DEEP CEREBELLAR TRANSCRANIAL ELECTRICAL STIMULATION: HYPOTHESIS AND THEORY FOR CANNABIS USE DISORDER

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Cannabis is the most widely cultivated, trafficked and abused illicit drug ("WHO | Cannabis," n.d.; "World Drug Report 2020," n.d.). In 2018, an estimated 192 million people aged 15-64 years used cannabis for nonmedical purposes globally (Degenhardt et al., 2013). The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2016 estimated that, across the globe, there were more than 22.1 million people with cannabis dependence (Degenhardt et al., 2018). Moreover, the same study calculated that cannabis dependence could be accounted for 646 thousand Disability Adjusted Life Years, globally. Importantly, cannabis dependence mostly affects young adults (20-24 years), and thus has significant negative impact on the growth and productivity of not only these individuals but also to the societies and nations (Degenhardt et al., 2013). In addition to the dependence syndrome, cannabis use is associated with increased risk of psychosis, cognitive dysfunction, academic problems, and road side accidents (Volkow et al., 2014). A review showed a fairly consistent associations between cannabis use and both lower educational attainment and increased reported use of other illicit drugs (Macleod et al., 2004). In the United States, Cannabis Use Disorder (CUD) is an escalating problem in young adults by legalization (Cerdá et al., 2020) where National Survey on Drug Use and Health reported increased prevalence from 5.1% in 2015 to 5.9% in 2018 in 18-25 year olds ("2019 NSDUH Detailed Tables | CBHSQ Data," n.d.).

The psychoactive effects are due to type 1 cannabinoid receptor (CB1), the cannabinoid binding protein, that are highly expressed in the cerebellar cortex (Marcaggi, 2015). CB1 is primarily found in the molecular layer at the most abundant synapse type in the cerebellum (Marcaggi, 2015) that can shape the spike activity of cerebellar Purkinje cell (Brown et al., 2019). Moreover, granule cell to Purkinje cell synaptic transmission can trigger endocannabinoid release (Alger and Kim, 2011), which may be important for information processing by cerebellar molecular layer interneurons (Dorgans et al., 2019). This suggests that endocannabinoids could be essential to neurocognitive aspects of cerebellar function (Di
Marzo et al., 2015)-(Marcaggi, 2015)-(Alger and Kim, 2011). Accumulating evidence also suggests cerebellar modulation of the reward circuitry and social behaviour, via direct cerebellar innervation of the ventral tegmental area (VTA) including dopamine cell bodies (A1) in the VTA (Carta et al., 2019). The VTA-dopamine (DA) signalling in the nucleus accumbens (NAC) and the medial prefrontal cortex (mPFC) (Lohani et al., 2019) play a key role in motivated behaviours and cognition. Cerebellar neuropathological changes can result in aberrant dopaminergic activity in the NAc and mPFC (ROGERS et al., 2011)-(Lohani et al., 2019). Therefore, there is a critical need to determine how cerebellum modulate limbic VTA-DA signalling. Cerebellar Non-Invasive Brain Stimulation (NIBS) is postulated to be most relevant in CUD since endocannabinoids are essential to cerebellar function that includes reward-related behaviours, information processing, and cognitive control. (Di Marzo et al., 2015)-(Marcaggi, 2015)-(Alger and Kim, 2011). Furthermore, cerebellar NIBS can facilitate training of cognitive control in CUD during a visual cue reactivity paradigm using a mobile virtual reality (VR) interface that can also allow remote delivery of cerebellar NIBS in conjunction with VR-based cognitive training for home-based intervention. Specifically, transcranial electrical stimulation (tES) can be translatable to low-cost (<$150) mobile devices that can be used in a low resource home-based setting (Carvalho et al., 2018).

**Non-invasive brain stimulation approach in cannabis use disorder**

Research on repetitive Transcranial Magnetic Stimulation (rTMS) for the treatment of substance dependence showed encouraging results so far, especially with regard to the reduction of craving for drug use and improving cognitive outcomes (Makani et al., 2017)(Ekhtiar et al., 2019) (Stein et al., 2019). However, the effect of NIBS has been shown to be only transient and fades rapidly after the termination of treatment (Stein et al., 2019). Craving is postulated as the failure of the normal inhibitory processes mediated by prefrontal regions, including the dorsolateral prefrontal cortex (DLPFC), to control reward processes mediated by the limbic system (Goldstein and Volkow, 2011). Therefore, excitatory rTMS to the executive control network (DLPFC)(Sahlem et al., 2018), or, inhibitory rTMS to the reward
network would result in decreased craving. Left DLPFC was found to be the most frequent anatomical target followed by the right DLPFC (Ekhtiari et al., 2019). Figure 1 shows the competing neurobehavioral decision systems (CNDS) based approach with relative activation of executive control network via DLPFC and relative inhibition of the frontal–striatal circuits involved in limbic (the amygdala, nucleus accumbens, ventral pallidum, and related structures) reward and impulsive action mediated by ventromedial prefrontal cortex (vMPFC). Excitatory rTMS at the left DLPFC has shown activation of executive control network to reduce craving in substance use disorders (Claire Wilcox, 2019), while inhibitory rTMS at the vMPFC leads to relative inhibition of the frontal–striatal reward network. Excitatory rTMS interventions results in an increased neuronal activation (also, regional hemodynamics) of DLPFC while inhibitory rTMS should lead to a reduced activation of vMPFC that can be measured using functional near-infrared spectroscopy (fNIRS) (Huhn et al., 2019). Additionally, electroencephalogram (EEG) delta power has been postulated to be linked to increased activity of the dopaminergic brain reward system (Wacker et al., 2009) and increased craving (Pripfl et al., 2014) so reduced EEG delta power should be related to therapeutic benefit. Multi-modal fNIRS-EEG joint-imaging (Sood et al., 2016) can capture the subject-specific response for dosing NIBS.

A similar inhibition of the reward network may also be achieved by cerebellar rTMS (Fernandez et al., 2020) via cerebellar innervation of the dopamine cell bodies in the VTA (Carta et al., 2019). Low-intensity rTMS is postulated to primarily affect the Purkinje cells in the cerebellum (Morellini et al., 2015) that is GABA-mediated inhibition of the deep cerebellar nuclei (DCN) in the fronto-cerebellar circuit (Middleton and Strick, 2001). Therefore, we augmented the CNDS theory (Koffarnus et al., 2013) (Hanlon et al., 2018) with recent
evidence from neuroimaging studies that fronto-cerebellar circuit, that interacts with brain’s default network, is relevant in cognitive functions (ROGERS et al., 2011), and that cognitive control (Zhang and Volkow, 2019) may be diminished in the addicted brain where components for memory, reward/saliency, and motivation/drive can be amplified (Moulton et al., 2014). Furthermore, it may be possible to exert a long term effect by cerebellar rTMS because of its wider connections with the memory circuit and role in habit formation (Moulton et al., 2014).

**Neuroimaging guided non-invasive brain stimulation in cannabis use disorder**

Human functional neuroimaging have showed segregated fronto-cerebellar circuits (Krienen and Buckner, 2009), e.g., DLPFC-correlated activity was shown to span cerebellar Crus I/II lobules in its lateral and ventral extent while MPFC-correlated activity spanned cerebellar Crus I lobe. Here, Crus I preferentially correlated with MPFC while Crus II preferentially correlated with DLPFC. Such lobule specific rTMS will require a neuroimaging guided individualized approach with Cerebellar Lobules Optimal Stimulation (CLOS) pipeline (Figure 2) for the delivery of neuroimaging guided cerebellar non-invasive brain stimulation (NIBS). CLOS pipeline uses structural magnetic resonance images (MRI) images (T1, T2) to create anatomically accurate subject-specific head model that can be used for computing electric field distribution in the brain for a given electrodes or TMS coil location. CLOS pipeline uses freely available computational packages (simNIBS (Saturnino et al., 2018), ROAST (Huang et al., 2017)) along with freely available brain atlases (AAL (Rolls et al., 2020, p. 3), SUIT (Diedrichsen, 2006)) for a leadfield based approach to optimize (convex optimization (Boyd and Vandenberghe, 2004)) the electrodes or TMS coil location. The optimization is
based on the quasi-uniform assumption that local polarization effect is proportional to the local electric field strength (Bikson et al., 2013). If we consider a set of N bipolar electrodes or TMS coil locations then the quasi-stationary Ohmic relation from the stimulation array, s, to the average electric field at a certain brain location, \( \vec{E} \), can be written in a matrix form, \( \vec{E} = \vec{LF} \cdot s \), where \( \vec{LF} \) is the leadfield. One way to write the objective function for least squares fitting of an unknown stimulation array, x, viz. arg min \( ||\vec{LF} \cdot x - \vec{E}||^2 \), is to minimize the L2-norm of the error, \( (\vec{LF} \cdot x - \vec{E}) \), given a desired electric field distribution, \( \vec{E} \), e.g., to target the Purkinje cells of Crus I/II in the fronto-cerebellar circuits (ROGERS et al., 2011). Here, it is important to limit the TMS generated electric field to the Purkinje cells in the Crus II to target for DLPFC executive network (Krienen and Buckner, 2009), which was achieved with cerebellar region-specific electric field modelling (Rezaee and Dutta, 2019) and neurophysiological validation (Batsikadze et al., 2019). Spill-over of TMS generated electric field to the dentate nuclei (DN) at higher TMS intensities will affect the recruitment curve (from inhibition to facilitation of the cerebellar-brain connection). For example, the left panel of Figure 3 shows the recruitment of the cerebellar-primary motor cortex (M1) connection, or the cerebellar-brain inhibition (CBI) recruitment curve, at different intensities of the cerebellar TMS conditioning stimulus - from our prior work (Batsikadze et al., 2019). The conditioning TMS intensity was reduced in 5% steps below the brainstem motor threshold (BST) up to -25%. BST was determined by the

![Figure 3](image-url)
activation of the corticospinal tract (see left bottom brain image in the Figure 4) by single-pulse TMS with the double-cone coil placed over the inion. The left panel of the Figure 3 also shows the computed mean electric field (EF) at Crus II and DN, normalized by the maximum, at various conditioning TMS intensities (-5%, -10%, -15%, -20%, -25% BST). A “knee” was noticed around -15% BST when the slope of the CBI recruitment curve decreased (became flatter) for further increase in the conditioning TMS intensity. This is postulated to be due to the stimulation of the DN (that is excitatory) in addition to the Purkinje cells (that are inhibitory) resulting in a slower increase in CBI with increasing conditioning TMS intensity. The right panel shows the computed mean electric field (V/m) at Crus II and DN using CLOS where the horizontal line denotes the DN mean electric field (V/m) at -15% BST which is postulated to be the electric field (EF) threshold for DN activation. Here, all the mean EF (V/m) values at Crus II, that resulted in CBI (see left panel of Figure 3), were found to be higher than the EF threshold for DN activation. Since motor evoked potential (MEP) cannot be generated at the frontal areas so lobule-specific cerebellar NIBS (Batsikadze et al., 2019; Rezaee et al., 2020a; Rezaee and Dutta, 2020, 2019) can be combined with portable fNIRS-EEG (Sood et al., 2016) to identify individual NIBS response (also, non-responders) (Dutta et al., 2015; Guhathakurta and Dutta, 2016; Rezaee et al., 2020b; Sood et al., 2016). Animal studies can confirm the cerebellar TMS evoked dose response at the dopaminergic circuits using a novel approach (Park et al., 2013, 2012, 2011, 2017; Wickham et al., 2015; Zachek et al., 2010) by incorporating extracellular electrophysiology and fast-scan cyclic voltammetry (FSCV) (Rodeberg et al., 2017) (tip diameter, ~1μm). Simultaneous multi-modal monitoring of (i) a local view (<100 μm) of rapid changes in dopamine (DA) concentration (≤10 ms), which will provide rTMS effects on VTA-DA regulation in MPFC and NAc subregions, and (ii) simultaneous electrophysiological data at the VTA, NAc, and MPFC over multiple spatial scales spanning individual neuronal spiking, population ensemble activity, and local field potential (LFP) oscillations can be performed (Lohani et al., 2019).

TMS based neuromodulation approaches are not amenable to home-based settings so transcranial electrical stimulation (tES) should be investigated as an adjuvant treatment where
deep cerebellar transcranial direct current stimulation (ctDCS) of DN has been shown feasible (Rezaee et al., 2020a). Also, cerebellar transcranial alternating current stimulation (ctACS) has been shown feasible in modulating motor behaviour (Koganemaru et al., 2020); however, evidence for addiction medicine is limited (Ekhtiari et al., 2019). Recently, tES for deep brain stimulation has been shown feasible via temporally interfering electric fields (Grossman et al., 2017).

**fNIRS-EEG guided tTIS of cerebellum in CUD**

The neuronal sensitivity in transcranial temporal interference stimulation (tTIS) depends on the neuronal membrane time-constant (Esmaeilpour et al., 2020). The tTIS can play an important role in psychiatric conditions (Grossman et al., 2018) for focused modulation of deep brain structures (Lee et al., 2020) that may stimulate deeper brain regions including anterior cingulate cortex and deep cerebellar nuclei.

Based on the leadfield from our prior work on deep tDCS (Rezaee et al., 2020a) – details in the Supplementary Materials, we investigated tTIS with 3.14cm² (1cm radius) circular electrodes placed at PO9h(-55.6, -70.1, -6.8) – Exx7(-54.6, -45.0, -54.0) location (shown in red in Figure 4) for tACS at 1kHz with 2mA peak current as well PO10h(61.7, -69.7, -5.8) – Exx8(59.8, -49.3, -52.9) location (shown in blue in Figure 4) for tACS at 1.03kHz with 2mA peak current. We will write f1=f−Δf and f2=f+Δf, and two tACS current sources as s1(t)=A · cos(f1 · t) and s2(t)=B · cos(f2 · t). At any region of the brain atlas, based on the leadfield (Rezaee and Dutta, 2019), the mean electric field \( \vec{E} = \frac{L \cdot F_1}{L} \cdot \cdot s1 + \frac{L \cdot F_2}{L} \cdot \cdot s2 \) for the cerebellar cortex near tACS electrodes, either \( \|L \cdot F_1\| \gg \|L \cdot F_2\| \) or \( \|L \cdot F_2\| \gg \|L \cdot F_1\| \) so the peak electric field was primarily...
determined by the individual tACS current sources, \( s_1(t) \) or \( s_2(t) \), which was \(<0.2\text{V/m} \) at high frequency of 1kHz or 1.03kHz – details in the Supplementary Materials. Here, neuronal stimulus response functions (Meyer et al., 2017) play an important role in neuromodulation (Dutta and Nitsche, 2013) as well as filtering operations (Heeger, 2017) where low pass properties of the membrane can drastically attenuate high (\(~\text{kHz}\) tACS frequencies (Deans et al., 2007). In fact, only stimulation frequencies below 100Hz have been found effective for neuromodulation via neuronal membrane (Deans et al., 2007).

In cerebellum, the dentate nucleus (DN) cells are under intensive inhibitory drive from Purkinje cells (PCs) while the excitatory inputs are from mossy fiber and climbing fiber collaterals. However, the excitatory inputs from mossy fiber and the climbing fiber collaterals are not strong enough for the generation of the burst activity in DN that is necessary to initiate motor behaviour (Ishikawa et al., 2014). We postulate that tTIS may drive the burst activity in DN without significantly affecting the PCs which is a challenge with rTMS and transcranial electrical stimulation (tES) (Batsikadze et al., 2019). We further postulate that tTIS of the DN can be combined with tES of the PCs to coordinate PCs population activities for dynamic synchronization (Shin and De Schutter, 2006) where inhibitory input will be important for the fine control of the excitatory-inhibitory balance (Dagar et al., 2016) at the target DN neurons to ameliorate dysrhythmia in the cortico-cerebello-thalamo-cortical (CCTC) loop. We investigated tTIS using a CCTC loop model (Zhang and Santaniello, 2019) that considered the average firing rate of PCs and deep cerebellar neurons (DCN) as 63Hz and 56.6Hz respectively, so for computational modelling of thalamocortical basal ganglia with cerebellum (Yousif et al., 2020), we selected \( f_2-f_1=63\text{Hz} \) for the amplitude modulation of DCN by tTIS (Grossman et al., 2017) – see Figure 4. At deeper brain regions distant from tACS electrodes with comparable electric fields, \( \overrightarrow{LF_1} \approx \overrightarrow{LF_2} \) and we can write \( \overrightarrow{E} = (\vec{a} + \vec{b}) \cdot \cos(f_1 \cdot t) + (\vec{a} - \vec{b}) \cdot \cos(f_2 \cdot t) \). Therefore, \( \overrightarrow{E} = 2\vec{a} \cdot \cos\left(\frac{f_1 + f_2}{2} \cdot t\right) \cdot \cos(f_1 \cdot t) + 2\vec{b} \cdot \sin\left(\frac{f_1 + f_2}{2} \cdot t\right) \cdot \sin\left(\frac{f_2 - f_1}{2} \cdot t\right) \) where \( \frac{f_2 - f_1}{2} = \Delta f \) and \( \frac{f_1 + f_2}{2} = f \). Here, \( \overrightarrow{E} = 2\vec{a} \cdot \cos(f \cdot t) \cdot \cos(\Delta f \cdot t) + 2\vec{b} \cdot \cos\left(\frac{p}{2} - f \cdot t\right) \cdot \cos\left(\frac{p}{2} - \Delta f \cdot t\right) \), which presents summation of two beats of \( \Delta f \) frequency but \( \frac{p}{2} \) phase apart, where
\( \vec{b} \approx 0 \) results in a single beats at certain deeper brain regions, i.e.,
\[ \vec{E} = 2\vec{a} \cdot \cos(f \cdot t) \cdot \cos(\Delta f \cdot t) \]. Here, the tTIS beats can provide the burst stimulation of the DCN.

A thalamocortical basal ganglia with cerebellum (Yousif et al., 2020) integrated two thalamic populations, the excitatory ventralis intermedius (Vim) nucleus and the inhibitory reticular nucleus (nRT), with an excitatory population of the deep cerebellar nuclei (DCN), an excitatory population representing the subthalamic nucleus (STN), and two inhibitory populations representing the external part of the globus pallidus (GPe) and the internal part of the globus pallidus (GPI), as shown in Figure 4. The model consisted of seven first-order coupled differential equations that could simulate the gamma-band oscillations (>30 Hz) for a constant external input to the DCN. It is postulated that this external input to DCN may be dysfunctional in CUD that can be related to psychosis and schizophrenia, e.g., increased CB1 expression (Marcaggi, 2015), (Alger and Kim, 2011) in the molecular layer (Marcaggi, 2015) can shape the spike activity of Purkinje cell (Brown et al., 2019) that can lead to a decrease in Purkinje cell density in CUD related maladaptive plasticity (Bernard and Mittal, 2014). Prior work (Hong et al., 2004) has identified gamma-to-beta frequency shift as a marker of sensory gating that was found deficient in schizophrenia. Additionally, prior works have shown that gamma and beta frequency oscillations occur in the neocortex in response to sensory stimuli over a range of modalities (Haenschel et al., 2000). Here, computational modelling of tTIS effects showed that 63Hz amplitude modulation of DCN can lead to this gamma-to-beta frequency shift, as shown in Figure 5 (details in the Supplementary Materials). In Figure 5, the top panel shows the gamma frequency oscillations at the cortex with constant input to the DN (can be...
modulated with transcranial direct current stimulation (Rezaee et al., 2020a)) whereas tTIS of DN at 63Hz beats frequency (burst stimulation) led to beta frequency oscillations at the cortex as shown in the bottom panel of Figure 5.

The effects of cerebellar stimulation on the fronto-cerebellar circuits (ROGERS et al., 2011) and sensory gating have not been investigated systematically in CUD during a during visual cue reactivity paradigm for VR-based cognitive training for home-based intervention. Combined fNIRS-EEG (Oxymon+ with Starstim Enobio, Artinis, Netherlands) sensors can be placed over bilateral rostral prefrontal cortex (Brodmann Area 10) and bilateral ventrolateral/DLPFC that showed fNIRS response during visual cue reactivity paradigm (Huhn et al., 2019). Visual cue reactivity paradigm (Huhn et al., 2019) consisted of five pictures from a single category (cannabis, as well as positive reward and neutral pictures sourced from International Affective Picture System) presented in 25-s blocks (5 pictures/block, each picture displayed for 5 s) via a 16-inch monitor (75 Hz refresh rate) delivered via E-Prime software (Psychology Software Tools Inc., PA). Subjects viewed the imagery in an upright, seated position, and the order of images within blocks and the order of blocks within the experiment were randomized for each individual and counter-balanced across individuals. Between blocks, a crosshair centered on a black screen was displayed for 10–15 s to allow hemodynamic flow to return to baseline (Huhn et al., 2019). In this block-design paradigm (Huhn et al., 2019), with each block of cannabis cue, positive reward, or neutral cues, the fNIRS measures can consist of mean deoxygenated hemoglobin (HbR), mean oxygenated hemoglobin (HbO2), and mean total hemoglobin (total Hb). Here, mean HbO2 change can be extracted for the duration of each 25-s block (cannabis cue, positive, and neutral) with baseline correction to the beginning of the block (Huhn et al., 2019). Also,
frontal EEG bandpower, with each block of cannabis cue, positive reward, or neutral cues, is postulated to be modulated (Wacker et al., 2009). Here, markers of sensory gating (Hong et al., 2004), i.e., post first stimulus beta frequency response in the sensorimotor EEG bandpower inversely correlated to the second stimulus P50 response, which may be found dysfunctional in CUD. We postulated that the tTIS with 63Hz amplitude modulation of DCN can lead to normative gamma-to-beta frequency shift during visual cue reactivity (Huhn et al., 2019). These innovations in lobule-specific cerebellar NIBS (Batsikadze et al., 2019; Rezaee et al., 2020a; Rezaee and Dutta, 2020, 2019) and portable fNIRS-EEG of the NIBS effects (Dutta et al., 2015; Guhathakurta and Dutta, 2016; Rezaee et al., 2020b; Sood et al., 2016) can measure individual response (also, identify non-responders), which should be evaluated for home-based NIBS approach in CUD and psychosis/schizophrenia.

Conclusion

The transcranial temporal interference stimulation of cerebellum combining burst stimulation of the deep cerebellar nuclei (DCN) with the tDCS/tACS of the superficial Purkinje cells can be used for the modulation of the Excitation–Inhibition balance at DCN. VR-based cognitive training as a home-based intervention can be facilitated with cerebellar tES as an adjuvant treatment for reducing craving in cannabis use disorders and enhancing cognitive controls. The dual effect of cerebellar NIBS on the reward and cognitive control circuitry makes it a promising target. The role of cerebellum in long-term habit formation presents an opportunity of lasting effect of NIBS even after the termination of treatment. A study on an animal model should be a starting point, followed by a proof-of-concept study in humans.

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Potential conflicts of interest
Authors declare no potential conflicts of interest.
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