The role of repetitive transcranial magnetic stimulation (rTMS) in the treatment of behavioral addictions: Two case reports and review of the literature

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ABSTRACT

Background: Several behaviors, besides consumption of psychoactive substances, produce short-term reward that may lead to persistent aberrant behavior despite adverse consequences. Growing evidence suggests that these behaviors warrant consideration as nonsubstance or "behavioral" addictions, such as pathological gambling, internet gaming disorder and internet addiction. *Case presentation:* Here, we report two cases of behavioral addictions (BA), compulsive sexual behavior disorder for online porn use and internet gaming disorder. A 57-years-old male referred a loss of control over his online pornography use, started 15 years before, while a 21-years-old male university student reported an excessive online gaming activity undermining his academic productivity and social life. Both patients underwent a high-frequency repetitive transcranial magnetic stimulation (rTMS) protocol over the left dorsolateral pre-frontal cortex (l-DLPFC) in a multidisciplinary therapeutic setting. A decrease of addictive symptoms and an improvement of executive control were observed in both cases. *Discussion:* Starting from these clinical observations, we provide a systematic review of the literature suggesting that BAs share similar neurobiological mechanisms to those underlying substance use disorders (SUD). Moreover, we discuss whether neurocircuit-based interventions, such as rTMS, might represent a potential effective treatment for BAs.

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INTRODUCTION

Behavioral addictions (BA) are increasingly recognized as a valid category of psychiatric disorder with relevant socio-cultural and economic implications (Robbins & Clark, 2015). Despite the substantial progress in research on the neurobiology and clinical definition of addictive behaviors, our understanding of the potential neurobiological mechanisms related to specific non-substance addictive behaviors is still at an early stage and no proven specific

pharmacotherapies are available (Marazziti, Presta, Baroni, Silvestri & Dell'Osso, 2014). A large body of findings suggest that BAs share similar clinical, phenomenological, genetic, and neurobiological features with substance use disorders (SUD), supporting the inclusion of these disorders in the category of "Substance-related and Addictive disorders" of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (Grant, Potenza, Weinstein, & Gorelick, 2010). Similar to SUD, alterations in brain network activity related to reward processing, executive functions, inhibitory control response and habit formation and in neurotransmitter signaling, including dopamine, may underlie the development and maintenance of addictive behaviors (Brand et al., 2019). The identification of brain network activity dysfunctions could have important implications for the development of neurobiologically based treatments for both behavioral and drug addiction. Recently, repetitive transcranial magnetic stimulation (rTMS), is emerging as a promising therapeutic approach for SUD (Diana et al., 2017) and could potentially be an effective treatment for behavioral addictions. To our knowledge, we describe for the first time two cases of patients diagnosed with behavioral addictions (compulsive sexual behavior disorder for online porn use and internet gaming disorder) who received a multidisciplinary treatment including a rTMS protocol stimulating the left dorsolateral prefrontal cortex (l-DLPFC). Moreover, we provide a systematic review of the literature suggesting that BAs resemble SUD in many domains, including the phenomenology, the neurobiology and the clinical response and support the hypothesis that non-invasive neuromodulation techniques, such as rTMS might represent a potential effective treatment for BAs.

CASE PRESENTATION

Patient 1

The first patient, a 57-year-old sales representative Italian man, attended our outpatient clinic for addiction treatment from May 2019 to May 2020. His personal record stated an academic degree and a 22-years marriage with daughter.

At the first consultation, the patient complained of a loss of control over his online pornography use, started 15 years ago. After losing his job 5 years ago, he referred a very pervasive daily use which persisted until the month prior the visit: on average about 1 hour and a half a day with frequent binge-watching episodes, lasting 8 hours often without self-maturbation. He was also absorbed by watching pornographic videos, spending a consistent amount of time to feel the desired level of excitement. This excessive level of engagement was reported as a way to relieve negative mood states as boredom, frustration, or depression. He progressively lost interest in other daily activities, including sexual activities, and repetitively lied to his wife and daughter to justify his behavior jeopardizing the relationship with them. He also referred to have been abstinent from using pornography for the first time in 15 years during the last month. The

period of abstinence was associated to intense feelings of sadness, anxiety, irritability. Furthermore, he was spending a growing amount of time in thinking of sex scenes, thus avoiding any stimuli which could trigger the urge for pornography, as watching romantic movies with his wife or using internet alone. When admitted to our clinic, the patient met full diagnostic criteria for Compulsive Sexual Behavior Disorder (CSBD) according to the 11th edition of the International Classification of Diseases (ICD-11) as assessed by a clinical psychiatrist specialized in addiction disorders (World Health Organization, 2018). A standardized clinical evaluation was conducted using the following self-reported scales: Beck Depression Inventory –II (BDI - II) (Beck, Steer, & Brown, 1996), Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989), Self-rating Anxiety Scale (SAS) (Zung, 1971), Symptoms checklist 90 - Revised (SCL-90-R) (Derogatis, 1994) and a Visual Analogue Scale measuring craving for porn use (VAS craving). The patient was assessed at the first consultation, immediately before the rTMS treatment (nearly 20 days after the first consultation), after 5, 30, 60, 90 days of rTMS treatment and 1 month after the end of the treatment. The clinical outcomes scores of the patient during the observation period are summarized in Table 1.

The patient reported symptoms of social anxiety disorder from a young age, such as hand sweating, palpitations, redness, stammering, hot flashes, and muscle tension in the presence of unfamiliar people or when he felt under judgment. Consistently, the standardized clinical assessment revealed mild to moderate anxiety severity levels (SAS Score > 45, Table 1). His further medical history was not significant for any other mental disorder or medical condition. In the past, the patient referred unsuccessful psychotherapeutic attempts to face the addictive behavior and anxiety problems. To manage anxiety-related symptoms, we started an off-label pharmacological therapy with propranolol (Inderal, AstraZeneca spa, Milan, Italy) 60 mg/d. After 20 days, the patient reported a significant improvement of anxiety and depression symptoms with a reduction in palpitations and fainting feelings. He also noted to spend less time on thinking about sex scenes; however, the intrusive thoughts for pornography persisted in the everyday life situations (e.g. watching romantic movies with his wife) and the patient was continuously adopting avoidance behaviors. The persistence of cue-induced intrusive thoughts lead us to administer, following the acquisition of patient's informed consent approving the use of clinical data for research purposes, including the protocol approved by the Ethical Committee at Padua Teaching Hospital (protocol number: 4,743/U6/19), an rTMS protocol treatment that has been associated to anti-craving effects in other addictive disorders (Gómez Pérez et al., 2020; Terraneo et al., 2016).

The rTMS protocol was carried out using a medical device (MagPro R30, MagVenture, Farum, Denmark) targeting the l-DLPFC (MNI coordinates: x = −50, y = 30, z = 36) throughout an optical TMS Navigator (LOCALITE, St. Augustin, Germany) and a magnetic resonance image (MRI) template. Resting motor threshold (rMT) was determined using visual observation of muscle twitch (OM-MT) monthly. The stimulations parameters were set as previously

Table 1. Patient 1 Clinical Outcome Scores

	1st Consultation Assessment	Baseline	Day 5	Day 30	Day 60	Day 90	1st month Follow-up	Score Interpretation
GSI	75.00	50.62	43.98	40.67	40.33	40.33	41.66	45–55: normal 55–65: moderate 65–75: severe
PSQI	4.00	3.00	5.00	1.00	3.00	5.00	4.00	> 5: Poor Sleep Quality
BDI-II	19.00	-[§]	0.00	2.00	3.00	4.00	6.00	14–18: mild-moderate 19–29: moderate-severe 30–63: extremely severe
SAS	50.00	41.25	35.00	36.25	36.25	35.00	40.00	45–59: mild-moderate. 60–55: moderate-severe ≥75: severe
VAS craving	9.00	1.00	0.00	0.00	0.00	0.00	0.00	0–9

Data are presented as raw scores, except for the GSI (T-Score) and the SAS (Index score). [§] BDI-II was not administered at day 5 because it refers to the last two weeks; BDI-II: Beck Depression Inventory-II; VAS craving: Visual Analogue Scale measuring craving for porn use induced by imagined environmental cues; GSI: Global Severity Index of the Symptoms checklist 90 - Revised; PSQI: Pittsburgh Sleep Quality Index; SAS: Self-rating Anxiety Scale.

reported (Terraneo et al., 2016): 15 Hz frequency, 100% of rMT, 40 trains, 60 pulses per train, 15 s intertrain interval, and 2,400 pulses per session. The subject received 2 daily sessions for the first consecutive 5 days of treatment (10 sessions), and then 2 weekly sessions for the next 8 weeks. The time interval between two sessions each day was at least 30 min. Moreover, individualized psychological counselling was daily provided by an addiction expert clinical psychologist. During the treatment no adverse event or subjective complaint was reported.

Following the rTMS treatment protocol, the patient has no longer manifested urges to use pornography, even in situations that were described as trigger (e.g. being alone in a hotel with his laptop or watching romantic movies with sex scenes). Pornography was no longer used to escape from unpleasant feelings and of intrusive thoughts about porn videos were not present. The patient also referred a consistent improvement of mood disturbances with normalization of anxiety levels and a significant enhancement of mood and a better relationship with his relatives.

At the 1-year follow-up examination, despite stressful situations, including the request for a salary increase, the unexpected diagnosis of Peyronie's disease and the Coronavirus Disease 2019 (COVID-19)-related lockdown, that could have represented a trigger for a relapse, the patient maintained the clinical improvement achieved. At this timepoint, it was not possible to perform the assessment using standardized self-reported scales due to the COVID-19 lockdown.

Patient 2

The second patient was a 21-year-old Italian male university student admitted to our addiction clinic from November 2018 to November 2019.

At the clinical intake interview, the patient referred an excessive online gaming activity, about 9 daily hours on weekdays and about 15 daily hours during the weekend, often losing the sense of time and neglecting other daily activities such as studying or engaging in social relationships. He was experiencing increasing difficulties in concentrating and being focused, as in 2-years of academic study he failed to pass his examinations. He was also less interested in hanging out and having physical interactions with friends and other people, rather preferring the social media chats to communicate with them. Over the time the patient attempted to suspend the online gaming activity experiencing anxiety, irritability and sadness associated to an increased need of gaming online and feeling guilty when not able to stop the use. The patient attributed the loss of control over gaming to an increased anxiety and sadness caused by a feeling of loneliness related to a recent move far from friends and family.

Investigating his medical history, an overuse of online gaming without negative consequences on his school performances or social interactions, was already present during the middle school, particularly when her mother was diagnosed with a severe neurological disease. Since childhood he referred mild problems to engage in stable peer relations and often feeling embarrassed in social contexts. The medical history was devoid of other significant mental or medical condition. A standardized clinical assessment was conducted at baseline and 3 and 12 months after the beginning of the rTMS treatment by using the following self-reported scales: BDI - II (Beck et al., 1996), PSQI (Buysse et al., 1989), SAS (Zung, 1971), SCL-90-R (Derogatis, 1994), Internet Gaming Disorder Scale – Short-Form (IGDS9-SF) (Monacis, Palo, Griffiths, M. D. & Sinatra, 2016), Internet Addiction Test (IAT) (Servidio, 2017), Stroop Color Word Test-Short version (SCWT-SV) (Caffarra, Vezzadini, Dieci, Zonato, &
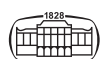
Venneri, 2002) and a Visual Analogue Scale measuring current craving for gaming (VAS craving). The clinical outcomes scores of the patient during treatment are shown in Table 2. At baseline, a high degree of internet gaming disorder was present as indicated by the high IGDS9-SF score (> 21, Table 2).

We hypothesized that the persistent and dysfunctional addictive-like behavior could benefit from a rTMS protocol treatment over the l-DLPFC. After obtaining the informed patient's consent approving the use of clinical data for research purposes, including the protocol approved by the Ethical Committee at Padua Teaching Hospital (protocol number: 4,743/U6/19), an rTMS protocol treatment, as previously described was administered. He also received psychological support by a clinical psychologist trained in addiction, whereas no pharmacological treatment was prescribed. No subjective complaint or adverse event was observed during or after rTMS protocol. After the first week of treatment, the patient reported a significant reduction of the time spent on internet, up to only 2 hours per week. Internet was no longer used for gaming, rather for study purposes. Furthermore, the patient was experiencing an unprecedent capacity to interrupt internet use once started and the resumption to be engaged in healthy leisure activities outside (e.g. going to the bookstore, hanging out with friends). At the end of the 9-weeks rTMS treatment, the subjective clinical improvement persisted and no irritability, anxiety, or recurrent thoughts about online gaming were reported. He managed to reorganize his daily routine activity mainly focusing on his academic goals, re-establishing old friendship or meeting new people. However, the progressive clinical improvement of gaming maladaptive behavior was accompanied by mood deflection and psychological distress related to a pre-existing and marked perfectionism attitude and low self-esteem, manifesting especially during social interaction. Therefore, the patient was referred to a psychotherapist. At the 1 year follow up, he demonstrated a significant improvement of his emotional state and relational skills, while symptoms of internet gaming addiction were no longer present.

DISCUSSION

Here, we describe two cases of BA, online pornography addiction and internet gaming disorder, diagnosed by applying the existing criteria for "substance-related and addictive disorders" in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (Vinet & Zhedanov, 2010) and the CSBD criteria in the International Classification of Diseases Eleventh Edition (World Health Organization, 2018). Both patients came to our attention complaining of symptoms resembling those of addictive disorders, including a pattern of persistent and excessive behavior (porn watching or internet gaming), several failed attempt to control the behavior, tolerance, and craving. This clinical picture was accompanied of withdrawal symptoms, including negative mood and increased stress reactivity, and an impairment of

Table 2. Patient 2 Clinical Outcome Scores

	Baseline	Day 90	1-year Follow-up	Score Interpretation
GSI	51.57	61.14	48.04	45–55: normal
				55–65: moderate
				65–75: severe
PSQI	4.00	6.00	1.00	> 5: Poor Sleep Quality
BDI-II	13.00	25.00	4.00	14–18: mild-moderate
				19–29: moderate-severe
				30–63: extremely severe
SAS	32.50	50.00	36.25	45–59: mild-moderate
				60–55: moderate-severe
				≥75: severe
VAS craving	75.00	55.00	5.00	0–100
IGDS9-SF	32.00	16.00*	0.00	> 21: Disordered gaming
IAT	59.00	30.00	26.00	31–49: mild problems
				50–79: moderate problems
				80–100: severe problems
SCWT-SV: Interference time score	4.00	4.00	4.00	0: below the norm
				1: lower limit of the norm
				2–4: within the norm
SCWT-SV: Interference error score	1.00	1.00	4.00	0: below the norm
				1: lower limit of the norm
				2–4: within the norm

Data are presented as raw scores, except for the GSI (T-Score), the SAS (Index score) and the SCWT-SV (Equivalent score). *This scale was administered at day 90 referring to the last three months for clinical reasons; BDI-II: Beck Depression Inventory-II; VAS craving: Visual Analogue Scale measuring current craving for gaming; GSI: Global Severity Index of the Symptoms checklist 90 - Revised; PSQI: Pittsburgh Sleep Quality Index; SAS: Self-rating Anxiety Scale; IGDS9-SF: Internet Gaming Disorder Scale – Short-Form; IAT: Internet Addiction Test; SCWT-SV: Stroop Color Word Test-Short version.

their personal, professional, and social life. In contrast to SUD, no approved medication for the treatment of behavioral addictions is available (Mouaffak et al., 2017). However, since underlying neural processes as well as clinical symptoms are found to be similar in BA and SUD (Grant et al., 2010), we sought that non-invasive neuromodulation intervention might be a promising candidate for the treatment of behavioral addictions as well. To our knowledge, these two cases are the first description of internet addiction treated with a rTMS protocol treatment targeting the l-DLPFC.

There is a general consensus suggesting etiological, cognitive and personality features similarities between SUD and non-substance related addictions (Brand et al., 2019; Brand, Young, Laier, Wölfling, & Potenza, 2016). However, the pattern of impulsivity and compulsivity of addictive behaviors might underlie different endophenotype that can critically differentiate SUD from non-substance related addiction (Wareham & Potenza, 2010). Although additional studies employing larger samples and a wider array of imaging modalities are needed to investigate the neurobiological similarities and differences of individuals with SUD and behavioral addiction, these internet-use related disorders share with substance addiction personality traits, including impulsivity, sensation seeking, and neuroticism (Antons & Brand, 2018; Dayan, Bernard, Olliac, Mailhes, & Kermarrec, 2010; Ko et al., 2014; Lejuez et al., 2010; Liu et al., 2014; Ma et al., 2010; Mehroof & Griffiths, 2010; Müller, Beutel, Egloff & Wölfling, 2014; Uhl et al., 2008) and escapism to avoid hassles and distress as negative reinforcement mechanism for maintaining abuse behaviour (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Hagström & Kaldo, 2014). Interestingly, both patients reported escaping from unpleasant feelings as an essential driving motivation to engage in overuse behaviour.

Similarly, cognitive disturbances, typically associated to SUD, such as impaired decision-making ability, biases toward addiction related stimuli and lower response inhibition (Bechara & Martin, 2004; Field, Mogg & Bradley, 2004; Field, Munafò & Franken, 2009; Goldstein & Volkow, 2011; Jovanovski, Erb & Zakzanis, 2005; Koob & Volkow, 2016; Spronk, van Wel, Ramaekers & Verkes, 2013; Verdejo-García, Bechara, Recknor & Perez-Garcia, 2006) have also been reported in people with non-substance addictions (Mechelmans et al., 2014; Pawlikowski & Brand, 2011; Zhou, Yuan & Yao, 2012). The cognitive function impairment might be related to an imbalance between the increasing incentive-oriented urges and the decreasing situation-specific inhibitory control over these urges, that plays a key role for the onset and maintenance of addictive behaviors (Brand et al., 2019). Furthermore, brain imaging studies have demonstrated similar alterations in cortico-limbic-striatal and prefrontal control circuits, involving ventral striatum, amygdala, and dorsolateral prefrontal areas, in either SUD or BA indicating an enhanced activation of these networks during cue-induced craving processing but a blunted response during executive control processing (Brand, Snagowski, Laier, & Maderwald, 2016; Chen et al., 2015;

Han, Hwang & Renshaw, 2010; Ko et al., 2014, 2009; Liu et al., 2014; Zilverstand, Huang, Alia-Klein & Goldstein, 2018).

Thus, prolonged exposure to addictive agents or engaging in persistent addictive behaviors are associated to neural circuit dysfunctions implicated in reward, salience attribution, motivation, inhibitory control, learning and memory consolidation, suggesting a common neurobiological basis for SUD and BA. Preclinical studies manipulating corticostriatal circuits by using optogenetics provided foundation to explore neuromodulation as an effective treatment for stimulant use disorder (Chen et al., 2013). rTMS represents a novel and promising therapeutic approach for addiction (Spagnolo, Gómez Pérez, Terraneo, Gallimberti & Bonci, 2019) as it modulates neural activity in the short and long term period by inducing neuroplastic changes (Fox, Halko, Eldaief & Pascual-Leone, 2012). This approach has been associated to clinically relevant behavioral changes in patients with addictive disorders (Ekhtiari et al., 2019), affecting craving, intake and relapse (Diana et al., 2017). To date, high-frequency rTMS protocols over the dorsolateral prefrontal cortex, a key node for the executive control network (Shirer, Ryali, Rykhlevskaia, Menon & Greicius, 2012), are effective in reducing craving, substance consumption and withdrawal symptoms of SUD, including alcohol (Addolorato et al., 2017; Mishra, Nizamie, Das & Praharaj, 2010; Mishra, Praharaj, Katshu, Sarkar & Nizamie, 2015), tobacco (Amiaz, Levy, Vainiger, Grunhaus & Zangen, 2009; Eichhammer et al., 2003; Hayashi, Ko, Strafella & Dagher, 2013; Johann et al., 2003; Li et al., 2013), cocaine (Gómez Pérez et al., 2020; Hanlon et al., 2015; Madeo et al., 2020; Pettorruso et al., 2019; Politi, Fauci, Santoro, & Smeraldi, 2008; Sanna et al., 2019; Steele, Maxwell, Ross, Stein, & Salmeron, 2019; Terraneo et al., 2016), methamphetamine (Liang, Wang & Yuan, 2018; Su et al., 2017) and heroin (Shen et al., 2016). Preliminary findings also suggest that these protocols might ameliorate gambling disorder symptoms (Cardullo et al., 2019; Pettorruso et al., 2020).

In our cases, both patients regained the ability to control their behavioural urges and craving-like thoughts after the rTMS protocol treatment. Following the treatment, they also reported an internet use for professional purposes, as university or work assignments. We hypothesized that the clinical improvement of behavioral addictive symptoms might be related to the rTMS-induced neuromodulatory effect over the brain networks areas mediating response inhibition and control of impulsive behaviour (Dunlop, Hanlon & Downar, 2017; Gorelick, Zangen, & George, 2014).

In medicine and in some therapeutic areas, including psychiatric disorders, a possible placebo response might influence the final outcome of clinical trials. From a psychological point of view the placebo response may be triggered by various interrelated environmental and psychosocial factors, such as patient's expectations of the benefit of a treatment, behavioural conditioning, and the quality of the patient–physician relationship (Enck, Bingel, Schedlowski & Rief, 2013). We took into account all these elements and we adopted some procedures to minimize as much as possible

the placebo effect. Both patients were given clear and exhaustive information regarding the off-label use of the rTMS treatment, for whom no evidence of efficacy is still available in the literature. This approach allowed to balance the patients' expectations towards the treatment final outcome. Indeed, Patient 1 started an off-label pharmacological treatment with the beta-blocker propranolol before the rTMS protocol obtaining an improvement only of his anxiety-related symptoms whereas the cue-induced intrusive thoughts persisted.

Notably, the clinical recovery persisted at 1-year follow-up after the treatment although both patients experienced unpleasant situations, recognized as triggers for inducing craving for gaming or porn watching in the past. This long-lasting clinical improvement over the addictive behaviours with no relapses in both patients is in support of a minimized placebo response and is in line with our previous findings showing that rTMS treatment is accompanied by long-lasting reductions of substance consumption behaviours in a large cohort of patients with cocaine use disorder clinically followed-up for 2 years and 8 months (Madeo et al., 2020).

Patient 2 required a psychotherapic support to address some of his personality features, including perfectionism and low-self-esteem, that emerged during the treatment. Several finding now suggest that cognitive, personality and mood features are associated with internet addiction (Şenormancı et al., 2014; Younes et al., 2016) and might play a role in developing addictive behavior as a coping strategy to be relieved from their negative beliefs (Şenormancı et al., 2014). The improvement of cortical function through the neuromodulatory intervention might have allowed a more successful psychotherapeutic approach (Bajbouj & Padberg, 2014) (Donse, Padberg, Sack, Rush & Arns, 2018), as seen in patient 2.

Likewise, in patient 2 we observed prominent autonomic symptoms associated with social anxiety, a frequent comorbidity in internet-related disorders (Bernardi & Pallanti, 2009). We efficaciously controlled the autonomic-related symptomatology by administering propranolol, a nonselective beta-blocker blocking the catecholamines action through the beta-1 and beta-2 adrenergic receptors (Routledge & Shand, 1979). Propranolol effectively suppresses the autonomic hyperactivity and hyperarousal associated with anxiety disorder, reducing thereby its physical symptoms (Brantigan, Brantigan, & Joseph, 1982; Mealy et al., 1996). Consistently with the pharmacological effects, after 20 days of treatment patient 1 experienced an improvement of autonomic-related symptoms but the intrusive thinking and cue-induced craving persisted. A substantial improvement of addictive related behaviors was observed after the rTMS treatment. In both substance and porn addictions, increased reactivity towards appetitive cues is associated with a reduced connectivity between dorsal prefrontal regions, mediating cognitive control, and limbic areas, relevant for the motivational salience (Berlingeri et al., 2017; Klucken, Wehrum-Osinsky, Schweckendiek, Kruse & Stark, R., 2016; Ma et al., 2010; Schmidt et al., 2017). Thus, the rTMS

treatment strategy focused on amplifying activity in frontal-striatal circuits might improve cognitive functions and reduce craving (Hanlon et al., 2015).

In conclusion, the reported cases describe how BAs, sharing clinical core symptoms with SUD may benefit from a neuromodulatory intervention using a rTMS protocol stimulating the DLPFC. Hence, further studies are needed to validate these preliminary observations and investigate whether rTMS could be a treatment option for non-substance addictions, such as internet gaming disorders or online porn-addiction.

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