



## Revisión

### Effects of neuromodulation on executive functions and food desires in individuals with obesity: a systematic review

*Efectos de la neuromodulación sobre las funciones ejecutivas y los deseos alimentarios en pacientes con obesidad: revisión sistemática*

Marta Maria da Silva Lira-Batista<sup>1</sup>, Marcela Lima Silagi<sup>2</sup>, Gleydson Wesley Freire Lima<sup>3</sup>, Jaynara Keylla Moreira da Silva<sup>4</sup>, Maria Rita Carvalho Silva<sup>5</sup>, Laurení Dantas de França<sup>6</sup>, Ricardo Galhardoni<sup>7</sup>, Janyerson Dannys Pereira da Silva<sup>8</sup>, Maria Ivone Mendes Benigno<sup>9</sup>, Oseas Florêncio de Moura Filho<sup>10</sup>, Maria do Carmo de Carvalho e Martins<sup>11</sup>

<sup>1</sup>Department of Speech Therapy. Faculdade de Ensino Superior do Piauí. Hospital Universitário do Piauí. Universidade Federal do Piauí. Teresina, Piauí. Brazil. <sup>2</sup>Department of Speech Therapy. Universidade Federal de São Paulo. São Paulo, SP. Brazil. <sup>3</sup>Internal Medicine Program. Hospital Universitário do Piauí. Universidade Federal do Piauí. Teresina, Piauí. Brazil. <sup>4</sup>Clinical Nutrition Practice. Teresina, Piauí. Brazil. <sup>5</sup>Faculdade de Ensino Superior do Piauí. Teresina, Piauí. Brazil. <sup>6</sup>Dental Sciences Doctoral Program. Faculdade de Odontologia São Leopoldo Mandic. Campinas, São Paulo. Brazil. <sup>7</sup>Neuromodulação em Foco. Universidade Cidade de São Paulo. São Paulo, SP. Brazil. <sup>8</sup>Faculdade Maurício de Nassau. Aracaju, Sergipe. Brazil. <sup>9</sup>Department of Morphology. Universidade Federal do Piauí. Teresina, Piauí. Brazil. <sup>10</sup>Instituto de Ensino, Pesquisa e Pós-Graduação em Fisioterapia Clínica. Teresina, Piauí. Brazil. <sup>11</sup>Department of Biophysics and Physiology. Universidade Federal do Piauí. Teresina, Piauí. Brazil

### Abstract

**Objective:** to describe the effects of neuromodulation on the performance of executive functions in overweight and/or individuals with obesity.

**Methods:** articles published in PubMed, ScienceDirect, BIREME, and Web of Science databases were selected using the following combination of descriptors: ("problem solving" OR "executive function" OR memory) AND (tDCS OR TMS) AND obesity. After applying the selection criteria, 08 articles were included for analysis.

**Results:** the articles included had an average of 30.1 participants per study, with a minimum of 12 and a maximum of 76. The overall nutritional status ranged from underweight to grade 3 obesity, and the general mean body mass index was 28,1 kg/m<sup>2</sup>. Regarding the instruments used to assess executive functions, the most frequent were: the flanker paradigm; binocular rivalry for Continuous Flash Suppression (bCFS/NoCFS); Stroop task; Go/No-Go task; and N-back task. The primary outcomes were dependent on the neuromodulation target site. Reduced food craving and improved performance in the active group were observed from decreased response time and increased precision in cognitive tasks.

**Conclusion:** neuromodulation can generate changes in executive functions, reducing food cravings in overweight and individuals with obesity.

#### Keywords:

Systematic review.  
Neuropsychology.  
Transcranial direct current stimulation. Transcranial magnetic stimulation.  
Obesity management.

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#### Correspondence:

Marta Maria da Silva Lira-Batista. Rehabilitation Unit. Department of Speech Therapy. Hospital Universitário do Piauí. Avenida Universitária s/n, Campus Ministro Petrônio Portela. CEP 64048-550 Teresina, Piauí. Brazil  
e-mail: fgamarthaira@gmail.com

## Resumen

**Objetivo:** describir los efectos de la neuromodulación en el desempeño de funciones ejecutivas en pacientes con sobrepeso y/o obesidad.

**Métodos:** se seleccionaron artículos publicados en las bases de datos PubMed, ScienceDirect, BIREME y Web of Science utilizando la siguiente combinación de descriptores: ("resolución de problemas" O "función ejecutiva" O memoria) Y (tDCS O TMS) Y obesidad. Después de aplicar los criterios de selección, 08 artículos fueron incluidos para el análisis.

**Resultados:** los artículos incluidos tuvieron un promedio de 30,1 participantes por estudio, con un mínimo de 12 y un máximo de 76. El estado nutricional general osciló entre bajo peso y obesidad grado 3, y el índice de masa corporal promedio general fue de 28,1 kg/m<sup>2</sup>. En cuanto a los instrumentos utilizados para evaluar las funciones ejecutivas, los más frecuentes fueron: paradigma del flanqueador; rivalidad binocular para la supresión continua de flash (bCFS/NoCFS); tarea de Stroop; Tarea Go/No-Go; y tarea N-back. Los resultados primarios dependieron del sitio objetivo de la neuromodulación. Se observó una reducción del antojo de alimentos y un mejor rendimiento en el grupo activo debido a la disminución del tiempo de respuesta y al aumento de la precisión en las tareas cognitivas.

**Conclusión:** la neuromodulación puede generar cambios en las funciones ejecutivas, reduciendo el antojo de alimentos en personas con sobrepeso y obesidad.

### Palabras clave:

Revisión sistemática.  
Neuropsicología.  
Estimulación transcraneal de corriente directa.  
Estimulación magnética transcraneal. Manejo de la obesidad.

## INTRODUCTION

The brain is more sensitive to oxidative stress than other organs. It has low defensive antioxidant potential, high oxygen consumption, low oxidation resistance of neurotransmitters and their precursors, and lipid constitution of the neuronal membrane with unsaturated fatty acids that are very susceptible to lipid peroxidation to the active process of immune defense. These factors can trigger an excitotoxic process with the free radical generation, edema formation, and activation of cellular apoptosis (1-3).

Oxidative stress and inflammatory processes can negatively affect cognitive functions. The cumulative effect can potentially impact deterioration, especially of executive functions; disability manifests itself mainly in senescence. The term "executive function" corresponds to skills, including planning, organization, problem solving, self-monitoring, and decision making. These skills require integrating information from various cognitive domains to perform more complex tasks. These functions imply several skills, such as attention, concentration, abstraction, behavior initiation, cognitive flexibility, inhibiting control, working memory, and selectivity of stimuli (2,4,5).

Working memory is fundamental for the execution of several tasks involving executive functions, such as self-regulation, inhibition, and cognitive flexibility, influencing various behaviors. One of these behaviors is the decision about food intake. Such skills, when recruited in an integrated way, can restrict the properties that encourage inadequate eating cues resulting from impulsivity, remaining interdependent with cortical excitability, that is, the favorable situation to the inhibitory pattern is reinforced at the time of hyperpolarization; on the other hand, the excitatory pathway occurs favorably in cases with continuous neuronal depolarization (2,3,6).

Experimental studies with rats demonstrated that manipulations that weakened the inhibition of working memory also reduced rodent self-control over food intake and increased the likelihood of overeating (6-9). Rodents with a deficit in the inhibition of working memory presented greater food impulsivity, weight gain and/or overweight; the inverse finding was also validated. When rodents had more significant memory inhibition, they showed less food impulsivity (6,7,10,11).

Neuroplasticity and cortical excitability changes may contribute to neural activity regulation. Both could be modified by applying direct electric current in the sensory-motor cortex, with results dependent on the type and modality of the polarity of the current. Its effect would last for days after the end of stimulation (12,13).

In the context of invasive stimulation, deep brain stimulation and vagus nerve stimulation, performed only surgically, are examples of this type of stimulation. Regarding noninvasive brain stimulation patterns, Repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial direct current stimulation (tDCS) can be mentioned. Noninvasive methods are more attractive for humans because they have the best cost-benefit ratio and allow painless modulation of cortical activity and excitability, applied through the intact skull (13,14).

For didactic purposes, the cerebral hemispheres are delimited with points; the right hemisphere is marked with even numbering and the left hemisphere with odd total. The letters correspond to the cerebral lobes; therefore, in this logic used internationally by the 10-20 system in the electroencephalogram, the Right Dorsolateral Prefrontal Cortex (CPFDL) will be registered as F4. The left one will be recorded as F3, both cortices belonging to the most central frontal lobe region (letter F).

Among the described effects of using ETCC, the following stand out: increased reaction time and mental flexibility accuracy scores (problem solving or constantly changing situations) and working memory (phonological and visuospatial loops). And although the variability of the protocols used is extensive, anodic stimulation in the right dorsolateral prefrontal cortex seems to have better results (13,15-19).

Although there are many publications on food desire and assessment of nutritional status or executive functions, there is little information on the effect of brain stimulation on executive functions in overweight or obese individuals. It is known that metabolic syndrome and its related components (obesity and chronic non-communicable diseases such as hypertension and type 2 diabetes *mellitus*) incarnate high long-term costs (20,21).

Considering the application of low-intensity electrical and/or magnetic current excitation modulation in cortical regions, the following question arises: How can noninvasive neuromodulation influence the performance of executive functions in overweight or obese individuals?

However, few studies simultaneously analyze the influence of noninvasive neuromodulation on the executive functions of overweight or obese individuals. Given the above, the research aimed to verify, through a literature review, the effects of neuromodulation on the performance of executive functions when applied to overweight or obese individuals.

## METHODS

This is a systematic review article based on articles selected from the databases PubMed, ScienceDirect, BIREME (Latin American and Caribbean Center for Information in Health Sciences), and Web of Science. The search was performed using the following combination of descriptors: (“troubleshooting” OR “executive function” OR memory) AND (tDCS OR TMS) AND obesity.

Only controlled and/or randomized clinical trials published in any language were analyzed between 2011 and May 31, 2022, using the PICOS (Population, Intervention, Comparator, Outcome, and Study Design) strategy to assist in the proper construction of the review question, as it follows: (P) adults; (I) use of tDCS and/or rTMS; (C) simulated or false treatment; (O) reduction of altered neuropsychological symptoms; (S) controlled and/or randomized clinical trial to answer the following question: What is the influence of noninvasive neuromodulation on the performance of executive functions in overweight or obese individuals?

Inclusion criteria were: original articles from controlled and/or randomized clinical trials whose main subject matter was related to ETCC and/or rTMS in the treatment and/or rehabilitation of executive functions in adult humans, considering the context of variations in nutritional status. Incomplete studies, systematic reviews, articles outside the time frame of the research and studies without relevant results on diagnosis and rehabilitation of executive functions in obese individuals using ETCC and/or transcranial magnetic stimulation were excluded.

The selection was initially made by reading the titles and abstracts of the articles and applying the inclusion and exclusion criteria. A review was conducted by a pair of researchers (MMSLB and MRC) independently to ensure greater accuracy and credibility in selecting articles. In cases of disagreement, there was communication between the evaluators for a decision, by consensus, about the inclusion or not of the article. The study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42021261770.

The bias risk assessment tool proposed in the Cochrane Handbook for Systematic Reviews of interventions evaluated the included studies based on the criteria. These were used to minimize the risks of selection, performance, detection, wear, and reporting risks. Each item was scored as having low risk, uncertain risk, or high risk of bias. After analyzing each domain in the Cochrane Risk of Bias tool, each study was classified as having a general risk of bias, and the score was classified (22).

## RESULTS

Using the descriptors above, 763 articles were identified in the databases defined for the search. After the selection and analysis of the studies found, 08 articles were selected for systematic review (Fig. 1).

Table I summarizes the studies selected to make up this systematic review. The main items were listed: author(s) and year of publication; study design, target population, sample size, type, and qualifiers of the proposed intervention (both the neuromodulation protocol and the tests for evaluating the executive function, comparator group, and primary outcomes).

The results are organized according to the presentation of the sample variables (sample size, characteristics of the participants regarding age, gender, classification of global nutritional status), research design, type of intervention (with the description of procedures related to noninvasive neuromodulation and executive functions), type of control for the treatment group and characterization of primary outcomes (changes in overall nutritional status and functioning of the process evaluated in the participants, before and after the intervention).

The number of people included in the eight selected studies was 301 participants. The majority were female (235 participants), and 44 were left with an indeterminate gender definition. A survey sample size obtained an average of 30.1 participants per study (minimum of 12 and 76), as seen in table I.

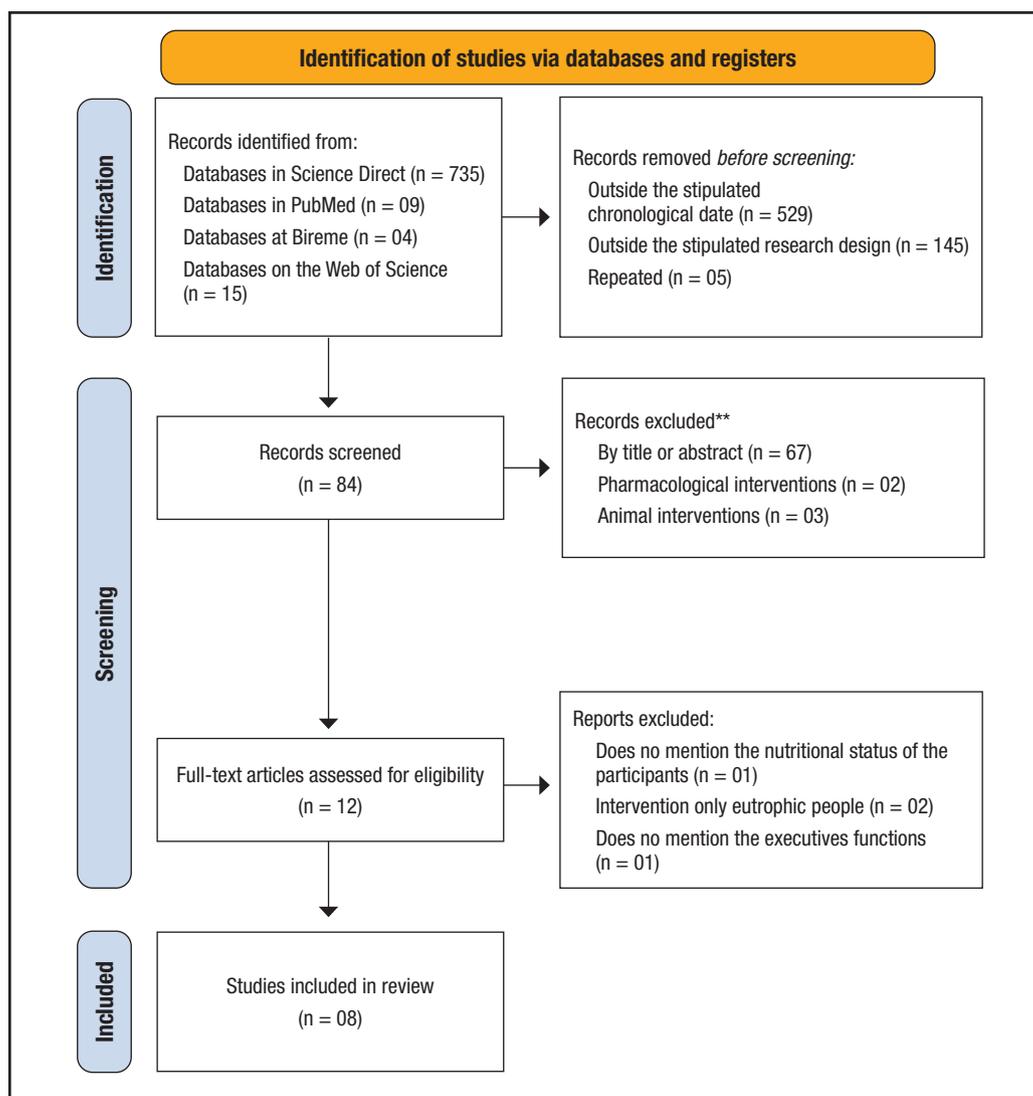
There was variability in the age group of the participants in the different studies, as described below: 1) sample was composed of 38 women between 45 and 65 years (23); and 2) another sample included a smaller and younger selection (28 women between 19 and 22 years) (24), and we believe the difference between ages may have influenced the results.

The first demonstrated a favorable result of neuromodulation in reducing binge eating and increasing the agility of executive functions. At the same time, the second observed an increase in the number of calories ingested by participants and worse performance in inhibition control. The overall nutritional status varied between low weight and obesity grade 3, and the overall body mass index (BMI) average of the participants recruited by the selected studies was 28.1 kg/m<sup>2</sup> (minimum of 19 and maximum of 40).

Regarding the type of stimulation modality, the proportion between noninvasive neuromodulation strategies as a form of treatment was 75 % (n = 6) with the use of tDCS (electric current) (23,25-29) and 25 % (n = 2) rTMS (magnetic pulses) (24,30).

Considering only the results of the articles that evaluated the effects of noninvasive neuromodulation in the modality of electric current (n = 6), there was the evaluation of the result after the application of anodic currents, with the most recurrent stimulation site being the left dorsolateral prefrontal cortex (F3) (83.3 %; n = 5) (23,25,28,29).

As for the studies that evaluated the effects of non-invasive neuromodulation using the magnetic pulse modality, in both studies the area of excitatory stimulation “theta-burst” was the left dorsolateral prefrontal cortex (F3) (24,30).



**Figure 1.** Schematic representation of the study selection steps according to the methodological recommendations of the "Preferred Reporting Items for Systematic Reviews" (PRISMA). Flow diagram specific for systematic reviews.

**Table I. Summary of the main findings in the selected articles**

Author and year	Type of study/population and sample/objective/outcome	Intervention	Control	Results
Ljubisavljevic et al. (2016) (26)	A randomized, double-blind, controlled, parallel clinical trial comparing active versus sham tDCS in eutrophic (13), overweight (8), and individuals with obesity (6) college students (21.3 ± 2 years of age). Objective: to assess food cravings in subjects after tDCS sessions and 30 days later. Executive Function: Resisting foods shown (inhibitory control)	Five consecutive sessions (anodic active tDCS group) OR one real session and four simulated sessions (sham tDCS group); F4 and FP2 (cathode) for 20 min, 2mA for 35 cm <sup>2</sup> or sham (same assembly, with the active current for the 30 sec)	Sham group	tDCS reduced cravings for sweet foods, fast food, and fat, but not carbohydrates. Food cravings were reduced for up to one month after the end of the intervention regardless of baseline body weight or sex and were not associated with changes in body weight

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**Table I (Cont.).** Summary of the main findings in the selected articles

Author and year	Type of study/population and sample/objective/outcome	Intervention	Control	Results
Lowe et al. (2018) (24)	A randomized, single-blind, crossover clinical trial was conducted on 28 healthy college students (only 1 was overweight and not individuals with obesity). Objective: To examine the role of tDCS in behavioral and visceral responses to high-calorie foods. Executive function: pre and post-stimulation flanker paradigm (FP)	A cTBS TMS session at F3. Continuous 40 sec trains of 600 pulses are applied in the theta-burst pattern (50 Hz repeated at 5 Hz frequency) (bursts of three stimuli at 50 Hz repeated at a frequency of 5 Hz)	Sham group	PF task performance was worse after active cTBS. Participants consumed more calories after active cTBS than sham cTBS ( $p < 0.001$ )
Lowe & Hall (2018) (30)	A randomized, single-blind, crossover clinical trial in university students ( $n = 76$ ; $26 \pm 1.6$ years): (underweight (2), eutrophic (56), overweight (15), and obesity (3). Objective: to assess the reproducibility of the effects of TMS cTBS on the performance of executive functions. Executive function set: Stroop task and pre-and post-stimulation PF	A cTBS TMS session at F3. Continuous 40 sec trains of 600 pulses are applied in the theta-burst pattern (50 Hz repeated at 5 Hz frequency) (bursts of three stimuli at 50 Hz repeated at a frequency of 5 Hz)	Patient pre and post-stimulation	Baseline executive function was the only predictor of the magnitude of mitigating effects observed; more significant variations were obtained after cTBS induction in executive functions in subjects with lower baseline interference scores
Fassini et al. (2019) (29)	A randomized, double-blind, parallel clinical trial was conducted for 30 days with 38 women with obesity (20 to 39 years, BMI between 30 to 35 kg/m <sup>2</sup> ), differing in the presence of catechol-O-methyl transferase (COMT) enzyme. Objective: To determine whether tDCS influences the appetite of individuals with the COMT enzyme with Val158Met polymorphism. Executive function: N-back task	Study in 3 phases: phase 1 - memory assessment after 1 tDCS session at F3 (if anodic: 2 mA for 30 min; if sham: only 30 sec); phase 2 10 tDCS sessions; phase 3: 06 sessions of tDCS + hypocaloric diet. It does not mention the area of stimulation in cm <sup>2</sup>	Sham group	Participants with the Val158Met polymorphism with a low-functioning COMT responded better to tDCS (less hunger, desire to eat, and prospective consumption over time). Polymorphism did not influence memory
Marron et al. (2019) (28)	A randomized, single-blind, crossover clinical trial with 12 participants with grade 1 obesity (BMI, $32.7 \pm 1.9$ kg/m <sup>2</sup> ). Objective: To examine changes in appetite in individuals with obesity after applying cerebellar tDCS. Executive function: Food-modified N-back with 3 levels of cognitive load	Two tDCS sessions (one active and one simulated), 2 mA, with a stimulation area of 25 cm <sup>2</sup> , 20 min/session. Anodic current in F3 and cathode in the right cerebellar hemisphere	Sham group	Active tDCS caused a relative increase in overall hunger status compared to simulated tDCS. Increased desire to eat and hunger triggered by stimuli and possible impairment in working memory tasks (for food)
Osimo, Korb & Aiello (2019) (25)	Age was a randomized, double-blind clinical trial with 44 participants ( $24.5 \pm 3.2$ years) of both sexes (underweight, eutrophics, overweight, and obese). Objective: To investigate the role of the prefrontal cortex in image processing and inhibition of responses to food images. Executive Function: Evidence: Binocular Rivalry by Continuous Flash Suppression (bCFS/NoCFS), Go/No-Go Task	Three sessions on alternate days, 1.5mA, being: anodic, cathodic or sham tDCS; where: F3 (cathode) and FP2 (cathode); Anodic F4 and FP2 (cathode) of 25 cm <sup>2</sup> ; and, Cathodic in Mm. Deltoid and F4 (cathode) of 70 cm <sup>2</sup> total. Sham groups only 15 sec of active stimulation; anodic or cathodic had 30 minutes	Sham group	Positive correlation between participants' BMI and reaction times to foods [ $p = 0.02$ ], but not for non-foods [ $p = 0.09$ ]. There was greater accuracy for Test Go compared to NoGo tests

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**Table I (Cont.).** Summary of the main findings in the selected articles

Author and year	Type of study/population and sample/objective/outcome	Intervention	Control	Results
Usanos et al. (2019) (23)	A randomized, double-blind, parallel, sham-controlled clinical trial with 38 women (45-65 years of age; BMI between 25-35 kg/m <sup>2</sup> ).  Objective: To examine the effects of tDCS on weight loss when associated with a hypocaloric diet. Assessment of pre and post-variation: body weight, appetite, and desire for food. Executive function: Go/No-Go task	Eight sessions of 2mA tDCS with anode in F3 and cathode in Fp2 + Mediterranean-type hypocaloric diet (20 kcal/kg/day), with stimulation area of 25 cm <sup>2</sup> for 20 minutes/session	Sham group	Reduction in body weight ( $p < 0.05$ ) and in the desire to eat ( $p = 0.062$ ); There was no effect on hunger, fullness, or potential consumption. Speed on the Go/No-Go task was positively correlated with reducing the food craving state ( $< 0.05$ )
Fassini et al. (2020) (27)	Double-blind, randomized, parallel-design clinical trial with 38 women (20 to 40 years; BMI 30-35 kg/m <sup>2</sup> ), categorized by the presence or absence of COMT enzyme polymorphisms.  Objective: To investigate the effects of tDCS when applied to the prefrontal cortex in young women with obesity. Executive function: N-back task in 3 conditions	The anode in F3 and cathode in F4; 2mA, with a stimulation area of 25 cm <sup>2</sup> for 30 min/session, with 17 sessions, subdivided into Phase I: 1 session (working memory assessed), Phase II: tDCS only (10 sessions/2 weeks), Phase III: tDCS + hypocaloric diet (6 sessions/2 weeks), Phase IV: follow-up + genotyping	Sham group	Participants who did not have the COMTMet enzyme in the subgroup were responsible for the pattern of weight recovery. During the study, there was no difference in change in appetite, body weight, and food cravings

COMT: catechol-O-methyl transferase; Ctbts: TMS in excitatory theta-burst continuous mode; FP: flanker paradigm; RCT: randomized clinical trial; tDCS: transcranial direct current stimulation.

It is noteworthy that the study (25) sought to evaluate possible different results for the same result after the application of stimuli in other areas in the same group of participants, with the following assemblies: in F3 (anodic) with the cap on Fp2; in F4 (anodic) with the cathode in Fp2; and in F4 (cathodic) with the anode in the deltoid muscle. In the comparator group there was simulated stimulation (with the same settings mentioned above; however, there were only 30 seconds of active stimulation); in this group, only favorable results were obtained with anodic currents aiming at inhibition (interference control and selective attention).

The sites chosen for anodic direct current stimulation were: 1) F3 – 60 % ( $n = 3$ ), using the Fp2 point as the cathode; 2) F4 and cerebellum – 20 % of studies ( $n = 1$ ; each). In the TMS, the two studies used the same stimulation configuration: “theta-burst” mode in F3, with continuous trains of 600 pulses for 40 sec applied at 50 Hz.

Regarding the design of the study, half of the studies were of the clinical, randomized, parallel type (23,26,29), and the other half were of the cross-over type (24,25,28,30). Regarding blinding, 62.5 % ( $n = 5$ ) were double-blind studies (23,25–27,29) and the rest (37.5 %) were single-blind studies (24,28,30).

Among all the studies selected, when considering the relationship between executive functions and binge eating and/or nutritional status, 62.5 % ( $n = 5$ ) of the studies pointed to inhibition as the main way to influence the result of reduced binge eating and/or inhibitory control to resist impulsive behaviors/dietary

temptations (23-26,30); the other studies (37.5 %) focused their interventions on observing changes in working memory before and after the intervention (27-29).

Regarding the instruments used to evaluate executive functions, in the included studies they were more frequent for the pre- and post-stimulation evaluation of inhibitory control (to measure interference control): flanker paradigm (PF) (24,30); binocular rivalry for continuous flash suppression (bCFS/NoCFS) (25); Stroop task (30), and Go/No-Go task (23,25).

To evaluate inhibition control (resistance to temptations and impulsive behaviors), only one study used visual tasks to elicit the ability to resist the foods shown, using questionnaires and visual analog scales to measure the variation in the intensity of inhibitory control (26).

Notably, only 37.5 % observed the influence of working memory response (27-29). However, considering that there are studies that have analyzed more than one aspect of executive function, including working memory and binge eating (food inhibition control) (25,27-29), the results exceed 100 % ( $n = 8$ ). No article sought to establish the relationship between the influence of cognitive flexibility variability (via neuropsychological tests), before and after neurostimulation, in patients with binge eating, nor from the perspective of nutritional status.

After the interventions, the most commonly observed primary outcomes were described: reduction of food craving (23,26,29), improved performance in the active group from

reduced response time, and increased accuracy in cognitive tasks (23,25,27,30).

On the other hand, the intervention group (participants who received real stimulation) showed increased hunger and food desire, as well as worsening working memory performance (28). In another study (30), the intervention group participants performed worse in the flanker paradigm (inhibiting and interference control). In addition, they had a higher calorie consumption when compared to shams.

The results of the methodological quality assessment for each of the 8 included studies are shown in table II. Five studies were considered to have a low risk of bias in all four domains: performance bias, detection bias, reporting bias, and trend data friction, as shown below (23,25,26,29,30). A high risk of bias was

found in three studies. The risk was related to the researcher's allocation of participants and no random sequence generation or allocation concealment (selection bias) (27).

The tendency towards attrition and reporting bias was evidenced by the fact that one participant was allowed to have a longer interval between stimulations compared to that established and performed on the others (24). Furthermore, there was no blinding of results evaluation (detection bias) and selective reports were present (report bias) (28).

There was no specific mention in the above-mentioned studies on allocation concealment (selection bias), the method of blinding participants and researchers (performance bias), or the conditions of execution or values obtained after measurement. However, the authors mentioned that it was carried out.

**Table II. Summary of the analysis of the authors' judgments on each risk of bias domain for each included study**

	Ljubisavljevic et al. (2016)	Lowe et al. (2018)	Lowe e Hall (2018)	Fassini et al. (2019)	Marron et al. (2019)	Ostimo, Korb e Aiello (2019)	Usanos et al. (2019)	Fassini et al. (2020)
Random sequence generation (selection bias)	(?)	(?)	(?)	(+)	(?)	(?)	(+)	(-)
Allocation concealment (selection bias)	(+)	(?)	(?)	(+)	(?)	(?)	(+)	(-)
Blinding of participants and researchers (performance bias)	(+)	(+)	(+)	(+)	(?)	(?)	(+)	(+)
Blinding of outcome evaluation (detection bias)	(+)	(+)	(+)	(+)	(-)	(+)	(+)	(+)
Incomplete result data (attrition trend)	(+)	(-)	(+)	(?)	(?)	(+)	(+)	(?)
Selective reporting (report submission)	(+)	(-)	(?)	(?)	(-)	(+)	(+)	(+)

(+): low risk of bias; (-): high risk of bias; (?): uncertain risk of bias.

**DISCUSSION**

Non-invasive neuromodulation influences the reduction of food craving and promotes improvement in the performance of executive functions, especially cognitive inhibition.

Regarding the relationship between age and performance of executive functions, a study with older participants (23) demonstrated the Go/No-Go task and a reduction of food desire. Differently, in a survey with young patients, an increase in the consumption of calories and worse performance in the flanker paradigm task were demonstrated. It should be noted that both used the same target (anodic at F3) but in different modalities: electrical and magnetic, respectively (24).

The use of non-invasive neuromodulation has consistently reduced food cravings, especially for sweet foods, fast food. However, a clear impact on changes in body weight has not been demonstrated. Furthermore, it improved performance of the participants' executive functions, especially in the groups of subjects with overweight or obesity (23,25-27,29).

The mechanism for weight loss is complex and involves other variables that are often not considered in studies, partly due to limitations in the methodological design itself or due to high costs that make genotyping unfeasible. Therefore, we recommend that during the clinical evaluation process of an obese person several factors can be considered as adjuvants in the weight loss process, from biological aspects (chewing, nutritional/dietary selection), to genetic study, to rehabilitation aiming at cortical biochemical adjustment (noninvasive neuromodulation).

The genotyping of the catechol-O-methyltransferase (COMT) enzyme showed that weight loss might be linked to specific enzyme polymorphisms, leaving the individual susceptible to easier weight recovery, resulting in higher energy expenditure (27).

COMT acts on the breakdown of catecholamines in the synaptic cleft, and is responsible for a large part of the metabolism of the neurotransmitter dopamine present in the prefrontal cortex. Therefore, this enzyme plays a vital role in the dopaminergic and noradrenergic balance. The COMT gene Val158Met polymorphism, caused by an amino acid exchange, promotes the

phenotypic heterogeneity found in attention deficit hyperactivity disorder. There is evidence that it is involved in the emergence of disruptive energy behavior disorders, directly influencing food decisions. Higher appetite levels and weight loss were observed in participants with no polymorphism (29,31).

The food decision is a critical moment and precedes the oral processing of mastication or the process of bioavailability or storage of nutrients. It is conscious and dependent on brain inhibitory control, especially in the interference control modality (14,32).

Therefore, because executive functions are interdependent, from the change in self-regulation, memory inhibition can occur and vice versa, allowing individuals to suppress or ignore unwanted or outdated associations, thus helping them to use information relevant to dietary goals and disregard irrelevant information (33).

Judgment capacity and also executive functions are closely related to frontal lobe activity. This lobe is associated with the motor, perceptual and limbic regions, subdivided into four components: the premotor cortex, the primary motor cortex, the prefrontal cortex, and the supplementary motor area. Five major functional areas are recognized for the prefrontal cortex: dorsolateral prefrontal (CPF<sub>DL</sub>), ventrolateral (CPF<sub>VL</sub>), orbitofrontal (CPF<sub>OF</sub>), ventromedial (CPF<sub>VM</sub>), and anterior cingulate (ACC) cortex (10,34).

Highlighted cortical areas and correlated actions/functions, reasoning, social control of behavior, and action planning, are related to the CPF<sub>VL</sub> and CPF<sub>OF</sub> regions (10), while the modulation of emotions and control of attentional processes are related to the CCA. The CPF<sub>VL</sub> region is involved in working memory, but there is an input from the CPF<sub>DL</sub> region during manipulation of information.

The network functioning of cortical functions provides the substrate for choosing which test is the most appropriate, considering the process or subfunction to be evaluated. The N-back task, for example, aims to bombard working memory using increasing memory spans (items that must be retrieved shortly after successive updating of similar information). The letter 'N' reveals the number of spans that will be used: 0-back, the stimulus presented in the current one; 1-back, the stimulus presented on the previous screen; 2-back, the stimulus given two screens back, and so on (35).

On the other hand, the Go/No-go tasks and the flanker paradigm (FP) require a response selection process with execution/inhibition of the motor response, triggered by a movement of pressing or not pressing a key. The task requires agility and a high cognitive level between response selection, decision making, or attention and response inhibition (36,37).

In the context of the influence of executive functions, there is a relationship between impulsivity derived from low performance of inhibitory control influencing the low oral processing of food. Cognitive functions are highly influenced by reversible biological processes such as nutritional intervention and traditional speech therapy, concomitant with non-invasive neuromodulation (38).

## LIMITATIONS AND STRENGTHS

A limitation of this study was the impossibility of performing a meta-analysis due to lack of data in the articles. It was possible to apply specific statistical tests. The mastication efficiency metric was another point that deserved discussion and was not considered in any article. This is because overweight and individuals with obesity tend to have changes in masticatory behavior, which can contribute to more difficulties in performing masticatory functions when compared to eutrophic individuals.

Furthermore, individuals with obesity tend to have a chewing pattern with few chewing cycles, which in turn leaves the surface area for the action of digestive enzymes smaller, which can decrease the efficiency of the digestive and absorptive process, reducing satiety and increasing signaling for a pattern of hunger, since digestibility is involved in the control of the glycemic response. One hunger and satiety control mechanism involves glucostatic management (32,39,40).

## CONCLUSION

This systematic review showed that neuromodulation generates changes in food desire (decrease or increase) and can influence executive functions in people with obesity. However, due to the heterogeneity found in the assembly of the stimulation protocols used, as well as the different executive functions evaluated in the studies included in this work, there is a need for additional research using masticatory efficiency measures concomitant with the food desire profile, as well as the evaluation of all executive functions to highlight which component prevails in food decisions.

## REFERENCES

- Barbosa KBF, Costa NMB, Alfenas R de CG, Paula SO DE, Minim VPR, Bressan J. Estresse oxidativo : conceito , implicações e fatores modulatórios Oxidative stress: concept, implications. *Rev Nutr Campinas* 2010;23(4):629-43. DOI: 10.1590/S1415-52732010000400013
- Saleem U, Sabir S, Niazi SG, Naeem M, Ahmad B. Role of Oxidative Stress and Antioxidant Defense Biomarkers in Neurodegenerative Diseases. *Crit Rev Eukaryot Gene Expr* 2020;30(4):311-22. DOI: 10.1615/CritRevEukaryotGeneExpr.2020029202
- Chavda V, Chaurasia B, Garg K, Deora H, Umana GE, Palmisciano P, et al. Molecular mechanisms of oxidative stress in stroke and cancer. *Brain Disord* 2022;5:100029. DOI: 10.1016/j.dscb.2021.100029
- Diamond A. Executive functions. *Annu Rev Psychol* 2013;64:135-68. DOI: 10.1146/annurev-psych-113011-143750
- Franzoni F, Scarfò G, Guidotti S, Fusi J, Asomov M, Pruneti C. Oxidative Stress and Cognitive Decline: The Neuroprotective Role of Natural Antioxidants. *Front Neurosci* 2021;15:729757. DOI: 10.3389/fnins.2021.729757
- Martin AA, Davidson TL, McCrory MA. Deficits in episodic memory are related to uncontrolled eating in a sample of healthy adults. *Appetite* [Internet] 2018;124:33-42. DOI: 10.1016/j.appet.2017.05.011
- Davidson TL, Monnot A, Neal AU, Martin AA, Horton JJ, Zheng W. The effects of a high-energy diet on hippocampal-dependent discrimination performance and blood-brain barrier integrity differ for diet-induced obese and diet-resistant rats. *Physiol Behav* [Internet] 2012;107(1):26-33. DOI: 10.1016/j.physbeh.2012.05.015

8. Egea J, Fabregat I, Frapart YM, Ghezzi P, Görlach A, Kietzmann T, et al. European contribution to the study of ROS: A summary of the findings and prospects for the future from the COST action BM1203 (EU-ROS). *Redox Biol* 2017;13:94-162. DOI: 10.1016/j.redox.2017.05.007
9. Beaumont JD, Smith NC, Starr D, Davis D, Dalton M, Nowicky A, et al. Effective Transcranial Direct Current Stimulation Parameters for the Modulation of Eating Behavior: A Systematic Literature Review and Meta-Analysis. *Psychosom Med* 2022;84(6):646-57. DOI: 10.1097/PSY.0000000000001074
10. Stuss DT, Levine B. Adult clinical neuropsychology: lessons from studies of the frontal lobes. *Annu Rev Psychol* 2002;53:401-33. DOI: 10.1146/annurev.psych.53.1.00901.135220
11. Kendig MD. Cognitive and behavioural effects of sugar consumption in rodents. A review. *Appetite [Internet]* 2014;80:41-54. DOI: 10.1016/j.appet.2014.04.028
12. Antal A, Alekseiuk I, Bikson M, Brockmüller J, Brunoni AR, Chen R, et al. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. *Clin Neurophysiol [Internet]* 2017;128(9):1774-809. DOI: 10.1016/j.clinph.2017.06.001
13. Lefaucheur JP, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol [Internet]* 2017;128(1):56-92. DOI: 10.1016/j.clinph.2016.10.087
14. Fregni F, Orsati F, Pedrosa W, Fecteau S, Tóme FA, Nitsche MA, et al. Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite* 2008;51(1):34-41. DOI: 10.1016/j.appet.2007.09.016
15. Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses ZT, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *J Neurosci* 2009;29(16):5202-6. DOI: 10.1523/JNEUROSCI.4432-08.2009
16. Rueger MA, Keuters MH, Walberer M, Braun R, Klein R, Sparing R, et al. Multi-session transcranial direct current stimulation (tDCS) elicits inflammatory and regenerative processes in the rat brain. *PLoS One* 2012;7(8):e43776. DOI: 10.1371/journal.pone.0043776
17. Hall PA, Vincent CM, Burhan AM. Non-invasive brain stimulation for food cravings, consumption, and disorders of eating: A review of methods, findings and controversies. *Appetite [Internet]* 2018;124:78-88. DOI: 10.1016/j.appet.2017.03.006
18. Surowka AD, Ziomber A, Czyzycki M, Migliori A, Kasper K, Szczerbowska-boruchowska M. *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy* Molecular and elemental effects underlying the biochemical action of transcranial direct current stimulation ( tDCS ) in appetite control. *Spectrochim Acta Part A Mol Biomol Spectrosc [Internet]* 2018;195:199-209. DOI: 10.1016/j.saa.2018.01.061
19. de Oliveira C, de Freitas JS, Macedo IC, Scarabelot VL, Ströher R, Santos DS, et al. Transcranial direct current stimulation (tDCS) modulates biometric and inflammatory parameters and anxiety-like behavior in obese rats. *Neuropeptides [Internet]* 2019;73(July 2018):1-10. DOI: 10.1016/j.npep.2018.09.006
20. Nilson EAF, Andrade RDCS, de Brito DA, de Oliveira ML. Custos atribuíveis a obesidade, hipertensão e diabetes no Sistema Único de Saúde, Brasil, 2018 [Costs attributable to obesity, hypertension, and diabetes in the Unified Health System, Brazil, 2018] Custos atribuíveis a la obesidad, la hipertensión y la diabetes en el Sistema Único de Salud de Brasil, 2018]. *Rev Panam Salud Publica* 2020;44:e32. Portuguese. DOI: 10.26633/RPSP.2020.32
21. Lira-Batista MM da S, Dias RSC, Barros GM de, Lima GWF, Silva JKM da, Silva MRC, et al. Qualidade de Sono, desejos alimentares e marcadores bioquímicos de inflamação em profissionais de Saúde. *Res Soc Dev [Internet]* 2021;10(14):e245101422419. Available from: <https://rsdjournal.org/index.php/rsd/article/view/22419>
22. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343(7829):1-9. DOI: 10.1136/bmj.d5928
23. Usanos CA, Valenzuela PL, de la Villa P, Navarro SM, Melo Aroeira AE de, Amo Usanos I, et al. Neuromodulation of the prefrontal cortex facilitates diet-induced weight loss in midlife women: a randomized, proof-of-concept clinical trial. *Int J Obes [Internet]* 2020;44(3):568-78. DOI: 10.1038/s41366-019-0486-x
24. Lowe CJ, Staines WR, Mannochio F, Hall PA. The neurocognitive mechanisms underlying food cravings and snack food consumption. A combined continuous theta burst stimulation (ctBS) and EEG study. *Neuroimage [Internet]* 2018;177(September 2017):45-58. DOI: 10.1016/j.neuroimage.2018.05.013
25. Osimo SA, Korb S, Aiello M. Obesity, subliminal perception and inhibition: Neuromodulation of the prefrontal cortex. *Behav Res Ther* 2019;119:103408. DOI: 10.1016/j.brat.2019.05.005
26. Ljubicavljovic M, Maxood K, Bjekic J, Oommen J, Nagelkerke N. Long-Term Effects of Repeated Prefrontal Cortex Transcranial Direct Current Stimulation (tDCS) on Food Craving in Normal and Overweight Young Adults. *Brain Stimul* 2016;9(6):826-33. DOI: 10.1016/j.brs.2016.07.002
27. Fassini PG, Das SK, Magerowski G, Marchini JS, da Silva Junior WA, da Silva IR, et al. Noninvasive neuromodulation of the prefrontal cortex in young women with obesity: a randomized clinical trial. *Int J Obes [Internet]* 2020;44(6):1279-90. DOI: 10.1038/s41366-020-0545-3
28. Marron EM, Viejo-Sobera R, Cuatrecasas G, Redolar-Ripoll D, Lorda PG, Datta A, et al. Prefronto-cerebellar neuromodulation affects appetite in obesity. *Int J Obes (Lond)*. 2019;43(10):2119-24. DOI: 10.1038/s41366-018-0278-8
29. Fassini PG, Das SK, Suen VMM, Magerowski G, Marchini JS, da Silva Junior WA, et al. Appetite effects of prefrontal stimulation depend on COMT Val158Met polymorphism: A randomized clinical trial. *Appetite* 2019;140:142-50. DOI: 10.1016/j.appet.2019.05.015
30. Lowe CJ, Hall PA. Reproducibility and sources of interindividual variability in the responsiveness to prefrontal continuous theta burst stimulation (ctBS). *Neurosci Lett* 2018;687:280-4. DOI: 10.1016/j.neulet.2018.09.039
31. Saloner R, Cherner M, Sundermann EE, Watson CW, Iudicello JE, Letendre SL, et al. COMT val158met genotype alters the effects of methamphetamine dependence on dopamine and dopamine-related executive function: preliminary findings. *Psychiatry Res* 2020;292:113269. DOI: 10.1016/j.psychres.2020.113269
32. Hollis JH. The effect of mastication on food intake, satiety and body weight. *Physiol Behav [Internet]* 2018;193(October 2017):242-5. DOI: 10.1016/j.physbeh.2018.04.027
33. Dohle S, Diel K, Hofmann W. Executive functions and the self-regulation of eating behavior: A review. *Appetite [Internet]* 2018;124:4-9. DOI: 10.1016/j.appet.2017.05.041
34. Lent R. *Cem bilhões de neurônios*. 2ª. Vol. 2, Editora Atheneu. Rio de Janeiro; 2010. p 1.
35. Cohen JD, Perlstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, et al. Temporal dynamics of brain activation during a working memory task. Vol. 386, *Nature*. 1997. p. 604-11.
36. Luria AR. *The working brain*. New York: Basic Books. New York: Basic Book; 1973. p 1-2.
37. Zelazo PD., Reznick JS., Pinon D. Response control and the execution of verbal rules. *Dev Psychol*. 1995;31:508-17. DOI: 10.1037/0012-1649.31.3.508
38. Horie NC. Mudança cognitiva em obesos com comprometimento cognitivo leve submetidos à perda intencional de peso [Internet]. Faculdade de Medicina da Universidade de São Paulo; 2014. Available from: <http://www.teses.usp.br/teses/disponiveis/5/5135/tde-11052015-114427/publico/NidiaCelestehorie.pdf>
39. Pedroni-Pereira A, Araujo DS, Scudine KG de O, Prado DG de A, Lima DANL, Castelo PM. Chewing in adolescents with overweight and obesity: An exploratory study with behavioral approach. *Appetite [Internet]* 2016;107:527-33. DOI: 10.1016/j.appet.2016.08.122
40. Blanquet-Diot S, François O, Denis S, Hennequin M, Peyron MA. Importance of oral phase in vitro starch digestibility related to wholegrain versus refined pastas and mastication impairment. *Food Hydrocoll [Internet]* 2021;112(July 2020):106277. DOI: 10.1016/j.foodhyd.2020.106277