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Interhemispheric paired associative stimulation targeting the bilateral prefrontal cortex of subjects with obesity and food addiction modulates food-related emotional reactivity and associated brain activity

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ABSTRACT

Purpose: Behavioral and neurobiological abnormalities in addiction and obesity have led to the theory of food addiction in obesity (FAOB) and brain-behavior association studies. Transcranial magnetic stimulation (TMS) studies and treats various brain disorders. Cortico-cortical paired associative stimulation TMS protocol, in which left lateral prefrontal cortex (LPFC) stimulation follows right LPFC stimulation, can reduce emotional reactivity to visual triggers and modulate prefrontal asymmetry in healthy adults. Accordingly, we examined the effects of acute ccPAS on food cravings and brain responses in FAOB.

Methods: Twenty-two adults (12 Active, 10 Sham) with FAOB participated in this single-blind, sham-controlled pilot study. Electroencephalogram was recorded during rest and a Food Stroop task, which were conducted before and after a single active or sham ccPAS session, consisting of 600 paired stimulation pulses of the right, then left LPFC, with inter-pulse interval of 8ms and a 3sec inter-pair-interval. Stroop bias changes following exposure to food images, alterations in the associated (emotionally laden) late positive event-related component (LPPb) total brain activity power, and frontal alpha band asymmetry during rest and task performance were investigated.

Results: No baseline differences were detected between the groups, except for education level. Active (but not Sham) ccPAS elevated the Stroop bias and the total brain activity power over the left LPFC while no stimulation-related influence was found on the LPPb or prefrontal brain asymmetry during task and the resting state. However, the stimulation-induced change in the Stroop bias was negatively correlated with the change in LPPb magnitude, positively correlated with changes in asymmetrical activity during the task, and negatively with left frontal alpha asymmetry during rest.

Conclusions: The ccPAS affected food-related emotional regulation, probably due to general reduction of inhibitory control during task performance. Further studies are needed to affirm the results with larger samples and to elucidate the development of beneficial ccPAS protocol for obesity with food addiction.

1. Introduction

1.1. Obesity epidemic

Obesity is a global epidemic prevalent in children and adult worldwide (World Health Organization (WHO). Significant co-morbidities such as diabetes, cardiovascular diseases, cancer, and depression, are associated with this condition, weighing heavily on the global economy and public healthcare. To reduce the prevalence of obesity, traditional remedies such as diet and physical activity are often prescribed, but only about 5% of individuals with obesity who seek care, successfully achieve and maintain healthy body weight in the long run (J. W. Anderson et al., 2001). Over the past decade, the clinical construct of "food and eating addiction" (FA) has been suggested as a theory that explains why some individuals with obesity are resistant to conventional weight management or are unable to sustain weight loss goals in the long run. Indeed,

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data support FA as a contributing factor to the severity and chronicity of obesity (Pedram et al., 2013; Tompkins et al., 2017).

1.2. Food addiction

The validity of FA as a stand-alone clinical construct is under debate. Opponents claim that this construct is highly related to other overeating disorders, such as binge-eating disorder (BED) or bulimia nervosa (BN) (Davis, 2013; Hauck et al., 2020), and argue that the term "addiction" is inappropriate since food is a necessity, not something individuals can abstain from (Fletcher & Kenny, 2018; Ziauddeen et al., 2012). However, several studies have demonstrated that FA uniquely shares striking behavioral and neurobiological resemblance to other addictive conditions (Davis & Carter, 2009; Passeri et al., 2023). Symptoms of FA include frequent and excessive cravings for highly palatable ultra-processed food (HPUF) (Meule & Kübler, 2012); an urgency to consume these foods to relieve stress and negative affect (negative urgency) (Wolz et al., 2016); hypersensitivity to external cues signaling rewarding food (Volkow et al., 2017); impulsivity (Jasinska et al., 2012); disinhibition of dietary restraint in response to HPUF cues (Lubman et al., 2004); recurrent overeating past the point of satiety (Lavagnino et al., 2016); and reduced inhibitory control over eating (Batterink et al., 2010). As in drug addiction, these symptoms occur despite the adverse consequences of such behavior and patients' significant efforts to do otherwise (Moore et al., 2017). About a decade ago, the Yale Food Addiction Scale (YFAS) was established to quantify FA symptoms and the associated daily functional disruption (Gearhardt et al., 2009; Meule & Gearhardt, 2014). Based on the YFAS scores, FA has been repeatedly demonstrated as a significant factor contributing to weight gain and maintenance failure in overeating disorders and obesity (Lerma-Cabrera et al., 2016; Sawamoto et al., 2017). Therefore, the study of the mechanisms behind the symptoms of FA in obesity (FAOB) is warranted.

1.3. Altered neurobiological systems in obesity and food addiction

Recent advancements in brain imaging techniques have significantly enhanced our understanding of maladaptive brain circuits in obesity and FA (Albayrak et al., 2012). These include the ventral striatum and the prefrontal cortex (PFC) in the reward and executive systems, respectively (Volkow et al., 2017). The sensory attributes of highly palatable energy-dense food, such as its taste, image, or smell, are all active reinforcers, leading to intense dopaminergic secretion in the striatum and the PFC. In disorders of overeating, such as obesity and binge eating disorder, the function of meso-limbic and meso-cortical brain systems often becomes maladaptive, resulting in high, often uncontrollable, responsiveness to environmental or sensory cues signaling highly palatable food. This intense response to a salient cue is termed attention bias, linked to an over-sensitized dopaminergic system in frontostriatal circuits (B. A. Anderson et al., 2017). The imbalance between motivational drives emerging from the striatum and inhibitory control systems in the lateral PFC (mainly the dorsolateral PFC) results in loss of control over food intake and eventual weight gain (Passamonti et al., 2009; Shank et al., 2015).

Cognitive regulation of eating also entails a functional balance between the left and right prefrontal cortices (lPFC and rPFC, respectively) (Gable & Harmon-Jones, 2007). The right and left PFC play mutual and specialized roles in executive functions that regulate eating (Lowe et al., 2019). They work cooperatively to regulate eating-related drives and decision-making, aligning with long-term health and weight management goals (Lowe et al., 2019). They also communicate with lower brain structures, which receive metabolic signals from the periphery, to drive or terminate eating (Plassmann et al., 2021). In addition to their collective role in eating regulation, they also have specialized functions. The left PFC (lPFC) plays a pivotal role in cognitive reappraisal, including emotional regulation and the drive to approach food (Alonso-Alonso & Pascual-Leone, 2007; Dixon, 2015). The right PFC, specifically the right lateral PFC, however, is essential for self-control and the inhibition of impulsive tendencies (Alonso-Alonso & Pascual-Leone, 2007), the impairment of which is a hallmark of addiction (Kozak et al., 2019). For example, the right LPFC is crucial for inhibiting the drive to eat in response to food-related cues (Lowe et al., 2019), especially in environments where high-calorie foods are easily accessible.

In line with the approach-avoidance motivational direction theory, left-sided lateral prefrontal asymmetry (i.e., greater left LPFC compared with right LPFC activity) is associated with a tendency to impulsively respond to a salient cue and an impaired ability to avoid (or inhibit) behaviors generating undesirable outcomes, such as those that do not align with long-term goals (Kelley et al., 2017). In the digestive research domain, enhanced left LPFC oxygenated blood flow in fMRI studies, or reduced alpha band EEG activity in a resting state, are usually a proxy for prefrontal brain asymmetry. For example, left LPFC fMRI asymmetry has been observed in chronic overeaters (Brooks et al., 2013; Ely et al., 2013, 2013, 2013), and in obese binge eaters (Karhunen et al., 2000), while left LPFC EEG alpha band asymmetry has been demonstrated in participants with high hedonic hunger (van Bochove et al., 2016; Winter et al., 2016). In these conditions, individuals tend to discount the delay of highly palatable food rewards, despite the absence of physiological hunger (Kishinevsky et al., 2012). Particularly in stressful situations, or those that elicit negative affect (Sinha & Jastreboff, 2013; Yau & Potenza, 2013), these individuals might impulsively overeat, failing to account for the long-term consequences of their behavior (Moore et al., 2017).

In contrast to left LPFC asymmetry, right-sided lateral prefrontal asymmetry (i.e., greater right LPFC activity compared with left LPFC activity) is associated with successful self-control of eating (Alonso-Alonso & Pascual-Leone, 2007; Ely et al., 2013) and cognitive inhibition of the desire for food reward (McGeown & Davis, 2018; Silva et al., 2002). Therefore, manipulating prefrontal asymmetry rightward might help regulate eating (McGeown & Davis, 2018) by reducing the intense responsivity to and cravings for highly palatable foods, and/or increasing the inhibition of the impulsive tendencies to overeat these foods. However, this has not yet been tested in FAOB participants.

1.4. Non-invasive brain stimulation (NIBS) in obesity

One approach to test and modulate maladaptive brain systems is non-invasive brain stimulation (NIBS), such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Despite inconsistencies between study methodologies, such as the protocol and modality utilized, the site and frequency of the stimulation, and the study population, TMS appears slightly more effective than tDCS in reducing food cravings but not necessarily body weight (Gouveia et al., 2021) in obesity. This is particularly true for studies examining repetitive TMS (rTMS) for food craving reduction, binge eating frequency, and overall eating disorder psychopathology in binge eating disorder (BED) and obesity (Hall et al., 2018). Although differing stimulation methodologies complicate drawing firm conclusions about the most effective protocol for these conditions, they consistently underscore the role of inhibitory control systems in the LPFC. For instance, a single session of continuous theta burst stimulation (cTBS) to the left LPFC attenuated inhibitory control activity and increased rewarding food intake (Lowe et al., 2018). Conversely, multiple sessions of excitatory high-frequency rTMS to the same area strengthened inhibitory control, resulting in decreased food intake and body weight at the end of the sessions (Kim et al., 2019). Considering the central role of interhemispheric communication in brain functional asymmetry (Nowicka & Tacikowski, 2011), a neuromodulation technique directly targeting the interconnectivity between the right LPFC and left LPFC may be even more potent than the regular single-site stimulation rTMS methods. This has not yet been tested in the context of eating behavior.

A TMS protocol termed paired associative stimulation (ccPAS) can target cognitive-emotional circuits in the PFC, by coordinating timed stimulation of two interconnected cortical areas (hence, cortico-cortical PAS, ccPAS) (Veniero et al., 2013; Zibman et al., 2019). The ccPAS is based on Hebbian plasticity, according to which connections are strengthened or weakened depending on the timing of the pre- and post-synaptic stimuli (Müller-Dahlhaus et al., 2010; Song et al., 2000). In a recent study applying ccPAS in healthy adults, we tested the coordinated stimulation of the right LPFC and left LPFC, aiming to alter the connectivity between these two homologous brain regions. Results indicated that repeated stimulation of the right LPFC 8 ms prior to the left LPFC (R-L ccPAS) reduced emotional reactivity to angry faces in an emotional Stroop paradigm, compared to both L-R ccPAS protocol and sham stimulation. It additionally enhanced interhemispheric signal propagation and directed coherence from the right to the left LPFC, and induced a leftward shift in alpha band resting state activity compared to the L-R (but not sham) ccPAS, suggesting a rightward shift in brain activity (Zibman et al., 2019).

In another study, we conducted the food Stroop task to measure the influence of rewarding food cues on attentional bias and associated brain activity (Aviram-Friedman et al., 2020). Participants were presented with food and control images 500 ms before each Stroop trial, and we measured their reaction time along with EEG components related to image processing. The study found that the FAOB participants exhibited reduced attentional Stroop bias (i.e., less interference from incongruent Stroop words) following images of rewarding foods compared to healthy controls and individuals with obesity but without food addiction. Additionally, the study identified early and late components, emerging after image presentation and before the Stroop word, which were associated with the image content. Among these components, only the late positive potential (LPP), known to reflect the emotional processing of arousing affective pictures (Schupp et al., 2000), was associated with the Stroop bias. Moreover, the LPP magnitude, initially consistent across the study groups (LPPa, 300–450 ms post-image onset), was abruptly reduced before introducing the Stroop word (LPPb, 450–495 ms) in the FAOB group only. We interpreted these results as FAOB participants' efforts to regulate their intense emotional reactions to triggering cues to enhance task performance. The early recruitment of inhibition processes presumably drifted toward the Stroop task and reduced the Stroop bias.

Considering the findings from both studies, we hypothesized that R-L ccPAS might reduce intense emotional reactivity toward triggering food cues in individuals with obesity and food addiction, alleviating their need to regulate their initial response, and aligning their bias in the food Stroop task with that of healthy participants. We also hypothesized that R-L ccPAS might affect their LPFC activity and asymmetry, similar to the effect observed in healthy controls (Zibman et al., 2019). Therefore, we examined attentional bias and electrophysiological responses to highly palatable food images during the food Stroop task, and we measured right and left LPFC resting activity before and after a single session of R-L ccPAS.

2. Material and methods

2.1. Participants

Twenty-two adults with overweight, obesity, and food addiction were recruited and randomly assigned to Active (12 participants) or Sham (10 participants) stimulation, as part of a pilot clinical trial testing the efficacy of a 3-week TMS treatment on body weight (registration number: NCT02761369). Participants were asked to fill out the YFAS on a pre-study phone screening (Meule & Gearhardt, 2014), and had to have at least 3 FA symptoms and a positive score on the clinical significance scale [for a detailed description of the YFAS scale see Aviram--Friedman et al. (2020)]. On the pre-study phone screening, potential participants also filled out a general demographic questionnaire, requiring them to have had at least one prior conventional weight loss attempt, but no attempts currently or during the past three months. Other inclusion criteria were age between 20 and 65, stable health condition in the past three months, and a BMI between 28 and 40. Exclusion criteria were a cognitive or functional disability diagnosed in the past year; starting or changing a psychotropic prescription in the past three months; substance abuse, current or in the past 12 months; known or suspected pregnancy or lactation; or practicing veganism (due to the non-vegan food cues utilized in this study). Participants signed an informed consent form approved by the ethics committee at Soroka University Medical Center, and they filled out a short TMS safety questionnaire to ensure no contraindications with TMS (Rossi et al., 2009).

2.2. Study design

This was a single-blind, sham-controlled, proof-of-concept study. Eligible participants were allocated by an independent investigator to receive either active or sham TMS, utilizing a minimization method based on age and BMI (Scott et al., 2002; Treasure & MacRae, 1998). The participants were naïve to TMS and blind to their group assignment.

2.3. General procedures

Detailed preparatory procedures briefly described herein are further elaborated in Aviram-Friedman et al. (2020). Participants were asked to follow preparatory guidelines before arriving at the lab, which included a 48-hr abstinence from alcohol and recreational drugs, a dietary preparation to follow 24-h before their arrival, and an overnight fast. On the study day, participants arrived at the lab at ~9am, when baseline measures were taken, including body weight and several questionnaires assessing different psycho-behavioral parameters (see *2.7 Psycho-behavioral questionnaires* below). Thereafter, participants were provided with a standardized breakfast of bland food, to control metabolic hunger and intensify cravings for cafeteria food cues (Duncan & Northoff, 2013; Stockburger et al., 2009; Tapper et al., 2010).

Next, participants were prepared for EEG acquisition, and their brain activity was measured during the Food Stroop task and at rest, before and after the R-L ccPAS. In the present study we aimed to examine brain signals indicative of food cravings in the absence of hunger, necessitating close monitoring of metabolic hunger (Alsiö et al., 2012). Therefore, self-reported hunger of the participants was monitored before each Stroop task using a Visual analogue scale (VAS), and a snack of their choice (a small container of either plain yogurt or unsweetened apple sauce) was provided before the 2nd Stroop task, to standardize metabolic hunger (Aviram-Friedman et al., 2020). Procedural specification is detailed in Fig. 1A.

2.4. TMS: R-L ccPAS

The TMS was delivered using a multi-channel deep TMS system (Brainsway, Jerusalem, Israel) (Roth et al., 2014), which contains two H-D1 coils, one incorporated into each side of a helmet. These coils stimulate multiple portions of the anterior and posterior of LPFC, including BA #10, 9, and 8, with a maximal induction point over the dorsolateral prefrontal cortices (Fig. S1), which correspond to EEG electrodes F4 and F3 (Zibman et al., 2019).

Resting motor thresholds (RMT) of both hemispheres were assessed prior to the 1st resting EEG measurement (see Fig. 1 for the timeline and the sequence of procedures), by testing the lowest stimulation intensity at which 3 out of 6 TMS pulses produce a response in the abductor pollicis brevis muscle of the contralateral hand. This criterion was chosen for the larger clinical trial, where we conducted daily RMT assessments (Fitzgerald & Daskalakis, 2022). The TMS helmet was then centered and moved 6 cm forward from the motor hotspot, over the sagittal axis, to its final placement over the right and left LPFC (Zibman

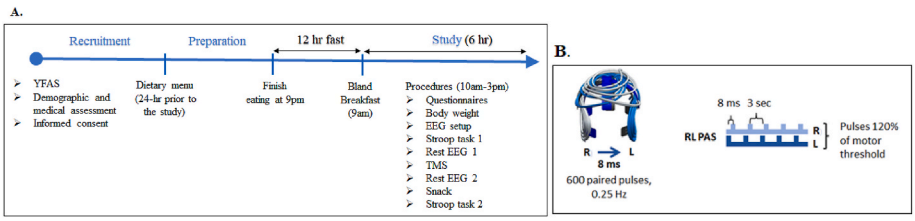

Fig. 1. A. Recruitment, preparation, and study procedures. **B.** The R-L ccPAS protocol. YFAS: Yale Food Addiction Scale; TMS: Transcranial Magnetic Stimulation.

et al., 2019). This in accordance with the 6 cm rule which has been established clinically in depressive patients for targeting the pathological LPFC (Herwig et al., 2001; Levkovitz et al., 2015; Zangen et al., 2023).

The R-L ccPAS consisted of 600, lagged pairs of pulses starting with the rLPFC and then the lLPFC, with inter-pulse interval of 8 ms and a 3-sec inter-pair-interval. This is summated to 1800 s (30 min) per session (Fig. 1B). The intensity of the stimulation was set as 120% or 40% of the RMT for the Active and Sham stimulation, respectively. Sham intensity was based on the previous studies indicating it is below any intensity shown to affect plasticity (Abrahamyan et al., 2015; Huang & Rothwell, 2004a; Todd et al., 2006; Zibman et al., 2019) yet still strong enough for the participants to experience some acoustic and scalp sensations, making blinding more efficient.

2.5. The Food Stroop task

For details regarding the Food Stroop task, the reader is referred to Aviram-Friedman et al. (2020). In short, the Food Stroop is a version of the combi-Stroop test (Fadardi & Bazzaz, 2011; Nijs et al., 2010), in which food images precede the Stroop stimuli, to test the image influence on participants' emotional attention. Each Stroop trial began with a fixation cross presented for 800 ms, followed by an image of either high-calorie food (HCF), low-calorie food (LCF), or non-food (NF) items (such as furniture), presented for 500 ms. Thereafter the Stroop word (congruent, incongruent, or neutral) was presented for a maximal duration of 2500 ms, or until the participant responded on the keyboard (Fig. 2). The inter-trial interval was randomly set between 1100 and 1900 ms.

There were 540 trials overall, sixty for each combination of picture type (HCF, LCF, or NF) and Stroop condition (congruent, incongruent, or neutral). Each of the 180 pictures was exposed once in combination with each Stroop condition. Participants were instructed to press as quickly and accurately as possible on the key associated with the color of the word, while ignoring the word's meaning.

Stroop bias scores were computed as the difference in mean reaction times (RT) between incongruent and congruent conditions, excluding error-response trials or ones with RT $>$ 1200 ms, to account for the full attentional bias elicited by the Stroop stimuli (Aviram-Friedman et al., 2020). Higher bias scores denote greater cognitive conflict, which delays response time in incongruent conditions.

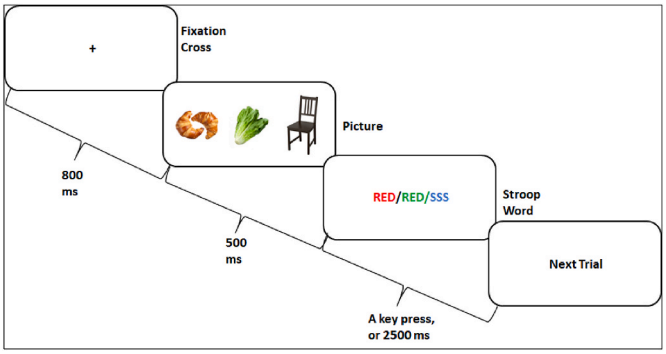

Fig. 2. The Food Stroop task experimental paradigm.

2.6. Electrophysiology (EEG) procedures

EEG was acquired using ASA™ version 4.7.3, a 64 electrode Wave guard cap (ANT neuro, Enschede, Netherlands) and a TMS-compatible EEG amplifier (TMSi, Oldenzaal, Netherlands), grounded to the POz electrode and referenced to the Cz (referenced offline to the average). Impedance was kept below 5 kOhm, the recording frequency was set to 2048 Hz, and data was digitized with a 24-bit AD converter. Off-line data processing was conducted using EEGlab 14.0.0 (Delorme & Makeig, 2004) and the FieldTrip toolbox in Matlab (version R2018a; MathWorksInc., Natick, USA) (Oostenveld et al., 2011), by a trained researcher.

The Stroop data were filtered using a 1–100 Hz band-pass and 45–55 Hz notch finite impulse response filters and then epoched and baseline-corrected around the appearance of the food image (regardless of the Stroop condition), starting at 500 ms before, and ending 1000 ms after image appearance. Noisy channels and epochs were detected automatically, followed by manual review and rejection (absolute amplitude threshold of $\pm$150 μV or improbability threshold of 3 standard deviations above the mean of the entropy value). Next, an infomax Independent Components Analysis (ICA) was conducted; eye blinks and eye movement-related ICA components were manually removed, and a second automatic and manual scan ensured no residual noisy segments were left, leaving an average of 147.74 $\pm$ 27.62 epochs per condition. Finally, rejected channels were interpolated using spline interpolation and data were analyzed in the time domain, as Event-Related Potentials (ERP).

Resting state EEG was recorded over a 5-min resting period (lights dimmed, eyes closed), segmented into 2-s epochs and further pre-processed in a similar manner as above, leaving an average of 140.92 $\pm$ 38.21 epochs per file. Data were then transformed into the frequency domain using a fast Fourier transform (1–100 Hz; 0.065 Hz frequency resolution), alpha power (8–12 HZ) was extracted for each electrode, and brain asymmetry scores were calculated as the decibel-transformed power ratio between each left electrode and its homologues right one.

One subject from the Active group and one from the Sham group were excluded from electrophysiological analysis of the Stroop and the Resting state, correspondingly, due to low quality of the EEG signal.

2.7. Psycho-behavioral questionnaires

The YFAS (Meule & Gearhardt, 2014) is a widely researched instrument aiming to assess food addiction symptoms and the clinical distress associated with the symptoms experienced. This instrument, which has good psychometric properties (Cronbach's alpha: 0. 84) (Lemeshow et al., 2016), can reliably distinguish between individuals showing symptoms of addictive eating and those who do not (Gearhardt et al., 2009).

For more details about the YFAS and other questionnaires employed in the study [the Three-Factor Eating Questionnaire (TFEQ), Binge Eating, Beck Depression Inventory (BDI), Positive Affectivity Negative Affectivity Schedule (PANAS), and a Visual Analogue Scale (VAS) of

hunger)], please refer to Aviram-Friedman et al. (2020).

2.8. Outcome measures and statistics

All statistical inference tests were performed using two-tailed tests requiring a-priory alpha level of 5%. Participants' demographic and baseline clinical data were tested for group differences using independent t and Chi-square tests.

The effect of R-L ccPAS on the Stroop bias in response to the attentionally relevant HCF images was tested using a 2-way mixed model ANCOVA (STATISTICA 13; TIBCO Soft Inc.) with time (pre-ccPAS, post-ccPAS) as a within-subjects' factor, and group (Active and Sham) as a between subjects' factor. Previous studies demonstrated the need to control individual hunger levels, and transitory mood states, when testing attentional bias to food cues (Cox et al., 2006; Rutters et al., 2009; Stockburger et al., 2009). Furthermore, baseline pre-ccPAS incidental significant and marginal group difference was detected in education level, YFAS-S, and TFEQ-CR scores (see Table 1). Yet, of those variables and in accordance with previous findings (Aviram-Friedman et al., 2020), only YFAS-S was found to interact with the baseline level or the treatment-related change in the food Stroop bias (Table S1). Hence, PANAS, hunger, and YFAS scores were entered into the ANCOVA as covariates.

The effect of R-L ccPAS on brain activity during the Stroop task was investigated using two approaches. The first was a task-based approach, focusing on the Stroop task indices and brain activity components sensitive to food addiction. Specifically, we tested the influence of brain stimulation on the Stroop bias and the LPPb component (the latest part of the late positive potential, just before the introduction of the Stroop word) elicited following HCF images. This is based on previous results (Aviram-Friedman et al., 2020) indicating that the Stroop bias of FAOB participants (differently from both obese participants with no food addiction and healthy controls) was specifically reduced by exposure to HCF images. The same work also found that the LPPb was the only component, among several earlier ones (namely, P100, N200, P300, and LPPa), that was associated with both food addiction and the Stroop bias elicited by food images. Following these results, we pre-defined the LPPb time window (450–495 ms), as well as two regions of interest (ROIs): frontal (electrodes: F1, Fz, F2, FC1, FCz, FC2) and right posterior (P2, P4, P6, P8, PO4, PO6, PO8, O2).

The second approach was stimulation-based, which assumes that the effect of ccPAS on brain activity (i.e., neuronal potentiation or depression) would be evident in the total EEG power of electrodes under the stimulation area in a generalized manner, unrelated to a specific event-related component elicited by the task stimuli or conditions. Thus, the activity power in electrodes F3 and F4 (Zibman et al., 2019), averaged over all food and Stroop conditions, was first calculated as the log transformed variance of the unrectified amplitudes in the entire time window, beginning at the appearance of the food image and ending 500 ms following the appearance of the Stroop word (i.e., 0–1000 ms; see Fig. 4). As ccPAS may additionally influence the activity balance between the two hemispheres (Zibman et al., 2019), we also calculated inter-hemispheric asymmetry as the log-transformed power ratio between these two electrodes (i.e. F3 and F4). The influence of RL-ccPAS on resting state alpha asymmetry under the stimulation electrodes was additionally investigated as a part of the stimulation-based approach.

ccPAS induced changes in brain activity and their correlation with ccPAS-induced changes in the Stroop bias were tested using non-parametric permutation tests (Monte-Carlo method) implemented via the FieldTrip toolbox (Oostenveld et al., 2011). Permutation tests repeatedly and randomly sample the data (10000 iterations) to evaluate the characteristics of the sampling distribution under the null hypothesis, obviating the need for prior assumptions. Following the ANCOVA logic, brain activity scores were first residualized from the influence of PANAS, hunger, and YFAS-S levels, using a linear regression model. Active-Sham group differences in correlation magnitude were tested using Fisher Z test.

Table 1
Demographic and clinical baseline levels.

	Sham TMS (M±SE)	Active TMS (M±SE)	*p* level
AGE	38.9 (4.29)	40.375 (4.33)	0.81
Gender (M, F)	2, 8	4, 8	0.48
Education	15.3 (0.60)	13.5 (0.54)	0.04*
BMI	34.74 (1.07)	34.6 (1.46)	0.94
YFAS-S	5.3 (0.47)	6.25 (0.30)	0.10
TFEQ-CR	11.85 (0.43)	14.65 (1.20)	0.06
TFEQ-UE	27.5 (1.80)	28.92 (1.00)	0.48
TFEQ-EE	10 (0.92)	9.33 (0.66)	0.55
BE	6.75 (1.67)	6.30 (2.08)	0.87
BDI	10.3 (1.65)	9.92 (2.42)	0.90
PANAS	17.9 (2.58)	19.08 (2.43)	0.74
VAS-hunger	4.6 (0.37)	5.03 (0.28)	0.36

*p < 0.05; YFAS-S: Yale Food Addiction Scale Symptoms; TFEQ-CR: Three Factor Eating Questionnaire Cognitive Restraint; TFEQ-UE: Uncontrollable Eating; TFEQ-EE: Emotional Eating; BE: Binge Eating symptoms; BDI: Beck Depression Inventory; PANAS: Positive and Negative Affect Schedule; VAS-hunger: Visual Analogue Scale - Hunger.

3. Results

3.1. Demographic and baseline data

Detailed demographic and clinical information of the participants are presented in Table 1. No baseline group differences were detected in the demographic and clinical data, except for education ($t_{(21)} = 2.23$, $p = 0.04$) and marginal incidental differences in the TFEQ-CR and YFAS-S. No baseline group differences were found in the other behavioral and electrophysiological measures (Table S2).

3.2. The effect of R-L ccPAS on the Stroop bias and LPPb amplitude in response to high-calorie food images (a task-based approach)

ANCOVA of the R-L ccPAS influence on the Stroop bias following presentation of HCF images revealed a significant time by stimulation group interaction ($F_{(1,17)} = 5.26$, $\eta^2_{partial} = 0.24$, $p = 0.03$). Post-hoc Bonferroni corrected tests indicated that the active but not the sham stimulation group, experienced an elevation in the (post-PAS) Stroop bias following HCF images ($F_{(1,17)} = 10.07$, $\eta^2_{partial} = 0.37$, $p = 0.008$; Fig. 3A).

The R-L ccPAS had no overall influence on the LPPb amplitude (between group tests, frontal ROI: $t_{(n = 21)} = 0.67$, $p = 0.50$; right posterior ROI: $t_{(n = 21)} = 0.06$, $p = 0.95$; Fig. 3B). Nevertheless, stimulation-related LPPb amplitude alterations correlated with those of the Stroop bias in the Active (frontal ROI: $r_{(n = 11)} = 0.72$, $p = 0.02$; posterior ROI: $r_{(n = 11)} = -0.77$, $p = 0.005$) but not in the Sham group (frontal ROI: $r_{(n = 10)} = -0.47$, $p = 0.17$; posterior ROI: $r_{(n = 10)} = 0.33$, $p = 0.35$; Fig. 3C and D). Fisher Z test confirmed the difference in correlation magnitudes between the two groups (frontal ROI: $Z = 2.74$, $p = 0.003$; posterior ROI: $Z = 2.63$, $p = 0.004$). Note that non-parametrical tests do not use F or t distributions; hence, sample size is detailed rather than the degrees of freedom. Additionally note that the LPPb polarity is positive in the right posterior ROI and negative in the frontal one (Aviram-Friedman et al., 2020), hence the correlations found in the active group reflect negative relationships between the LPPb magnitude change and the Stroop bias change.

3.3. R-L ccPAS influence on total activity power during the stroop task, and brain asymmetry during the resting state (stimulation-based approach)

R-L ccPAS enhanced total activity power during the Stroop task in LPFC electrodes under the stimulation area. This effect was observed in left but not in right stimulation electrode (between group differences in

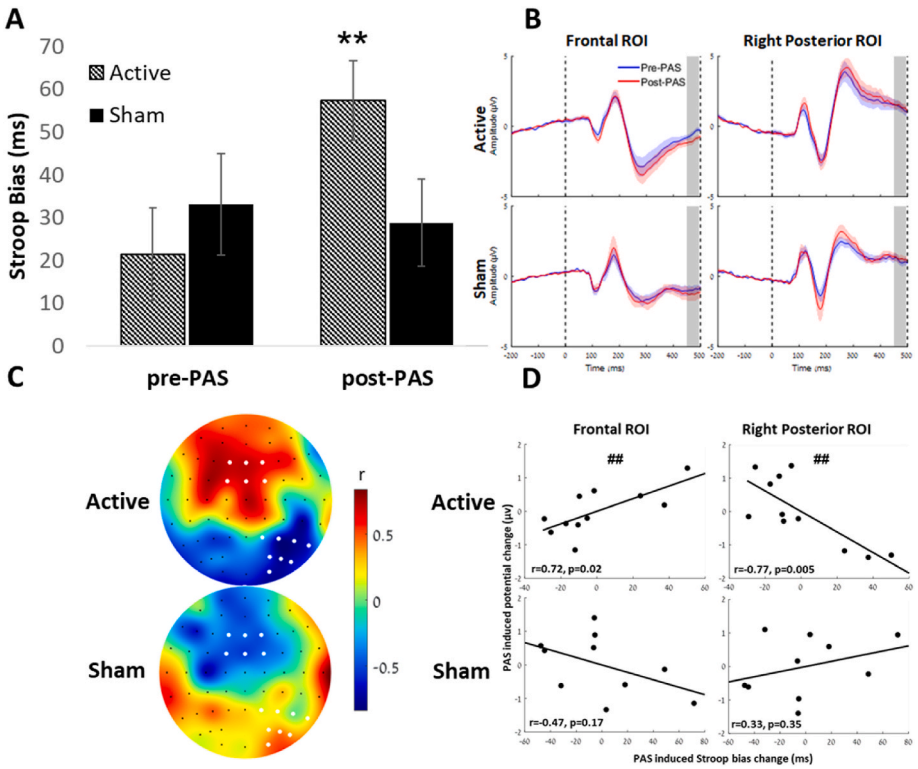

Fig. 3. The Influence of R-L ccPAS on the Stroop bias and its correlation with LPPb amplitude (a task-based approach). (A) Bar graph of the Stroop bias (Mean ± SEM) following high-calorie food images, before and after Active and Sham R-L ccPAS. (B) Event-related potential curves (±SEM), locked to image presentation, before and after Active and Sham R-L ccPAS in the frontal and right posterior ROI. Dashed lines represent the food cues and the Stroop word, respectively. Time window of the LPPb (450–495 ms) is marked gray. (C) Topographical plots of the correlation magnitude between the Stroop bias change and the LPPb amplitude change, induced by Active and Sham R-L ccPAS (ROI electrodes are marked white). (D) Scatter plots of the same as in C in the frontal and right posterior ROIs. All data presented in A, C, and D is controlled for PANAS, hunger level, and YFAS score. $^{**}p < 0.01$ pre-vs post-ccPAS; $^{\#\#}p < 0.01$ Active vs Sham.

the left electrode: $t_{(n = 21)} = 2.25$, $d_{conhen} = 0.98$, $p = 0.03$; Pre-post contrast in the active group: $t_{(n = 11)} = 2.76$, $d_{conhen} = 0.83$, $p = 0.01$, and in the sham group: $t_{(n = 10)} = 0.43$, $d_{conhen} = -0.13$, $p = 0.68$; Between-group differences in the right electrode: $t_{(n = 21)} = 1.17$, $p = 0.25$; Pre-post contrast in the active group: $t_{(n = 11)} = 1.48$, $p = 0.17$, and in the sham group: $t_{(n = 10)} = 0.26$, $p = 0.80$. Fig. 4: A, B, C). LPFC total power asymmetry scores during the task indicated only a trend level shift of power to the left hemisphere (between-group difference: $t_{(n = 21)} = 1.29$, $p = 0.22$; Pre-post contrast in the active group: $t_{(n = 11)} = 1.97$, $p = 0.09$, and in the sham group: $t_{(n = 10)} = 0.14$, $p = 0.89$). Nevertheless, it was the change in left asymmetry (Active group: $r_{(n = 11)} = 0.69$, $p = 0.03$; Sham group: $r_{(n = 10)} = 0.19$, $p = 0.59$; $Z = 1.27$, $p = 0.2$; Fig. 4D) rather than the change in total power (Active group: $r_{(n = 11)} = 0.33$, $p = 0.32$; Sham group: $r_{(n = 10)} = 0.37$, $p = 0.29$) which was found positively associated with the change in the Stroop bias following the stimulation.

Finally, the R-L ccPAS did not induce differences in resting state left alpha asymmetry (between group tests: $t_{(n = 21)} = 1.49$, $p = 0.15$; Fig. S2 in Supplements). Yet, a negative correlation was observed under the left stimulation area in the active but not in the sham group (Active group: $r_{(n = 12)} = -0.64$, $p = 0.03$; Sham group: $r_{(n = 9)} = -0.01$, $p = 0.97$; $Z = 1.42$, $p = 0.15$; Fig. 5: A,B).

4. Discussion

The present study examined the effect of a single R-L ccPAS session on emotional responsiveness to the presentation of highly palatable food images and brain electrophysiology, in participants with food addiction and obesity. This was evaluated as the change in the Stroop bias and the associated electrophysiological component (LPPb) following the presentation of the images (i.e., a task-based approach), and as the change in total brain activity power during the task, as well as alpha asymmetric activity during the resting state (i.e., a stimulation-based approach). We found a direct effect of the stimulation on the Stroop bias and on total brain activity during the task, but not on LPPb magnitude or prefrontal total power asymmetry. The Stroop bias following brain stimulation was higher in the active group but not in the sham group, and this was negatively correlated with the LPPb magnitude change over frontal and occipital electrodes. In the stimulation-based approach, a potentiation of total brain activity was detected in the active group but not in the sham group, over the left and, to a lesser extent, the right stimulation areas. No differences between the groups in alpha asymmetry in the resting state were detected. Additionally, stimulation-related changes in the total left asymmetric brain activation during the task, and in the left alpha asymmetry during the resting state, were positively and negatively correlated with the Stroop bias change, respectively.

The influence of ccPAS on emotional reactivity was previously indicated as bias toward angry faces (Zibman et al., 2019). Although arousing visual cues tend to draw attention similarly regardless of their valence (Cuthbert et al., 2000), the ability of ccPAS to affect the attentional appeal of positive stimuli had to be investigated. Likewise, ccPAS studies (Buch et al., 2011; Koch et al., 2013; Veniero et al., 2013), including interhemispheric ccPAS (Rizzo et al., 2009), repeatedly demonstrate its ability to alter the excitation level of the target area through the strengthening of the connectivity between the two stimulated brain areas. Yet, the potentiation of total activity power under the stimulation area is nontrivial, given the low stimulation frequency of the ccPAS (i.e., paired stimulation once every 3 s), which could be expected to cause long-term depression of brain activity similar to low-frequency repetitive TMS (Thut & Pascual-Leone, 2010). Finally, this influence of ccPAS on behavior and excitability is usually measured using motor-evoked responses to M1 stimulation (Rizzo et al., 2009). Thus, the current findings add to the accumulating evidence regarding the ability

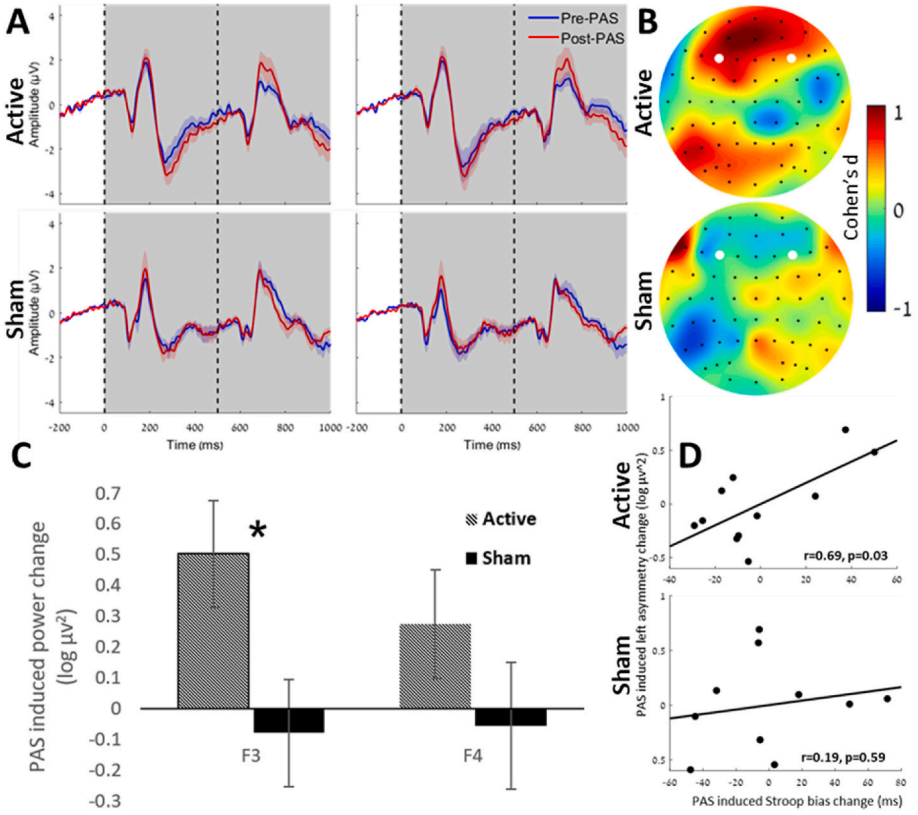

Fig. 4. The effect of R-L ccPAS on total activity power under the stimulation area (a stimulation-based approach). (A) Event-related potential curves (±SEM) locked to image presentation, before and after Active and Sham R-L ccPAS in electrodes under the left (F3) and right (F4) stimulation area (marked white in B). Dashed lines mark the presentation of the food images and the Stroop word, respectively. Yet curves are averaged over all the food and Stroop conditions. Hence, they reflect general activation unrelated to any task specifications. The time window used to calculate the power (0–1000 ms) is marked gray. (B) Topographical plots of power changes induced by the Active and Sham R-L ccPAS. Differences are expressed as Cohen's d effect size. (C) Bar graph (mean ± SEM) of the same as in B in electrodes F3 and F4. (D) Scatter plots of the correlation between changes in the Stroop bias and left asymmetry scores induced by the Active and Sham stimulations. Data presented in D is controlled for PANAS, hunger level, and YFAS score. *$p < 0.05$.

of ccPAS to causally alter brain activity outside of the motor cortex and affect related emotional behavior.

A neurobehavioral marker of food addiction is an intensified approach toward and failure to inhibit the overconsumption of highly palatable food (Lavagnino et al., 2016). These tendencies align with the approach-avoidance motivation theory, linking a leftward shift in prefrontal brain dominance with behavioral approach toward an appetitive stimulus or a reduction in the tendency to avoid an aversive stimulus (Kelley et al., 2017). While the approach-avoidance theory does not readily distinguish between these two motivational tendencies, the current results suggest a possible, more univocal explanation. In accordance with the study hypothesis, the active R-L stimulation induced prolongation of the Stroop bias of FAOB participants compared to their sham counterparts, "normalizing" it to that of participants with obesity without food addiction and healthy controls (Aviram-Friedman et al., 2020). Importantly, the change in the Stroop bias was negatively correlated with the change in the LPPb magnitude, suggesting reduced regulation of the emotional responses to the food cues. This interpretation is further supported by the correlations between Stroop bias changes and brain asymmetry changes during task performance and the resting state. While total power during the task indicates activity, alpha power during the resting state indicates inactivation (Alyagon et al., 2020; Jensen & Mazaheri, 2010). Thus, contrary to our expectations, both correlations indicate a positive association between the prolongation of the Stroop bias and enhanced left asymmetry, which may be linked to a reduction of inhibitory functions (Winter et al., 2016), rather than a reduction in the emotional response of FAOB participants to the food cues. The study results indicate successful modulation of inhibitory control systems in response to reinforcing foods in FAOB, which holds potential for future ccPAS studies in this population. However, the exact protocol that can benefit individuals with obesity or FAOB, remains unknown.

Various neuromodulation approaches have been employed to investigate the role of PFC mechanisms in food cravings and consumption, building on research that consistently highlights the involvement of this brain region in obesogenic behaviors (Brooks et al., 2013b; Lowe et al., 2019). For instance, Lowe et al. (2018) used continuous theta burst stimulation (cTBS) to inhibit the left LPFC in participants with either overweight or healthy body weight. They tested the effects of stimulation on food intake, neurocognitive functions related to inhibitory control (via the Flanker task) and electrophysiology measures (event-related components such as P3a, P3b, and N2). They observed that stimulated increased food intake, and, through a mediation analysis, found an indirect effect of inhibitory control on food consumption (Lowe et al., 2018). Another cTBS study demonstrated a prolonged Stroop bias following inhibition of the left LPFC (Lowe et al., 2014). The findings of the current study align with these and other neurobehavioral studies, underscoring the role of the LPFC in inhibitory control mechanisms related to obesity. While the results of the current study are preliminary, they contribute valuable insight by highlighting the involvement of bilateral interhemispheric prefrontal interactions in inhibitory control and emotional regulation in obesity and food addiction. Future research in this area should aim to standardize the population studied (healthy weight, obesity, eating disorders, food addiction), and the stimulation protocol used (e.g., unilateral right or left stimulation, inhibitory or excitatory, bilateral interhemispheric

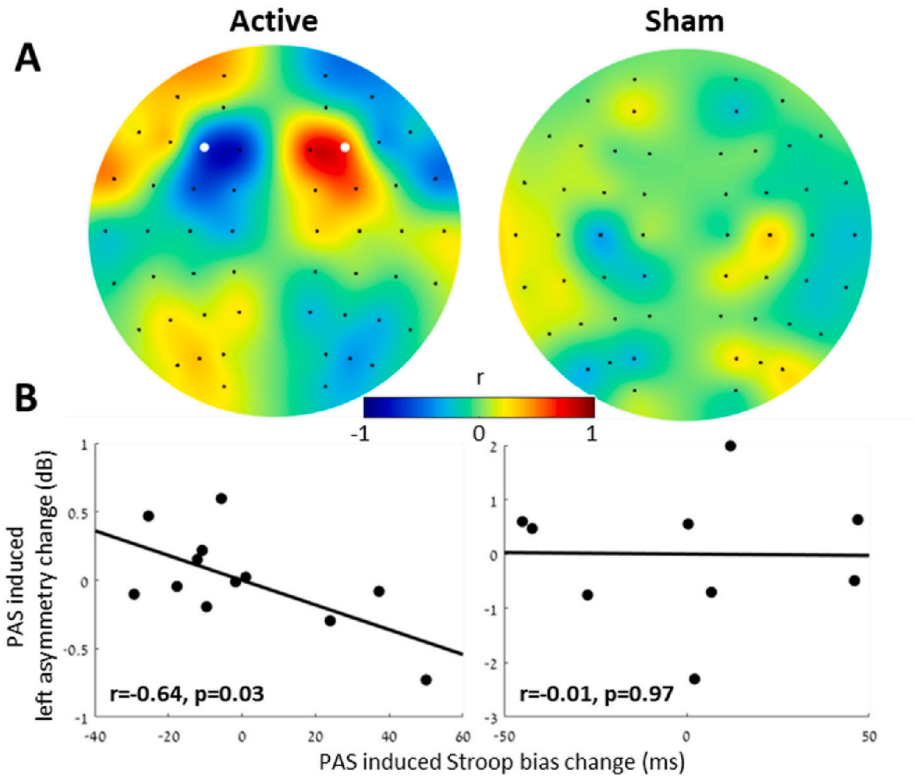

Fig. 5. Correlations between the R-L ccPAS stimulation-induced changes in the resting state alpha asymmetry and in the Stroop bias (a stimulation-based approach). (A) Topographical plots of the correlation magnitude between changes in Stroop bias and in alpha asymmetry during resting state, induced by Active and Sham R-L ccPAS (ROI electrodes are marked white). (B) Scatter plots of the same as in A in the left stimulation electrode (F3). Data presented in A and B are controlled for PANAS, hunger level, and YFAS scores.

stimulation), to draw more robust conclusions regarding the neurocognitive mechanisms underlying these conditions.

Food addiction (FA) may contribute to certain forms of obesity, as both conditions share similar neurobehavioral, neuroanatomical, and neurofunctional characteristics (García-García et al., 2020). Specifically, alterations in mesolimbic and mesocortical structures and functions have been observed in both conditions (Benton & Young, 2016; Volkow et al., 2008, 2011). However, these findings are primarily based on observational, cross-sectional studies. In contrast, the current causality-based study highlights the involvement of the bilateral PFC and the interhemispheric connections between them in inhibitory control among participants with food addiction and obesity. Future research may test the effects of ccPAS in two additional groups: one with food addiction only and the other with obesity only. This approach could help identify potential similarities and differences in inhibitory control systems across addiction, obesity, and the combined FAOB condition.

The current study has multiple strengths and limitations. It is novel, as it is the first to causally address interhemispheric modulation in FAOB participants. The methodology is well characterized by standardizing homeostatic hunger prior to brain stimulation and statistically controlling for possible variations between the participants. However, as a pilot study, it is subject to notable limitations that constrain its ability to draw strong conclusions. Chief among these is the small sample size, which lacks the statistical power needed to detect group differences or trend-level effects that might become significant with a larger sample (e.g., group differences in the correlation magnitude between task performance and brain asymmetry). Moreover, the small sample size may amplify the effects of interindividual variability known to exist in response to brain stimulation (López-Alonso et al., 2014), potentially leading to false positive findings. For instance, the absence of behavioral and brain responses to Sham stimulation compared to Active stimulation might reflect an incidentally high proportion of non-responders in a small group.

An additional source of ambiguity in the current study is the use of 40% RMT intensity for Sham stimulation. This intensity was selected to enhance the validity of blinding between study groups, based on prior findings (Zibman et al., 2019) suggesting that it produces some scalp sensation in the control group, with negligible cortical effects. However, the possibility of cortical influence at this intensity cannot be entirely ruled out. While numerous studies indicate that stimulation below 60% RMT does not affect cortical excitability or behavior (e.g., Abrahamyan et al., 2015; Huang & Rothwell, 2004b), some evidence suggests otherwise. For instance, low intensity stimulation (~30% MSO) has been shown to induce EEG oscillatory activity (Zmeykina et al., 2020), and even standard tilted-coil Sham stimulation—frequently used as a control condition—has been reported to have cortical effect (Opitz et al., 2015). Therefore, the possibility that 40% RMT stimulation induces some cortical influence cannot be entirely excluded. If this is the case, the results should be interpreted with a dose-control perspective, suggesting that supra-threshold ccPAS stimulation influences inhibitory control and brain activity in FAOB participants, whereas low-intensity subthreshold stimulation does not.

Taking study limitations into consideration, future studies shall replicate current findings using larger sample, use a separate sham coil and assess blinding efficacy, and may also examine the change in state food cravings following the TMS session with a validated questionnaire (Meule et al., 2014) (e.g., in the current protocol, following Stroop 1 versus following Stroop 2). Future research might also include disorders of binge eating and overeating, to characterize the short- and long-term outcomes of single and multiple ccPAS sessions in disordered eating conditions.

In summary, the current study characterizes the acute effect of interhemispheric R-L ccPAS on prefrontal brain activity and neurobehavioral reactivity to rewarding food images in FAOB participants.

The results indicate that this protocol is suitable for targeting reward and motivation-related inhibitory control systems, but it needs modifications to effectively benefit individuals with food addiction in obesity.

CRediT authorship contribution statement

Roni Aviram-Friedman: Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Uri Alyagon:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Lior Kafri:** Project administration, Investigation. **Shahar Atias:** Project administration. **Abraham Zangen:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

Ethical approval

An ethical approval for this study has been received from the ethics committee at Soroka University Medical Center (Beer-Sheva, Israel).

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Declaration of competing interest

None.

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All authors have approved the final article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.appet.2025.107863.

Data availability

Data will be made available on request.

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