LITERATURE REVIEW

Chronic Pain Management 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 chronic pain management. 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 peer-reviewed scientific journals.

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 in Toronto, the University of Ottawa, and the Saint Joseph's General Hospital Elliot Lake.

2. A New Modality for Chronic Pain Management

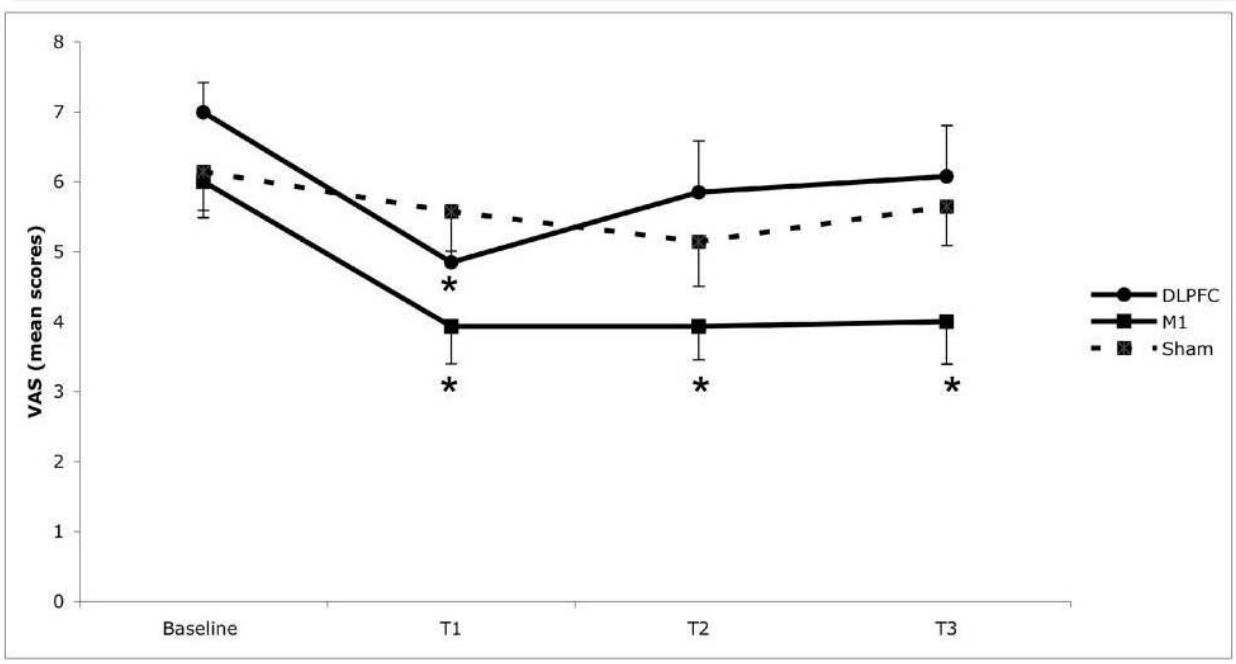
Neuromodulation is a revolutionary new set of neuroplasticity techniques that can be used to modify the human brain. One such technique is called transcranial direct current stimulation (tDCS). Nuraleve has developed a platform technology and service applying tDCS to reduce pain symptoms associated with many chronic pain indications, including (but not limited to) fibromyalgia, chronic headaches (including migraines), and painful diabetic neuropathy.

A promising feature of tDCS is its ability to induce neuroplasticity, engaging some of the same systems (e.g., glutamate, dopamine, and serotonin) that figure prominently in the pathological neuroplasticity resulting from chronic pain syndromes. TDCS has been shown to exert its beneficial effects via the induction of neuroplastic changes in brain regions responsible for pain management.

Double-blind, randomized trials conducted to date support the notion that cortical stimulation via tDCS significantly reduces pain associated with many chronic indications, including in patients suffering from fibromyalgia (Fregni et al., 2006b; Roizenblatt et al., 2007; Valle et al., 2009; Mendonca et al., 2011), **chronic headaches** (Chadaide et al., 2007; DaSilva et al., 2012; Auvichayapat et al., 2012; Viganò et al., 2013), **and** various forms of **neuropathic pain** (Fregni et al., 2006a; Antal et al., 2010; Kim et al., 2013; Gonçalves et al., 2014). In many of these studies, these effects persisted past the conclusion of stimulation, with studies showing pain improvements lasting up to four months post-stimulation (Valle et al., 2009, Antal et al., 2010; Auvichayapat et al., 2012; DaSilva et al., 2012; Viganò et al., 2013). Furthermore,

stimulation has shown to improve not only the intensity of experienced pain, but the duration of pain symptoms, as well (e.g., Viganò et al., 2013).

Several brain regions have been stimulated to reduce chronic pain symptoms, including motor, sensorimotor, prefrontal, and occipital areas. However, research suggests that stimulation of the motor cortex contralateral to the affected side provides the greatest improvements, as well as longer-lasting results, in comparison to stimulation of other regions (Fregni et al., 2006b; Valle et al., 2009; Kim et al., 2013). For example, in a study by Valle and colleagues (2009), while both motor cortex and prefrontal cortex stimulation resulted in pain reduction, only motor cortex stimulation provided relief for up to 60 days post-study (see Figure below).



Mean pain scores associated with the three conditions of stimulation: left M1 (primary motor cortex); left DLPFC (dorsolateral prefrontal cortex); and sham tDCS. Pain scores are reported on the Visual Analogue Scale for Pain; 0= no pain, 10= worst pain of life. * Indicates statistically significant ($p<0.05$) as compared with baseline. Each column represents mean score SEM (standard error of mean). T1: end of stimulation, T2: 30 day follow-up, T3: 60 day follow-up.

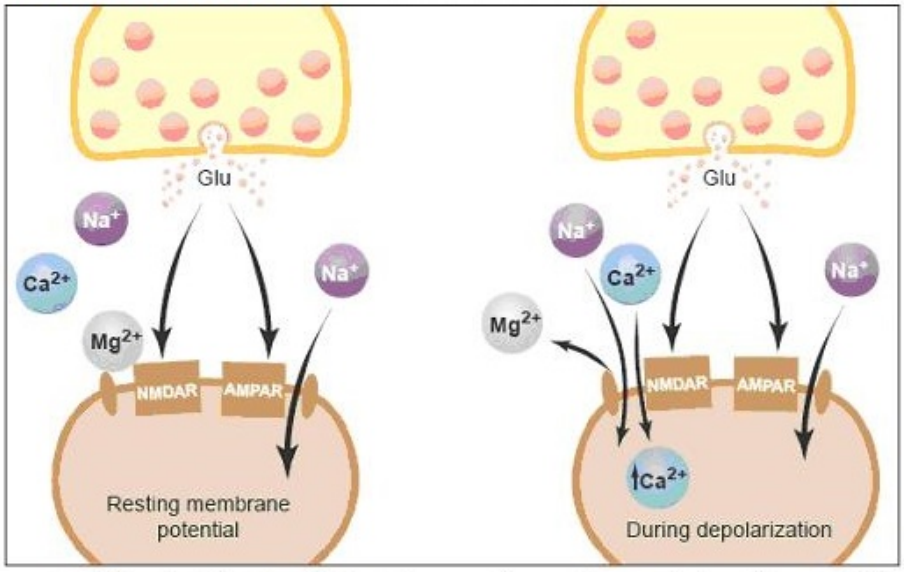
The beneficial effects of tDCS administration have been shown to exert a cumulative effect, with multiple tDCS sessions shown to be beneficial, with several studies showing 10 sessions to provide superior, longer-lasting pain management results (Valle et al., 2009; DaSilva et al., 2012) than single sessions or even 5 sessions (Fregni et al., 2006b; Antal et al., 2010; Viganò et al., 2013).

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 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.

Chronic pain has been shown to result in long-lasting brain changes, both structural and functional, at both cortical and subcortical levels, including somatotopic reorganization, sustained increases in neuronal excitability, and decreased cortical thickness in associated brain regions. These changes are believed to be due to maladaptive neuroplasticity, which results in the persistence of pain past the point of tissue healing and the development and preservation of chronic pain (Knotkova & Nitsche, 2013).

With this in mind, the effectiveness of tDCS for various types of chronic pain is believed to be due in part to the facilitation of beneficial neuroplastic changes (along with the reversal of maladaptive ones), resulting in both acute and long-term reductions in pain. More specifically, stimulation of the motor cortex via tDCS is believed to exert its analgesic effects most prominently via a) modulation of thalamic activity, b) indirect inhibition of the somatosensory cortex, and c) increases in endogenous opioid release (Knotkova et al., 2013).

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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