Impact of tDCS on persistent COVID-19 olfactory dysfunction: a double-blind sham-controlled study

INTRODUCTION

Loss of smell is a characteristic finding of COVID-19. It may outpersist the resolution of the disease, though recovery varies significantly, ranging from 15 to 180 days. Studies have purported central nervous system involvement in COVID-19 anosmia, mostly in the orbitofrontal cortex (OFC), the neural substrate for conscious olfactory perception. Given the high prevalence of COVID-19, an enormous number of patients worldwide are at risk of long-term loss of smell. Olfaction is essential for detecting environmental hazards and for enjoying food. Smell loss can cause mood disorders, even suicidal ideation. Treating olfactory dysfunction is therefore of paramount importance. Different interventions have been tried in order to alleviate COVID-19 hyposmia, but with limited efficacy.

Non-invasive brain stimulation techniques can be deemed as a promising alternative to traditional neurorehabilitative approaches for several diseases, including smell disturbances. In this double-blind, sham-controlled study, we implemented a 2-week session of combined olfactory training (OT) and anodal transcranial direct current stimulation (A-tDCS) in seven patients with persistent COVID-19 hypo/anosmia, with the aim of investigating the effect of tDCS on olfactory function.

MATERIALS AND METHODS

Seven consecutive patients were enrolled in the study, according to the following inclusion criteria: (1) persistent (at least 6 months) hypo/anosmia due to COVID-19; (2) a score below 12 on the ‘Sniffin’ Sticks’ identification subtest. The exclusion criteria were: (1) severe mood disorder; (2) rhinological diseases; (3) epilepsy; (4) sensitive scalp. No medications for alleviating olfactory symptoms were allowed. Patients’ smell performances were first assessed immediately preceding stimulation (t0). A visual analogue scale smell 0–10 (0=complete loss of smell, 10=full sense of smell) was employed as a subjective measure. As an objective measure, we used the ‘Sniffin’ Sticks’, a validated test consisting of three subtests (smell threshold, discrimination and identification). Smell identification can be separately used to assess olfactory function, with a shorter test time and a high test–retest reliability. It consists of 16 reusable pen-like odour-dispensing devices that the subject is asked to identify and characterise by choosing one of four options. No feedback is provided after each odour examination. The test is scored out of a total of 16 points (12–16, normosmia; 9–11, hyposmia; and 8 or below, anosmia). All the patients were classified as anosmic at baseline.

In the 20-minute OT session, patients had to carefully sniff 10 odours (rose, eucalyptus, lemon, star anise, rosemary, strawberry, coconut, vanilla, pine tree, bergamot) in a random order. After sniffing each odour for 10 s, the patients were asked to identify it and to rate its intensity. The training was applied once for each session. TDCS stimulation was concurrently administered with a battery-driven stimulator of 1.5 mA intensity. The anode was placed over the left prefrontal cortex (PFC), since the OFC is not directly accessible by tDCS. The PFC was chosen due to its close anatomofunctional connection with the OFC. Notwithstanding no general agreement is established about laterality of the olfactory processing, we chose the left side because of the functional hypoactivity of the left OFC in COVID-19 anosmia. The cathode was applied to the contralateral shoulder. Repeated sessions of combined OT and A-tDCS were carried out for 5 consecutive days, for 2 weeks. The same protocol was first used for the sham stimulation (S-tDCS). We did not include a control group, though this choice would have strengthened the power of the study. The order of S-tDCS and A-tDCS across subjects was not counterbalanced because we intended to avoid potential carryover effects if A-tDCS had been applied first. The patients and the assessors collecting the data were blinded as to the design of the study. The smell assessment was repeated immediately after S-tDCS (t1), A-tDCS (t2) and 3 months from the end of stimulation (t3), using the same odours and the same order of the first assessment.

The Wilcoxon test was used to compare each assessment (t1, t2 and t3) with baseline. A two-sided α less than 0.05 was considered statistically significant.

RESULTS

Both the subjective and objective measures showed a statistically significant improvement at t2 and t3, with average measurements doubled or even tripled compared with t0 and t1. Also, each individual demonstrated notable improvement in smell performance. All patients, except for

**Figure 1** Mean±SD of the Sniffin’ Sticks test (A) and VAS smell 0–10 (B) measurements at baseline (t0), after S-tDCS (t1), A-tDCS (t2) and 3 months later (t3). Time points marked with * showed significantly different (p<0.05) results compared with baseline based on the Wilcoxon test. At t1, the test statistics were z=1.732, p=0.2500 for (A) and z=2.193, p=0.0625 for (B). At t2, z=2.392, p=0.0156 for (A) and z=2.375, p=0.0156 for (B). At t3, z=2.388, p=0.0156 for (A) and z=2.384, p=0.0156 for (B). Dashed lines show the individual results of the seven patients. A-tDCS, anodal transcranial direct current stimulation; S-tDCS, sham transcranial direct current stimulation; VAS, visual analogue scale.
The implementation of stimulation at least of up to 3 months following the treatment. Importantly, the beneficial effect as compared with baseline and sham stimulation was maintained over a period of up to 3 months following the treatment. The implementation of stimulation at least at 6 months after a negative SARS-CoV-2 swab allowed us to generally rule out the possibility of spontaneous recovery, since the likelihood of improvement is significantly reduced after 2 months. Although placebo effects may play a non-trivial role in any trial, our data indicate that OT coupled with S-tDCS did not achieve any benefit. It is therefore tempting to speculate that the amelioration of smell in the current sample may be due to the effect of A-tDCS on the neuroplasticity of the OFC, or, alternatively, the PFC (the stimulated area). We cannot exclude a contribution of PFC stimulation to the observed results. However, given the essential role of OFC in olfactory perception, modulation of OFC connectivity induced by tDCS may be of foremost importance.

Caution is needed in drawing any definitive conclusions based on a study on a small group of patients. However, the significant and long-lasting improvement of olfactory function observed in the current sample suggests that this safe treatment could alleviate chronic post-COVID-19 hypo/anosmia. In addition, the results may support the hypothesis that the cortical areas involved in olfaction may have a non-negligible role in the development of COVID-19 smell loss. Larger studies are necessary to confirm this intriguing hypothesis.

DISCUSSION
This double-blind, sham-controlled study is the first attempt to use A-tDCS in the treatment of individuals with persistent hyposmia due to COVID-19. We found a significant improvement in all the patients, as compared with baseline and sham stimulation. Importantly, the beneficial effect of A-tDCS was maintained over a period of up to 3 months following the treatment. The implementation of stimulation at least at 6 months after a negative SARS-CoV-2 swab allowed us to generally rule out the possibility of spontaneous recovery, since the likelihood of improvement is significantly reduced after 2 months. Although placebo effects may play a non-trivial role in any trial, our data indicate that OT coupled with S-tDCS did not achieve any benefit. It is therefore tempting to speculate that the amelioration of smell in the current sample may be due to the effect of A-tDCS on the neuroplasticity of the OFC, or, alternatively, the PFC (the stimulated area). We cannot exclude a contribution of PFC stimulation to the observed results. However, given the essential role of OFC in olfactory perception, modulation of OFC connectivity induced by tDCS may be of foremost importance.

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Ethics approval The principles of the Declaration of Helsinki were followed. Patients provided signed informed consent at the beginning of the procedures. The study protocol was exempted by the Institutional Review Board because tDCS is considered a tool which is routinely used in rehabilitation and all the patients underwent the sham AND the real stimulation.

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REFERENCES