Machine learning identified therapeutic targets for transcranial magnetic stimulation as a treatment for cocaine use disorder

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There are no effective treatments for cocaine use disorder (CUD), a chronic, relapsing brain disease characterized by dysregulated circuits related to cue reactivity, reward processing, response inhibition, and executive control. Using machine learning classifiers, I identified executive control processes and specific neural circuitry predictive of outcomes after a drug treatment program. Specifically, executive control processing largely manifested by the anterior cingulate cortex (ACC), measured with event-related potentials (ERPs), elicited from a commission error in a Go/NoGo task was predictive of which individuals would (78.72%) and would not (75.00%) complete the treatment program. Greater post-error processing was predictive of individuals who subsequently completed the program. In a functional magnetic resonance imaging (fMRI) version of the Go/NoGo task, stronger functional connectivity (FC) between ACC and amygdala, hippocampus, and striatum predicted treatment outcomes. Similar to the ERP findings, the machine learning models of the fMRI FC measures successfully identifying who would (81.31%) and would not (78.13%) complete treatment. Together, the ERP and fMRI findings suggested cognitive and circuit-based targets for intervention that overlap with known dysregulated circuits in CUD and executive control processes. Recent advances in neuromodulation, specifically transcranial magnetic stimulation (TMS), allow specific modulation of circuits identified in my program of research toward developing an efficacious treatment. Targeting executive control and dysregulated circuits identified in my ERP and fMRI studies, I performed a first of its kind proof-of-concept study in active cocaine users by applying intermittent theta-burst stimulation (iTBS; a type of TMS) as a chronic intervention. I hypothesized that iTBS applied to modulate executive control would reduce cocaine use in this non-treatment seeking cohort. I recruited 19 individuals with CUD to receive three open-label iTBS sessions per day, with approximately a 60-minute interval between sessions, for 10 days over a 2-week period (30 total iTBS sessions). iTBS was delivered to left dorsolateral prefrontal cortex (dlPFC) with neuronavigation guidance. Compliance and safety were assessed throughout the trial. Cocaine use behavior was assessed before, during, and after the intervention and at 1- and 4-week follow-up visits. Of the 335 iTBS sessions applied, 73% were performed on participants with cocaine-positive urine tests. Nine of the 14 participants who initiated treatment received at least 26 of 30 iTBS sessions and returned for the 4-week follow-up visit. These individuals reduced their weekly cocaine consumption by 78% in amount of dollars spent and 70% in days of use relative to pre-iTBS cocaine use patterns. Similarly, individuals reduced their weekly consumption of nicotine, alcohol, and THC, suggesting iTBS modulated a common circuit across drugs of abuse. iTBS was well tolerated, despite the expected occasional headache. Participants reported reduced compulsive cocaine use and reduced cocaine-induced euphoria while maintaining alternative rewarding activities suggesting specificity in modulation of cocaine-related behaviors. Accelerated iTBS to left dlPFC administered in active, chronic cocaine users is both feasible and tolerable with preliminary indications of efficacy in reducing both the amount and frequency of cocaine (and other off-target drug) use. Results open the door to large-scale clinical trials assessing iTBS as the first effective treatment for CUD.

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