Machine Learning Identified Therapeutic Targets for Transcranial Magnetic Stimulation as a Treatment for Cocaine Use Disorder

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Background

Addiction is a chronic, relapsing brain disease characterized by dysregulated circuits related to cue reactivity, reward processing, and executive control (Volkow, Koob, & McLellan, 2016).

Targeting specific cognitive functions and related circuits may lead to positive treatment related outcomes.

First, we must know which cognitive functions and circuits are related to positive treatment outcomes.

Are executive control processes and related circuits predictive of substance abuse treatment outcomes?

In two studies, executive control was elicited with a Go/NoGo task (Keihl et al., 2000) in participants prior to initiation of a12-week substance abuse treatment protocol.

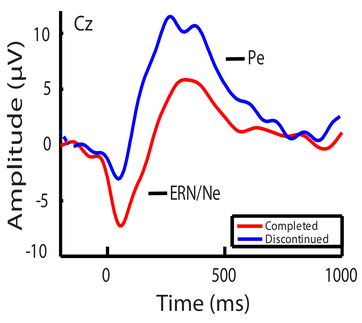
In each study, two-nested, cross-validated support vector models (SVM) were used to predict which individuals would and would not complete treatment.

The SVM models were implemented to identify specific cognitive functions and underlying circuits that could be targeted in novel treatments for addiction.

Study 1: Event-related potentials (Steele et al., 2014)

Executive Control Predicts Treatment Outcomes

****Those who discontinued treatment, compared to those who completed treatment, were deficient in both error-monitoring, as indexed by the error-related negativity (ERN) and adjusting response strategy post-error, as indexed by the error positivity (Pe) but only the Pe was predictive of treatment outcomes ****



SVM accurately predicted 78.72% of those who subsequently completed treatment and 75.00% of those who prematurely discontinued treatment

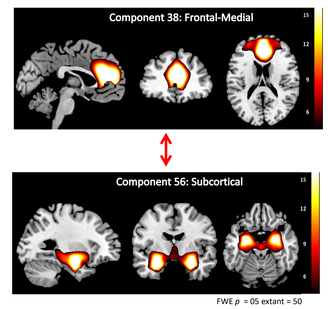
Post-error processing is predictive of treatment completion and thus an intervention target

Are the underlying circuits related to executive control similarly predictive of treatment outcomes?

Study 2: Functional magnetic resonance imaging (Steele et al., 2018)

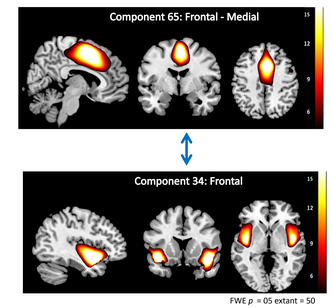
Functional Network Connectivity Predicts Treatment Outcomes

****The completed group exhibited increased connectivity between the rostral anterior cingulate cortex (RACC) and amygdala, hippocampal, and striatal regions compared to the discontinued group****



SVM accurately predicted 81.31% of those who subsequently completed treatment and 78.13% of those who prematurely discontinued treatment

****The discontinued group exhibited increased connectivity between the caudal anterior cingulate cortex (CACC) and insula and temporal regions compared to the completed group****



Circuits underlying executive control predict substance abuse treatment outcomes, extending findings from study 1

Studies 1 and 2 suggest cognitive and circuit-based targets for intervention that overlap with known dysregulated circuits in addiction

Current Study

In an open-label study (Steele et al., 2019), chronic intermittent theta-burst stimulation (iTBS; an excitatory transcranial magnetic stimulation, Huang et al., 2005) was applied as a treatment for cocaine use disorder (CUD) to:

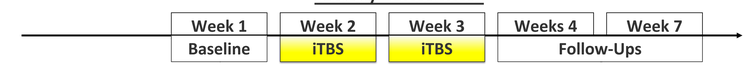
- Target the cognitive and circuit-based targets identified in studies 1 and 2
- Test the feasibility and tolerability of chronic iTBS in CUD participants
- Assess safety of applying iTBS to active cocaine users
- Assess efficacy of a novel intervention for CUD, which currently has no FDA-approved treatment.

Hypothesis

Chronic application of iTBS over left dorsolateral prefrontal cortex (l-dlPFC) will reduce cocaine use

Nineteen participants with CUD were recruited (non-treatment seeking)
Cocaine abstinence not required

Study Timeline



Baseline
- Consented 19 participants actively using cocaine
- Collection of clinical assessments (e.g., lifetime substance use)
- iTBS orientation (2 of 19 consented did not tolerate orientation)

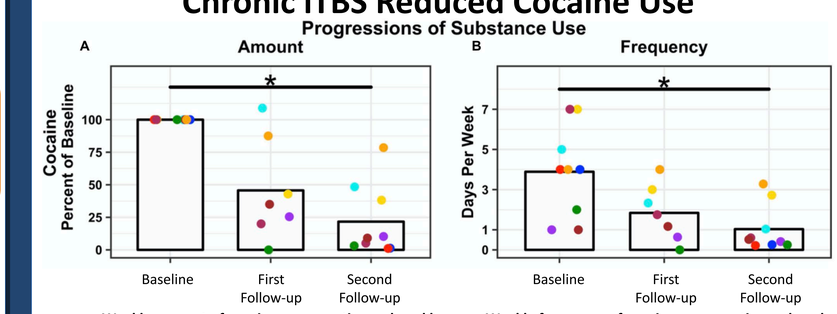
iTBS
- 10 iTBS days over a 2-week period
- Each iTBS day included 3 iTBS sessions with a 60-minute interval
- Each iTBS session included 600 pulses at 100% motor threshold applied to l-dlPFC
- During iTBS stimulation, participants down-regulated induced cocaine craving

Follow-Ups
- 1-week and 4-week post iTBS
- Collection of clinical assessments (e.g., substance use since iTBS)
- Monitoring of iTBS side-effects

Nine of 14 participants who initiated treatment completed at least 26 of 30 iTBS sessions and returned for the second follow-up visit

Of the 335 iTBS sessions applied, 73% were performed on participants with cocaine-positive urine tests

Chronic iTBS Reduced Cocaine Use



Weekly amount of cocaine consumption reduced by 78% post-iTBS treatment

Weekly frequency of cocaine consumption reduced by 70% post-iTBS treatment

Shaded bars represent group means; Dots represent individual participants

Chronic iTBS to left-dlPFC administered as a treatment for CUD in active cocaine users is, feasible, tolerable, and preliminarily efficacious in reducing both the amount and frequency of cocaine use

Future Directions

To address limitations, studies are currently underway that include:
- a sham condition to minimize potential placebo effects
- functional magnetic resonance imaging to assess neuroplastic change induced by chronic iTBS
- long-term follow-up to assess longevity of the behavioral effects
- assessment of neuroplasticity induced by an acute session of iTBS

Acknowledgments
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