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Prefronto-cerebellar neuromodulation affects appetite in obesity

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Abstract

Human neuroimaging studies have consistently reported changes in cerebellar function and integrity in association with obesity. To date, however, the nature of this link has not been studied directly. Emerging evidence suggests a role for the cerebellum in higher cognitive functions through reciprocal connections with the prefrontal cortex. The purpose of this exploratory study was to examine appetite changes associated with noninvasive prefronto-cerebellar neuromodulation in obesity. 12 subjects with class I obesity (mean BMI 32.9 kg/m^2) underwent a randomized, single-blinded, sham-controlled, crossover study, during which they received transcranial direct current stimulation (tDCS; active/sham) aimed at simultaneously enhancing the activity of the prefrontal cortex and decreasing the activity of the cerebellum. Changes in appetite (state and food-cue-triggered) and performance in a food-modified working memory task were evaluated. We found that active tDCS caused an increase in hunger and desire to eat following food-cue exposure. In line with these data, subjects also tended to make more errors during the working memory task. No changes in basic motor performance occurred. This study represents the first demonstration that prefronto-cerebellar neuromodulation can influence appetite in individuals with obesity. While preliminary, our findings support a potential role for prefronto-cerebellar pathways in the behavioral manifestations of obesity.

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Conflict of Interest

Drs. Abhishek Datta and Marom Bikson are co-founders of Soterix Medical. The City University of New York has patent applications in Drs. Datta and Bikson's name on brain stimulation. The rest of the authors declare no conflict of interest.

Introduction

Obesity is associated with brain changes and impaired performance in laboratory measures of neurocognitive functioning.[1–3] These alterations may contribute to the development and maintenance of maladaptive eating behaviors, but the specific mechanisms remain largely unknown. The cerebellum is one of the regions most consistently associated with body mass index (BMI) and obesity. A number of functional neuroimaging studies has identified cerebellar activation in response to hunger/satiation[4], gastric distension[5], and food cues.[6] Obesity and obesity risk status impact the structure of the cerebellum, with a high degree of heritability.[7] Additionally, the cerebellum is an important target for leptin action[8] and its gray matter volume is inversely associated with abdominal obesity and related inflammatory processes.[9] The animal literature also supports an important role for the cerebellum in homeostatic control of feeding and body weight.[10] Altogether, these data suggest an inverse association between BMI/obesity and cerebellar function and integrity, but no study has provided direct demonstration for such link in humans to date.

Notably, the cerebellum is well positioned to exert a broad coordinating role in the regulation of appetite and food intake, namely via access to the hypothalamus, reward centers and cognitive circuits.[10,11] Current models posit that the cerebellum may act as a multi-domain integrator, fine-tuning the quality of behavioral outputs and providing optimized shortcuts.[11–14] Emerging data suggest that beyond the well-recognized role of the cerebellum in motor control, this area can also contribute to cognition, learning, reward processing, habit formation and craving.[11–15] In particular, the human cerebellum has a highly developed system of contralateral, reciprocal connections (via thalamus and pons) with high-order brain regions, including the prefrontal cortex.[16] Prefronto-cerebellar interactions are believed to coordinate and temporally synchronize multiple cognitive representations with external stimuli and voluntary actions[12,14,17]; however, the extension of these functions to cognitive processes that support adaptive behavioral regulation of food intake is currently unknown.

In the present study we preliminarily examined acute effects of experimental manipulation of prefronto-cerebellar pathways in individuals with obesity. We used transcranial direct current stimulation (tDCS), a noninvasive neuromodulation technique that delivers weak direct currents to the brain via scalp electrodes[18], with the purpose of enhancing the activity of the left dorsolateral prefrontal cortex (DLPFC) and reducing the activity of the right cerebellum. Previous studies with tDCS in obesity have focused on the DLPFC[19,20]; however, the effects of modulating DLPFC-cerebellum interactions have not yet been explored. We selected a left DLPFC/right cerebellum tDCS montage based on past work in obesity (target: left DLPFC)[19], and some neuroimaging data pointing more specifically to the right cerebellum in association with BMI.[7] We hypothesized that this tDCS approach would facilitate prefronto-cerebellar interactions, by increasing the influence of the DLPFC on the cerebellum, leading to a reduction in appetite and an improvement of cognitive performance under the presence of food cues.

Materials and Methods

Twelve tDCS naïve participants (9 female, 3 male) with class I obesity (BMI 32.7 ± 1.9 Kg/m^2) aged 33–47 years (41.6 ± 4.8) took part in this pilot study. Participants were recruited from Clinica Sagrada Familia and Universitat Oberta de Catalunya (Barcelona, Spain). Exclusion criteria included BMI < 30 or > 35 Kg/m^2, unstable body weight (defined as ± 5% change within 6 months prior to participation), any history of neurological disorder, psychiatric illness, alcohol or drug abuse, and any known cause of secondary obesity (self-reported). Subjects gave written informed consent to participate at the beginning of the study. The study was approved by the Institutional Review Board of Universitat Oberta de Catalunya.

The study protocol involved two visits. In each visit, a different stimulation condition (active or sham) was applied in a randomized and counterbalanced order. Subjects were unaware of stimulation condition. Visits took place on two consecutive days, at the same time of the day, and within a postprandial period of 4 hours. tDCS (2 mA, 20 min) was administered with the cathode over the right cerebellum (1 cm below and 4 cm lateral to the inion, i.e. centered within the posterior cerebellar lobe[21,22]) and the anode over the left DLPFC (F3) (Fig. 1A). This montage, guided by our own computational modeling data (Fig. 1B), was planned with the intention of modulating prefronto-cerebellar pathways by simultaneously enhancing the activity of the left DLPFC and decreasing the activity of the right cerebellum. We used a Soterix Medical 1×1 tDCS device (Soterix Medical, New York, NY) equipped with 5×5 cm sponge electrodes soaked in 0.9% sodium chloride solution. During tDCS sessions, participants were awake, relaxed and seated in a comfortable chair. All technical aspects of tDCS application adhered to recent recommendations for safe and replicable use of this technique.[23]

Subjects were evaluated in three domains: a) subjective appetite, b) food-related cognitive performance, and c) general effects on motor performance and working memory. Fig. 1C depicts the time course of assessments for each session. For a) we evaluated both state and cue-induced changes in appetite using visual analogue scales (VAS) with questions on hunger, fullness, desire to eat and prospective consumption.[24] State appetite was defined as VAS scores obtained immediately before and after receiving tDCS. Cue-triggered appetite was defined as VAS scores obtained immediately before and after exposure to food cues. For b) we used a food-modified N-back task with 3 levels of cognitive load (1-back, 2-back, and 3-back). For c) we used a finger tapping task and a digit span test. Additionally, we evaluated tDCS adverse effects in each session and, at the end of the study, subjects also filled in questionnaires on personality, eating behavior and food craving. For more details about methods see Supplementary material section on IJO website.

Statistical analyses were performed as indicated, using $\alpha=0.05$, and two-tailed hypotheses. Normality was examined using Shapiro-Wilk test. All analyses were conducted in SPSS software (IBM SPSS Statistics 23, Chicago, IL).

Results

Fig. 2 shows all changes in appetite VAS scores. Repeated measures ANOVA of appetite state revealed an interaction effect time x stimulation condition for hunger ($F(1,11)=5.041$, $p=0.046$). Post hoc analyses using t-test with Bonferroni correction showed a decrease in score after sham stimulation (pre=42.5, post=31.67) nearly significant ($p=0.094$) but not after active stimulation (pre=39.45, post=40.33, $p=0.903$), indicating a relative increase in hunger following active tDCS. There were no other differences pre vs. post stimulation.

In the case of cue-triggered appetite (VAS scores pre/post cue exposure), there was a main effect of time on desire to eat, indicating a significant increase when comparing pre vs. post task scores ($F(1, 11)=5.919$, $p=0.033$). Even though this interaction was not significant, the increase was greater in the active stimulation condition (difference: active=9.13, $p=0.034$; sham=6.5, $p=0.202$). Paired-sample t-test comparing pre vs. post scores also revealed a significant increase in hunger for the active condition ($t(11)=-2.75$, $p=0.019$), but not for the sham condition ($t(11)=-1.019$, $p=0.299$).

Regarding performance in the n-back food task, paired-sample t test revealed a tendency towards more errors committed after active stimulation, compared to sham (5.25 % more, $t(11)=1.892$, $p=0.085$). No differences were found in reaction times (speed).

We found no effects on the finger tapping task. Digit span ANOVAs revealed a main effect of time on digit backward span ($F(1, 11)=10.385$, $p=0.008$) with higher scores the second time participants performed the task, both in active and sham sessions (mean 5.08 vs. 5.62). Paired-sample t test also revealed an increase in backward digit span only after sham stimulation ($t(11)=-2.345$, $p=0.039$). Evidence for a possible contribution of individual characteristics (personality factors and eating behavior trait) was also observed (Supplementary Material, Table S1). Only few -expected- side effects were reported at the end of each stimulation session, but with no differences between sham and active conditions (Fisher's exact test) (Table S2).

Discussion

In this study, we examined acute effects on appetite and food-related cognitive performance associated with noninvasive prefronto-cerebellar neuromodulation in obesity for the first time. Contrary to our hypothesis, we found that active tDCS caused a relative elevation in the general state of hunger, compared with sham tDCS. Additionally, there was an increase in cue-triggered desire to eat and hunger, and a trend suggesting impairment of performance in a food-specific working memory task. While preliminary and limited by the small sample size, our results support the notion that prefronto-cerebellar pathways may contribute to appetite regulation and mechanisms related to behavioral control over external food cues.

A number of scenarios could explain our unexpected findings. First, tDCS may have caused a more dominant impact on the cerebellum (reduced activity) than on the DLPFC (increased activity). The association between reduced activity in the cerebellum and increased hunger is compatible with the inverse relationship between cerebellar function/integrity and BMI that has been reported in the neuroimaging literature.[3] Furthermore, previous studies with tDCS

that showed decreases in appetite and food craving, i.e. opposite effects from our findings, used montages with the same anodal DLPFC location, but different positioning of the cathode, which here was placed over the cerebellum, versus the supraorbital/prefrontal region in prior studies.[19,20] The relative increase in hunger state that we found could also fit with a modulatory role of the cerebellum in basic appetite sensations driven by homeostatic and visceral regulation, conveyed by cerebellar-hypothalamic circuits[10], and more selectively related to the vermis sector.[25] Abnormalities in cerebellar-hypothalamic connectivity have recently been associated with obesity and difficulty achieving successful weight-loss.[26] A second scenario to explain our findings is that the prefronto-cerebellar tDCS montage that we used may have engaged a more ventral sector of the prefrontal cortex, or even reached components of the orbitofrontal cortex, which are more prominently involved in reward processing (see current density peaks predicted by computational modeling, Fig. 1B), and thus could have contributed to the observed increase in hunger. A third scenario to interpret our results is that the anodal DLPFC/cathodal cerebellum tDCS montage could have disrupted, rather than facilitated, the function of prefronto-cerebellar pathways, e.g. due to functional decoupling between DLPFC and cerebellum as a result of tDCS simultaneously increasing and decreasing the activity of these interconnected areas, or a reversal in the flow of information (DLPFC to cerebellum versus cerebellum to DLPFC). This third possibility is particularly intriguing, as prior research with a similar tDCS montage in patients with stable mood disorders showed improvements in neurocognitive performance.[21] Last, we also observed that active tDCS caused an increase in cue-triggered appetite (hunger and desire to eat) and a trend-level impairment of food-related working memory performance. These effects could be accounted for by the above scenarios, by an impact on cerebellar connections to reward centers -known to be altered in obesity[27], or simply as a result of elevated homeostatic motivation to eat.

Our study has a number of limitations. The prefronto-cerebellar tDCS montage that we used has poor topographic resolution, making it impossible to explain effects based on specific cerebellar subregions or brain circuits. Future studies should combine tDCS with fMRI, allowing for a detailed topographical characterization of the effects and their association with specific mechanisms. Also, we only examined the impact of tDCS on the left DLPFC/right cerebellum pathway. Whether the observed effects can be extended to the homologous pathway, i.e. right DLPFC/left cerebellum, remains unknown. We selected this specific side as a first investigation, but there is no clear evidence of lateralization, based on the available neuroimaging data.[22]

Given that our results were in the opposite direction as hypothesized, we cannot make conclusions on the potential of prefronto-cerebellar neuromodulation for the treatment of obesity. Our findings call for alternative strategies to influence prefronto-cerebellar pathways in the direction of appetite reduction and improvement of behavioral control over food cues. Future studies should examine the effects of reversing the polarity of the tDCS montage that we used here, and other higher resolution approaches to simultaneously enhance DLPFC and cerebellum activity. If a benefit can be confirmed, clinical trials evaluating the effect of repeated tDCS sessions on body weight are warranted. It is also unclear whether the effects that we found here are specific of obesity or, rather, can be extended to individuals with healthy weight or undereating conditions. Notwithstanding

these limitations, our study represents the first direct evidence that the human cerebellum, possibly via prefronto-cerebellar pathways, may be involved in the regulation of appetite and food cue reactivity, uncovering a role in processes that are central to the behavioral manifestations of obesity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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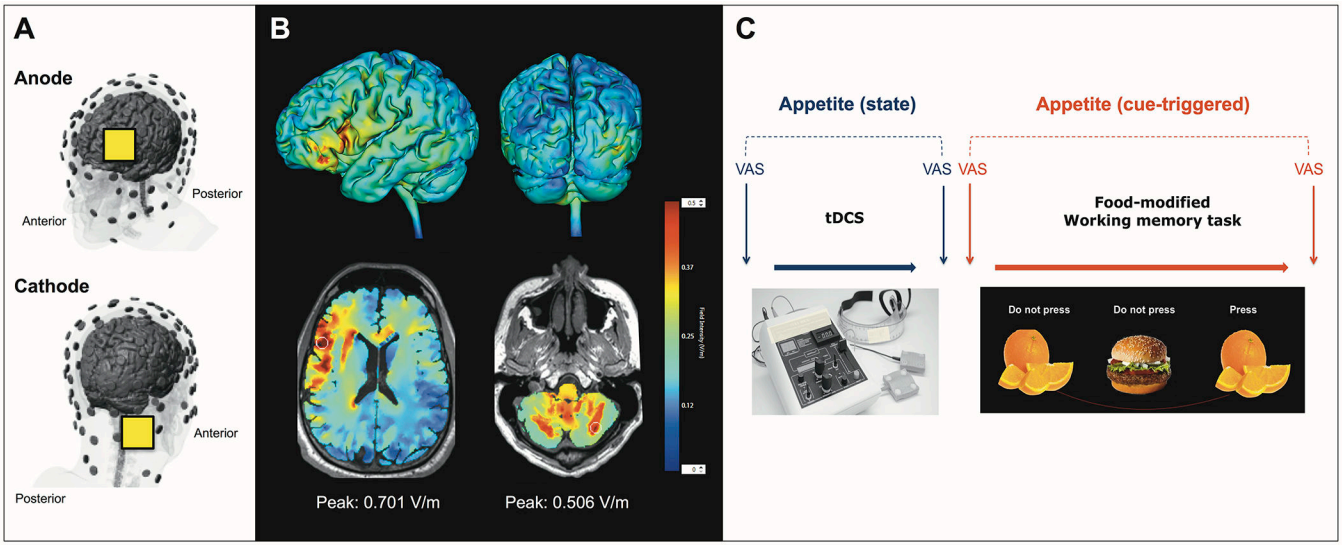

Figure 1.

A. tDCS montage used in the present study. 5×5 cm electrode pads were placed over right cerebellum (cathode) and F3 (anode). B. Computational model of the tDCS montage used. Peak electric field magnitude is shown at the approximate location of the electrodes (axial images, white circles). The scale bar on the right shows the color code for current density values (V/m). C. Study diagram showing the time course of measurements for each of the study visits. VAS: visual analogue scale.

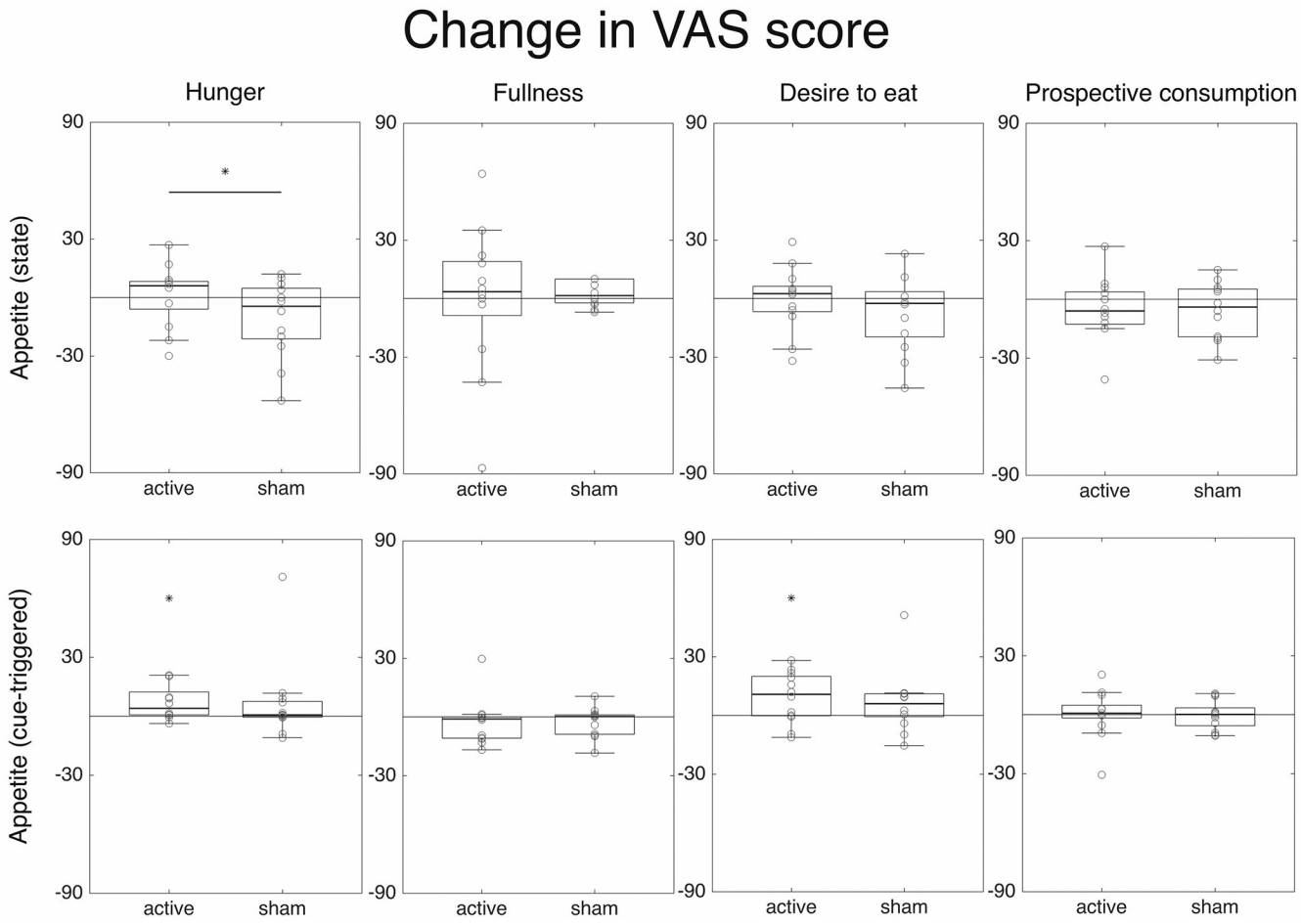

Figure 2.

Box and dot plots representing changes in the four VAS scores (Δ, columns) for the two appetite measurements: state and cue-triggered (rows). The horizontal line represents a significant main effect of stimulation condition (active vs. sham) and the asterisks (*) over one condition represent significant pre-post differences within that condition.