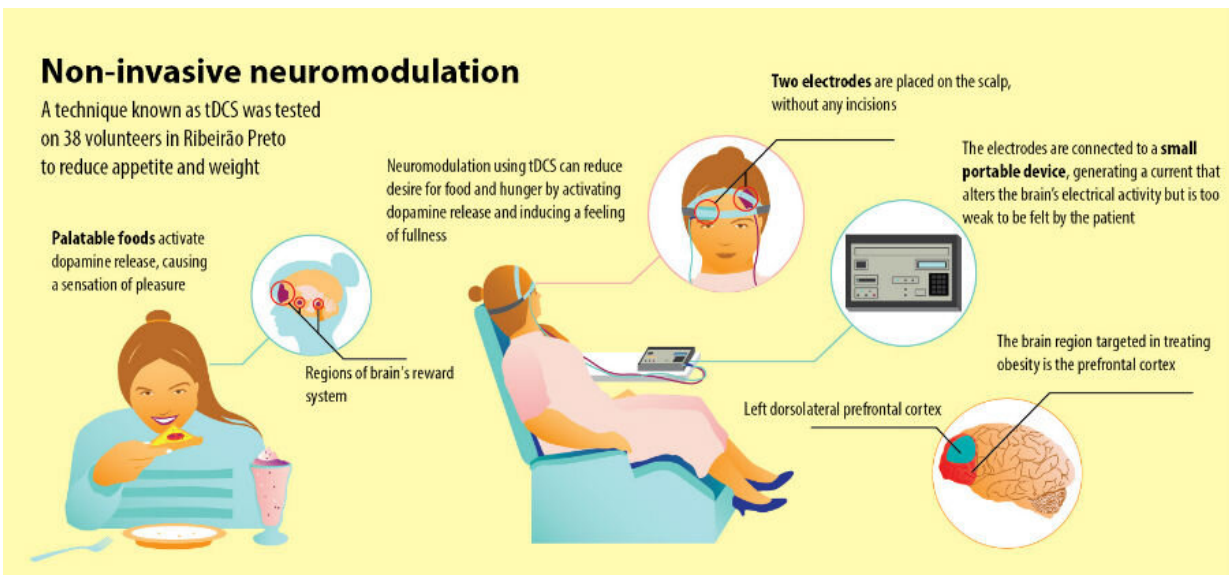


Study evaluates effects of noninvasive neuromodulation used to treat obesity

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Credit: Fabio Otubo

Novel approaches that have been tested to treat obesity include noninvasive neuromodulation techniques such as transcranial direct current stimulation (tDCS). Studies performed to date have suggested that this method does in fact help reduce appetite, food intake and body weight, but only in some subjects.

New findings published in the journal *Appetite* by researchers at the University of São Paulo (USP) in Brazil help elucidate the reason for the

variability in responses to tDCS treatment.

"The patient's genetic profile, especially variations in the gene COMT, appears to be a key factor in determining the outcome," Priscila Giacomo Fassini, first author of the article, told.

During her postdoctoral research at the University of São Paulo's Ribeirão Preto Medical School (FMRP-USP), Fassini conducted a double-blind sham-controlled randomized clinical trial to test the efficacy of tDCS in reducing appetite and weight, with São Paulo Research Foundation—FAPESP's support. In double-blind randomized [clinical trials](#), considered the gold standard for assessing new therapies, volunteers are divided randomly into two groups, and neither they nor the researchers know who receives the treatment or intervention versus the sham treatment or placebo. Fassini's study was supervised by Vivian Marques Miguel Suen a professor in FMRP-USP's Department of Internal Medicine.

In tDCS, two electrodes (a cathode and an anode) are placed on the scalp and are connected to a small portable device, generating a galvanic current that alters the brain's electrical activity in the area of interest. In the case of obesity, the aim is to modulate neuron excitability in the left dorsolateral prefrontal cortex.

"In our trial, we used a current of only 2 milliamperes, which is too weak to be felt by patients," Fassini said. Sham stimulation (placebo group) involved the same procedure, but the current lasted only 30 seconds, a timeframe that is too short to affect neurons.

Starting with a base sample of almost 9,000 volunteers, the researchers selected 38 women who were 20-40 years old as participants in the clinical trial. For all subjects, body mass index (BMI) was between 30 and 35, corresponding to class 1 (mild) obesity.

"The criteria for inclusion were rigorous. We excluded pregnant women and people who were using medications or had significant medical conditions that could influence the results. In addition, because the third stage of the trial involved hospitalization for two weeks, not all those who applied and were eligible had the free time to participate," Fassini said.

The selected volunteers were given 17 thirty-minute sessions of tDCS over the course of a month. Appetite and weight were monitored for six months. According to Fassini, previous trials had only investigated the immediate effects of tDCS on appetite, involved fewer sessions, and performed no follow-up.

The clinical trial comprised four stages. In the first stage, the volunteers were given a single tDCS session and then immediately took a test measuring working memory, the memory system that temporarily stores information for use in specific tasks. According to Fassini, the aim was to confirm that the correct brain region was being stimulated, since the left dorsolateral prefrontal cortex is associated with both working memory and the regulation of appetite.

In both cases, there is evidence that the effects of neuromodulation are mediated by the release of dopamine, a substance produced by neurons (neurotransmitters).

"Dopamine plays a crucial role in the regulation of food reward, feeding and [body weight](#)," Fassini said. "It's well established in the literature that palatable foods activate the brain's reward system, contributing to dopamine release. Neuromodulation is apparently capable of mimicking this effect."

In stage two, the volunteers were given ten tDCS sessions (once a day in the morning, Monday-Friday) and then returned to their normal routines

after each intervention. In stage three, volunteers were admitted to the hospital for two weeks and were placed on supervised, individualized low-calorie diets with a 30% reduction in energy intake. During this period, they were also given six more tDCS sessions (on Mondays, Wednesdays and Fridays).

The fourth stage consisted of weight and appetite monitoring for six months after the end of the intervention period. The effects of the treatment on appetite during and after neuromodulation were measured using standard scales for the assessment of hunger, fullness, desire to eat, and prospective food consumption.

Analysis of results

After completing data collection in Brazil, Fassini traveled to the US for a research internship at Harvard Medical School that was supported by FAPESP. The results were analyzed under the supervision of Professor Miguel Alonso-Alonso, one of the pioneers of obesity treatment using tDCS. Júlio Sérgio Marchini (FMRP-USP), Sai Krupa Das (Tufts University, Boston) and Greta Magerowski (Harvard Medical School) also participated in the analysis.

Genomic DNA obtained from whole blood samples taken during stage one was sequenced to genotype the volunteers. Because dopamine is known to be important for the tDCS mechanism of action, the research group decided to investigate variations (polymorphisms) in the gene COMT, which encodes catechol-O-methyltransferase, an enzyme that plays a critical role in the degradation of dopamine in the prefrontal cortex.

"Previous research showed that a polymorphism called Valine158Methionine [Val158Met] affects the enzyme's activity and makes it less effective at degrading dopamine. The availability of

extracellular dopamine in the prefrontal cortex is higher in people with this variant of the COMT gene," Fassini said.

The results of her trial did, in fact, point to a significant reduction in appetite over time only in individuals with the Met allele of COMT who also received active neuromodulation treatment. "These individuals responded better to treatment because of higher dopamine availability, displaying lower levels of hunger, less desire to eat, and less prospective food consumption over time," Fassini said.

However, the most striking discovery from the clinical trial, she continued, was the paradoxical effect observed in noncarriers of the COMT Met allele. In these women, tDCS had the opposite effect, increasing their hunger, desire to eat and food consumption throughout the intervention period.

"This paradoxical effect was consistently seen in repeated assessments. It was only present immediately before tDCS, i.e., 23 h after the administration of the previous tDCS session, not acutely after stimulation. The potential mechanisms underlying this effect are unclear," Fassini said.

The results also showed a correlation between performance in the working memory test during stage one and a COMT genotype-dependent subsequent appetite change. "Speed improvements during the memory tests predicted increased appetite in Met carriers and reduced appetite in Met noncarriers," Fassini said.

The effect of the treatment on body weight is still being analyzed and will be the focus for an article to be published shortly. "We did not observe a substantial difference between the groups during the intervention period, which was expected because all participants had a supervised diet. However, we're finding differences in body weight

maintenance during the six-month follow-up period," Fassini said.

She and her colleagues continue to follow the same group of volunteers, and the study will soon complete one year. "These first results help us understand why only some people respond to treatment with tDCS. We saw that differences in genotype affect the availability of dopamine and greatly influence the effect of neurostimulation," she said. "There may be other factors, and this possibility will be investigated in future studies."

Another question is whether the alterations in brain functioning induced by neuromodulation entail long-term changes to cerebral plasticity (how the brain is organized). Answers to questions such as these will be vitally important if the technique is to be prescribed safely and effectively as part of the treatment of obesity, Fassini stressed.

Although tDCS is still considered experimental in this context, it has been used to treat neuropsychiatric conditions such as depression and schizophrenia. The method is considered safe and has no known side effects.

More information: Priscila Giacomo Fassini et al, Appetite effects of prefrontal stimulation depend on COMT Val158Met polymorphism: A randomized clinical trial, *Appetite* (2019). [DOI: 10.1016/j.appet.2019.05.015](https://doi.org/10.1016/j.appet.2019.05.015)

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