Portable neuroimaging guided non-invasive brain stimulation in substance use disorder: computational modelling based medical hypothesis

Pushpinder Walia[a], Abhishek Ghosh[b], Shubhmohan Singh[b], and Anirban Dutta[a]*

[a]*University at Buffalo SUNY, USA;* [b]*Postgraduate Institute of Medical Education & Research, Chandigarh, India.*

Authors:

Pushpinder Walia
University at Buffalo SUNY, USA

Abhishek Ghosh MD, DM (Addiction Psychiatry)
Drug De-addiction & Treatment Centre & Department of Psychiatry
Postgraduate Institute of Medical Education & Research, Chandigarh, India

Shubhmohan Singh MD
Department of Psychiatry
Postgraduate Institute of Medical Education & Research, Chandigarh, India

Anirban Dutta PhD
Department of Biomedical Engineering, Surgery, Pathology and Anatomical Sciences
University at Buffalo SUNY, USA
Email: anirband@buffalo.edu

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Background: Maladaptive neuroplasticity in substance use disorder(SUD) can be ameliorated using non-invasive brain stimulation(NIBS); however, individual dosing of NIBS is challenging at the point-of-care.

Objective: In this computational modeling and methodological study, our first objective was to develop a hypothesis for NIBS for SUD related maladaptive plasticity based on competing neurobehavioral decision systems model. Next objective was to conduct computational simulation of NIBS of cortico-cerebello-thalamo-cortical(CCTC) loop in cannabis use disorder(CUD) related dysfunctional "cue-reactivity" – a closely related construct of "craving" that is a core symptom. Our third objective was to develop a rational approach guided by neuroimaging.

Methods: "Cue-reactivity" can be measured using behavioral paradigms and portable neuroimaging metrics where we conducted computational simulation to support NIBS of the CCTC loop based on its effects on the neuroimaging metrics of sensorimotor gating. We also developed a rational neuroimaging guided NIBS approach for cerebellar lobule (VII) and prefrontal cortex based on our published dataset.

Results: We simulated the CCTC loop for transcranial direct current stimulation(tDCS) and transcranial temporal interference stimulation(tTIS) of the cerebellum where tDCS induced gamma oscillations while tTIS induced gamma-to-beta frequency shift in the cerebral cortex. Here, dissociating NIBS effects on the cerebellar circuit, including Purkinje cells and dentate nuclei, is crucial which can be based on cerebellar-brain inhibition recruitment curve. Also, NIBS-related cortical activation was found feasible using published functional near-infrared spectroscopy(fNIRS) and electroencephalogram(EEG) data(5 males).

Conclusion: Effects of cerebellar tDCS and tTIS on the CCTC loop and its corresponding effects on the sensorimotor gating showed promise in simulation and need further experimental investigation in CUD using simultaneous portable neuroimaging.

Keywords: fNIRS; EEG; tDCS; rTMS; tACS; CUD; cerebellum

Introduction:

Neurobiological framework from misusing addictive drugs to substance use disorder (SUD) is increasingly shown to be related to neuroplastic changes in the structure and function that promote and sustain SUD, including addiction – the most severe form of SUD [1]. Onset, development, and maintenance of SUD show dysfunction in three main areas of the brain; the basal ganglia, the extended amygdala, and the prefrontal cortex [1]. Brain dysfunction can trigger different behavioral aspects of SUD, including substance-seeking triggered by substance-associated cues, reduced sensitivity to reward and heightened activation of brain stress systems, and reduced executive control. Here, adolescence is a critical "at-risk period" for all addictive drugs, including alcohol and cannabis, where neuroplastic changes due to a less potent drug may facilitate substance-seeking of a more potent addictive drug. The differential nature of the interactions between the substance use and brain structure maturation across adolescence and into young adulthood has been highlighted in a recent work [2].

Cannabis is the most widely cultivated, trafficked, and abused illicit drug [3,4]. In 2018, an estimated 192 million people aged 15-64 years used cannabis for nonmedical purposes globally [5]. 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 [6]. Moreover, the same study calculated that cannabis dependence could be accounted for 646 thousand Disability Adjusted Life Years globally. Significantly, cannabis dependence mainly affects young adults (20-24 years), which has a significant negative impact on these individuals' growth and productivity and the societies and nations [5]. In addition to the dependence syndrome, cannabis use is associated with an increased risk of psychosis [7], cognitive dysfunction, academic problems, and roadside accidents [8]. A review showed a consistent association between cannabis use and lower educational attainment and increased reported use of other illicit

drugs [9]. In the United States, Cannabis Use Disorder (CUD) is an escalating problem in young adults by legalization [10] 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 [11].

The psychoactive effects are primarily due to type 1 cannabinoid receptor (CB1), the cannabinoid binding protein, that is highly expressed in the cerebellar cortex [12]. CB1 is primarily found in the molecular layer at the most abundant synapse type in the cerebellum [12] that can shape the spike activity of cerebellar Purkinje cell [13]. Moreover, granule cell to Purkinje cell synaptic transmission can trigger endocannabinoid release [14], which may be important for information processing by cerebellar molecular layer interneurons [15]. This suggests that endocannabinoids could be essential to neurocognitive aspects of cerebellar function [16],[12],[14], and CB1 receptor downregulation in long-term chronic cannabis use may promote CUD [17]. Accumulating evidence also suggests cerebellar modulation of the reward circuitry and social behavior via direct cerebellar innervation of the ventral tegmental area (VTA), including dopamine cell bodies (A1) in the VTA [18]. The VTA-dopamine (DA) signaling in the nucleus accumbens (NAc) and the medial prefrontal cortex (MPFC) [19] play a crucial role in motivated behavior and cognition. Cerebellar neuropathological changes can result in aberrant dopaminergic activity in the NAc and MPFC [20],[19] leading to dysfunctional behavior and cognition. Therefore, there is a critical need to determine how the cerebellum modulate limbic VTA-DA signaling since endocannabinoid system is essential to cerebellar function, so, CUD related cerebellar dysfunction is postulated that can include reward-related behaviors, information processing, and cognitive control [16],[12],[14].

Cerebellar Non-Invasive Brain Stimulation (NIBS) can facilitate ameliorate CUD related maladaptive plasticity as an adjuvant treatment to cognitive control training during a visual cue-reactivity paradigm using a virtual reality (VR) interface. Specifically, transcranial electrical stimulation (tES), a NIBS modality, is translatable to low-cost (<$150) mobile devices that can allow remote delivery of cerebellar NIBS in conjunction with VR-based cognitive training in a low resource home-based setting [21]. In this computational modeling and methodological study, we aim to address dysfunctional sensory/sensorimotor gating, including prepulse inhibition, found to be deficient in chronic cannabis use [22] and schizophrenia [23]. In this study, tES with transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) were investigated with computational simulations. Here, tES applied low currents around 2mA that generated cortical electric fields less than 1 V/m [24], which has shown entrainment effects in the case of tACS [25]. We also present combined functional near-infrared spectroscopy (fNIRS) and electroencephalogram (EEG) approach to monitor and dose tES effects, including entrainment effects, based on prior works [26],[27],[28],[29]. This is crucial in SUD since both genetics and the environment influence schizophrenia, a neurodevelopmental disease, with a delayed post-pubertal onset [30]. AKT1 genotype has been shown to influence the risk of psychosis, especially in young cannabis users [31]. Also, an altered function of fibroblast growth factor receptors (FGFR) signaling can be associated [30] where FGFR uses endocannabinoid signaling system during neurodevelopment [32]. Here, FGF7 and FGF22 have been shown to differentially promote the formation of inhibitory or excitatory presynaptic terminals [33] that may play a role in Excitatory/Inhibitory (E/I) balance [34].

NIBS approach in cannabis use disorder based on competing neurobehavioral decision systems model:

Research on repetitive Transcranial Magnetic Stimulation (rTMS) for the treatment of substance dependence showed encouraging results so far, especially concerning the reduction of craving for drug use and improving cognitive outcomes [35][36,37]. However, NIBS's effect is only transient and fades rapidly after treatment termination [37]. Craving is postulated as the failure of the normal inhibitory processes mediated by prefrontal cortex (PFC) regions to control reward processes mediated by the limbic system [38]. Although neuroimaging studies have implicated diverse PFC regions; however, the right inferior frontal cortex has been implicated mainly by the human lesion-mapping [39]. Therefore, excitatory rTMS to the executive control network (dorsolateral prefrontal cortex – DLPFC)[40] or inhibitory rTMS to the reward network can be postulated to result in decreased craving. Indeed, left DLPFC is the most frequent anatomical target in clinical studies, followed by right DLPFC [36]. Figure 1 shows the competing neurobehavioral decision systems (CNDS) approach with relative activation of executive control network via DLPFC and relative inhibition of the frontal–striatal circuits involved in limbic (amygdala, nucleus accumbens, ventral pallidum, and related structures) reward and impulsive action mediated by the ventromedial prefrontal cortex (vMPFC). Excitatory rTMS at the left DLPFC has shown activation of the executive control network to reduce craving in substance use disorders [41], while inhibitory rTMS at the vMPFC leads to relative inhibition of the frontal–striatal reward network.

Besides DLPFC and vMPFC, the inferior frontal gyrus (IFG) in the ventrolateral prefrontal cortex (VLPFC) [42] is postulated to be crucial for memory retrieval (IFG pars orbitalis) [43] and post-retrieval control processes for amplifying the downstream inhibition from the subthalamic nucleus [44] when substance-seeking is triggered by substance-associated cues [45]. Dysfunctional response inhibition system following

substance-associated cues are postulated to trigger "automatic" goal-directed substance-seeking behavior where distinct neural circuits are responsible for the acquisition (during drug misuse) and "automatic" performance of the "learned" behavior (in SUD, addiction). Goal-directed behaviors are driven by brain structures including the medial prefrontal and orbitofrontal cortices, hippocampus, ventral and dorsomedial striatum, while sensorimotor cortices and dorsolateral striatum mediate the automatized/reflexive behavior. Within this brain network, the dorsomedial striatum (DMS) receives excitatory inputs from PFC, whereas the dorsolateral striatum (DLS) primarily receives inputs from the sensorimotor and premotor cortices. In primates, the caudate nucleus and the putamen correspond to the DMS and DLS in rodents, where DLS has been shown to mediate stimulus-response habits [46]. This network mapping can be related to habitual performance, i.e. when the response is no longer adaptive [47]. Animal studies have shown distinct DMS and DLS activity patterns during the early acquisition stage and become similar during an automatized performance. Extinction learning may enable learning of new contingencies via inhibition of the automatized response that will require facilitation of the inhibitory connections from the PFC to the subcortical regions to enable cognitive flexibility [48,49]. Here, a cortical-dorsomedial striatal circuit starting from PFC is responsible for acquiring goal-directed actions while a cortical-ventral striatal circuit mediates the performance [46]. Therefore, it is postulated that the response inhibition system can be facilitated by the activation of IFG for proactive control [45,50] during cue-exposure therapy [51], where a decrease in ventral striatum activity has been shown to correlate with the treatment effects [52].

In this study, we review NIBS methods to reduce "craving" – a core symptom of SUD; however, defining "craving" is challenging [36]. Therefore, "cue-reactivity" is used as a closely related construct that can be measured using behavioral paradigms and imaging

metrics (e.g., electroencephalogram, functional brain imaging, eye-tracking/pupilometry, heart rate) [36]. Besides medial prefrontal cortex (MPFC) and cingulate cortex, which may predict relapse across multiple substances [36], we postulate that the cerebellum may also modulate the allocation of the attentional resources [53] to cue stimuli relevant in "cue-reactivity." Therefore, cerebellar NIBS may facilitate attentive executive function [53] in the Posnerian model to reduce "cue-reactivity." Here, portable imaging metrics from eye-tracking [54], EEG [55], and fNIRS [56] can provide insights into NIBS effects during a "cue-reactivity" test that can be less challenging at the point-of-care settings than functional magnetic resonance imaging (fMRI) [57]. EEG delta power has been postulated to be linked to increased activity of the dopaminergic brain reward system [58] and increased craving [59] so reduced EEG delta power can be related to therapeutic benefit.

Multi-modal portable fNIRS-EEG joint-imaging [26] is also postulated to capture the subject-specific response for dosing NIBS. Here, inhibition of the reward network is postulated to be achieved by cerebellar rTMS [60] via cerebellar innervation of the dopamine cell bodies in the VTA [18]. Low-intensity rTMS is proposed to primarily affect the Purkinje cells in the cerebellum [61] that is GABA-mediated inhibition of the deep cerebellar nuclei (DCN) in the fronto-cerebellar circuit [62]. We augmented the CNDS theory [63] [64] (see Figure 1) with recent evidence from neuroimaging studies that fronto-cerebellar circuit, which interacts with brain's default network, is relevant in cognitive functions [20], and that cognitive control [65] may be diminished in the addicted brain with memory, reward/saliency, and motivation/drive components [66]. Therefore, it may be possible to exert a longer term effect via cerebellar NIBS because of its broader connections with the memory circuit and the role in habit formation [66]. In fact, animal studies have shown cerebellar contribution to extinction learning where the

motor memory preserved in the cerebellum needs to be inhibited by the forebrain structures via the amygdala complex [67] – see Figure 1. Therefore, neuroplastic changes at the cerebellum is postulated to be crucial for long-term therapeutic effects by reducing cerebellar "addiction" memory (lobule VIIb [66]). Indeed, human study showed detrimental effect of anodal cerebellar tDCS on the performance and timing of learned motor responses; however, the extinction learning was not affected during the acquisition phase [68]. Effects on motor learning can provide important insights since motor symptoms can be a characteristic of the disorder [69]. Based on these prior works, we postulate lobule VII (including Crus I, Crus II, and lobule VIIb) specific cerebellar NIBS [70],[71] to facilitate extinction learning toward substance-related cues in CUD.

Cerebellum in cannabis use related psychotic disorder:

Targeting maladaptive plasticity in the cerebellum was considered crucial due to significant FGFR1 and AKT1 gene expression, as shown in Figure 2. FGFR1 possesses mechanisms to activate the Akt signaling pathway relevant in neurodevelopment in schizophrenia [72]. Here, protein kinase Akt1's role in dopamine neurotransmission has been implicated in schizophrenia and psychosis [73]. Interestingly, FGF21 has been found to regulate sweet and alcohol preference correlated with reductions in dopamine concentrations in the nucleus accumbens, which coordinates reward behavior [74]. Also, excitation/inhibition (E/I) balance is disrupted in schizophrenia [75] that can affect the prefrontal cortex [76] and cerebellum [34]. In the cerebellum, the only output from the cerebellar cortex is represented by the inhibitory GABAergic Purkinje cells [77], while CB1 receptors are mainly expressed in the presynaptic terminals of granule cells molecular layer interneurons, and climbing fibers that synapses onto Purkinje cells. Here, CB1 receptor activity is required for long-term plasticity at parallel fiber-Purkinje cells synapses relevant for cerebellar learning. CB2 receptors in Purkinje cells may mainly

participate in pathophysiological responses to exogenous cannabinoid compounds that can inhibit GABA receptor-mediated currents potentially causing cerebellar dysfunction [78]. This will reduce the inhibitory tone the cerebellum that can be investigated based on the primary motor cortex, i.e., CBI, that can be impaired in CUD [79] and schizophrenia [69]. Therefore, ameliorating maladaptive neuroplasticity in the cerebellum using NIBS is crucial in CUD since brain-wide AKT1 and FGFR1 gene expressions show hot-spot at the cerebellum, as shown in Figure 2 (from https://neurosynth.org/), which makes it relevant for progression to psychotic disorder.

Methods - transcranial electrical stimulation of the cerebellum:

We postulate NIBS based amelioration of dysrhythmia in the cortico-cerebello-thalamo-cortical (CCTC) loop as an extension to thalamocortical dysrhythmia [80]. We investigated tTIS using a CCTC loop model [81] that considered the average firing rate of PCs and deep cerebellar neurons (DCN) as 63Hz and 56.6Hz, respectively. So, for computational modeling of thalamocortical basal ganglia with cerebellum [82], we selected f2-f1=63Hz for the amplitude modulation of DCN by tTIS [83] – see Figure 3 (details in Supplementary materials). Thalamocortical basal ganglia model with cerebellum [82] 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 3. The model consisted of seven first-order coupled differential equations that 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 increased risk of psychosis and schizophrenia with familial/genetic risk factors

[7,84,85], e.g., increased CB1 expression [12],[14] in the molecular layer [12] can shape the spike activity of Purkinje cell [13]. In CUD, a decrease in Purkinje cell density [86] can lead to dysrhythmia in the CCTC loop. Prior work [87] has identified gamma-to-beta frequency shift as a marker of sensory gating that was found deficient in schizophrenia. Additionally, previous results have shown that gamma and beta frequency oscillations occur in the neocortex in response to sensory stimuli over various modalities [88]. Therefore, portable neuroimaging of the cerebellar tES response with combined fNIRS-EEG may guide the tES dosing based on general linear modeling of dose-response [29].

Methods - neuroimaging guided NIBS in cannabis use disorder:

Human functional neuroimaging has shown segregated fronto-cerebellar circuits [89], e.g., DLPFC-correlated activity was shown to span cerebellar Crus I/II lobules in its lateral and ventral extent. In contrast, MPFC-correlated activity spanned cerebellar Crus I lobule. 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 a Cerebellar Lobules Optimal Stimulation (CLOS) pipeline (Figure 4) for the delivery of neuroimaging guided cerebellar NIBS [70] – details in the Supplementary materials. In this study, we investigated the "knee" in 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 based on computational modeling and published experimental results [90].

Methods - fNIRS-EEG guided tES approach based on published dataset:

In a feasibility study [29], we hypothesized that the combination of fNIRS and EEG would allow for non-invasive and simultaneous assessment of cerebral response to bilateral deep cerebellar transcranial direct current stimulation (tDCS) of the dentate nucleus (DN) and the lower-limb representations (lobules VII-IX). Cerebellar tDCS

(ctDCS) optimized for targeting the dentate nucleus [91] stimulated combined anterior and posterior lobes of the cerebellum, including cerebellar hemispheric lobules Crus I–Crus II and the dentate nucleus [91], which was postulated to modulate the cerebrum activity differently than ctDCS of the posterior lobes of the cerebellum consisting of the hemispheric lobules VIIb-IX [24], [26].

The research protocol was approved by the All India Institute of Medical Sciences, New Delhi, India Institutional Review Board (IEC-129/07.04.2017). We performed fNIRS-EEG joint-imaging covering the prefrontal cortex, the primary motor cortex, and the supplementary motor area to investigate the deep ctDCS effects on cerebrum activity. This was based on fMRI studies [89] that showed distinct PFC regions functionally connected to the multiple areas of the human cerebellum, e.g., Crus I with MPFC, Crus II with DLPFC. We applied a novel approach using latent variables (from CCA) for fNIRS and EEG using a general linear model (GLM) [92] to study the effects of ctDCS. This was based on our prior works that showed ctDCS electrode montages could be optimized to stimulate different parts or lobules of the cerebellum [7,21]. Specifically, we found [29] that bilateral ctDCS of combined anterior and posterior lobes of the cerebellum, including cerebellar hemispheric lobules Crus I–Crus II and the dentate nucleus, resulted in increased canonical scores of oxy-hemoglobin (O2Hb) concentration changes as well as an increased canonical scores of EEG from pre-ctDCS baseline at the contralateral (to the anode) PFC. In contrast, bilateral ctDCS of the hemispheric lobules VIIb-IX resulted in a small decrease in the canonical scores of O2Hb concentration changes and EEG from pre-ctDCS baseline at the contralateral PFC from pre-ctDCS baseline. Here, distinct areas of PFC are functionally connected to lobule VII of the cerebellum [55], i.e., Crus I with MPFC, Crus II with DLPFC, ventral VIIB with anterior prefrontal cortex (APFC) [29]. However, lesion heterogeneity led to inter-individual

variability in the fNIRS-EEG response [29], so we selected best five subjects (Table 1) with the greatest post-ctDCS change in the canonical scores of O2Hb concentration from pre-tDCS baseline to determine brain activation [93], as shown in Figure 5 and described in the supplementary materials. Open-source realistic volumetric-approach to simulate transcranial electric stimulation-ROAST pipeline [95] was used with maximal-focality optimization criteria to target the response inhibition brain activation with 4x1 high-definition (HD) tDCS montage [94] using – see Figure 5.

Results:

The left panel of Figure 6 shows the CBI recruitment curve at different intensities of the cerebellar TMS conditioning stimulus based on prior work [90]. The conditioning TMS intensity was reduced in 5% steps below the brainstem motor threshold (BST) up to -25%. BST was determined by the corticospinal tract activation (shown in the left bottom brain section in Figure 3) by single-pulse TMS with the double-cone coil placed over the inion. The left panel of Figure 6 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 CBI recruitment curve slope decreased (became flatter) for further increase in the conditioning TMS intensity – change point detection. This is postulated to be due to the stimulation of the DN (that is excitatory, shown by a blue marker in Figure 6) in addition to the Purkinje cells (that are inhibitory, shown by a red marker in Figure 6), 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, which resulted in CBI (see left panel of Figure 6), were higher

than the EF threshold for DN activation. Since motor evoked potential (MEP) cannot be generated at the non-motor areas, so lobule-specific cerebellar NIBS [70,90,91,96] was combined with portable fNIRS-EEG joint-imaging [26] to identify individual NIBS response (also, non-responders) [26–28,97].

The top panel of Figure 7 shows the post-ctDCS change in the canonical scores of O2Hb concentration from pre-tDCS baseline for contralesional anode based on the dataset from our published work [29]. The bottom panel of Figure 7 shows the brain activation at the inferior frontal gyrus (Figure 7A) that can be targeted with 4x1 HD-tDCS with cathodes at ‘F7', 'F3', 'C3', 'T7', and an anode at 'FC5,' as shown in Figure 7B, to facilitate post-retrieval control processes during VR-based extinction learning by amplifying downstream inhibition from the subthalamic nucleus for sensory gating [98]. Here, gamma-to-beta frequency shift can be considered a marker of sensory gating. We postulated an effect of cerebellar transcranial electrical stimulation on substance-seeking triggered by substance-associated cues since interactions between sensory and motor cortices can be modulated by the cerebellum [99]. While tDCS induced gamma oscillations, computational modeling of tTIS effects showed that 63Hz amplitude modulation of DCN could lead to this gamma-to-beta frequency shift, as shown in Figure 8 (details in the Supplementary Materials). In Figure 8, the top panel shows the gamma frequency oscillations at the cortex with constant input (i.e., tDCS [91],[29]) to the DN. In contrast, 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 8.

Discussion

This study presented a computational modeling and methodological approach for portable neuroimaging guided NIBS, including cerebellar tTIS in CUD. NIBS intervention can be important at the early stages since CUD plays a causal role in the

development of psychosis [7] in certain genotypes with expression in cerebellum, as shown in Figure 2. The neurobiological substrate can be Δ(9)-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, where chronic administration produced significant reductions in prepulse inhibition (PPI) that resemble those of schizophrenia [100]. However, cannabidiol in cannabis can have opposite effects on PPI [101], which may be related to the antagonist of the human CB2 receptor [102,103]. Here, in cannabis use related psychotic disorders, we postulate a role of dysrhythmia of CCTC loop (as an extension of thalamocortical dysrhythmia [80]) in sensorimotor gating including negative and positive symptoms. We also postulate that cerebellar NIBS may ameliorate the maladaptive plasticity as an adjuvant to cue-reactivity training where cerebellar maladaptive plasticity may promote cannabis use related psychotic disorders in certain genotypes with expression in the cerebellum.

A key feature of psychotic disorders is the involvement of subcortical dopaminergic dysfunction [104]. Here, fundamental invasive neuroimaging studies in animal models can confirm the change of the cerebellar-brain connection using cerebellar TMS evoked dose response at the dopaminergic circuits based on multi-modal approach [105–110] by incorporating extracellular electrophysiology and fast-scan cyclic voltammetry (FSCV) [111] (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 [19]. However, TMS-based neuromodulation approaches are not amenable to home-based settings, so, tES should be investigated as an adjuvant treatment where cerebellar tDCS of Purkinje

cells DN has been shown feasible [91]. Also, cerebellar tACS has been shown feasible in modulating motor behavior [112]; however, evidence for addiction medicine is limited [36]. Recently, tES for deep brain stimulation has been shown feasible using temporally interfering electric fields [83], so we presented proof-of-concept computational simulation results in Figure 8. Also, NIBS of IFG (see Figure 7) can facilitate proactive control [45,50] during cue-exposure therapy [51] which needs to be evaluated in experimental study. Based on our computational results, we presented methodological approaches (Figure 4 and 5) for future experimental studies to investigate transcranial electrical stimulation of the cerebellum that can ameliorate CUD-related maladaptive plasticity and related dysfunctional cortical inhibition [79]. Furthermore, NIBS of the cerebellum in conjunction with the IFG as an adjuvant treatment during early cue-exposure therapy may ameliorate chemical dependency as well as habit formation [113].

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Tables

Table 1: Subject details (all male) from retrospective data from our prior work [29]

Name	Age and age-group for CLOS (years)	Post Stroke Period (years)	Hemiplegic Side	Cerebellar tDCS (Anode-Cathode)
P1	44 (40-44)	2	Right	PO10h-PO9h
P2	53 (50-54)	3	Right	PO10h-PO9h
P3	40 (40-44)	1	Left	PO9h-PO10h
P6	50 (50-54)	2	Left	PO9h-PO10h
P7	61 (60-64)	1	Left	PO9h-PO10h

Figures

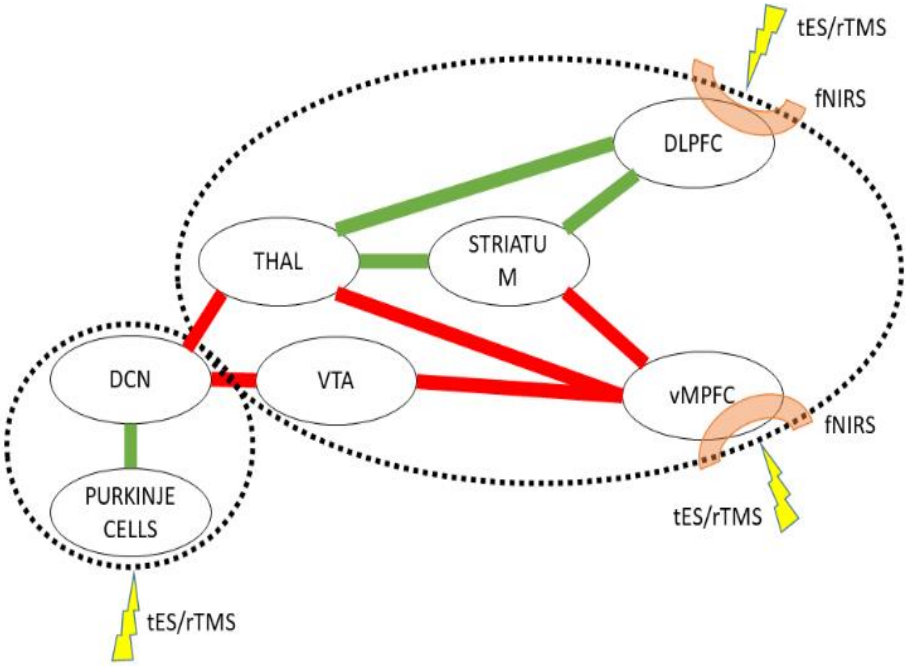

Figure 1: Competing neurobehavioral decision systems (CNDS) with cerebellum. Green links show the activation of executive control network via dorsolateral prefrontal cortex (DLPFC) and relative inhibition of the frontal–striatal circuits involved in limbic (amygdala, nucleus accumbens, ventral pallidum, and related structures) reward and impulsive action via ventromedial prefrontal cortex (vMPFC) and Purkinje cells in the cerebellum.

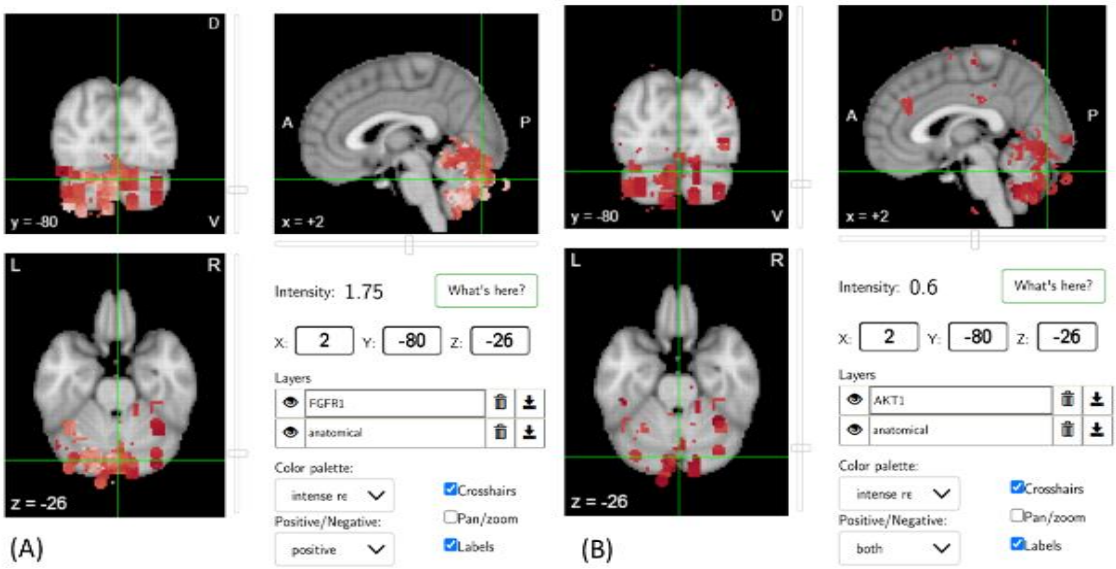

Figure 2: Brain-wide gene expression level of gene FGFR1 (A) and AKT1 (B) as made available from Allen Human Brain Atlas (from https://neurosynth.org/).

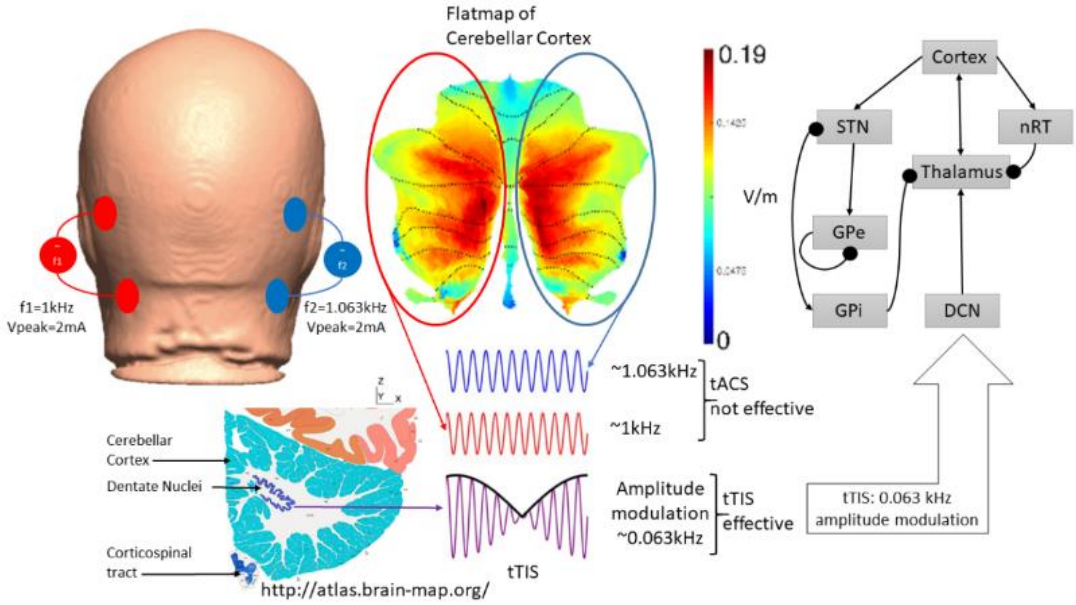

Figure 3: An illustrative picture of transcranial temporal interference stimulation (tTIS) approach where two tACS sources with frequencies f1=1kHz and f2=1.063kHz are combined for amplitude modulation at 0.063kHz at the deep cerebellar nuclei (DCN) regions. The thalamocortical basal ganglia network with DCN from (Yousif et al., 2020) is presented for tTIS modeling where arrows denote excitatory connections and round arrowheads denote inhibitory connections.

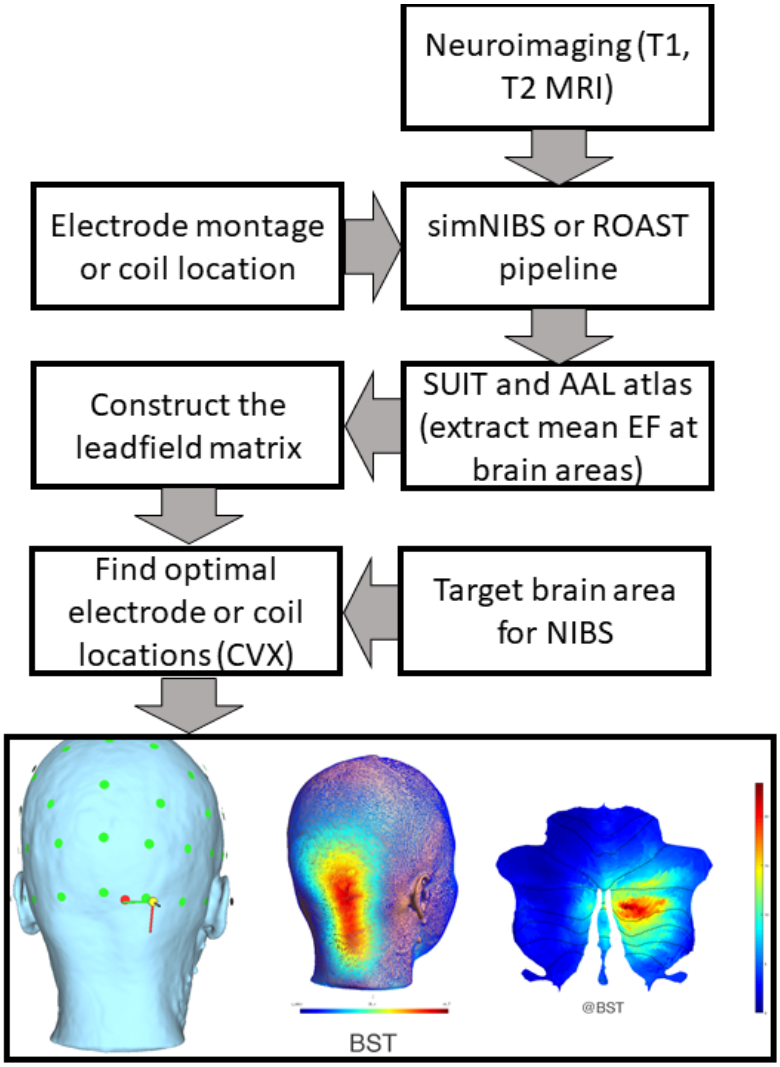

Figure 4: Computational pipeline for MRI based optimization of non-invasive brain stimulation for a target electric field (EF) distribution using convex optimization (CVX). Bottom panel shows an illustrative example of TMS targeting Crus II at brainstem threshold.

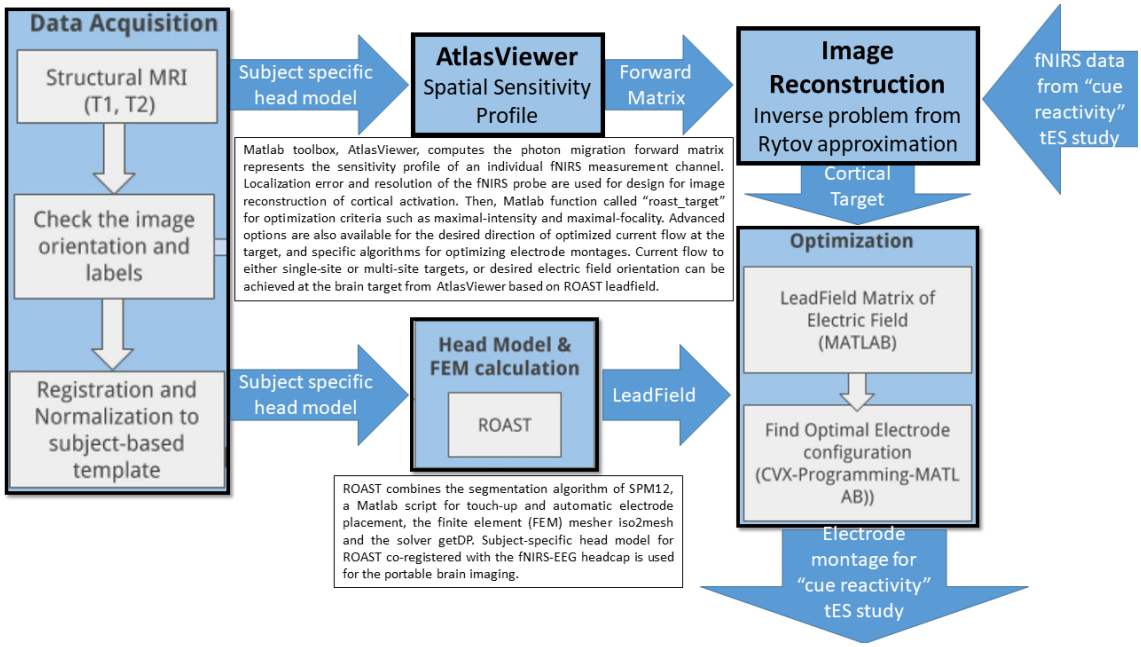

Figure 5: Computational pipeline for portable neuroimaging guided transcranial electrical stimulation

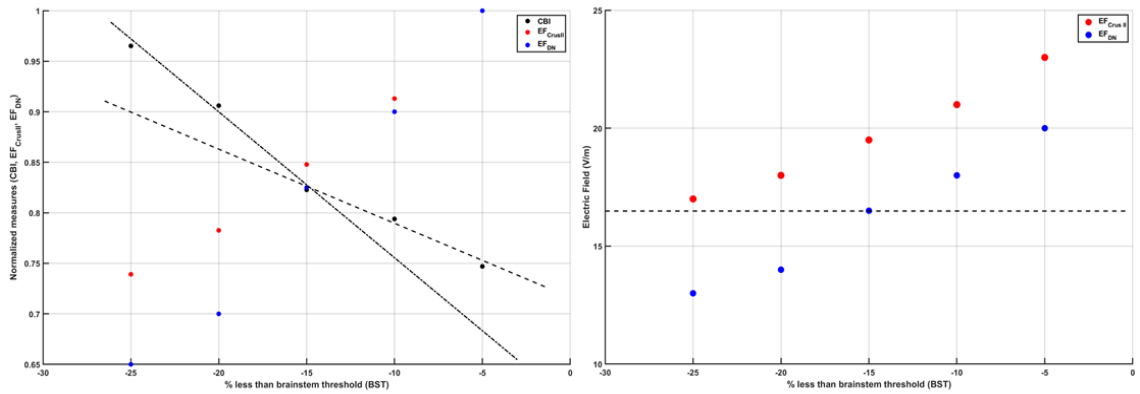

Figure 6: Left panel shows the change in the cerebellar brain inhibition (CBI) from a neurophysiological study and change in normalized (by maximum) electric field strength at Crus II and dentate nuclei (DN) with the change in the intensity of the transcranial magnetic stimulation (TMS) as a percent less than the brain stem threshold (BST). Right panel shows the electric field strength (V/m) at Crus II and dentate nuclei (DN) with the change in the intensity of the TMS as a percent less than the BST. -15% less that the BST is postulated to the TMS intensity (dash line in the right panel) at which DN starts getting activated by the TMS – change in the slope denoted by a dash and a dash-dot line in the left panel.

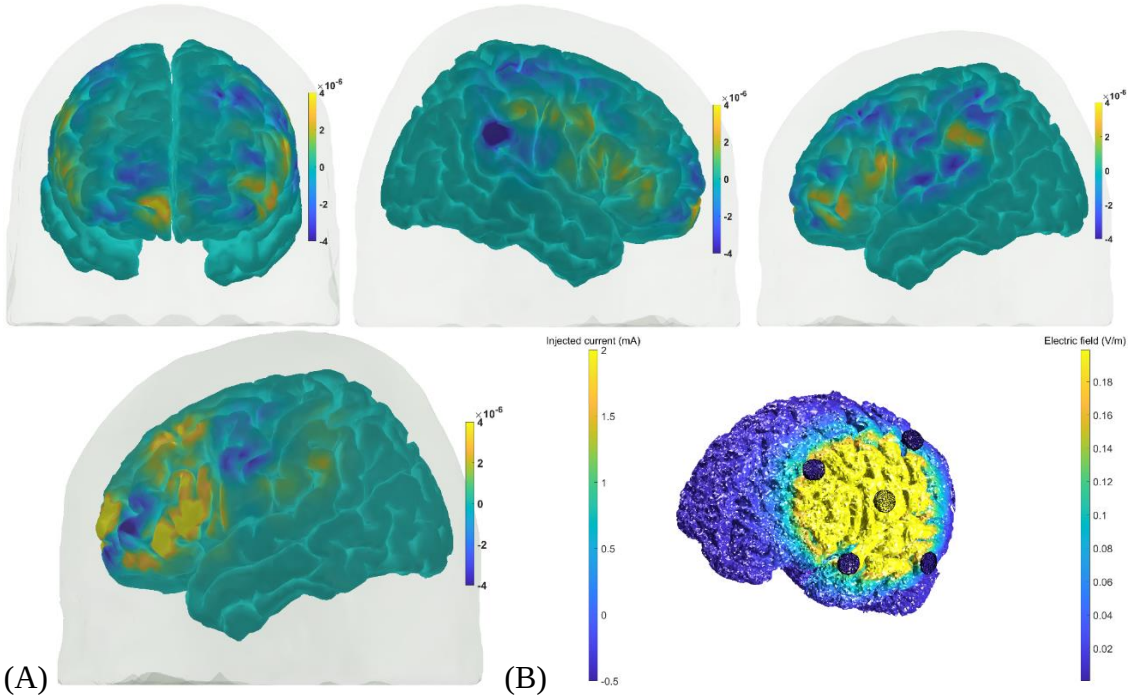

Figure 7: Top panel shows the change in the post-ctDCS change in the canonical scores of O2Hb concentration from pre-tDCS baseline for contralesional anode (right hemisphere is lesional hemisphere). The bottom panel (A) shows the brain activation at the inferior frontal gyrus that can be targeted with HD-tDCS (B) to facilitate downstream inhibition from the subthalamic nucleus when substance-associated cues trigger substance-seeking.

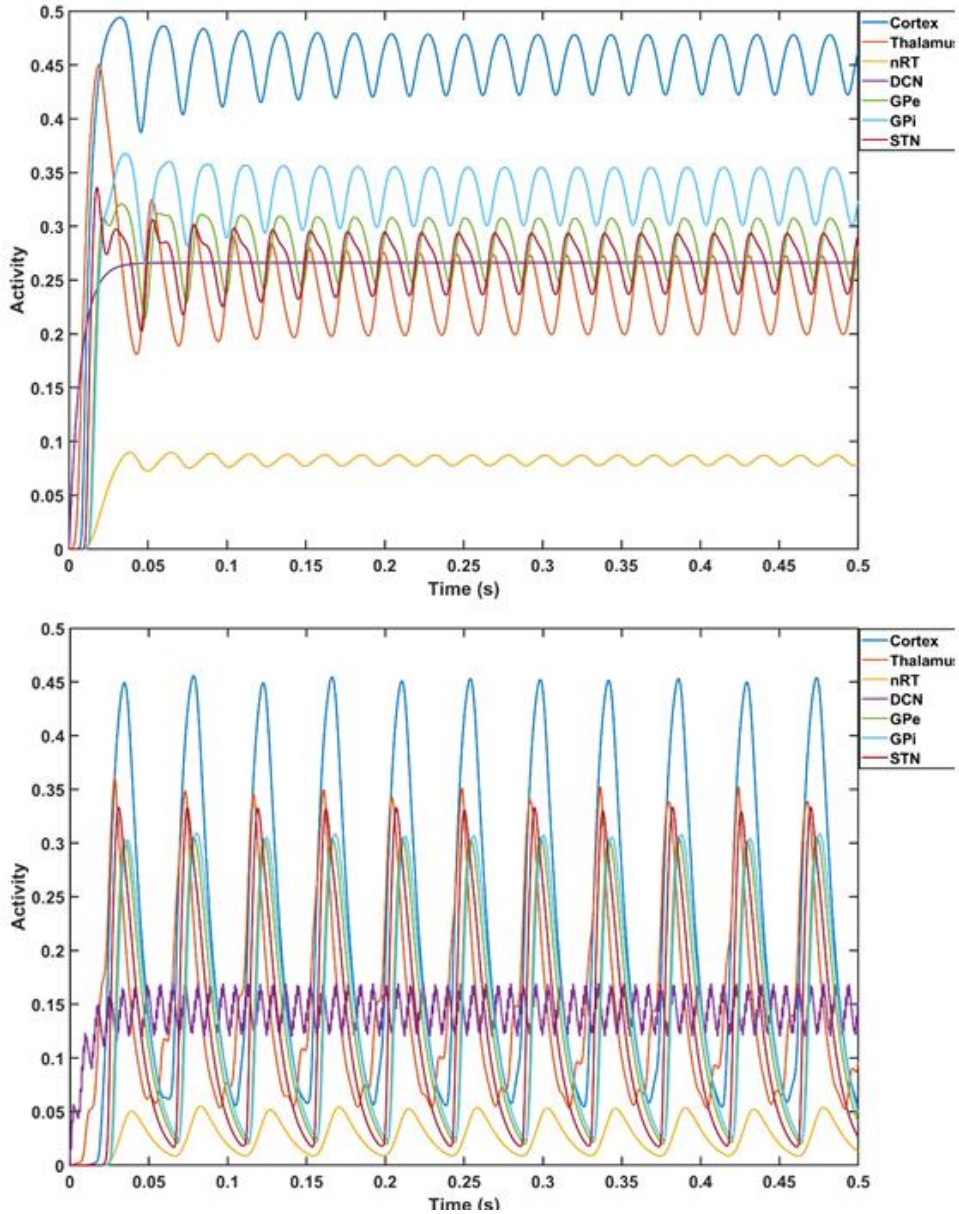

Figure 8: Computational modelling of thalamocortical basal ganglia with cerebellum (Yousif et al., 2020). Top panel shows cortical gamma frequency oscillations with a constant external input to the dentate nucleus (DN) which transitions to beta frequency oscillations with tTIS of DN at 63Hz beats frequency.