Effects of rTMS on Cannabis Use and Cognitive Function in Schizophrenia

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BACKGROUND

- Cannabis use disorder (CUD) is a significant risk factor for developing psychosis, with highest rates amongst schizophrenia (SZ) (~25%) versus the general population (~3%)[1].
- Increased hospitalizations, earlier onset/worsening of symptomology, antipsychotic non-adherence, and reduced cognitive/behavioural functional outcomes], have shown to improve with cannabis abstinence and contingency management (CM)[2,3].
- There are currently no optimal treatments for CUD.
- High frequency (20Hz) repetitive transcranial magnetic stimulation (rTMS) procedures DLPFC have shown tremendous promise/tolerability in preliminary short-term intervention trials by improving working memory deficits and drug craving in SZ [4,5] **(Figure 1)**.

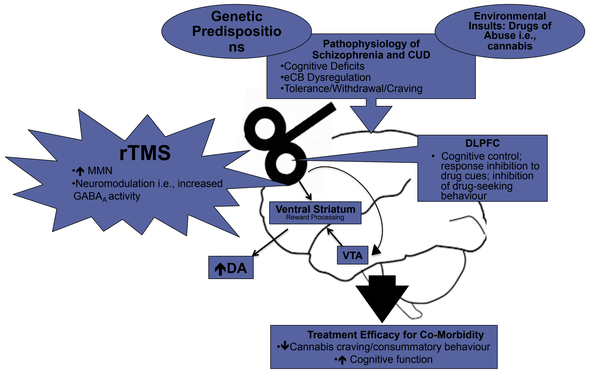

Figure 1. Brain mechanisms of rTMS targeting DLPFC address SZ and CUD co-morbidity [Adapted from Kozak et al. (6)].

OBJECTIVES

1. Primary Objective: Determine if active vs sham rTMS to DLPFC improves cannabis abstinence rates at end of trial (Day28);
2. Secondary Objective: evaluate if active vs sham rTMS improves neurophysiological/ neuropsychological function (verbal learning, working memory and mismatch negativity, MMN);
3. Exploratory: explore effects of active vs sham rTMS on cannabis withdrawal, craving and psychotic symptoms.

HYPOTHESES

1. Active rTMS will increase abstinence rates compared to the sham group;
2. Active rTMS treatment will improve neurophysiological/ neuropsychological function;
3. Withdrawal, craving and psychotic symptoms will be related to a decrease in severity with active rTMS treatment.

APPROACH

- Double-blind, randomized, parallel groups controlled study with 28-day cannabis abstinence paradigm (with a 2-week lead-in) in participants with comorbid SZ and CUD (N=40).
- 5x/week of high frequency rTMS using a standard Figure-8 TMS coil will be administered bilaterally to DLPFC for 4 weeks.
- Cannabis abstinence assessed weekly by timeline follow-back and cannabis urine toxicology tests (NarcoCheck).
- Behavioural support provided weekly for motivation towards abstaining/ reducing use.
- Progressive payments at the end of each rTMS treatment week and follow-up session to reinforce attendance/compliance with rTMS treatments.

STUDY DESIGN

DATA ANALYSES

- Primary Outcome: 28-day cannabis abstinence trial-endpoint self-reported cannabis use, assessed by timeline follow-back and confirmed by cannabis urine toxicology.
- Secondary Outcome: Cognitive outcomes (verbal learning HVLT-R, working memory (SDR) and MMN.
- Exploratory Outcome: cannabis craving and withdrawal, and psychosis symptom ratings (Positive and Negative Symptoms Scale for Schizophrenia, Calgary Depression Scale for Schizophrenia).
- **Statistical Analysis:** A mixed modeling procedure will be used to determine rTMS Treatment (active versus sham) x Time (Baseline and 28) effects on the aforementioned outcomes.

EXPECTED RESULTS

- Previous studies have shown improvement in cognitive performance after treatment with rTMS. Thus this study may result in participants experiencing an improvement in their working memory performance.
- Preliminary work has also demonstrated rTMS may decrease levels of cravings/consumption of drugs (i.e., tobacco cigarettes). This study may result in participants in decreased experience in the level and/or consumption of cannabis use and/or tobacco cigarette use.

SIGNIFICANCE & FUTURE DIRECTIONS

- This study may determine if a novel state-of-the-art neuroscience-based intervention (rTMS) may be both well-tolerated and efficacious for successful treatment of CUD in SZ patients.
- This will further our understanding of the pathophysiology of SZ and CUD, while also improve cognitive and functional outcomes for this debilitating comorbidity.

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