCS evidence, there are controversial results. As soon as anodic stimulation on the left dorsolateral prefrontal cortex (l-DLPFC)[18-21] as on the right prefrontal dorsolateral cortex (r-DLPFC)[22,23] or bi-hemispheric DLPFC[9,24], all showing big effect sizes (g > 0.30). The intensity of tDCS stimulation varied from 1 to 2 milliamperes being in most protocols with 2 milliamperes, with time of application from 19 to 40 minutes.

In relation to the rTMS evidence, the most size effects were observed applying around 1000 pulses with excitatory protocol (10 Hz) over the left DLPFC and 100% of motor threshold.[25,26] One RCT observed a big effect size applying an excitatory protocol of rTMS over bi-DLPFC and Insula.[27]

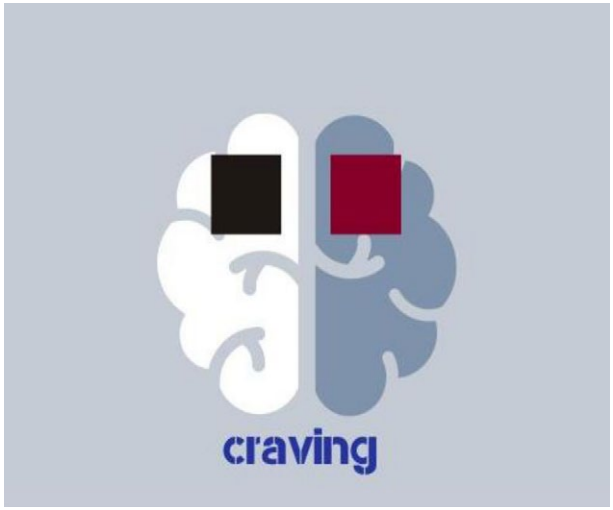
The protocols with the most size effects were anodal tDCS with 2mA by 30 minutes over the right DLPFC (g = 0.45; 95%CI 0.328-0.583; p<0.001), and high frequency of rTMS (10Hz), 100% motor threshold, over the left DLPFC (g = 1.116; 95%CI 0.597-1.634; p<0.001). The positions of coils and electrodes are in Figure 2 and 3 respectively.

Figure 2. Coil location in rTMS



Source: the authors (2023).

Figure 3. Electrodes of tDCS position



Source: the authors (2023).

4. Discussion

This study aimed to provide a major level of evidence on NIBS for the treatment of craving disorders, suggesting the best protocols. To the best of our knowledge, our study is the first umbrella review on this topic. Our results point to the efficacy of excitatory protocols of rTMS and tDCS to control craving in illicit/licit drugs and food consumption, being the major effect size with high-frequency rTMS protocols. However, a lack of knowledge remains in relation to the best protocol for the hemisphere side with controversial results in relation to the stimulation target.

The rationale for using NIBS as a treatment for craving is that the prefrontal cortex (PFC) plays a major role in top-down inhibitory control mechanisms. Almost all protocols have tested the effect of tDCS over the PFC (bi-hemisphere DLPFC, left DLPFC, right DLPFC or medium PFC). Several RCTs were positive regarding the effect of active tDCS taking to recommend level of evidence B-II for bi-hemispherical approach over the DLPFC (right anode + left cathode) in Lefaucheur guideline.[28] Our findings reinforce those previous data being major effect sizes with anodic tDCS over right DLPFC. It is possible that craving has similar results to some types of anxiety disorders in relation to the hemisphere side.[29,30] The amperage used in most of the studies was 2mA. This intensity is safe and well tolerated by patients. In relation to the time of application varied from 19 to 40 minutes, however in most protocols, 30 minutes showed to be sufficient to promote desired effects. The number of sessions are very different in the meta-analyses included. Certainly, multiple sessions are better than a single session in a minimum of 10 applications.

Different studies applied different intensities of stimulation of TMS. Any RCT used an inhibitory protocol (1Hz), reinforcing the rationale that stimulation needs to be excitatory on the prefrontal cortex areas. Excitatory protocols, using different frequencies (10, 20 or 50Hz) were tested. Functional or clinical effects outlast the period of rTMS stimulation for minutes or hours due to long-term potentiation for frequency rTMS. The direction of excitability changes induced by rTMS may vary according to the location of the cortical target and to the prior state of activation of the recruited brain circuits.[31] In the present study, from 1,500 to 3,000 pulses, 100%TM, 10Hz over the left DLPFC found the best effect sizes to treat craving.

In terms of stimulation sites, DLPFC was selected in most rTMS and tDCS studies. Proposed mechanisms underlying the behavioral effects include modulation of midbrain dopaminergic system, alterations of prefrontal functioning, or restoration of brain plasticity.[26] The DLPFC role in craving is related to the inhibition of the impaired response and the attribution of salience, which means that abnormalities in their function are associated with the increase in the search for and use of drugs, despite the negative consequences. Via amygdala and striatal connections, the ventromedial PFC and orbitofrontal cortex coordinate reward-related decision-making, value tracking, goal-directed control, and inhibitory control.[32]

High frequency over the left DLPFC stimulation demonstrated clear effects on rTMS studies, but on the tDCS studies it was observed the best results applying excitatory stimulation over the right DLPFC. The left and right sides have different biases, with the left side oriented more toward approach, positive goals, and emotions, and the right side specialized more in avoidance and negative emotions.[33] The balanced activity of both hemispheres is clinically relevant in several situations, bilateral tDCS protocols that may facilitate interhemispheric communication and symmetrical DLPFC activations between hemispheres can be an effective option to reduce craving by improving individual's decision-making capabilities.[34,35]

The insula is a target described in some studies, as it plays a role in motivational incentive processes that lead to addictive behavior, control processes that moderate or inhibit addictive behavior, and interoceptive processes that represent bodily states associated with drug use.[36] However, recent meta-analyses have found no differences to inhibitory, insula or medial prefrontal cortex targets, but the anti-craving effect may be associated with stimulation dose.[7]

Different patients answer to different kinds of treatment. NIBS is a possibility but not the single option. The possibility to realize NIBS simultaneously with cognitive tasks supports the use of tDCS with subtle sensation allowing the patient to keep attention focused on the task. The use of cognitive tasks with rTMS is more limited, but not impossible as demonstrated in recent studies.[37,38] On the other hand, rTMS produces effects of greater magnitude. We believe that the best results are obtained with NIBS associated with cognitive tasks during or after NIBS.

In fact, contemporary science has no solution to treat this serious phenomenon. Many drugs have been tested to manage craving with incipient results. The use of gabapentin is at least moderately effective[39,40] as soon as intranasal endogenous oxytocin41, antipsychotic[41,42] or anticonvulsants medications.[41-43] The use of cannabinoids might result in little or no increase in abstinence, and it probably increases adverse effects.[44] In summary, there is insufficient evidence to indicate any medication for the treatment of withdrawal[45] pointing to the possibility of NIBS use as the first line of treatment. However, motivational enhancement and cognitive-behavioral therapy interventions are effective as adjuncts of contingency management for abstinence.[46] Also, significant small-to-large effects were observed with mindfulness treatments in reducing craving for psychoactive substances and in increasing rates of posttreatment abstinence from cigarette smoking.[47] NIBS can potentialize these interventions - psychotherapy and mindfulness-, opening a brain window to improve the results of treatment.

5. Limitations

The heterogeneity of RCTs in relation to excitatory or inhibitory stimulation, and about outcomes, limited our analyses. The single database to our sources was another limitation despite most publications being deposited in the Pubmed database. Most studies assess the efficacy of NIBS as an incremental advantage to the medication, sustaining a lack of the underlying primary treatment without non-inferiority studies. The major limitations in the meta-analyses to produce high levels of evidence were the absence of registration, inconsistency due to high heterogeneity between the included studies, small sample sizes in the RCTs, and the consequent large confidence intervals. These limitations in the RCTs and meta-analyses impact our UR, limiting the evidence and possibility of producing a consistent guideline of NIBS in craving themes. The absence of adverse effect reports sustains a lack of risk-benefit assessment like its economic evaluation in the RCTs and meta-analyses.

6. Conclusion

In summary, the results of 10 meta-analyses assessing the efficacy of NIBS in controlling craving disorders are robust regarding the effect sizes; however, the methodological quality of the studies showed low to moderate levels of evidence. There remains doubt about the best side to be excitatory stimulation. Future RCTs and meta-analyses can be developed searching to fill in gaps identified in this UR.

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Authors' contributions

Baptista A, Tanaka C, Monte-Silva KK, Sá KN and Shirahige L developed the project, made training for the research team and registered the protocol. Sá KN and Sá Maristela Nunes were responsible per sources. Baptista RF made supervision and solved find divergences. Sá KN and Goulardins JB were responsible for methodological quality of evidence and recommendation grade assessment. All authors give relevant intellectual contributions to the final manuscript.

Conflicts of interest

Baptista A, Tanaka C, Monte-Silva KK, Sá KN are part of Brain Imaging and Stimulation's editorial team. All authors declare no other competitive interest.

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