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Effects of High Frequency Repeated Transcranial Magnetic Stimulation and Continuous Theta Burst Stimulation on Gambling Reinforcement, Delay Discounting, and Stroop Interference in Men with Pathological Gambling

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ABSTRACT

Background: Repeated transcranial magnetic stimulation (rTMS) can reduce cravings and improve cognitive function in substance dependent individuals. Whether these benefits extend to individuals with pathological gambling (PG) is unclear. High-frequency rTMS of the medial prefrontal cortex (PFC) and continuous theta burst stimulation (cTBS) of the right dorsolateral PFC can reduce impulsive choice in healthy volunteers.
Objective: This study aimed to assess the effects of these two protocols on gambling reinforcement and related responses in otherwise healthy men with PG.
Methods: Participants (n = 9) underwent active or sham treatments at weekly intervals in a repeated-measures, Latin square design. Subjective and physiological responses were assessed before and after a 15-min slot machine game on each session. Delay discounting and Stroop tasks measured post-game impulsive choice and attentional control.
Results: Multivariate analysis of covariance, controlling for winnings on the slot machine under each treatment, found that rTMS reduced the post-game increase in Desire to Gamble; cTBS reduced amphetamine-like effects, and decreased diastolic blood pressure. Treatment had no significant univariate effects on bet size or speed of play in the game; however, a multivariate effect for the two indices suggested that treatment decreased behavioral activation. Neither treatment reduced impulsive choice, while both treatments increased Stroop interference.
Conclusions: rTMS and cTBS can reduce gambling reinforcement in non-comorbid men with PG. Separate processes appear to mediate gambling reinforcement and betting behavior as against delay discounting and Stroop interference. Interventions that modify risky as opposed to temporal aspects of decision making may better predict therapeutic response in PG.

Introduction

Repeated transcranial magnetic stimulation (rTMS) is a procedure that uses magnetic pulses to evoke or inhibit action potentials in cortical neurons. This may rectify functional disturbances mediated by these neurons. By inducing neuroplasticity, rTMS can also confer enduring benefits [1].

Stimulation parameters critically influence rTMS effects: low frequencies (1–5 Hz) tend to inhibit, whereas high frequencies (10–20 Hz) tend to activate, target neurons [2]. Stimulation of dorsolateral regions, e.g., dorsolateral prefrontal cortex (DLPFC) tends to influence cognitive-executive functions, whereas stimulation of medial regions (mPFC) tends to influence affective-motivational functions [3]. Reward-related decision making involves both cognitive and affective-motivational processes and may therefore engage both DLPFC and mPFC [4]. This interplay may be especially important for addictions, where a bias to select short-term over long-term rewards is integral to the syndrome [5]. This bias has been operationalized

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with a procedure called delay discounting, in which participants choose between pairs of options that yield small, immediate vs. large, delayed rewards [6]. Substance dependent individuals consistently choose the former option [7], as do those with the behavioral addiction, pathological gambling (PG) [8]. A number of studies have found that rTMS of DLPFC can reduce cravings and use, and improve cognitive function in individuals addicted to cigarettes, alcohol, or cocaine [9]. However, delay discounting may not account for these changes in addictive behavior: In non-treatment seeking smokers, single sessions of high frequency (10 Hz, 20 Hz) rTMS of the left DLPFC significantly reduced delay discounting, but did not alter cigarette consumption relative to sham treatment [10]. To date, no other study appears to have compared effects of rTMS on delay discounting and addictive motivation or behavior in the same individuals. The correspondence between rTMS effects on these processes in substance dependent individuals and those with PG also remains unknown.

A literature review found one previous study of rTMS in individuals with PG [11]. Five PG patients underwent 15 sessions of low frequency (1 Hz) rTMS of left DLPFC. Despite a decline in self-reported gambling severity, effects were not statistically significant, and were not supported by collateral reports. Lack of a control condition and possible inhibition of right DLPFC were cited as limitations. In healthy controls, 1 Hz rTMS of right DLPFC increased risky decisions in a probabilistic risk taking task, consistent with a decreased constraining effect of right DLPFC on decision-making (adaptive avoidance) [12].

Cho and colleagues subsequently observed a benefit of two TMS protocols on adaptive decision-making in a delayed discounting task. The task presents a series of hypothetical choices (e.g., $10 now vs. $1000 in 6 months), from which a parameter (k) is derived that denotes increased preference for small, immediate versus large, delayed rewards as time from present increases. Cho et al. [13] found that high frequency rTMS of mPFC decreased k, denoting a shift toward large, delayed options. Thus, mPFC activation decreased impulsive choice in healthy volunteers.

A companion study investigated effects of continuous theta burst stimulation (cTBS) on delayed discounting in a separate sample of controls [14]. Like low frequency rTMS, cTBS is believed to inhibit neural activity. Given this, it is somewhat surprising that cTBS of right DLPFC also reduced delayed discounting. This appeared to contradict the previous finding of increased risky responding following standard low frequency rTMS of right DLPFC in the probabilistic risk-taking task [12]. The apparent discrepancy suggests that distinct neural systems may mediate tolerance of delay vs. uncertainty [15].

The present study applied Cho and colleagues' two stimulation protocols to men with PG, in a sham-controlled, repeated measures design. Along with delay discounting, risky decision making was assessed in terms of betting behavior on a commercial slot machine. The reinforcing properties of the game were assessed using validated self-report scales; cognitive control was assessed with the Stroop task; and physiological arousal was assessed in terms of blood pressure response to the game. Based on the results for volunteers, both rTMS and cTBS were expected to promote adaptive decision-making, enhance cognitive control, and reduce the subjective-motivational and arousing effects of the slot machine.

Materials and methods

Participants

Participants were nine community-recruited, non-treatment-seeking men with PG. They had no other Axis I disorder aside from nicotine dependence (n = 1), as confirmed by the Structured Interview for DSM-IV [SCID-I [16]]; were drug- and medication-free as determined by urinalysis; and had normal or corrected-to-normal vision (for computer tasks).

PG status (score ≥ 5) was determined by the National Opinion Research Center DSM Screen for Gambling Problems [NODS [17]]. PG severity was assessed with the South Oaks Gambling Screen [SOGS [18]]. The Beck Depression Inventory-short form [BDI-sf < 10 [19]], and Alcohol Dependence Scale [ADS < 13 [20]] measured sub-clinical depressive symptoms and alcohol-related consequences. The Drug Abuse Screening Test [DAST < 4 [21]] confirmed lack of non-alcohol related drug abuse. The Fagerstrom Test for Nicotine Dependence measured nicotine dependence [FTND [22]]. The Eysenck Impulsivity Scale [EIS [23]] measured impulsivity.

To help corroborate self-report measures, the validity scales of the Neuroticism–Extraversion–Openness–Five Factor Inventory [NEO-FFI [24]] assessed the tendency to dissimulate (fake good/fake bad) during the intake interview before testing.

To rule out structural brain lesions and identify anatomical targets for TMS stimulation, a T1-weighted MRI image was obtained for all participants using a 3T high-resolution MRI (GE Discovery MR750 3T, FSPGR with repletion time = 6.7 ms, echo time = 3.0 ms, flip angle = 8 mm, slice thickness = 1 mm, NEX = 1, matrix size = 256 ± 192).

Materials

A portable breathalyzer (ALERT; Alcohol Countermeasures Inc., Mississauga, ON) confirmed that blood alcohol was 0 at the start of each test session. A wrist-cuff monitor (HEM-601; Omron Inc., Vernon Hills, IL, USA) assessed blood pressure at test session baseline and immediately before and after the slot machine game.

Visual analog scales [VAS 0–10 [25]] assessed Desire to Gamble. The Profile of Mood States-short form [POMS-sf [26]] Vigor scale assessed subjective-behavioral activation. The Addiction Research Center Inventory [ARCI [27]] amphetamine scale assessed psychostimulant-like sensations. A series of 7-point Likert scales (–3 to +3; most unpleasant to most pleasant/normal), previously validated with these TMS protocols [28,29], assessed the subjective effects of treatment *per se* on 7 dimensions (comfort, fatigue, anxiety, mood, irritation, pain, nausea) immediately before and after stimulation. A Side Effect Checklist [30], used to gauge medication-related side effects, was administered at the end of each test session.

A commercial slot machine (Cash Crop, WMS Gaming, Detroit, MI), previously found to reliably increase Desire to Gamble in PG participants [31,32], assessed risky decision-making (credits bet per spin) and speed of play (spins/15-min), and served as the reinforcing stimulus. Participants received 400 credits before each game and were advised that an amount proportional to their final credit tally on each session would be added to their participation fee at the end of the study. This provided an incentive to play to win. All participants received an additional $80 as winnings.

The screen of the slot machine displayed an array of icons. Participants selected 1–9 lines of icons and bet 1–5 credits/line (1–45 credits) on each spin. Credits available, current payoff and current bet were shown on the screen. A spin was initiated by touching the screen. Bells and lights accompanied wins.

Stroop task

The Stroop task was administered on a PC with psychological testing software (Psychology Software Tools, Pittsburgh, PA, USA) that recorded vocal response latency with ms accuracy. Participants sat 60 cm from the screen and spoke into a microphone. On each trial a word (0.7 cm in height) or letter string appeared in the center of the screen in one of four colors: red, yellow, green, or blue. Participants were instructed to name the color of the stimulus aloud as soon as it appeared, rather than to read it. Twenty warm-up trials