Provocative repetitive transcranial magnetic stimulation to reduce craving in methamphetamine use disorder

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Dear Editor,

The global use of methamphetamine (METH), a highly addictive substance, is increasing (1). Initially, METH use produces feelings of euphoria, heightened alertness, and increased physical abilities (2). However, long-term use of METH can result in negative effects such as anxiety, agitation, decreased appetite, impaired cognitive function, paranoid delusions, hallucinations, and sleep disturbances (2–5). Furthermore, prolonged use of METH often leads to the need for higher doses as tolerance develops rapidly (6, 7). The craving for METH is a strong emotional state that can lead to an uncontrollable urge to obtain and use the substance (6). Triggers related to previous METH use can intensify this craving and contribute to the recurrence of substance use, playing a pivotal role in the development of METH dependence (7). METH is associated with high relapse rates, making the recognition and effective treatment of relapse crucial for successful outcomes. Craving is a complex concept that includes behavioral, cognitive, and emotional aspects and is closely linked to addiction and relapse. The natural cycle of craving plays a crucial role in precipitating relapse. Hence, the implementation of craving reduction techniques may serve as a viable approach to mitigating the risk of relapse with METH use disorder (MUD) (8).

In Turkey, the most common treatment for addiction rehabilitation takes place in alcohol and substance rehabilitation clinics. The clinical interventions include pharmacological and psychological therapy but do not incorporate specific neuroscientific procedures. When it comes to treating MUD, non-invasive methods such as repetitive transcranial magnetic stimulation (rTMS) have been suggested as a potentially supported alternative treatment (9). rTMS involves converting magnetic field impulses into electrical signals, which are then transmitted through the skull to exert an effect on the cortex. rTMS is a non-invasive therapeutic method with notable safety. It can either increase synaptic activity in specific brain regions (in high-frequency mode, defined as >5 Hz) or inhibit it (in low-frequency mode, defined as <1 Hz) (10).

The U.S. Food and Drug Administration (FDA) has approved rTMS for the treatment of major depression and obsessive-compulsive disorder (11). It has also been widely tried in the treatment of various psychiatric diseases, including MUD (9). Studies have shown that targeting the left dorsolateral prefrontal cortex (LDLPFC) with rTMS can be effective and safe for treating patients with MUD (9, 12). Craving is associated with the brain's reward circuitry, and METH use leads to excessive dopamine release in the limbic system, particularly in the nucleus accumbens, contributing to addiction. The DLPFC plays a role in inhibiting the reward circuit through mesofrontolimbic connections (13, 14). Research has demonstrated that rTMS stimulation of the DLPFC can reduce craving by increasing dopamine release and glutamate levels (15, 16). These findings support the use of rTMS in treating MUD, as it has been shown to reduce craving, improve cognitive functions, and alleviate withdrawal symptoms (12). In a recent study, MUD patients were shown pictures related to METH and asked to recall memories of their

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last METH use. Following this, rTMS and sham rTMS were randomly applied to different brain regions, and it was found that real rTMS significantly reduced craving compared to sham rTMS (9). Here, we aimed to present the provocative (craving after clues about METH) rTMS protocol in an MUD patient.

A 24-year-old male patient has been using METH for five years. When he first started using 1 gram of METH, he gradually increased this amount and consumed 3-4 grams of METH almost daily. The patient MET is used through a glass pipe. When he quit the substance, he complained of weakness, pain, fatigue, unhappiness, and increased appetite. The patient spends most of his time on substance use and has impaired functionality. Clues such as where he used the substance and the people he used with it caused him to crave it. When he wasn't using his METH, he was having dreams about METH. He tried to quit methamphetamine 3-4 times to date but was unsuccessful. The patient's cue-related craving visual analog scale (VAS) score at the first clinic examination was 9 out of 10 (representing severe craving). We diagnosed the patient with MUD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, diagnostic criteria in the outpatient clinic. The patient stated that although he had used different antidepressant medications before, he experienced a MET relapse and wanted a different treatment. We chose rTMS treatment because of the patient's preference and the growing body of supportive evidence in the literature about the efficacy of rTMS in treating cravings. We created 30 pictures related to METH. These pictures are METH use sites, METH paraphernalia, METH powder, and METH use scenarios. We showed the patient these pictures for 5 minutes and had them tell their memories of the last METH use. After the pictures, we evaluated the craving score with the VAS. After the pictures, rTMS was applied to the patient. The patient marked the VAS before and after every rTMS session on a scale of 0 = no craving to 10 = excessive craving. We applied ten seasons (one session per day) of rTMS to the LDLPFC via a neuro-MSX TMS device. One session was implemented as follows: rTMS session with the figure eight coil at 110% motor threshold, 10 Hz, 5 seconds on, 10 seconds off interval for 10 minutes (1,000 pulses). No side effects were detected during or after rTMS sessions. The patient's craving (VAS) scores after pictures are 8,9 in the first three rTMS sessions. The patient's (VAS) scores after rTMS decreased to 3,4 in three rTMS sessions. The patient's craving (VAS) scores after pictures are 4,5 in the fourth and fifth rTMS sessions. The patient's (VAS) scores after rTMS decreased to 2,3 in the fourth and fifth rTMS sessions. The patient's craving (VAS) scores after pictures were 2,3 in the sixth, seventh, and eighth rTMS sessions. The patient's (VAS) scores after rTMS decreased to 1,0 and 0 in the sixth, seventh, and eighth rTMS sessions. The patient's craving scores after pictures and after the last rTMS session were 0.The patient stated that the pictures related to METH did not cause him cravings and that METH no longer entered his dreams. This report proposed a promising treatment protocol for treating MUD. It provided additional support for studies showing that rTMS reduces craving in MUD patients. rTMS significantly reduced craving scores in our MUD patient.

MUD is a chronic, relapsing disorder and has emerged as one of the most quickly expanding novel psychoactive substances globally in the last few years (8). MUD patients frequently report craving METH, which may increase the risk of relapse (17). Vanoxerine (GBR12909) is considered one of the most promising agents for MUD treatments (18). It exhibits a potency that is 50-fold greater in inhibiting dopamine reuptake compared to cocaine. Vanoxerin consta is the injectable formulation of vanoxerine, a substance that helps maintain sobriety in individuals addicted to cocaine (19). Vanoxerine might be useful as a medication for MUD (18). Another treatment is bupropion and naltrexone combination therapy in MUD (20). Bupropion and naltrexone have demonstrated promising efficacy in clinical trials for treating MUD. Bupropion is an antidepressant with stimulant properties that works by affecting the norepinephrine and dopamine systems (21). Naltrexone is a pharmacological agent that acts as an antagonist to the opioid receptors, making it a useful treatment option for individuals with opioid use disorder (21). A small, open-label pilot trial suggested that the combination of naltrexone and bupropion could effectively treat severe MUD

(21). Unfortunately, there is no FDA-approved drug treatment for MUD (14). In addition, patients with MUD do not want to use drugs such as antidepressants and antipsychotics that we can use to treat substance use disorders (22). When substance-related cues hit the limbic circuit in patients with MUD, dopaminergic neurons in the ventral tegmental area send dopamine impulses to the ventral striatum (9). In addition, the executive control network also affects this process (9). Substance-related cues either overstimulate the limbic system, make the executive control network weak, or make cognitive control weak, all of which make people want to use substances again. Therefore, the application of rTMS to the DLPFC, which serves as a central component of the executive control network, or the ventromedial prefrontal cortex (VMPFC), which serves as a significant component of the limbic neural circuit, in patients diagnosed with MUD has the potential of reducing the recurrence of cravings associated with substance misuse (9). In previous rTMS studies in MUD patients, high-frequency rTMS of the LDLPFC reduced craving and impulsivity and improved decision-making ability. Furthermore, the application of 10 Hz rTMS on the LDLPFC has been found to have the potential to mitigate cravings in individuals diagnosed with substance use disorder, ease symptoms of depression, and enhance their cognitive abilities and quality of sleep (8,9). The advantages of TMS, such as not having serious side effects and being an alternative treatment for MUD patients with frequent medication noncompliance, suggest that it may be included in the treatment of MUD. However, there is uncertainty about the specific TMS protocol to be used, the frequency and duration of treatment, and the need for maintenance therapy. TMS alone may not be adequate for these patients, and drug therapy may still be necessary.

Our report had several limitations. Firstly, the patient subjectively scored the craving scores and scored them under the supervision of the doctor. As with other substance use disorders, MUD patients may want to make themselves look good. Because of this, he may have shown lower scores. Second, the lack of functional neuroimaging in this report led to changes in activity that can be shown to be related to cravings. Thirdly, the placebo effect of rTMS may have caused a decrease in craving scores. Finally, the patient may have gotten used to the METH-related pictures we have shown for cravings and may not have sufficiently triggered the craving.

In conclusion, high-frequency rTMS to the LDLPFC reduced craving in the MUD patient and showed no side effects. However, more research needs to be done that compares the effect of rTMS on reducing cravings in sham, provocative, and non-provocative rTMS applications on large groups of patients.

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