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Transcranial direct current stimulation over the tongue motor cortex reduces appetite in healthy humans

Obesity is a major concern in many societies for its impact on individual health and societal costs [1]. Therapeutic options however are still limited with respect to efficacy and applicability. Food impulsivity and hyperphagia play a key role in obesity [2] and are associated with alterations of the activity of several brain structures of the reward system, including orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC), insula, anterior cingulate cortex (ACC), and dopaminergic (DA) midbrain structures (e.g., [3,4]). Functional alterations of these brain areas are involved in reward processing-related disorders, including eating disorders (e.g., [5]).

Noninvasive brain stimulation provides an innovative tool for treating hyperphagia with the advantage of modulating neural activity in absence of surgical and/or pharmacological interventions, which have often limited applicability due to obesity-associated health complications.

Dorsolateral prefrontal cortex is the typical cortical target for treating eating disorders, given its key role in up-/downregulation of the reward circuitry [6] and inhibitory control functions [7]. Most studies in the field describe short-term improvements [8,9]. However, no studies tackling alternative cortical targets more specifically associated with the reward circuit are currently available.

Here, we tested whether downregulation of the tongue muscle-representing area of the primary motor cortex (tnM1) via transcranial direct current stimulation (tDCS) – a plasticity-inducing non-invasive brain stimulation tool - reduces hunger in healthy humans. This research hypothesis originates from the evidence that tnM1 is directly connected with key regions of the reward system [10], including OFC, ACC, insula, ventral putamen, caudate nucleus and the amygdala. On the other hand, limb regions of the motor cortex do not project to OFC or insular regions. Remarkably, we have documented that tnM1 excitability is modulated by nicotine craving [11], distaste [12], and moral disgust [13], which supports a functional link between tnM1 and reward-relevant processes in humans.

We applied 1 mA tDCS for 15 minutes over the tnM1 in twenty-four food-deprived (fasting for 6h) healthy humans (mean age 29, standard deviation 5.56, 15 females). Participants were recruited by the Leibniz Research Centre for Working Environment and Human Factors (IfADo) by online advertisements, and compensated with 10 euros/h for their time spent and travel expenses. They provided written informed consent and procedures were approved by the local ethics committee. Participants were excluded from the study if they met any of the following criteria: intake of psychoactive medication, presence of a metal object/implant in their brain, skull, scalp, or neck, implantable devices (e.g. cardiac pacemaker), any neurological or psychiatric diseases, epilepsy or cardiac disease, history of traumatic brain injury, pregnancy.

In line with neuroimaging evidence [14], documenting greater activation of the OFC, insula, ACC, amygdala and striatum in obese humans, we hypothesized that downregulation of tnM1 via inhibitory (i.e., cathodal) stimulation would reduce self-reported appetite. Participants took part in 3 stimulation sessions (anodal, cathodal, sham), separated by at least 48 hours. In each session, participants were first asked to rate their hunger (baseline) via a visual analogue scale (VAS), with the indication of the minimum and maximum at the ends of the segment (not hungry vs. extremely hungry). Participants were asked to bisect the line according to their subjective sensation of hunger.

Next, the left tnM1 hotspot was identified using Transcranial Magnetic Stimulation as described previously (e.g., 11, 12, 13). Next, they provided a short verbal description of the content of a set of 40 photos showing individuals eating different types of foods. To administer tDCS, 2 rubber electrodes (5 × 7 cm) were covered with saline-soaked sponges and positioned on the scalp region overlying the left tnM1 (target electrode) and the right mastoid process (return electrode). For sham stimulation, current was ramped up (30 s) and then immediately ramped down (30 s), and then maintained at 0 mA. Participants were blind to the stimulation condition. The order of stimulation conditions was counterbalanced among participants (latin square balancing). During tDCS, we drove participants' attention to the photos by asking to observe and verbally describe each photo. Following tDCS, participants provided another VAS rating of their hunger.

Self-report ratings were analyzed using repeated measure ANOVAs. Two participants provided an outlier response (>3 SD) in the anodal and cathodal sessions. Therefore, we decided to remove these data from the analysis. In a first analysis we ensured that no difference in baseline hunger ratings could be found across the three sessions [$F_{2,42} = 2.590$, $p = 0.087$, $\eta_p^2 = 0.109$]. Ratings following tDCS were then computed relative to baseline ratings (i.e., $\frac{(tDCS\ score - Baseline\ score)}{Baseline\ score}$ x 100). A second analysis showed significant changes in post-tDCS ratings between sessions ($F_{2,42} = 3.349$, $p = 0.044$, $\eta_p^2 = 0.137$; Fig. 1A).

Scheffe post-hoc tests documented a significant difference in hunger following cathodal-tDCS ($M = 11.75\% \pm 3.85$) relative to sham-tDCS ($M = 30.85\% \pm 6.94$; $p = 0.047$). No significant difference emerged by comparing anodal vs. cathodal ($p = 0.277$) or sham ($p = 0.651$) stimulations. Finally, we observed no significant correlation between self-reported hunger ratings, Body Mass Index (BMI) and Council on Nutrition Appetite Questionnaire (CNAQ) scores (Table 1).

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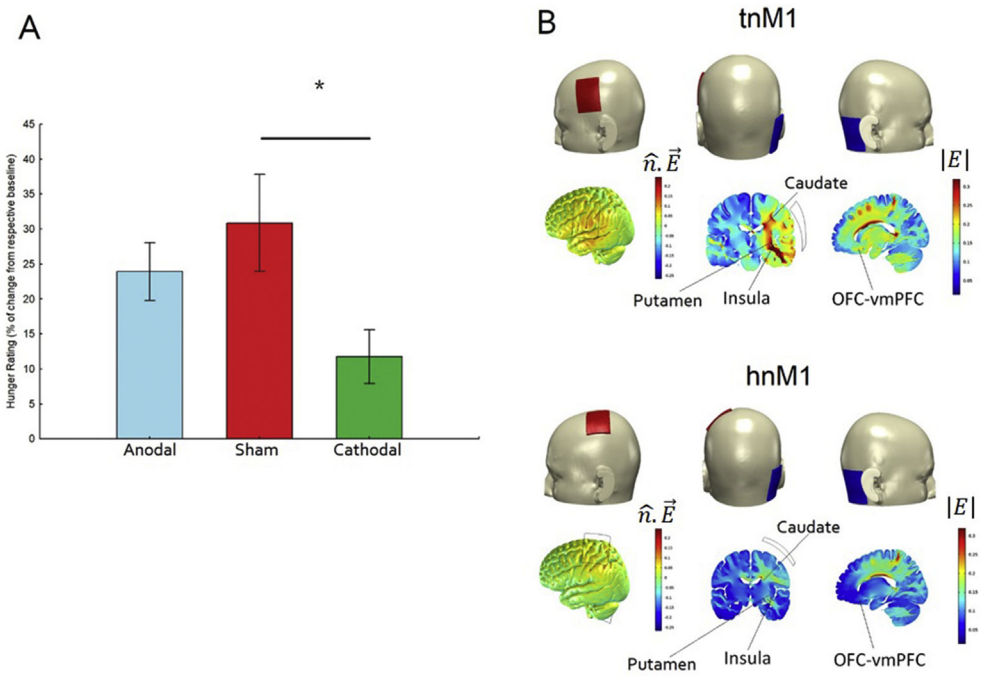

Fig. 1. A) Self-reported hunger rating following anodal, sham and cathodal tDCS. The results show that cathodal stimulation reduced hunger compared to sham stimulation. Asterisks indicate significant differences. Error bars denote standard error of means; B) Simulated electrical current flow associated with placement (top figure) of the target (cathodal) electrode over tnM1 and over a hypothetical control target, i.e., the hand muscle-representing area of the primary motor cortex (hnM1 - bottom figure). The return electrodes are placed over the contralateral mastoid. The modeling results show stronger electrical fields at the level of the caudate, putamen, insula, OFC-vmPFC, which are strongly involved in appetite regulation (3), for tnM1 compared to hnM1 stimulation.

Table 1
Results of correlation analyses plotting BMI and CNAQ scores with self-reported hunger ratings in the three stimulation sessions.

	Anodal	Sham	Cathodal
BMI	$r = 0.194$, $p = 0.374$	$r = -0.264$, $p = 0.212$	$r = 0.042$, $p = 0.855$
CNAQ	$r = -0.027$, $p = 0.900$	$r = -0.086$, $p = 0.687$	$r = 0.047$, $p = 0.828$

Overall, cathodal-tDCS over the left tnM1 selectively reduced self-reported hunger, as compared to sham-tDCS. Interestingly, Siep et al. [15] have shown that cognitive suppressing of food palatability thoughts and craving reduces activity in the striatum, insula, and OFC/vmPFC. Lower self-reported hunger ratings following cathodal (inhibitory) stimulation might be explained by a similar downregulation of mesocorticolimbic networks. This hypothesis is supported by anatomical evidence of direct connections between these networks and tnM1 [10], and, importantly, by our modeling results (Fig. 1B). Indeed, tnM1 stimulation affected the striatum, insula and OFC/vmPFC, i.e., key regions of a mesocorticolimbic network involved in controlling appetite (e.g., 3), and such involvement was not observed when modeling a nearby control region. Therefore, cathodal-tDCS over tnM1 might have resulted in a direct suppression of mesocorticolimbic activity, leading to a reduction of subjective hunger.

In conclusion, our findings highlight tnM1 as a potential cortical target for hunger downregulation. These findings may have implications for treating disturbed appetite control and/or eating disorders, and possibly for treating other disorders of the mesocorticolimbic system.

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Declaration of competing interest

Michael A Nitsche is on the Scientific Advisory Boards of Neuroelectrics, and Neurodevice. There are no other conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2020.05.008.

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