Addictive Behaviors 93 (2019) 246–249

Contents lists available at ScienceDirect

Addictive Behaviors

journal homepage: www.elsevier.com/locate/addictbeh

Dopaminergic and clinical correlates of high-frequency repetitive transcranial magnetic stimulation in gambling addiction: a SPECT case study

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HIGHLIGHTS

- We described cessation of gambling behavior and craving in a GD patient over a six month follow up period after treatment with repetitive Transcranial Magnetic Stimulation (rTMS) over the left dorsolateral prefrontal cortex; no craving or relapses were reported over the six-month follow-up period.
- After two weeks of treatment, we found changes in DAT availability that possibly reflect dopaminergic pathways modulation by rTMS.
- Neuromodulation of brain circuitries implicated in the executive control network may impact the clinical course of GD.

ABSTRACT

Repetitive Transcranial Magnetic Stimulation (rTMS) shows the potential to modulate local brain activity, thus resulting in a modulatory action on neurocircuitries implicated in the pathophysiology of Gambling Disorder (GD).

We report the case of a GD patient treated with two weeks of high frequency (15 Hz) rTMS over the dorsolateral prefrontal cortex (DLPFC). At baseline and after rTMS treatment the patient underwent a SPECT examination with (123)I-FP-CIT tracer, to test changes in dopamine transporter (DAT) availability. The patient was followed up for six months, to explore safety and clinical correlates of a weekly high frequency rTMS maintenance treatment.

Over the six-month follow-up the patient reported no episodes of gambling relapse. Also, the patient did not report craving for gambling or gambling-related symptoms. After two weeks of left DLPFC-rTMS treatment, we found a decrease in DAT availability in striatal regions, that represents a putative neurobiological substrate of dopaminergic pathways modulation.

This study suggests that high frequency DLPFC-rTMS deserves further investigations in larger samples, using controlled study designs, to assess its real potential as a treatment for GD.

1. Introduction

To date, no pharmacological treatment has proven to change the chronic course of gambling disorder (GD) and evidence-based treatment guidelines are lacking (Lupi et al., 2014). It is urgent to open up new treatment approaches to treat GD. Neuromodulation treatments show promise for the reduction of craving and substance use in alcohol and cocaine addiction (Diana et al., 2017), as well as in behavioral addictions (Martinotti et al., 2018; Sauvaget et al., 2015). Inducing a magnetic field that produces an electrical field in the brain, repetitive Transcranial Magnetic Stimulation (rTMS) modulates local brain activity, resulting in the stimulation or disruption of brain neurocircuitries. Applied over the dorsolateral prefrontal cortex (DLPFC), several studies demonstrated its potential to modulate mesolimbic pathways (Addolorato et al., 2015; Strafella, Paus, Barrett, & Dagher, 2001).

The altered interaction between prefrontal structures and the

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https://doi.org/10.1016/j.addbeh.2019.02.013
Received 21 October 2018; Received in revised form 3 February 2019; Accepted 13 February 2019
Available online 14 February 2019
0306-4603/

Table 1
Clinical and dopaminergic correlates of rTMS treatment in a GD subject.

	T0	T1	T2	T3	T4	T5	T6	% ΔT2-T0	% ΔT6-T0
	Baseline	One-week	Two-week	1 month	2 months	3 months	6 months		
Clinical correlates									
AUDIT	3	0	1	0	1	0	1	−66.7%	−66.7%
BDI	13	10	5	2	3	2	2	−61.5%	−84.6%
G-SAS	28	0	0	0	0	0	4	−100%	−85.7%
PG-YBOCS	24	6	2	2	2	3	4	−91.7%	−83.7%
ISI	7	0	1	0	1	1	0	−85.7%	−100%
YMRS	4	3	4	4	4	6	3	−0.0%	−25%
Dopaminergic correlates (DAT availability 123 I-FP-CIT SBR)									
Right caudate	2.42		1.72					−28.9%	
Left caudate	2.25		1.95					−13.3%	
Right putamen	2.14		1.66					−22.4%	
Left putamen	2.27		1.67					−26.4%	

Abbreviations. AUDIT: Alcohol Use Disorders Identification Test; BDI: Beck Depression Inventory; G-SAS: Gambling Symptom Assessment Scale; PG-YBOCS: Pathological Gambling Adaptation of the Yale-Brown Obsessive-Compulsive Scale; ISI: Insomnia Severity Index; YMRS: Young Mania Rating Scale; DAT: Dopamine transporter; 123 I-FP-CIT SBR: Specific to non-specific 123 I-FP-CIT binding ratio.
Cut-off scores: BDI: < 13 minimal, 14–19 mild, 20–28 moderate, 29–63 severe depressive symptoms; G-SAS ranges from 0 to 48, gambling severity: extreme = 41–48, severe = 31–40, moderate = 21–30, mild = 8–20; PG-YBOCS ranges from 0 to 40; ISI: > 10; YMRS: > 20.

mesolimbic reward system in GD shares similarities with the functional organization reported in substance addiction, suggesting a more general pathophysiology for addictive disorders (Moccia et al., 2017). Dysfunctions in dopaminergic pathways have been found to be critically involved in GD (Clark, Boileau, & Zack, 2018), particularly in presynaptic structures (Pettorruso et al., 2018; van Holst et al., 2018). Recently, we reported reduced dopamine transporter (DAT) availability in GD subjects (Pettorruso, Martinotti, et al., 2018). The DAT terminates dopamine signaling at the synapse through high affinity reuptake of dopamine into presynaptic terminals, thereby controlling the spatial and temporal dynamics of dopaminergic neurotransmission (Pettorruso, Martinotti, et al., 2018). It plays a key role in regulating dopamine homeostasis (Vaughan & Foster, 2013) and its function is crucially dependent on tonic extracellular dopamine concentration. Low DAT levels in GD may represent a neurobiological correlate of reduced dopaminergic tone, consistent with the hyporeactivity in the dorsal striatum during reward anticipation and outcome reported in fMRI studies (Luijten, Schellekens, Kuhn, Machielse, & Sescousse, 2017).

DLPFC rTMS was found to increase ipsilateral striatal dopamine release (Strafella et al., 2001). Monosynaptic projections from the DLPFC to the ventral tegmental area (VTA) and to midbrain dopaminergic neurons may ultimately determine an enhancement in DA availability in the synaptic cleft in the nucleus accumbens (Diana, 2011).

In the present study, we hypothesize that stimulating the DLPFC with rTMS may restore a physiological basal dopaminergic activity, thus determining an increase in DAT levels. Consistent with a stimulation protocol previously used to treat cocaine dependence (Pettorruso et al., 2018; Terraneo et al., 2016), we studied the case of a GD patient treated with two weeks of high frequency rTMS over the DLPFC. Also, we explored the dopaminergic correlates of the treatment, in terms of changes in dopamine transporter (DAT) availability. Finally, we followed up the patient for six months, to explore safety and clinical correlates of the weekly rTMS maintenance treatment.

2. Case report

The patient is a 40-year-old Caucasian male with a 12-year history of DSM-5 diagnosis of GD. He reported continuous involvement in gambling activities, without remission periods. Subthreshold mood reactivity and mild impulsive personality traits were present. The patient did not take any pharmacological treatment. Scores on gambling severity assessment at baseline were as follows: G-SAS: 28, PG-YBOCS: 24 (Obsession subscale: 11; Compulsion subscale: 13). In the previous month, the patient was involved in slot machine gambling for 28 out of 30 days and had spent 1800 Euros.

The patient underwent a nuclear medicine visit and a SPECT examination, in order to assess DAT availability. SPECT acquisition and processing were performed as previously published (Addolorato et al., 2015; Pettorruso, Martinotti, et al., 2018). 185 MBq of ^{123}I-FP-CIT (DaTSCAN™, G.E. Healthcare, United Kingdom) were administered intravenously and SPECT was carried out using a dual-head gamma camera system Symbia Intevo - Siemens Healthineers Global equipped with high-resolution low-energy, parallel hole collimators. We performed a semi-quantitative assessment using specific to non-specific 123I-FP-CIT binding ratio (SBR) calculated through Volumes of interest (VOI) placed over the bilateral caudate and putamen (as radiotracerspecific binding), and over the occipital cortex (as non specific binding reference area). Specific to non-specific 123 I-FP-CIT binding ratio (SBR) was obtained employing the following formula: [(mean counts in striatal VOI)-(mean counts in occipital VOI)]/ (mean counts in occipital VOI). The VOI technique is considered highly reliable and reproducible, with a low mean test/retest variability (7.47%) (Booij et al., 1998).

rTMS was initiated 5 days after the baseline SPECT and it was delivered using a MagPro R30 with the Cool-B80 figure-of-eight coil (MagVenture, Falun, Denmark). Such coil allows for a focal stimulation of the DLPFC. The left DLPFC was located with BeamF3 method (Beam, Borckardt, Reeves, & George, 2009). The stimulation protocol included 20 sessions (twice a day, 5 days/week, 15 Hz frequency, pulse intensity 100% of the resting motor threshold, 60 pulses per train, inter train pause of 15 s, 40 stimulation trains, 2400 pulses/session).

The week following rTMS treatment completion, SPECT examination was repeated (three weeks after the baseline).

Finally, we applied a weekly maintenance protocol (two applications/week) for twelve weeks, using the same stimulation settings. Overall, the patient was followed-up for six months.

Dopaminergic and clinical correlates of rTMS treatment are presented in Table 1. The patient did not report any adverse events during the study period. After two weeks of treatment we observed reduced DAT levels in the striatal regions (Fig. 1). Over the six-month follow-up the patient reported no episodes of gambling relapse. No psychopharmacological treatment was administered during the six-month period. In addition, the patient reported a marked reduction in craving for gambling. The patient gave written informed consent for the

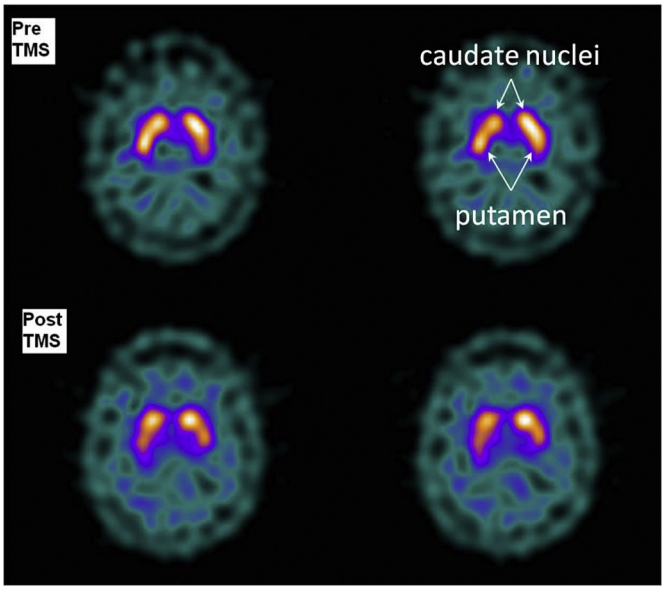

Fig. 1. Dopamine Transporter availability in a patient with Gambling Disorder (GD) before and after rTMS treatment. 123 I-FP-CIT SPECT images: transaxial slices showing striatum (caudate nucleus and putamen) radioligand uptake in a GD subject before and after rTMS treatment. The 123I-FP-CIT tracer uptake is correlated to DAT availability. The patient received two weeks (five days twice a day, for a total of twenty sessions) of high frequency rTMS over the dorsolateral prefrontal cortex. In comparison with baseline (PreTMS), the GD patient displayed reduced radiotracer uptake in the bilateral striatum, correlated to reduced DAT availability, after rTMS treatment (PostTMS).

procedure and subsequent case publication.

3. Discussion

In this case study we report the successful treatment of a subject with GD diagnosis, using high frequency rTMS applied over the DLPFC. The patient stopped gambling behavior over the six-month follow-up period, with an improvement in gambling craving and related-symptoms, as well as in hedonic tone and social functioning.

To date no studies ever explored the potential utility of multiple sessions of high-frequency rTMS as a possible treatment in GD in a clinical setting. A previous study demonstrated no efficacy of low frequency deep-TMS to the left DLPFC in the treatment of five GD patients (Rosenberg, Klein, & Dannon, 2013). Recently, two studies explored single sessions of high frequency rTMS in a laboratory setting (Gay et al., 2017; Zack et al., 2016), suggesting a potential utility to reduce cue-induced gambling craving (Zack et al., 2016) and no significant difference in gambling behaviors (Gay et al., 2017). Based on the rationale we recently provided (Moccia et al., 2017; Pettorruso, Spagnolo, et al., 2018), the protocol we applied was designed as a potential treatment for GD. We observed the complete interruption of GD behaviors in the case studied and continued remission over a six-month follow up period.

Also, we preliminarily explored dopamine function correlates of rTMS treatment in the GD patient. It has been postulated that rTMS modulates dopaminergic and glutamatergic transmission, both involved in the pathophysiology of GD (Pettorruso et al., 2014). The case showed a reduction in DAT availability after two weeks of treatment. Contrary to our hypothesis, these data do not show that treatment with rTMS could increase reduced levels of DAT in the striatum. Current evidence allows us to hypothesize that rTMS may enhance tonic dopaminergic transmission (Diana, 2011; Strafella et al., 2001), thus inducing a substrate-mediated DAT down-regulation. The mechanism of action of rTMS could imply modulation of gene expression of monoamine transporters (Ikeda, Kurosawa, Uchikawa, Kitayama, & Nukina, 2005) determining changes in DAT availability, and it has recently reported in subjects with alcohol use disorder (Addolorato et al., 2015). Nevertheless, it is not possible to exclude DAT reductions could be related to gambling withdrawal. At the moment no studies ever explored monoamine transporters' expression during the clinical course of GD. The absence of a control group limits data interpretation on DAT availability. Future studies assessing DAT function changes associated with rTMS treatment could benefit from a within-subjects crossover design to control the impact of study procedure and gambling withdrawal.

Our findings suggest that high frequency DLPFC rTMS deserves further investigations aimed at exploring its potential in the treatment of GD symptoms. By targeting the DLPFC, a node in the executive control network, rTMS should restore frontal-striatal circuitry abnormalities occurring in GD (Moccia et al., 2017). Additional studies in large samples using controlled designs are necessary to clarify rTMS neurobiological action in addictive behaviors.

Declaration of interest

The authors have no interests to disclose.

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