HHS Public Access

Author manuscript

J Addict Med. Author manuscript; available in PMC 2021 July 01.

Published in final edited form as:

J Addict Med. 2020 ; 14(4): 272–274. doi:10.1097/ADM.0000000000000575.

A light in the darkness: repetitive transcranial magnetic stimulation (rTMS) to treat the hedonic dysregulation of addiction

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Abstract

The present paper discusses the potential use of repetitive transcranial magnetic stimulation (rTMS) for the treatment of addiction, within a conceptual framework that includes the "dark side" of addiction. New findings suggest that rTMS may rescue specific reward system dysfunction that underlies the pathophysiology of addiction by exposing widely under-recognized and untreated key clinical and psychopathological aspects of addictive disorders. Our paper sheds light on the relevance of these hidden dimensions for the development of effective treatment interventions. In particular, we argue that rTMS may have an impact on craving by reversing the allostatic load of hedonic dysregulation.

Addiction is a chronic disorder, characterized by the progressive accumulation of allostatic load (Koob and Volkow, 2016). In recent years, the addiction field has seen important advances at the preclinical and conceptual levels, but has been slow to engage in efforts to reconfigure treatment interventions. New frameworks that fill this gap need to inform future treatment strategies.

1. "Dark side" of addiction and homeostatic hedonic dysregulation

The cumulative psychopathological burden of addiction, termed allostatic load, has been referred to as the "dark side" of addiction (Koob, 2009), which may account for the persistence of addictive behaviors that are mainly driven by negative reinforcement. This allostatic load is reflected by chronic deviation of the reward set point that results from

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repeated drug use and corresponds to the dysfunction of specific neurological circuits and recruitment of brain and hormonal stress systems (Ahmed et al., 2002). The shift in reward set point is hypothesized to mediate the transition from occasional drug use to compulsive drug seeking, particularly in patients with psychiatric comorbidity (Pettorruso et al., 2014). As such, the emergence of negative emotional states and withdrawal symptoms can be considered a hallmark of this transition. Under this framework, compulsive use is hypothesized to represent an attempt to offset negative affective states, such as dysphoria, the loss of motivation, and anhedonia. One can argue that impairments in hedonic tone are a core element across all stages of addiction (i.e., binge/intoxication stage, withdrawal/negative affect stage, and preoccupation/anticipation [craving] stage) and contribute to relapse during withdrawal and protracted abstinence (Ahmed et al., 2002).

Hedonic allostasis has been widely linked to underlying dopaminergic circuit dysfunction. Deficits in dopaminergic striatal circuitry are associated with low neural responsiveness to natural rewards in cocaine use disorder and during acute and protracted withdrawal in substance use disorders (Diana, 2011) and gambling addiction (Pettorruso et al., 2019). Moreover, an anti-reward system has been hypothesized to counteradaptively exert physiological actions that impose a constraint on the duration of activation of the reward system. Pathological hyperactivation of the corticotropin-releasing factor and dynorphin systems significantly contributes to the “dark side” of addiction, including stress-surfeit phenomena. Fundamental relationships between these alterations and addiction-related disorders appear to involve dysfunctional activation and connectivity of the prefrontal cortex, prefrontal-striatal networks, extended amygdala systems, and other limbic systems (Koob and Volkow, 2016). The conceptualization of addiction as a neurocircuitry disorder lays the groundwork for considering novel interventions that specifically seek to reverse some of these alterations.

2. Non-invasive brain stimulation and addiction

Non-invasive brain stimulation interventions have been proposed for the treatment of various psychiatric disorders, including major depression and anxiety disorders. Recently, repetitive transcranial magnetic stimulation (rTMS) has emerged as a promising treatment for addiction (Diana et al., 2017). rTMS is a neuromodulation technique that utilizes localized magnetic fields to focally modulate cortical excitability. It can either stimulate or inhibit local cortical activity, depending on the application of high (> 5 Hz) or low (< 5 Hz) frequencies, respectively (Valero-Cabré et al., 2017). These interventions have the benefit of not exposing the individual to untoward chemical effects of various substances and medications and circumventing drug-induced cognitive side effects.

The mechanisms that underlie the therapeutic effects of rTMS remain under study, but it appears to directly target and remodel brain circuit dysfunctions that are associated with addictive behaviors. rTMS over the dorsolateral prefrontal cortex (dlPFC) has been shown to re-equilibrate dopamine release in prefrontal and striatal regions that are involved in reward processing (Diana, 2011). Although the activity of the magnetic field that is produced by rTMS reaches a depth of only a few centimeters by following neuronal projections of targeted areas, it can have a wider range of action (Valero-Cabré et al., 2017). Changes in

extracellular dopamine levels can be measured *in vivo* using such techniques as positron emission tomography with the radiotracer [^{11}C]raclopride. Through monosynaptic projections to the ventral tegmental area and midbrain dopaminergic neurons, rTMS of the dLPFC was shown to drive the release of endogenous dopamine in the ipsilateral caudate nucleus (Strafella et al., 2001), thus ultimately enhancing dopaminergic transmission in healthy human subjects. As a result, rTMS may reduce negative affective states that are associated with several disorders (Aleman et al., 2018; Pettorruso et al., 2018). In subjects with cocaine use disorder, dlPFC rTMS reduced craving and anhedonic symptoms and restored the physiological response to natural rewards, consistent with the well established role of the dlPFC in higher cognitive functions and inhibitory control (Pettorruso et al., 2018). Studies of nicotine addiction have also reported a reduction of cue-induced craving after neuromodulation treatments, and studies of alcohol-dependent subjects reported increases in the function of dopaminergic pathways after rTMS (Diana et al., 2017).

Current neuromodulation strategies do not only focus on amplifying the activity of frontal-striatal circuits. Other approaches support the notion that inhibition of the medial PFC decreases striatal and insula activity, thereby weakening drug-related craving and transdiagnostically attenuating frontostriatal reactivity to substance-related cues (Kearney-Ramos et al., 2018). Thus, by exerting actions on an imbalance between competing neurobehavioral decision systems (Bickel et al., 2016), apparently opposite rTMS strategies may reverse addiction-related alterations in different stages of the addiction cycle.

To date, the application of rTMS to treat addiction is a nascent field of study. The vast majority of studies have been uncontrolled and exhibit high variability of the methods that are utilized and the outcomes that are measured, with consequently mixed results. For further development of the field, more efforts need to be made to test well-defined hypotheses in larger, sham-controlled trials.

3. rTMS to modulate the dark side of addiction: a proposed framework

The application of rTMS within the addiction field requires the conceptualization of deeper and more thorough hypotheses about the rationale for such application and the elaboration of different competing yet possibly complementary intervention models. The hypothesis that is proposed herein is that rTMS has the potential to restore drug-induced dopaminergic dysfunction (Diana, 2011), thus possibly reversing, at least partially, the allostatic load of hedonic dysregulation (Fig. 1). This dopaminergic “boost” is hypothesized to lead to the modulation of many of the core components of the dark side of compulsivity in addiction. Such protocols may ultimately utilize TMS as a tool to increase responses to alternative reinforcers that have been progressively overcome by drug-related dysregulation. rTMS may thus reawaken diminished reward-system reactivity to natural rewards. By enhancing responses to natural non-drug rewards, rTMS has the potential to dampen negative affective states that drive compulsivity.

Recently, through a dissection of anhedonia into different components, a motivational dimension was described (Treadway and Zald, 2011). Motivational anhedonia and craving may represent highly interconnected phenomena, whereas hedonic dysregulation and

craving may represent faces of the same disrupted coin. By modulating anhedonia, we hypothesize that rTMS may allow one to accentuate the downregulation of craving symptoms in subjects with addiction. This process may also involve the potentiation of prefrontal-driven cognitive control and the activation of plasticity-related glutamatergic projections. Nevertheless, the resulting “craving downregulated” therapeutic interval may allow the possibility of breaking the addiction cycle by allowing patients to gain more benefits from detoxification and rehabilitation programs. As such, TMS offers the additional advantage of not administering drugs, thereby circumventing drug-induced cognitive side effects.

Existing frameworks, grounded in a symptom-based approach, do not address fundamental elements of the dark side that drives the addictive process as a whole. A neuroscience-based framework, including the domains of incentive salience, negative emotionality, and executive function, has been proposed at the clinical level to better understand the development and maintenance of addiction (Kwako et al., 2016). The largely ignored complex interplay between the “hidden” dark side dimensions that drive the negative reinforcement component of compulsivity should be recognized as key future treatment targets of intervention programs. Translating these approaches into clinical practice may confer enormous benefits for patients who suffer from addiction.

Acknowledgments

The authors would like to thank Michael Arends for assistance with manuscript preparation and editing.

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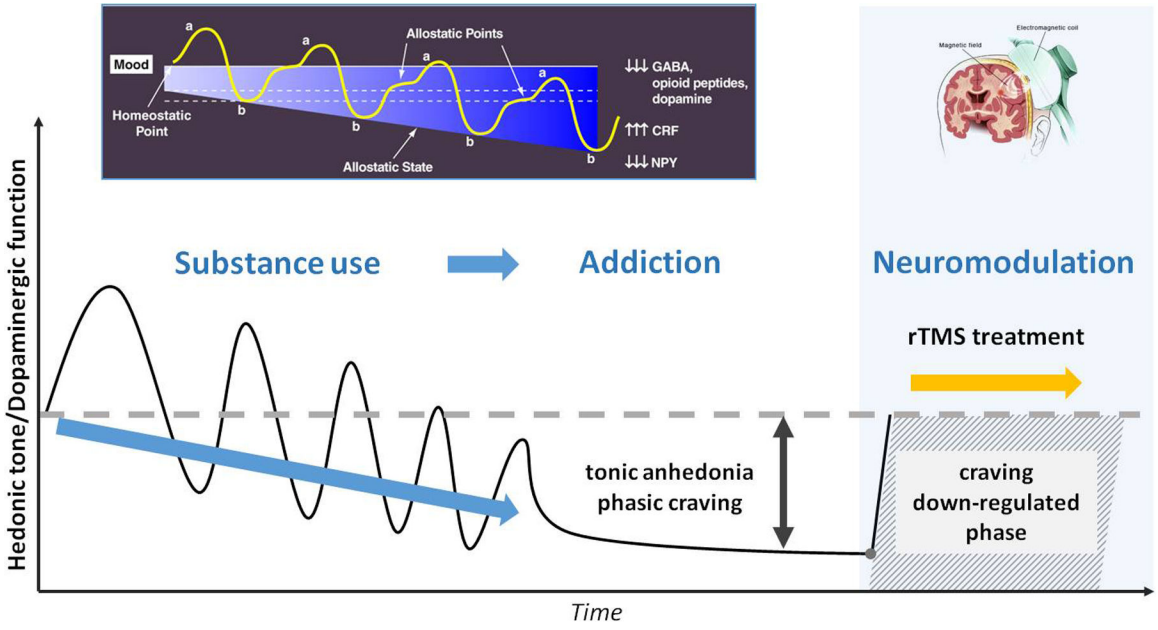

Figure 1.

Addiction reflects progressive dopamine system dysregulation and the sensitization of corticotropin-releasing factor and dynorphin brain stress systems, which interact, are subjectively experienced as hypohedonia, and support craving from a negative reinforcement perspective (Koob, 2013). We hypothesize that a neuromodulatory approach can restore these alterations, thus reversing the allostatic load of hedonic dysregulation. Dorsolateral prefrontal cortex stimulation with repetitive transcranial magnetic stimulation possibly produces a “craving downregulated” therapeutic interval, during which compulsivity phenomena (craving driven by hypohedonia) do not interfere with progress in rehabilitation programs. CRF, corticotropin-releasing factor; GABA, γ-aminobutyric acid; NPY, neuropeptide Y.