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 symptoms, antipsychotic non-adherence, and reduced cognitive/behavioural functional outcomes2, 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 SZ4-6 (Figure 1).

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

Randomized (1:1) ACTIVE or SHAM rTMS Day 1-28 (5X/week)

<table>
<thead>
<tr>
<th>Day</th>
<th>Clinical Assessment</th>
<th>Behavioural Support</th>
<th>THC-COOH Toxicology (2X/week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DLPFC Stimulation</td>
<td>Day -15 Screen</td>
<td>N=40</td>
</tr>
<tr>
<td>14</td>
<td>Clinical Assessment</td>
<td>Day -14 (Week 1)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Clinical Assessment</td>
<td>Out cannabis</td>
<td>12-hrs prior to Day 1</td>
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<tr>
<td>28</td>
<td>Clinical Assessment</td>
<td>Day 1 (Week 2)</td>
<td></td>
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<tr>
<td>21</td>
<td>Clinical Assessment</td>
<td>Day 14 (Week 4)</td>
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<tr>
<td>28</td>
<td>Clinical Assessment</td>
<td>Day 28 (Week 6)</td>
<td></td>
</tr>
<tr>
<td>56</td>
<td>Clinical Assessment</td>
<td>Day 28 (F/U)</td>
<td></td>
</tr>
</tbody>
</table>

Neuropsychological Outcomes: Training Day, Day 0 (Baseline), Day 28
Neuropsychological Outcomes: Days 6, 28

Contingency Management

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.

REFERENCES


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