Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

Brain Research

Research Report

What goes up, can come down: Novel brain stimulation paradigms may attenuate craving and craving-related neural circuitry in substance dependent individuals

Colleen A. Hanlon[a,b,c,*], Logan T. Dowdle[a,b], Christopher W. Austelle[a], William DeVries[a], Oliver Mithoefer[a], Bashar W. Badran[a,b], Mark S. George[a,b,c,d]

[a]Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, USA
[b]Department of Neurosciences, Medical University of South Carolina, USA
[c]Center for Biomedical Imaging, Medical University of South Carolina, USA
[d]Ralph H Johnson Veterans Affairs Medical Center, USA

ARTICLE INFO

Article history:
Accepted 10 February 2015
Available online 11 March 2015

Keywords:
Brain stimulation
Functional MRI
Orbitofrontal cortex
BA 10
Caudate

ABSTRACT

Vulnerability to drug related cues is one of the leading causes for continued use and relapse among substance dependent individuals. Using drugs in the face of cues may be associated with dysfunction in at least two frontal-striatal neural circuits: (1) elevated activity in medial and ventral areas that govern limbic arousal (including the medial prefrontal cortex (MPFC) and ventral striatum) or (2) depressed activity in dorsal and lateral areas that govern cognitive control (including the dorsolateral prefrontal cortex (DLPFC) and dorsal striatum). Transcranial magnetic stimulation (TMS) is emerging as a promising new tool for the attenuation of craving among multiple substance dependent populations. To date however, nearly all repetitive TMS studies in addiction have focused on amplifying activity in frontal-striatal circuits that govern cognitive control. This manuscript reviews recent work using TMS as a tool to decrease craving for multiple substances and provides a theoretical model for how clinical researchers might approach target and frequency selection for TMS of addiction. To buttress this model, preliminary data from a single-blind, sham-controlled, crossover study of 11 cocaine-dependent individuals is also presented. These results suggest that attenuating MPFC activity through theta burst stimulation decreases activity in the striatum and anterior insula. It is also more likely to attenuate craving than sham TMS. Hence, while many TMS studies are focused on applying LTP-like stimulation to the DLPFC, the MPFC might be a new, efficacious, and treatable target for craving in cocaine dependent individuals.

This article is part of a Special Issue entitled SI:Addiction circuits.

*Corresponding author at: Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, USA. Fax: +843 792 5702.
E-mail address: hanlon@musc.edu (C.A. Hanlon).

http://dx.doi.org/10.1016/j.brainres.2015.02.053
0006-8993/

1. Frontal-striatal circuits involved in addiction

Chronic cocaine use is among the most difficult substance-use disorders to treat. Nearly 1 in every 7 people seeking treatment for drug abuse is dependent upon cocaine (Abuse N.I.O.D, 2010) and short-term cocaine relapse rates can reach 75% (Sinha, 2011). There are no FDA-approved pharmacotherapy approaches for cocaine dependence and traditional behavioral treatment strategies often have limited success in cocaine dependent populations. This chronic cycle of use, abstinence, and relapse is likely due to factors that involve limbic and executive circuits in the brain, including vulnerability to salient cues and loss of cognitive control (Back et al., 2010; Poling et al., 2007).

1.1. *Anatomical connectivity between the frontal cortex and the striatum.*

In healthy individuals, limbic drive and executive control are modulated by at least two frontal-striatal neural circuits in the brain—the limbic circuit, which includes projections from the medial prefrontal cortex (MPFC) to the ventral striatum, and the executive control circuit, which includes projections from the dorsolateral prefrontal cortex (DLPFC) to the dorsal striatum (Alexander et al., 1986) (Fig. 1, left). Among treatment-seeking cocaine users, vulnerability to drug related cues could theoretically be due to: (1) elevated functional activity within limbic neural circuitry (including the MPFC and ventral striatum) in the presence of a salient cue (Ersche et al., 2012; Moeller et al., 2010; Moreno-Lopez et al., 2012) or (2) depressed activity in executive control circuitry (including the DLPFC and dorsal striatum) (Goldstein et al., 2004; Kubler et al., 2005; Moeller et al., 2010) which is likely required to resist the limbic drive for the drug. These frontal-striatal connections represent the first stage of the frontal-striatal-thalamic loops which were classically characterized based on anatomical connectivity between the frontal cortex, striatum, pallidum and thalamus (Alexander et al., 1986, 1989). Through advances in imaging technology in the past 20 years, these circuits have been further refined (Haber 2003; Lehéricy et al., 2004) and interpreted in relationship to their role in psychiatric disease (Haber and Rauch 2010).

The framework for using TMS as an innovative treatment option for addiction presented in this review will capitalize on the *anatomical connectivity* between the frontal cortex and striatum. Complementing this anatomical connectivity however, are models of functional connectivity in limbic and executive control circuits. The development of functional MRI acquisition and analysis techniques over the past 20 years has led to a rich, emerging literature on intrinsic networks of functional connectivity. These functional connectivity models typically measure temporally correlated changes in BOLD signal in disparate areas of the brain while an individual is resting. Unlike anatomical connectivity studies, functional connectivity studies are typically not constrained by neural architecture. That said, it is appealing to see that these 'anatomically agnostic' functional connectivity models have isolated intrinsic networks which are similar to the anatomically defined limbic and executive frontal-striatal-thalamic loops (e.g. default mode network, salience network, and the executive control network) (Seeley et al. 2007). When developing TMS as a tool for addiction however, we have chosen to focus on the anatomical connectivity between frontal and striatal areas. This is because TMS induces a change in BOLD signal in the area immediately under the TMS coil as well as areas monosynaptically connected (Bohning et al., 1999; Thickbroom, 2007). Consequently, any causal effect of TMS on subcortical structures with traditional figure-of-eight coils currently requires anatomical connectivity between the cortical region stimulated and the subcortical target.

1.2. *Tools available to modulate frontal-striatal circuits in addiction.*

Our understanding of the neural circuitry that governs drug seeking and cue-induced reinstatement has significantly advanced via developments in optogenetics (Cao et al., 2011; Steinberg and Janak, 2013) and designer receptors exclusively activated by designer drugs (DREADD) (Ferguson and Neumaier, 2012; Aston-Jones and Deisseroth, 2013). With optogenetics, populations of neurons that have been infected with channel rhodopsin (Boyden et al., 2005) or halorhodopsin (Zhang et al., 2007) can be selectively activated or inhibited through exposure to different frequencies of light. In an analogous approach, DREADDs involve the mutation of muscarinic acetylcholine

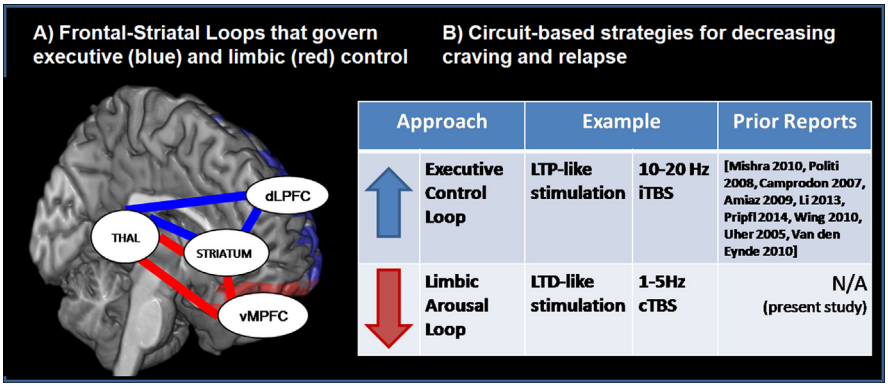

Fig. 1 – Frontal-striatal circuits that contribute to vulnerability to cues and brain stimulation strategies to modulate these circuits.