LITERATURE REVIEW

Cravings Reduction Program

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1. Introduction

This document is a comprehensive review of the scientific literature on the tDCS modality, limited to safety and cravings reduction. The reader is encouraged to read the cited articles. Statements in this document are intended to inform the reader on the subject of tDCS, and should not be considered as marketing claims. All claims in this document are cited appropriately using primary sources. The key work in this area of research has been conducted at world-class research centres using double-blind randomized controlled trials, published in top scientific journals. Note that the data in this document are presented and discussed in a manner that preserves the integrity and intent of the authors' work; no misrepresentation or falsification of data is presented.

Nuraleve's medical device is licensed by Health Canada for the treatment of chronic pain. Nuraleve continues to research applications of tDCS in Health Canada cleared clinical trials with the Centre for Addiction and Mental Health, the University of Ottawa, and the Saint Joseph's General Hospital. Nuraleve's consumer product is classified as such for claims related to smoking cravings reduction in a formal Health Canada classification letter.

2. A New Modality for Cravings Reduction

Neuromodulation is a revolutionary new set of neuroplasticity techniques that can be used to modify the human brain. One such technique is called transcranial direct current stimulation (tDCS). Nuraleve has developed a platform technology and service applying tDCS to reduce cravings associated with smoking cigarettes.

A promising feature of tDCS is its ability to induce neuroplasticity, engaging some of the same systems (e.g., dopamine, glutamate) that figure prominently in the pathological neuroplasticity caused by addictive drugs such as nicotine. Drug-induced neuroplasticity is thought to underlie the cravings for cigarettes, and by extension, the long-lasting vulnerability to relapse that characterizes addiction. By enhancing neuroplasticity, tDCS offers the potential to reverse some of the motivational consequences of cravings and reduce the risk of relapse.

Double-blind, randomized trials conducted to date support the notion that anodal tDCS stimulation significantly reduces several types of cravings, including those for cigarettes (Boggio et al., 2009; Fregni et al., 2008a), food (Fregni et al., 2008b; Goldman et al., 2011), and marijuana (Boggio et al., 2010). It has also been shown to improve related aspects of cognitive functioning such as decision making (Fecteau et al., 2007a,b; Hecht et al., 2010) and inhibitory

control (Hsu et al., 2011; Ditye et al., 2012). Given that a similar addiction pathway, which includes the left dorsolateral prefrontal cortex (DLPFC) region, is responsible for cravings for nicotine, alcohol and food (Wilson et al., 2004; Olbrich et al., 2006; McBride et al., 2006; Boggio et al., 2010), as well as for the cognitive deficits seen in drug-addicted individuals (Manes et al., 2002; Fecteau et al., 2007b; Hecht et al., 2010), it is not surprising that tDCS stimulation to the left DLPFC results in these beneficial effects.

With respect to nicotine specifically, while a single session of tDCS has been shown to be beneficial, repeated administration of tDCS has revealed a cumulative effect on the reduction of craving in cigarette smokers (Boggio et al., 2009; Fregni et al., 2008b). The study looking at a single session of tDCS was conducted at Harvard Medical School, and showed tDCS to reduce cigarette cravings by 20% when comparing craving at baseline and after stimulation (Fregni et al., 2008b). In another study, it was shown that after five sessions, craving levels decreased steadily over the 5 sessions (see figure below), with a difference in day 5 of 62% when comparing the stimulation and control groups; in addition, 11 of the 13 subjects in the active stimulation group showed a cigarette smoking decrease of 30% or more (Boggio et al., 2009).

Source: Boggio et al., 2009

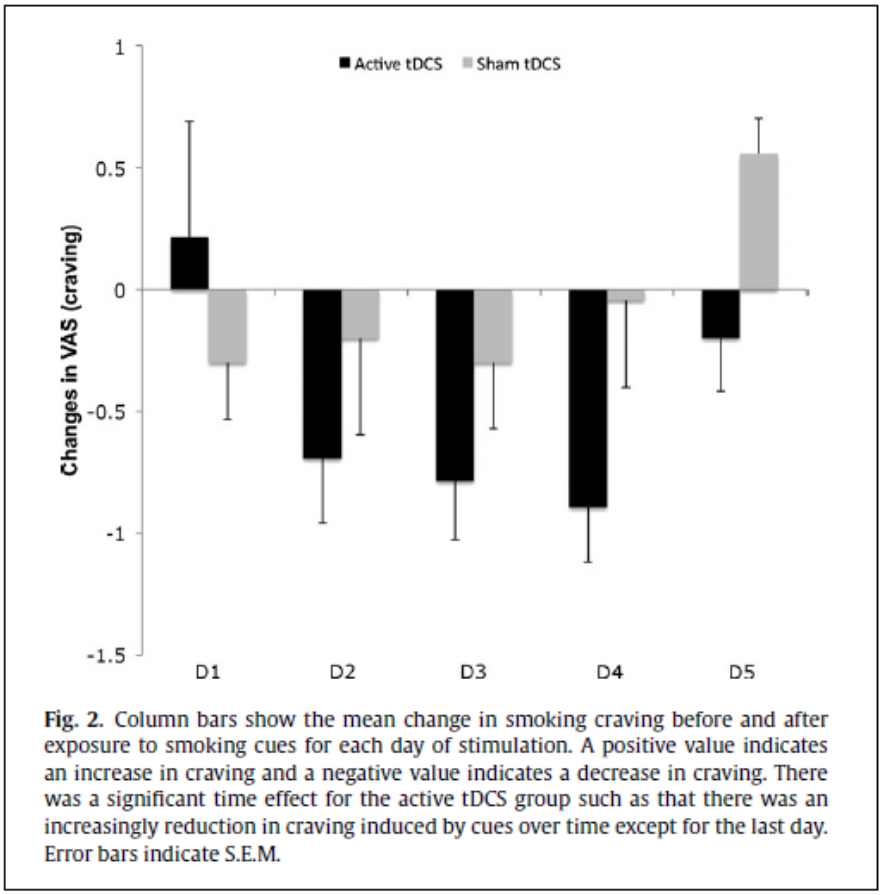


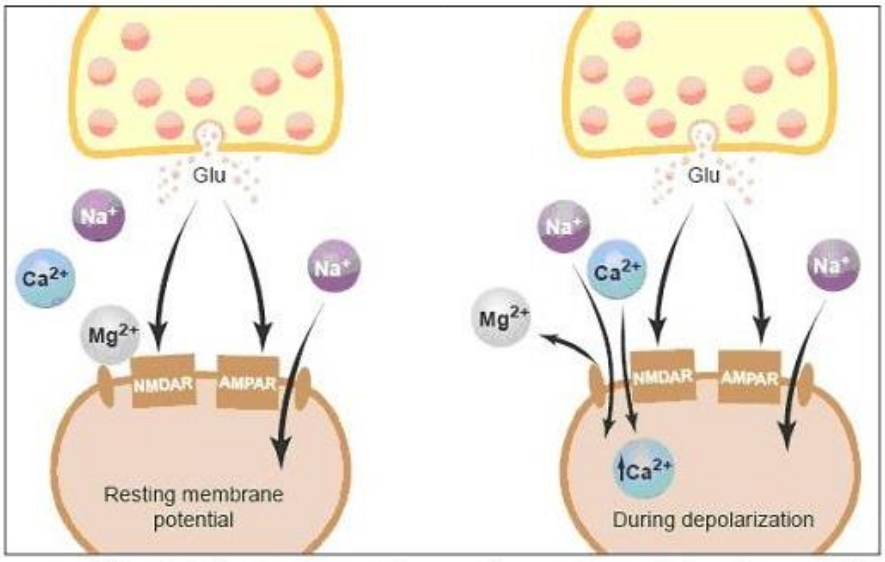
Fig. 2. Column bars show the mean change in smoking craving before and after exposure to smoking cues for each day of stimulation. A positive value indicates an increase in craving and a negative value indicates a decrease in craving. There was a significant time effect for the active tDCS group such as that there was an increasingly reduction in craving induced by cues over time except for the last day. Error bars indicate S.E.M.

3. Proposed Mechanism of Action

(tDCS) is a non-invasive brain stimulation technique that results in the modulation of neuronal excitability in both the central and peripheral nervous systems, and subsequently in the establishment of enduring changes in cortical functioning. The reason for the effectiveness of tDCS is not fully understood.

This technique involves the delivery of a weak electrical current to the brain via surface (i.e., scalp) electrodes, and affects brain activity by modulating the threshold of the neuronal resting membrane potential (Feil et al. 2010). The resting state potential can be hyperpolarized by cathodal stimulation (causing a decrease in cortical excitability) or depolarized by anodal stimulation (resulting in an increase in cortical excitability). Anodal stimulation is believed to exert its excitatory neuromodulatory effects mainly via long-term potentiation (LTP). This type of stimulation results in the release of the neurotransmitter glutamate, which binds to both and NMDA and AMPA receptors in the post-synaptic neuron; this results in an increase of the latter, and by extension, the expression of LTP (see figure below). The modulation of cortical excitability is influenced by the strength and duration of the applied current (Nitsche & Paulus, 2000; Nitsche et al., 2003a,c; Nitsche et al., 2008). As tDCS stimulation induces current below the action potential threshold, these effects are produced without inducing action potentials.

Source: Malenka & Nicoll, 1999



Model for the induction of LTP. During normal synaptic transmission, glutamate (Glu) is released from the presynaptic bouton and acts on both AMPA receptors (AMPARs) and NMDA receptors (NMDARs). However, Na^+ flows only through the AMPA receptor, but not the NMDA receptor, because Mg^{2+} blocks the channel of the NMDA receptor. Depolarization of the postsynaptic cell relieves the Mg^{2+} block of the NMDA receptor channel, allowing Na^+ and Ca^{2+} to flow into the dendritic spine by means of the NMDA receptor. The resultant rise in Ca^{2+} within the dendritic spine is the critical trigger for LTP.

4. Safety of tDCS in Humans

With well over 200 randomized controlled trials conducted since 1998, tDCS has been shown to be a safe and effective means of neuromodulation in humans. Current protocols for tDCS administration vary slightly from study to study. However, studies assessing the safety of tDCS have shown stimulation within standard parameters (that is, 1-2mA intensity, 25-35cm^2 anode electrode sizing, and up to 30 minutes of stimulation per session) to be safe (McCreery et al., 1990; Nitsche et al., 2003b; Iyer et al., 2005; Poreisz et al., 2007; Liebetanz et al., 2009). Current density (i.e., stimulation intensity/electrode size) below 25 mA/cm^2 does not result in tissue damage, even over a period of several hours. Recent studies (including those specifically related to substance abuse as well as cognitive functioning) have shown current densities of up to .094 mA/cm^2 to result in little to no side effects reported (Fertonani et al., 2011; Goldman et al., 2011). Furthermore, a study by Iyer et al. (2005) showed that frontal cortex stimulation in the range of 1-2mA was safe, with no adverse effects reported, a notion substantiated by the plethora of studies utilizing tDCS in both healthy and clinical populations, including those addressed in this literature review, reporting only minor side effects (e.g., tingling and itching at the electrode site).

5. References

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