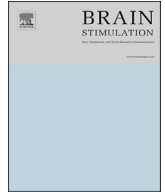




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Repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex may improve symptoms of anhedonia in individuals with cocaine use disorder: A pilot study

Letter to the editor:

Cocaine use disorder (CUD) is characterized by positive symptoms, such as craving, and negative affective states, all of which may drive drug taking and relapse. One prominent symptom that is part of the negative affective states is termed anhedonia, and is defined as an impaired ability to experience pleasure from natural rewards such as food, water, sex, and nurturing. From a neurobiological standpoint, disruption in dopaminergic mesocorticolimbic reward processing plays an important role in the development of

anhedonia [1]. Clinically, anhedonia is an important factor contributing to relapse to cocaine use and therefore it represents an important treatment outcome [2].

Recently, repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) has emerged as a potentially promising treatment for CUD [3,4]. rTMS appears to have unique therapeutic applications to directly target and remodel dysfunctions in brain circuits altered by chronic exposure to cocaine, including circuits implicated in reward processing, craving, inhibitory and cognitive control, mood, and learning [5].

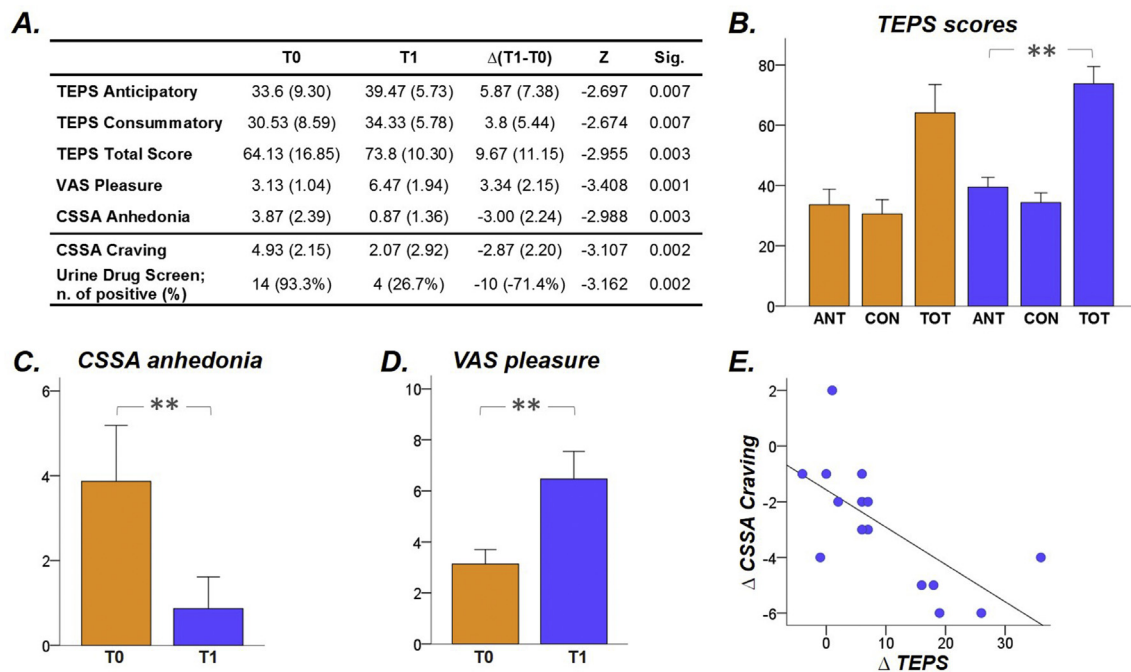


Fig. 1. A) Pleasure experience/anhedonia and drug craving and use before and after five-day (10 sessions) of high frequency rTMS treatment. B) Anticipatory, Consummatory Pleasure, and the Temporal Experience of Pleasure Scale (TEPS) total score, before (orange) and after (blue) rTMS treatment. C) Anhedonia subscale of the Cocaine Selective Symptoms Assessment (CSSA) scores, before (T0; orange) and after (T1; blue) rTMS treatment. D) VAS pleasure scores, before (T0; orange) and after (T1; blue) rTMS treatment. E) Correlation between the improvement in hedonic tone and the reduction of craving after rTMS treatment. The TEPS is composed of 18 items rated on a Likert-type scale ranging from 1 to 6, and yields two subscales measuring anticipatory and consummatory pleasure. Lower scores indicate greater levels of anhedonia. The CSSA is an 18-items clinician-administered instrument that measures early cocaine abstinence signs and symptoms, including anhedonia and craving (subscales ranging 0–7). All analyses were conducted using non-parametric testing (A–C: Wilcoxon Test for paired variables; D: Spearman's rank correlation coefficient), $**p < 0.01$. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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Furthermore, rTMS of the DLPFC has been found to increase dopamine release in the caudate/dorsal striatum [6]. Thus, we hypothesized that DLPFC neuromodulation via rTMS would improve symptoms of anhedonia in individuals with CUD. We tested this hypothesis in fifteen patients (13 M; 2 F; mean age 36.67 ± 7.04 years) with longstanding history of CUD (disease duration 16.80 ± 5.62 years) and seeking treatment for their cocaine use. The Ethic Committee of the University of Chieti approved the study and all patients signed a written consent form before the rTMS sessions began. Consistent with previous work [6], the stimulation protocol included 10 sessions (twice a day, 5 days/week, 15 Hz frequency, pulse intensity 100% of the resting motor threshold, 60 pulses per train, inter train pause of 15 s, 40 stimulation trains, 2400 pulses/session) and targeted the left DLPFC, located with the BeamF3 method [7]. At baseline and on the day of the last rTMS session, hedonic tone was assessed using the Temporal Experience of Pleasure Scale (TEPS; [8]), a Visual Analogue Scale (VAS) for pleasure experience, and the *anhedonia subscale* of the Cocaine Selective Symptoms Scale (CSSA; [9]). Cocaine craving and use were assessed by the *craving subscale* of the CSSA and urine drug screen (UDS), respectively. All statistical analyses were conducted using non-parametric testing (Wilcoxon Test for paired variables and Spearman's rank correlation). All patients completed the five-day (10 sessions) rTMS protocol on schedule, with only mild and transitory side effects (e.g., headache) reported by three patients.

Following rTMS treatment, on the TEPS, both the anticipatory and consummatory components of the hedonic experience significantly improved (17.47% and 12.45% mean increase, respectively; Fig. 1A–B). Similarly, CSSA scores decreased and VAS scores for pleasure experience increased after rTMS treatment (Fig. 1C–D). Furthermore, we observed a 71.4% reduction in positive UDS (Fig. 1A) and a 51.45% mean reduction in CSSA scores for craving, compared to baseline (Fig. 1A), with an inverse correlation between the reduction in craving and the improvement in the symptoms of anhedonia ($r_s = -0.739$; $p = 0.002$; Fig. 1E).

In summary, by targeting the DLPFC, a key brain node in the frontal-striatal network that governs executive control [10], rTMS may enhance cognitive control over craving and negative affect by restoring frontal-striatal circuitry abnormalities. In addition, anhedonia may play a key role in moderating the response to rTMS treatments, as suggested by the relationship between craving and anhedonic symptoms observed in our patients. To the best of our knowledge this is the first study preliminarily evaluating the effect of rTMS on hedonic tone in cocaine addicts. Repeated drug use results in a shift in hedonic set point that could mediate the transition from occasional drug abuse to compulsive cocaine seeking. In this study we provide preliminary findings that the rTMS therapeutic effect in treating CUD could be determined by its potential in rescuing hedonic tone dysfunction.

In conclusion, our findings suggest that DLPFC rTMS may be an effective intervention for treating CUD symptoms like anhedonia and craving. By reversing anhedonic symptoms, rTMS might allow to set cocaine detoxification protocols in CUD patients. This pilot study provides a strong rationale for larger follow up studies that will need to employ sham-controlled double-blind designs.

Conflicts of interest

None.

Clinical trial registration

URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT03333460.

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