Abstracts
Applying Neuromodulation to Accelerate Training Effects: Designing a Translational Validation for Experimental Therapy

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Keywords: transcranial direct current stimulation, cognitive training, motivation

Background
This study seeks to identify any potential effects of a specific modality of non-invasive brain stimulation, transcranial direct current stimulation (tCS), on domains of human ability such as executive control and decision-making.

Methods
In terms of executive control more specifically, this includes constructs such as working memory or the ability to maintain and manipulate information in your mind, as well as sustained attention or the ability to focus on a particular task for an extended period of time. In terms of decision making more specifically, we will ask participants to choose between a number of options such as possible hypothetical outcomes (e.g., "Which of these options would you rather have?") or choices between activities that they may do to earn a reward (e.g. performing an easier task for less points or money, versus a harder task for more points or money). The research will also address the relationship between these factors and questionnaires that ask about different experiences they may have had, preferences, or beliefs, such as how quickly they usually make choices, substance use, or personality. The experiment will consist of placement of electrodes to deliver tCS to targeted areas of the brain such as the dorsolateral prefrontal cortex (Brodmann area 9). Participants will receive multiple sessions of anodal (positive charge) stimulation to the targeted area while they complete the tasks. Participants will complete both cognitive tasks and those more specifically related to decision-making. Following stimulation, participants will fill out questionnaires that ask about different experiences they may have had, preferences, or beliefs.

Results
This is a presentation of a design concept for feedback on methodological issues and eventual analysis.

Conclusions
Exploring the effectiveness of intervention in a healthy population may implicate safe alternatives to existing treatment options. The piloting of these tasks in a readily available population before clinical populations is important to monitor effects of a new potential treatment and to work through any psychometric or interpretive confounds that may arise.

Funding
$10,000 – Sambol Family Foundation Grant.
Exposure Therapy and Simultaneous Repetitive Transcranial Magnetic Stimulation (rTMS): A Controlled Pilot Trial for the Treatment of Posttraumatic Stress Disorder (PTSD)

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Keywords: transcranial magnetic stimulation, exposure therapy, posttraumatic stress disorder, combination treatment

Background
Little is known about treatment paradigms that combine talk therapies with rTMS treatment. One large naturalistic study found that a combination treatment of rTMS and cognitive behavioral therapy (CBT) for MDD was feasible and appeared to positively influence outcomes1. To our knowledge there is but a single case report2 describing a combined psychotherapy and rTMS treatment approach to PTSD. This study’s objective was to pilot, test and develop the technique of using standard left or right prefrontal rTMS during PE to potentially acutely treat PTSD symptoms. The intervention would be considered feasible if at least 64% of consented participants completed all required sessions, equaling the national pooled average of adherence to traditional PE therapy in OEF/OIF veterans with PTSD3.

Methods
A prospective, randomized, double-blinded, active sham-controlled design combined weekly sessions of rTMS and standard PE at a Veterans Administration Hospital. Eight adult patients received a full course of protocol-driven PE therapy and were randomly assigned to receive either rTMS or sham rTMS. rTMS was delivered to the right or left prefrontal cortex with a figure-eight solid core coil at 120% motor threshold, 10 Hz, 5s train duration, 10s intertrain interval for 30 minutes (6000 pulses) weekly for 5 weeks (30,000 stimuli).

Results
Of the 12 veterans consented, 8 completed the study treatment protocol. The dropout rate was 34%, roughly equivalent to the pooled, average dropout rates observed in traditional PE therapy with OEF/OIF veterans with PTSD, suggesting that veterans had no difficulty tolerating the addition of rTMS to PE therapy, and that this is a feasible study design for larger trials in the future. Clinician Administered PTSD Symptom (CAPS) scores reflected a general non-significant trend toward improvement, and subjects with comorbid major depression appeared to experience significant antidepressant benefit with treatment despite the fact that the doses used in this protocol were much smaller than those used to treat patients with MDD.

Conclusions
This pilot study demonstrates the safety and feasibility of rTMS delivery to PTSD patients while they simultaneously receive PE. This unique approach to the treatment of PTSD highlights the need for further studies with larger sample sizes to assess treatment outcomes.

References
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Funding
This study was funded by the United States Department of Defense (DoD) through Telemedicine and Advanced Technology Research (TATRC). Funding # Award Number W81XWH-10-2-0194); (UNCLASSIFIED).
Motor learning under artificially elicited multiple brain states fosters the stability of motor memories

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Keywords: context-dependent memory, force-field learning, transcranial direct current stimulation (TDCS)

Background
Recollection of memory is strongly affected by the context in which memory is created. We recently demonstrated that contexts in motor memories are shifted according to the activities of the sensorimotor cortex while participants learn motor skills [1]. Given that a study showed that declarative memory can more readily be recalled when learnings under variable environmental contexts [2], a motor skill practiced under multiple activation patterns of the sensorimotor cortex may lead to better retention through more robust memory representation.

Methods
We tested whether a motor memory formed under multiple cortical activation patterns, artificially elicited by transcranial direct current stimulation (TDCS), is well retained than one created under a single activation pattern. Twenty-four participants performed reaching movements to a visual target in a velocity-dependent curl force field (FF) while holding a robotic manipulandum. They were assigned to one of the two conditions. One condition applied four different TDCSs to the sensorimotor cortex in which current flowed anterior-to-posterior (AP), posterior-to-anterior (PA), medial-to-lateral (ML), and lateral-to-medial (LM) directions relative to the central sulcus during FF learning. The other used one of the four TDCSs throughout the learning period. Following the FF learning, all participants performed reaching movements to the visual target in a channel in which errors were absent with sham TDCS. These error-clamp trials enabled to quantify motor memories using the force exerted against the channel.

A follow-up experiment examined whether the four TDCSs targeting sensorimotor cortex manipulate cortical activities involved in the retrieval of motor memories. Twenty participants were divided into two experimental groups. One group learned the FF with sham TDCS and the other learned with the AP TDCS. In-between the FF learning, both groups were exposed to five blocks of the error-clamp trials, each of which applied the AP, PA, LM, ML, or sham TDCS. We also assessed changes in the corticomotor excitability by the AP, PA, LM, ML, and sham TDCSs before the FF learning started.

Results
The main experiment demonstrated that decay of motor memories was less in the participants who were exposed to FF with multi-pattern TDCSs than those exposed with single pattern TDCS. The amount of motor memories at the end of FF learning and the learning rate was not different between the conditions. The follow-up experiment showed that motor memory was most recalled when TDCS intervention during FF learning and error-clamp tests was matched. The TDCSs might act as a context for motor memories. The ML and LM TDCSs significantly modulated the corticomotor excitability, but these changes were not associated with the amount of the memory retrieval.

Conclusions
The results of motor memory retention and recollection could not be accounted for by the changes in the excitability. Rather, we presumed that variable brain states practice (i.e., variability in cortical activity during motor learning), elicited by externally applied electric fields, helped to compose a stronger schema of the motor task [3], resulting in facilitation of the memory stability.

References

Funding
A Grant-in-Aid for JSPS Fellows to MT (#16J02485) and a Grant-in-Aid for Scientific Research (A) to DN (#17H00874).
Bimanual skill acquisition during combined bimanual training and transcranial direct current stimulation in pediatric unilateral cerebral palsy

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Keywords: transcranial direct current stimulation, motor learning, cerebral palsy, rehabilitation

Background
Bimanual skills are an important aspect of everyday hand use. Children with unilateral cerebral palsy (UCP), producing weakness on one side of the body, benefit from bimanual training to achieve goals requiring use of both hands1, 2. Transcranial direct current stimulation (tDCS) may be a complementary intervention to bimanual training to enhance motor learning and neuroplasticity. The direct effects of tDCS on bimanual skill acquisition have not been examined in children with UCP. Thus, the objectives of this study were to measure changes in performance, specifically the timing, of a novel bimanual skill before, during, and after a combined tDCS and bimanual motor training intervention.

Methods
Eight children and young adults (mean age=12.3±4.0 yrs) with UCP, and without contraindications to non-invasive brain stimulation or other medical interventions, participated. This was an open-label study consisting of multiple baseline assessments (Pre1-Pre4), followed by a 10 day intervention (D1-D10) and immediate post-intervention assessment (Post). The intervention included 20 minutes of 1.5 mA cathodal contralesional tDCS concurrently with 120 minutes of bimanual motor training focused on individual goal achievement. Bimanual skill acquisition was examined using a novel, modified Speed Stack task3, which requires assembly of plastic cups using both hands in a pre-specified pattern.

Results
Change in completion time from Pre4 to Post ranged from -9.3-18.8s (µ=-2.2s, 95% CI=[-9.74, 5.35], p=0.51), with six of eight participants showing improvement. Variability in performance (Fig 1) was marginally significantly reduced from Pre4 to Post (µ=-2.5 s, 95% CI=[-5.31, 0.29], p=0.07). The average daily (D1-D10) improvement during the intervention was 0.3s (95% CI=[-2.79, 2.21], p=0.82).

Conclusions
Acquisition of bimanual skills is a key part of upper-extremity rehabilitation in UCP. Reduced variability, while not statistically significant in this sample, may be a functionally-relevant signal of improved bimanual performance. Comparing bimanual motor learning in larger groups of children with and without tDCS will help elucidate the role of brain stimulation to enhance learning of motor skills.

References

Funding
This study was funded the National Institutes of Health (NIH) Eunice Kennedy Shriver National Institutes of Child Health and Development K01 Award (HD078484-01A1), the Cerebral Palsy Foundation, the Foundation for Physical Therapy Magistro Family Grant, Minnesota’s Discovery, Research, and Innovation Economy (MnDRIVE) Initiative. The project described was also supported in part by awards UL1 TR000114 and KL2 TR000113.
Pacing hippocampal sharp-wave ripples with weak electric stimulation

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Keywords: hippocampus sharp wave-ripples, pacing stimulation, mouse

Background  Sharp-wave ripples (SWRs) are spontaneous neuronal population events that occur in the hippocampus during sleep and quiet restfulness, and are thought to play a critical role in the consolidation of episodic memory [1]. SWRs occur at a rate of 30 - 200 events per minute. Their overall abundance reduces with aging and neurodegenerative disease [2]. We explore to increase the abundance of SWRs by “pacing”, i.e. to initiate SWR events by low intensity electrical shocks given at a rate similar to the spontaneously occurring rate.

Methods  Experiments were done in mouse hippocampus slices. The pacing stimuli were delivered by an electrode placed outside of the CA3 tissue, to provide a mild depolarization to large number of neurons. Single pulses of 0.1ms width, given at a rate of 0.8 - 4Hz. The stimulus intensity for reliably pacing SWRs is weaker than the intensity for evoking detectable field potentials in CA1.

Results  Pacing induced SWRs are morphologically indistinguishable from spontaneous SWRs. Large variations in sharp wave amplitude, ripple patterns and spike timing are observed, despite identical stimulus parameters which presumably activate the same CA3 neurons surrounding the electrode. Pacing faster than the spontaneous occurring rate can significantly increase the SWR abundance, especially when the spontaneously occurring rate is low or compromised. Repetitive ~1 Hz stimuli with low intensity can reliably evoke thousands of SWRs without detectable LTD or “habituation”.

Conclusion  Our results suggest that weak stimuli may promote the spontaneous emergence of SWRs without altering their spatiotemporal architecture. In contrast, high intensity stimulus to the hippocampus is known to destroy SWRs and to compromise hippocampus dependent memory [3]. Pacing SWRs with weak electric stimuli may be useful for improving memory consolidation by restoring the abundance SWRs in compromised hippocampus.

Reference

Funding  Supported by Georgetown University Dean’s Toulmin Pilot award to JW, National Natural Science Foundation of China No.61302035 to XG, Chinese State Scholarship No.201606175113 to HJ and No.201606175114 to SL, NIH NS083410 to KC, TL1 TR001431 to AC.
Evoking slow oscillation after sleep spindle activity by acoustic stimulation during a nap: a pilot study

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Keywords: acoustic stimulation, sleep spindle, motor memory, closed-loop system

Background
Many studies reported driving effect of spindles and slow oscillations (SO) by electrical [1] or acoustic stimulations [2] and enhancement on memory consolidation by such stimulation during sleep. Meanwhile, there is argument that temporal relationship between sleep spindle and slow oscillation is a key mechanism for memory consolidation [3]. In this study, we attempted to evoke K-Complex (KC) by acoustic stimulation after sleep spindle activity. We set a hypothesis that SO after sleep spindle activity can be a benefit for the memory consolidation during a nap.

Methods
Four male participants (age: 27 ± 1.4 years) were recruited for this study. Each of participants took an adaptation nap in an experimental environment during 90 minutes. We calculated a threshold of root mean square (RMS) of spindle activity from adaptation nap EEG data for real-time sleep spindle detection. Each of subjects proceeded to stimulation nap and sham nap in a pseudo-random order. During the stimulation nap, pink noise stimuli were delivered right whenever sleep spindle is detected, but there was no stimulation during the sham nap. Subjects conducted finger tapping task before and after the nap.

Results
We averaged the whole trials of EEG epochs for each of conditions (sham and stimulation). In time domain analysis, we found clear pattern of KC for the stimulation nap, but there was no evident pattern for sham nap. In time-frequency analysis, we observed phase-locked response in delta (1 – 4 Hz) frequency range from the stimulation onset to 1000 ms after the onset during the stimulation nap. Finger tapping speed got increased notably during the stimulation nap (0.0352 ± 0.0167 ms) compared to the sham nap (0.0142 ± 0.0282 ms).

Conclusions
Pink noise stimulation after sleep spindle activity may induce KC activity. There was evident phase-locked response in delta frequency range after the acoustic stimulation. From the behavioral result, it is believed that there is notable motor memory consolidation effect induced by acoustic stimulation, however, our study is quite limited by the small number of subjects. We continue to conduct additional experiments to get more evidences for the effect of pink noise after sleep spindle activity.

References

Funding
This work was supported by GIST Research Institute (GRI) grant funded by the Gwangju Institute of Science and Technology (GIST) in 2017 and the National Research Foundation of Korea (NRF-2016R1A2B4010897).
Peri-stimulus EEG power and coherence during paired associative stimulation predicts subsequent potentiation

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Keywords: transcranial magnetic stimulation, paired associative stimulation, eeg

Background
Paired Associative Stimulation (PAS) is a method to induce plasticity using transcranial magnetic stimulation. PAS is measured via the hand EMG, comparing the amplitude of the motor evoked potential (MEP) before PAS induction to that after PAS. The induction of PAS consists of repeatedly pairing median nerve stimuli with cortical TMS, timed with an ISI of 20 to 25 ms so the median nerve stimulus arrives at cortex simultaneously with the TMS pulse. The EEG can be recorded during PAS induction and because of the large number of PAS induction pulses, analysis of the EEG recorded during PAS induction is feasible.

Methods
We employ mass-univariate correlations with peri-stimulus time-frequency windows to analyze event-related spectral perturbation and coherence and determine statistical correlations using threshold free cluster estimation to demonstrate the pre-median nerve stimulation paired TMS pulse baseline, as well as the TMS-EEG evoked potential recorded during PAS induction significantly correlate with the amount of plasticity subsequently induced (post-PAS).

Results
The EEG recorded during the induction of paired associative stimulation is demonstrated here to have predictive power for the amount of plasticity subsequently measured using the electromyogram at the targeted hand muscle.

Conclusions
These results demonstrate the EEG recorded during PAS is suitable to predict subsequent plasticity at the hand EMG and may provide utility as a neurofeedback gate to increase the efficiency of PAS.

References

Funding
Funding provided by the NIMH Intramural Research Program
Is Neurological Disease due to Dysfunctional Brain Oscillators?

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Keywords: caloric vestibular stimulation, neuromodulation, migraine, Parkinson's disease

Background
There is now general recognition that brain dynamics are underpinned by collective oscillatory states [1]. It follows, therefore, that neurological disease can be modeled as dysfunctional brain oscillators. The test of any model is whether it has predictive power and, clinically, whether it informs delivery of therapy. The advent of vestibular sensory neuromodulation as a treatment for episodic migraine (EM) headache provides a specific example with which to examine this model.

Methods
The vestibular system innervates, directly or indirectly, extensive brainstem, subcortical and cortical regions, including the sensory cortices via thalamic relays [2]. Migraine pathophysiology is associated with hyperexcited sensory responses and some have hypothesized that aberrant sensory sensitivity precipitates the subsequent cascades resulting in headache [3]. It is therefore reasonable to hypothesize that vestibular neuromodulation is interrupting or regularizing sensory hyperexcitability, but what is the mechanism of action (MOA)? Examining previous results using time-varying CVS therapy is supportive of a model whereby CVS entrains endogenous neuronal pathways, leading to neuroplastic modification over time.

Results
Black et al. [4] demonstrated entrainment of a pontine pacing network using a CVS therapy device. Significantly, induced oscillations in cerebral blood flow velocity had a period matched to B waves, which show abnormal dynamics in migraineurs. Black et al. showed that the time-varying character of applied CVS was crucial for entrainment and that the effect was clearly vestibular in origin. Wilkinson et al. [5] presented evidence of the efficacy of CVS therapy for EM as an adjuvant, suggesting that it acts through a parallel MOA. Recently, a study of Parkinson's disease patients, using the same CVS treatment paradigm as the EM study, provided strong evidence of durable gains in motor and non-motor assessments, strongly suggesting neuroplastic modification of the brain.

Conclusions
Current neuromodulation approaches deliver stimulation via implanted electrodes, induced cortical currents, or conduction between large-area scalp electrodes. In these approaches, the applied stimulus is adjusted empirically, heedless of the actual underlying, fine-scale oscillatory dynamics. Vestibular neuromodulation is categorically different from current forms of neuromodulation in that it acts via a sensory system. Applied oscillatory modulation is carried and transformed via endogenous pathways so that the modulation effectively entrains distant oscillatory networks. A reasonable hypothesis, therefore, is that repeated entrainment with time-varying vestibular stimulation drives aberrant oscillatory networks back to ontogenetic baseline configurations through neuroplastic modification, reducing hyperexcitability in the case of migraine and, more generally, bringing network activity closer to pre-disease function. The extensive literature around the dynamics of collective oscillators will also be discussed in this context.

References

Funding
Scion NeuroStim funded the work described.
ROAST: an open-source, fully-automated, Realistic vOlumetric-Approach-based Simulator for TES

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Keywords: transcranial electrical stimulation, computational models

Background
Research in the area of transcranial electrical stimulation (TES) often relies on computational models of current flow in the brain. To build such a model, the magnetic resonance images (MRI) of the human head have to be segmented, electrodes have to be placed, the volume is then meshed into a finite element model and solved numerically to estimate the current flow. Various software tools are available for each step, and processing pipelines that connect these tools for batch processing. However, existing pipelines are either not fully automated or difficult to use. Recently SimNIBS [1] becomes popular for its ease of use, but it’s based on the surface approach to represent the anatomy, which is limited to capture detailed structures such as the skull. Also it requires advanced computer skills to install and operate. Here we propose a new software, ROAST, to provide an easy end-to-end solution.

Methods
We put together the segmentation algorithm in SPM8 [2], our in-house Matlab script for segmentation touch-up and automatic electrode placement [3], the open-source finite element mesh generator iso2mesh [4] and solver getDP [5]. The complete pipeline is a Realistic vOlumetric Approach to Simulate Transcranial electric stimulation and has therefore been named ROAST. We tested it on the MNI-152 standard head [6] and compared the results with those obtained with a commercial mesher and solver (ScanIP and Abaqus), and with SimNIBS.

Results
ROAST only leads to a small difference of 9% in the estimated electric field in the brain compared to the results obtained with other commercial software (ScanIP, Abaqus). We obtain a larger difference of 47% when comparing with SimNIBS, mainly because SimNIBS builds the model based on the surface segmentation of the MRI, as opposed to the volumetric segmentation generated by SPM.

Conclusions
We release ROAST as a new, fully-automated TES simulator based on free software (except Matlab). It can be downloaded at https://www.parralab.org/roast/

References

Funding
This work was supported by the NIH through grants R01MH111896, R44NS092144, R41NS076123, and by Soterix Medical Inc.
Electric field model of transcranial alternating current stimulation in ferret

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Keywords: transcranial alternating current stimulation, finite element method, ferret, electric field model

Background
In transcranial alternating current stimulation (tACS), weak, oscillating electrical currents are applied via scalp electrodes for non-invasive modulation of brain activity. tACS is a promising tool for research and therapeutics, but reaching its full potential requires further understanding of the mechanism of rhythmic brain activity modulation with tACS and interactions with endogenous neuronal network activity. Computational models including geometric and electric properties of head tissues can assess current flow through various head tissues and help optimize tACS protocols. We investigated tACS-generated electric field for a ferret anatomy and validated the model predictions with measurements collected from intracranial recordings.

Methods
The electric field distribution was calculated for current of 40 µA in inhomogeneous finite element ferret head models. Two geometric models were generated from ex-vivo CT and in-vivo MRI of an intact ferret head: an intact head model (IM) with tACS electrode pads and a modified version of the model with a craniotomy (CM) representing the experimental recording setup [1]. In total, we generated 4 models, based on geometric aspects (IM, CM) and different sets of tissue conductivity values [2,3]. We assessed the averaged electric field magnitude for thalamocortical network regions of interest (ROIs), including lateral posterior thalamic nucleus (LPI), posterior parietal cortex (PPC), and primary visual cortex (V1). These values were compared to the literature for human tDCS studies [3].

Results
As expected, there were stronger electric fields in the brain for CM than IM models. Lee et al [2] conductivity values provided both more uniform current distribution and stronger electric fields than those of Huang et al [3]. ROI average electric fields ranged 0.10–0.15 V/m for IM and 0.12–0.19 V/m for CM. Maximum electric fields in grey matter were 0.62 V/m for IM and 0.81 V/m for CM for Lee et al [2] conductivity values and 0.29 V/m for IM and 0.34 V/m for CM for Huang et al [3] conductivities.

Conclusions
The simulated electric fields in the ferret brain for conventional tACS settings in this animal model (40–80 µA) were comparable to the electric fields in human applications (peak ~ 0.4 V/m and 95th percentile = 0.14 V/m at 1 mA) [3]. In the future, validation of the ferret tACS models with experimental recordings would be advantageous to resolve uncertainties about the conductivity values for the ferret head tissues.

References

Funding
This work was supported by the National Institutes of Health under grant R01MH111889.
The effects of transcranial alternating current stimulation on heightened cocaine seeking following prolonged abstinence in rats

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Keywords: transcranial alternating current stimulation, addiction, animal models, abstinence

Background
In cocaine addicts, the length of time away from drug use plays a critical role in the propensity to relapse. In animal models, the ability of cocaine-associated stimuli to elicit heightened drug-seeking increases as a function of abstinence duration, a finding that has been attributed to alterations in neural activity in brain reward circuitry [1]. One cocaine-induced adaptation believed to contribute to relapse is a reduction in frontal cortical function, which has been reported in cocaine addicts even after extended periods (3-4 months) of abstinence [2]. This ‘hypofrontality’ is believed to be linked with impaired inhibitory control over drug-seeking behavior and devaluation of non-drug reinforcers [3]. Here, preliminary studies examined if heightened cocaine-seeking and underlying alterations in neural activity in the prelimbic cortex (PrL) to nucleus accumbens (NAc) circuit following 1 month of abstinence could be restored with non-invasive transcranial alternating current stimulation (tACS).

Methods
Adult male rats (n=15) were surgically implanted with intrajugular catheters, with a subset (n=8) also receiving multielectrode arrays (8 channels/region) into the PrL and ipsilateral NAc. Rats were trained to self-administer cocaine (0.33 mg/inf, ~25 mg/kg) or saline/water (2 h/day, 14 days), paired with an audiovisual cue (20 s). Rats then underwent 1 month of abstinence with tACS (80 Hz, 10 s on/off, 20 stims/day) or sham administered for three days (abstinence days [AD] 27-29) prior to behavioral testing. One day (AD30, test 1) and one week (AD37, test 2) post-treatment, animals were given a test session consisting of 10 noncontingent presentations of the audiovisual cue (test 1 and 2), extinction and self-administration (test 2 only). Resting state neural activity was simultaneously recorded from PrL and NAc on the first and final day of tACS/sham treatment, and prior to both test sessions.

Results
Preliminary data show that 1-month cocaine abstinence led to reduced PrL—NAc coherence in the high gamma range (80 Hz) compared with saline/water controls (n=5 for cocaine, 3 for saline/water), with higher cocaine self-administering rats showing larger deficits. Following three days of 80 Hz tACS, gamma80 coherence in cocaine-tACS rats (n=2) was restored to the level of saline/water controls (n=3), and this was maintained through at least 1-week post-tACS (test 2). Interestingly, gamma80 coherence prior to behavioral testing was significantly positively correlated with cocaine-seeking during extinction (n=2 for cocaine-tACS and 3 for cocaine-sham, collapsed across treatment). While tACS increased approach toward the cocaine lever-associated quadrant and did not affect cocaine-seeking under extinction, when drug became available during self-administration, there was a trend toward decreased cocaine intake in the cocaine-tACS versus cocaine-sham group (n=4 per group).

Conclusions
Our preliminary data suggest that 1-month cocaine abstinence leads to decreased high gamma coherence in the PrL—NAc circuit, and tACS may restore these values to saline control levels. Further, tACS reduced cocaine intake during the second test session, despite increasing approaches toward the cocaine lever-associated quadrant. Ongoing investigations will more fully characterize the relationship between PrL—NAc connectivity and cocaine-seeking, as well as uncover effective tACS parameters for decreasing drug-seeking following abstinence.

References

Funding
R01 DA034021 (RMC), K99 DA042934 (EAW), T32 DA007244 (RMH)
tDCS Paired With Exercise and Attention Training for mTBI and PTSD Symptoms: A Case Report

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Keywords: 1) Transcranial Direct Current Stimulation, 2) Exercise, 3) Cognition, 4) Brain Injuries, 5) Neuronal Plasticity

Background
The purpose of this study was to investigate the effects of combining transcranial direct current stimulation (tDCS) with exercise and direct attention training on cognitive, behavioral, and emotional functioning of a patient with mild traumatic brain injury (TBI) and post-traumatic stress (PTS). There is evidence that both tDCS and exercise modulate neural network excitability, thus creating an enhanced therapeutic window following execution.

Methods
A 30-year old male, active duty Marine status post multiple concussions with loss of consciousness and sentinel injury occurring 6 years prior secondary to IED blast presented to a multidisciplinary outpatient day program for veterans with mild to moderate TBI and PTSD. His primary complaints were cognitive symptoms including: attention, memory and executive functioning; PTS; depression; dizziness; and migraine. The patient completed 4 weeks of therapy prior to the use of tDCS. tDCS was then applied at 1.5 mA for 26 minutes during moderate aerobic exercise, 5 days a week, for 4 weeks directly prior to attention training in order to maximize the potential for neuromodulation. The Test of Everyday Attention, Repeatable Battery for the Assessment of Neuropsychological Assessment, Attention Training Questionnaire, Key Behaviors Change Inventory, Beck Depression Inventory, and PCL-5 were used to assess changes in cognitive, behavioral, and emotional functioning. These assessments were completed on admission to the program, pre-intervention, post intervention, and at 1 and 4 weeks post intervention.

Results

tDCS paired with exercise directly prior to attention training resulted in significant improvements in attention, apathy, awareness, communication, emotional adjustment, depression, and PTSD. These changes were maintained at 4 weeks post-intervention.

Conclusion

tDCS combined with exercise prior to direct attention training resulted in functional cognitive improvement in a patient with mild TBI and PTSD and should be further investigated in a more rigorous, controlled study.

References


Funding
No funding source was used for this case study investigation.
Transcranial alternating current stimulation of the dorsolateral prefrontal cortex improves inhibitory control among substance users

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Keywords: transcranial alternating current stimulation, tACS, substance use, inhibitory control

Background
Cognitive control deficits contribute to the inability to maintain abstinence following substance use treatment. Non-invasive brain stimulation has shown promise in modulating cognitive control neuronal networks. Transcranial alternating current stimulation (tACS) allows for more targeted stimulation of specific brain network oscillations. The aims of the current study were twofold; (1) to examine the acceptability and feasibility of administering tACS at an intensive outpatient substance use treatment setting, and (2) to test the effect of tACS on inhibitory control.

Methods
In a randomized, sham-controlled, double-blinded design, treatment-seeking substance users (n=25; M age=45.7 years, 84.0% male, 20.0% African American) attended two sessions during which they completed an inhibitory control (Go/No-Go) task while receiving tACS administered over the dorsolateral prefrontal cortex of both hemispheres. Participants received the tACS sham condition during session 1 and were randomized to sham, 10Hz, or 40Hz during session 2.

Results
Session 2 retention was 95%, with one participant ineligible due to a positive urine screen. The effect of stimulation condition during session 2 on inhibitory control (Go/No-Go d-prime) was tested using hierarchical linear regression. Session 1 dprime during sham was entered in Step 1 and condition in Step 2. The full models comparing 10Hz to sham and 10Hz to 40Hz were significant (10Hz vs sham, F(2,13)= 15.22, p<.001; 10Hz vs 40Hz; F(2,15)= 5.46, p<.05), with the inclusion of condition in Step 2 explaining significant incremental variance in both models (10Hz vs sham, \(R^2\Delta=0.47, F(1,11)=19.36, p<.001\); 10Hz vs 40Hz; \(R^2\Delta=0.20, F(1,13)=4.85, p<.05\)). Participants in the tACS 10Hz condition demonstrated significantly greater inhibitory control compared to both sham (\(B=0.75, SE=0.19, 95\% CI=0.33,1.17\)) and 40Hz (\(B=0.58, SE=0.26, 95\% CI=0.46,2.20\)). There was no effect of condition on d-prime when comparing 40Hz to sham.

Conclusions
Results demonstrate the feasibility of recruiting and retaining participants enrolled in an intensive outpatient substance use treatment center for on-site tACS repeated administration of tACS, with evidence indicating a positive effect of 10Hz tACS on inhibitory control.

References

Funding
None.
A Single Session of High Definition Transcranial Direct Current Stimulation Does Not Alter Lower Extremity Neurophysiological Variables in Stroke

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**Keywords:** HDtDCS, stroke, resting motor threshold, MEP, amplitude, latency

**Background**
In stroke, transcranial direct-current stimulation (tDCS) has been shown to improve lower extremity force production but changes in walking speed, endurance, and balance remain unaffected\textsuperscript{1}. It has been suggested that tDCS is not effective due to nonspecific stimulation of large cortical areas. To overcome this limitation, High Definition (HD) tDCS was designed to deliver targeted current flow. Standard HDtDCS setups have a central electrode surrounded by four reference electrodes of opposite polarity\textsuperscript{2}. The central electrode can be setup to deliver current (anodal/excitatory) or receive current from the reference electrodes (cathodal/inhibitory). The purpose of this pilot study was to determine if HDtDCS affects lower extremity neurophysiological and biomechanical variables in individuals post-stroke.

**Methods**
Eighteen stroke survivors underwent biomechanical and neurophysiological assessments pre-/post-HDtDCS. Participants received excitatory, inhibitory, and sham stimulations in visits spaced three to five days apart. Biomechanical assessments were performed with motion capture. Participants walked at a self-selected comfortable speed on an instrumented treadmill for two 30 second trials. Participants then underwent neurophysiological testing using TMS. Neuronavigated single pulse TMS was used to determine resting motor threshold (rMT) of the paretic and non-paretic tibialis anterior muscles using parameter estimation by sequential testing. Once rMT was established, 10 TMS pulses were delivered at 120% rMT to elicit motor evoked potentials (MEP). After biomechanical and neurophysiological testing participants pedaled on a recumbent cycle ergometer for 20 minutes at a self-selected pace while receiving HDtDCS. Excitatory stimulation consisted of 2 mA applied through the central electrode and during inhibitory stimulation 0.5 mA was applied through each of the four reference electrodes. The central electrode was placed over the affected motor cortex at either C1 or C2 standard EEG references. Immediately following HDtDCS participants underwent neurophysiological and biomechanical testing. The effects of HDtDCS were analyzed using Repeated Measures ANOVA. Within-subject factors included treatment (excitatory, inhibitory, sham), timepoint (pre-, post-HDtDCS) and leg (paretic, non-paretic).

**Results**
Several biomechanical and ground reaction forces differed pre-/post-HDtDCS (N=18, main effect timepoint, $P<0.05$) but were not affected by HDtDCS (main effect treatment, $P>0.05$). In two participants paretic MEPs were unobtainable. Pre-HDtDCS rMT (N=16) was similar across visits (main effect Day, $P=0.15$) and was not altered by the treatment (main effect of timepoint, $P=0.15$), however rMT was greater for the paretic leg (main effect leg, $P<0.01$). Out of 2160 stimulations, 1887 (87\%) valid MEPs were elicited. Trials with <4/10 valid MEPs were removed from the analysis (N=12). Normalized latency was shorter in the non-paretic leg (main effect leg $P=0.05$) but neither MEP amplitude nor normalized latency changed with HDtDCS (main effect timepoint, $P>0.25$, main effect treatment $P>0.18$).

**Conclusions**
A single session of excitatory or inhibitory HDtDCS does not appear to alter lower extremity neurophysiological or biomechanical variables post stroke. HDtDCS was applied to a standard location and not to the neuro-navigationally identified hotspot. Also, all HDtDCS was delivered to the lesioned side. Due to the known interactions between the hemispheres contralesional stimulation should be investigated. Future work is required to determine the usefulness of HDtDCS in rehabilitative settings.

**References**

**Funding**
Veteran’s Administration Career Development Award-2, NO787-W, awarded to Bowden, Mark G. and Institutional Development Award from the National Institute of General Medical Sciences under grant number P20-GM109040 (MGB). The contents do not represent the views of the Dept. of Veterans Affairs or the United States Government.
The effects of transcranial alternating current stimulation on cocaine-induced deficits in behavioral flexibility in rats

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Keywords: transcranial alternating current stimulation, addiction, animal models, behavioral flexibility

Background
A history of cocaine impairs the ability to adjust behavior away from reward-predictive cues following reward devaluation, a canonical test of behavioral flexibility [1]. The ability to shift behavior in this task depends on prefrontal cortex (PrL) and the nucleus accumbens (NAc). Neural encoding in the NAc core, a predictor of flexible behavior [2] and a primary target of PrL, is abolished in cocaine-exposed rats during pavlovian conditioning [3]. Preliminary studies suggest that cocaine-induced deficits in behavioral flexibility are accompanied by a shift in the neural encoding of reward predictive cues from predominately increases to decreases in neuronal firing in PrL neurons. This is accompanied by a loss in synchronized, high gamma oscillatory dynamics (>50 Hz) between the PrL and NAc. Here, we sought to determine whether altered behavioral flexibility and underlying oscillatory dynamics following cocaine could be restored with non-invasive, transcranial alternating current stimulation (tACS).

Methods
Multielectrode arrays (8 channels/region) were implanted into the ipsilateral PrL and NAc in cocaine-exposed (14 days of 2-hr cocaine self-administration; 0.33 mg/inf, ~25 mg/kg) or control rats (saline/water self-administration [3]) and single unit activity and local field potentials were recorded across the behavioral paradigm. Two stainless steel screws with attached leads were positioned on the surface of the skull at midline (above the PrL). Eighteen days later, rats received either sham (n=8 cocaine and 9 control) or tACS (n=6 cocaine and 4 control) for three days (80hz; 10s on/off; 20 stims/day) via the steel screws. Next, rats underwent pavlovian conditioning over 10 days with two cues as conditioned stimuli (CS+; one predicting a sugar pellet and one predicting a food pellet) and two cues that did not predict a reward (CS-); 10 trials each. Next, sugar pellets were devalued by pairing with lithium chloride to induce a conditioned taste aversion. Rats were tested on the same pavlovian task (under extinction) to evaluate their ability to the avoid CS+ associated with the devalued outcome, a measure of behavioral flexibility.

Results
On the last day of conditioning, all experimental groups spent significantly more time in the food cup during both CS+ vs. to CS-. Post-devaluation, controls successfully avoided the CS+ associated with the devalued reward showing intact behavioral flexibility. In contrast, rats with a history of cocaine continued to go to the CS+ that predicted the devalued reward, suggesting habitual behavior. Preliminary studies show that tACS pretreatment attenuated these cocaine-induced deficits in behavioral flexibility and increased synchronized high gamma oscillatory dynamics (>50 Hz) between the PrL and NAc.

Conclusions
These preclinical experiments demonstrate the utility of tACS in ameliorating cocaine-induced deficits in behavioral flexibility and altered oscillatory dynamics within the PrL to NAc circuit. Non-invasive brain stimulation may serve as an effective treatment strategy in patients with substance use disorders by restoring maladaptive decision making associated with underlying disruptions in neural activity.

References

Funding
R01 DA034021 (RMC), K99 DA042934 (EAW), T32 DA007244 (RMH), McNair Scholars Program (HKO)
Transcranial Direct Current Stimulation Lessens Dual Task Cost In People With Parkinson’s Disease

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Keywords: Non-Invasive Brain Stimulation, Dual task interference, Gait, Executive function

Background
Parkinson’s disease (PD) is characterized by progressive motor and non-motor impairments including cognitive deficits in attention and executive function [1]. Dual-task walking requires divided attention and intact executive function through motor-cognitive interplay [2]. Transcranial direct current stimulation (tDCS), a form of noninvasive brain stimulation, has demonstrated isolated facilitation of motor and cognitive processing in people with PD [3]. Our purpose was to identify if application of bilateral brain hemisphere protocol of tDCS improved the ability to divide attention during walking in people with PD.

Methods
Participants with PD were assessed at baseline for disease severity [Unified Parkinson’s Disease Rating Scale (UPDRS)] and executive function [Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)]. Participants received a single 20-minute session of bilateral tDCS (dorsolateral prefrontal cortex; left=anode, right=cathode) at 2mA (tDCSactive) and one sham session (tDCSsham) separated by 7 ± 2 days. Following each condition, participants performed Timed Up and Go (TUG) single and dual task conditions (TUGalone, TUGmotor, TUGcognitive). Order of tDCS sessions and TUG conditions were randomized.

Results
Twenty-six people with PD were included [M=68.85±8.69, UPDRS M=40.69±16.39, RBANS M=83.23 (13th percentile)]. No differences between tDCSactive and tDCSsham were observed on dependent t-test for TUG conditions. Gait velocity dual task cost for TUGmotor was 18.80% (tDCSactive), 20.01% (tDCSsham); for TUGcognitive was 6.68% (tDCSactive), 25.00% (tDCSsham). Cognitive dual task cost for TUGcognitive was 22.30% (tDCSactive), 26.68% (tDCSsham).

Conclusions
Our bilateral tDCS protocol in PwPD did not significantly improve dual task gait. However, dual task cost following tDCS was lessened, most dramatically in the presence of a cognitive distractor. A larger sample size is warranted to draw further conclusions about our bilateral tDCS approach.

References

Funding:
This study was partially funded by Texas Woman’s University Research Enhancement Program
Continuous theta-burst stimulation dose and motor cortex excitability

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Keywords: transcranial magnetic stimulation, theta burst stimulation, motor evoked potential

Background
Theta burst stimulation is a form of repetitive transcranial magnetic stimulation which is used to change cortical excitability. Several previous studies have shown that continuous theta burst stimulation (cTBS) can reduce motor cortex excitability following 600 pulses of stimulation [1] but may increase excitability at higher doses (1200 pulses) [2]. This study extends the previous literature by investigating the relationship between cTBS dose (number of pulses) and motor cortex excitability in 30 young right-handed healthy subjects.

Methods
Four theta burst stimulation doses (600, 1200, 1800 and 3600 pulses) were administered at 80% of active motor threshold for 30 subjects on different days in a within subject randomized cross over design. Sham cTBS was administered to a subset of 10 participants. Motor evoked potentials (MEPs) were collected at baseline, directly following stimulation and at 10 minute intervals following stimulation for 60 minutes.

Results
A two-way within subjects ANOVA of MEP amplitude (dose x time, n=30) did not reveal a main effect of time (F(7, 203)=1.776, p=0.094), dose (F(1,87)=1.890, p=0.137) or interaction between dose x time (F(21,609)=1.088, p=0.356). The sham condition did not show a significant main effect of time (F(7,70)=1.051, p=0.404). To determine whether MEP amplitude variability was influenced by cTBS dose a second two-way within subjects ANOVA revealed a significant main effect of time across protocols (F(7,203)=2.629, p=0.013), wherein MEP variance was significantly greater than baseline directly following stimulation. No interaction between time and protocol administered was observed.

Conclusions
Continuous theta-burst stimulation has emerged as a popular rTMS paradigm being investigated for a number of neuropsychiatric diseases. The goal of this study was to determine how various cTBS doses (600 pulses, 1200 pulses, 1800 pulses, and 3600 pulses) effect the excitability motor cortex by measuring motor evoked potentials (MEPs). The primary results from this study demonstrate that 1) motor cortex excitability is not reliably decreased relative to baseline directly following cTBS at a variety of doses and 2) there is not a clear relationship between cTBS dose and motor cortex excitability following cTBS. The high level of variability in motor cortex in response to cTBS indicates the need for more standardized methodology and increased caution when planning research or interpreting the effects of cTBS on cortical excitability.

References

Funding
This work was supported by the National Institutes of Health (T32 TL1TR001451, T32 AA007474) and the American Heart Association (17PRE33660857).
Biophysics of multi-electrode tACS for phase-driven de/synchronization

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Keywords: transcranial alternating current stimulation, mechanisms of action

Background
Transcranial alternating current stimulation (tACS) is an emergent method of non-invasive neuromodulation due to its ability to engage frequency-specific brain oscillations. One recent application of multi-electrode tACS is the hyper- or de-/synchronization of distant brain regions. To do so, researchers vary the phase of applied stimulation currents between the stimulation electrodes at different scalp sites. However, the effectiveness of this manipulation in modulating the phase of intracranial electric fields has not yet been demonstrated. Here, we perform intracranial measurements of multi-electrode TACS electric fields and systematically evaluate the effect of varying input phases.

Methods
We performed intracranial recordings of electric fields during three-electrode TACS in two non-human primates. Monkeys were implanted with three recording arrays each with multiple recording sites at 5 mm intervals along the anterior-posterior axis. Three stimulation electrodes were placed on the scalp over the medial prefrontal (anterior brain target), left occipital (posterior brain target), and left temporal locations. We applied TACS with phase differences of 0° to 360° in 15° steps between the prefrontal and occipital stimulation electrodes, while the left temporal electrode served as “return” electrode. The electric field in the brain during tACS was calculated as the numeric gradient along the recording electrode array.

Results
We found that phase differences between the stimulation electrodes significantly affect the electric field magnitude in the brain in a systematic, albeit non-linear fashion (non-parametric ANOVA, sbj 1: χ²(224,700) = 396.2, p = 4.5×10⁻⁶⁹; sbj 2: χ²(224,525) = 164.3, p = 6.95×10⁻²⁸). The weakest field was found for the 0°/360° stimulation condition (RMS E(abs)₁ = 0.37 V/m; E(abs)₂ = 0.74 V/m per 1 mA p-to-b). The electric field for 180° stimulation condition is twofold stronger (RMS E(abs)₁ = 0.57 V/m; E(abs)₂ = 1.3 V/m per 1 mA p-to-b). Noteworthy, changes between the stimulation conditions (from 0° to 15°, to 30° etc.) following a sinusoidal curve, rather than a linear function (sinusoidal fit: R²(adj) = 0.99; linear fit: R²(adj) = 0.95). Similarly, non-linear behavior was also found for the phase angles of the electric field. The stimulation at 0° phase difference generates an “anti-phase” electric field with opposite phase angles at its anterior and posterior ends. In contrast, the stimulation at a 180° phase difference leads to an “in-phase” electric field with a zero-degree phase difference along the whole volume. Moreover, the intermediate stimulation conditions, such as 90° or 270°, creates a mixed picture where the electric field changes its spatial configuration in a traveling wave like manner.

Conclusions
The phase configuration during multi-electrode TACS has a significant impact on the generated electric field. Previous studies using “in-phase” or “out-of-phase” stimulation conditions are not in concordance with basic biophysics of TACS electric fields. Nevertheless, our measurements demonstrate the ability to create stimulation conditions with varying phase relationships. Further, we identify novel stimulation parameters leading to the creating of traveling-wave like stimulation fields. Accompanying computational efforts will enable future stimulation protocols that will allow to stimulate remote brain regions in a phase-specific manner based on validated biophysical principles.

Funding
Supported by NIH funding MH110217, MH111439, and by pilot funding from NKI. Research was further supported by the University of Minnesota’s MnDRIVE (Minnesota’s Discovery, Research and Innovation Economy) initiative.
Searching Further and Wider: Single Pulse TMS Still Leads to Elevated BOLD Activity in the ACC and Caudate

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Keywords: transcranial magnetic stimulation, interleaved, brain stimulation, multiband, multiecho

Background
Interleaved TMS/fMRI presents researchers with a powerful technique that combines the causal effects of TMS pulses with the ability to record brain-wide activity changes. Our group has recently published support for TMS/fMRI, showing that active TMS leads to greater BOLD activity in areas such as the ACC and caudate, relative to well-matched control stimulation (1). This prior report, however, had a limited field of view, making it impossible to draw conclusions regarding activity in much of the brain. Here, we present data to address this concern, while also implementing acquisition techniques that improve the signal to noise ratio of interleaved TMS/fMRI (2).

Methods
We delivered 4 runs of 10 TMS pulses to participants (n=10), of which two were active stimulation with the TMS coil positioned over the left DLPFC, while the other 2 runs used 3cm of padding to preserve the sensory aspects while dramatically reducing magnetic field entry (identical to the previous methods). The order of events was counterbalanced amongst participants. Rapid whole brain fMRI data was collected using a multiband multiecho imaging sequence (MB 2, TR 1.2, TEs 11.28,8.45,56 ms; 3.7x3.7x3.7 mm). We confirmed the perceptual similarity of stimulation conditions after each session. Data underwent standard preprocessing in AFNI. Subject level modeling was performed using both a conventional double gamma hemodynamic response, as well as using AFNI’s TENT functions to estimate hemodynamic responses without prior shape constraints. Mixed effects multilevel analyses methods were used for inference at the group level (3).

Results
As in our earlier work using a rapid TR with a limited slice prescription, we found that both active and control TMS led to activation in the insulae, thalamus, anterior cingulate, somatosensory regions and lateral prefrontal cortex. With the larger field of view, we are able to confirm similar activation also occurs in the inferior parietal lobule, paracentral lobule, cerebellum, and middle temporal gyrus (voxel threshold, p<0.005). Examining the TENT model, we find greater BOLD activity in response to active TMS relative to sham in the anterior cingulate, caudate and putamen (voxel threshold p<0.01).

Conclusions
This data represents a conceptual replication of our prior work, showing that interleaved TMS/fMRI activates putatively connected regions. It also bolsters the argument that interleaved TMS/fMRI requires appropriately controlling for the non-specific effects of delivering TMS within the MRI environment. Future studies may benefit from using multiband/multiecho techniques to obtain full brain coverage with better signal to noise characteristics. Furthermore, unconstrained modeling approaches may offer a better way to determine the areas that respond to active TMS, though this remains to be tested in a larger sample.

References

Funding
This work was supported by the National Institutes of Health (T32 DA007288, R01 DA036617, R21 DA041610, P20 GM109040, UL1 TR001450, F31 DA043330 and P2 CHD086844)
Computational Exploration of Stimulation Mechanism of Temporally Interfering Electric Fields

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Keywords: transcranial alternating current stimulation, temporally interfering electric field, computational modeling

Background
Temporally-interfering electric fields (E-fields) were recently reported as a non-invasive and steerable method for deep brain stimulation [1]. Two high frequency (kHz) sine-wave E-fields with a small frequency difference (a few Hz to tens of Hz) were used, forming a beat signal with a low frequency envelope. Experiments suggested that the interfering E-field activated neurons at the difference frequency with the same order-of-magnitude thresholds as low frequency stimulation, but the underlying mechanism remains unknown. This study explores potential mechanisms of interfering E-field stimulation using computational models of extracellular neuronal stimulation.

Methods
Theoretical analysis and computational simulation were performed to explore neuronal stimulation using the interfering E-fields and a range of parameters for the stimulation waveform were considered. We used a single-compartment model and realistic cortical neuron models from the Blue Brain Project [2] to analyze membrane depolarization and obtain extracellular stimulation thresholds for interfering kHz stimulation and two control conditions of low frequency stimulation and regular kHz stimulation.

Results
For either linear and non-linear membranes, theoretical analysis and simulations showed that the interfering kHz E-fields required higher stimulation amplitudes to reach similar subthreshold transmembrane depolarization compared to low frequency stimulation, ranging from 5–500 fold dependent on the membrane time constant and carrier frequency of the interfering E-fields. The interfering E-fields had higher relative thresholds normalized to low frequency stimulation (8–80 times for 10 Hz low frequency and 2 kHz carrier) than reported experimentally (3 times). Moreover, the single-frequency kHz stimulation and interfering kHz stimulation had similar thresholds and did not agree with the experimental reports that regular kHz stimulation elicited no response (threshold too high to be measured).

Conclusions
Computational models using conventional E-field–neuronal coupling mechanisms and activation of single neurons appear insufficient to explain the experimentally-reported effects of interfering E-field stimulation. Additional studies that include intrinsic neural activity and/or network-level interactions may be necessary to explore more fully the effects of temporally-interfering E-fields.

References

Funding
National Institutes of Health, Grant No. R01NS088674.
Ictal EEG Expression and Relation to Antidepressant Response in Electroconvulsive Therapy and Magnetic Seizure Therapy

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Keywords: ictal EEG, electroconvulsive therapy, magnetic seizure therapy

Background
Magnetic seizure therapy (MST) is under investigation as an alternative to electroconvulsive therapy (ECT), offering the promise of more focal seizure induction and fewer adverse neurocognitive effects than ECT(1). There has been great interest to determine differences in seizure expression between ECT and MST to shed light on their differential mechanisms(2), however the literature on this topic is limited. Furthermore, there is significant utility in identifying EEG biomarkers of clinical response after ECT and MST treatment, although previous attempts have been inconclusive(3,4). The objective of this study was to characterize neurophysiological differences between MST and ECT seizure expression, testing prior observations that ECT elicits greater ictal expression that MST, particularly in the theta, alpha, and beta frequency bands(2,5). Furthermore, we sought to determine whether patterns of ictal EEG expression at the start of treatment were predictive of antidepressant response (>50% reduction in HDRS-24) within each group.

Methods
A two-center, randomized controlled trial was conducted to contrast the antidepressant efficacy of right unilateral ECT and circular coil MST in treatment-resistant depressive patients. The 24-item Hamilton Depression Rating Scale (HDRS-24) was administered at baseline and after each treatment session. Four channel ictal EEG (Fp1, Fp2, P3, P4) was recorded at each treatment session for ECT (n=17) and MST (n=19) patients. Ictal EEG was manually screened for artifacts. Discrete wavelet transformation was performed using 4th order Daubechies wavelet, which decomposed the ictal EEG into 5 frequency bands (delta, theta, alpha, beta, gamma). Nonparametric unpaired permutation testing was performed to compare ictal EEG power.

Results
MST and ECT induced differential patterns in ictal EEG expression during the first treatment session. Specifically, ECT demonstrated significantly greater mean ictal power than MST in the theta, alpha, and beta bands over Fp1, Fp2, P4 (p<0.05, 50,000 repetitions). There was a significant difference in ictal delta power between ECT and MST patients in regions Fp2 and P4 (p<0.05, 50,000 repetitions); however delta power was indistinguishable between groups in regions Fp1 and P3. During the first treatment session, ECT responders (n=7) had a significantly higher ictal beta and gamma power (p<0.05, 50,000 repetitions) compared to ECT non-responders (n=10) over Fp1 and P3. This relationship was not observed within the MST cohort.

Conclusions
These results corroborate previous findings that ECT induces greater ical power than MST, particularly in the theta, alpha, and beta frequency bands. Increased ictal beta and gamma power in the ECT group was associated with antidepressant response. While the clinical utility of these findings awaits replication with larger sample size, ictal EEG may provide a potential biomarker of clinical response to seizure therapy.

References

Funding
The Stanley Research Foundation sponsored this study. AVS, ZD, and SHL are supported in part by the NIH Intramural Research Program.
Respiratory-gated auricular vagal afferent nerve stimulation modulates the stress response circuitry in major depression

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Keywords: major depressive disorder, transcutaneous auricular vagus nerve stimulation, respiration, stress response circuitry, autonomic function

Background
Transcutaneous auricular vagus nerve stimulation (taVNS) has shown promise in the treatment of major depressive disorder (MDD)¹, however, the mechanisms of action and neural pathways implicated are still unclear and its optimization needs investigation. Neuroimaging studies have suggested that taVNS modulates the activity of the nucleus tractus solitarii (NTS), from which projections synapse with brain regions involved in mood and stress regulation². Further, as NTS operates in response to changes in cardiopulmonary function, we propose that gating vagal afferent stimulation to respiration will yield a novel neuromodulation approach that may effectively optimize taVNS effects in major depression (MDD). The aim of this study was to evaluate the effects of respiratory-gated auricular vagal afferent nerve stimulation (RAVANS) in the modulation of the stress response circuitry, mood symptomatology and autonomic function in MDD.

Methods
Twenty women (30.3±4.7 yrs) with recurrent MDD, unmedicated and in an active episode were included. Functional MRI data were acquired on a Siemens Tim Trio 3T MRI scanner (TR=1250 ms, TE=33 ms, slice thickness 2 mm). Subjects attended two imaging visits within one week in which they were exposed to a visual stress challenge that preceded and followed expiratory- (eRAVANS) or inspiratory-gated (iRAVANS) stimulation. Group level analyses were performed using non-parametric permutation analysis (Randomise, FSL) followed by cluster-based correction for multiple comparisons (p<0.05). The High Frequency component of heart rate variability (HF-HRV, 0.15 to 0.4 Hz) was estimated as an indicator of parasympathetic cardiac tone. In addition, a Beck Depression Inventory (BDI) was administered before and after each fMRI session. A paired Student’s t-test was used to evaluate significant differences in HF-HRV and BDI changes after stimulation.

Results
Depressed women presented a significantly greater activation in NTS, raphe nuclei, anterior insula, anterior cingulate cortex and putamen following eRAVANS while an increased activation of hypothalamus and subgenual cingulate cortex was observed after iRAVANS. In addition, a significant reduction in BDI values (28.1±6.9 vs 19.9±9.1, p<0.01) and a significant increase in cardiovagal output (HF-HRV: 43.3±9.3 vs 52.2±10.6, p<0.01) was observed after eRAVANS, whereas no significant differences were observed following iRAVANS.

Conclusions
Modulation of cortical and subcortical areas involved in mood and stress regulation, such as NTS, raphe nuclei, putamen,insula and cingulate cortex, may constitute an underlying mechanism supporting the effects of RAVANS in depressive symptomatology reduction and cardiac autonomic regulation. Future neuroimaging studies may help in the evaluation of optimal stimulation parameters for a clinical course of therapy in MDD.

References

Funding
NIMH R21MH103468
Learning not to avoid: effects of cathodal tDCS to the DLPFC to modulate generalization of reversal learning

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Keywords: transcranial direct current stimulation, anxiety, generalization

Background
Avoidance of anxiety-provoking situations plays a central role in the maintenance of anxiety and fear-based disorders, such as obsessive-compulsive disorder and posttraumatic stress disorder. Extinction of avoidance behaviors is essential for success of exposure-based psychotherapy. While initial fear acquisition and instrumental avoidance generalize easily across contexts, subsequent extinction of avoidance is context-bound and does not readily generalize to novel contexts. Rodent and human studies point towards the importance of the prefrontal cortex and hippocampus in extinction learning/memory and the modulation by context, respectively. Here we used a reversal learning task to test whether cathodal transcranial direct current stimulation (tDCS) during reversal can reduce the impact of contextual encoding to facilitate generalization of extinction of avoidance behavior.

Methods
Participants (N=15) completed a contextual reversal learning task with the goal to avoid losing points as much as possible. During the first phase (initial learning) participants saw two sets of images either presented in Context 1 (images A/B) or Context 2 (images C/D). Selecting images A and C resulted in losing points, on average, over stimulus B and D, which generally resulted in no points lost. After meeting a learning criterion participants started the reversal phase. During reversal, image pair A/B now appeared in new Context 3 (context-dependent reversal), whereas image pair C/D continued to appear in Context 2 (context-independent reversal). Regardless of context, all contingencies reversed, i.e. images B and D resulted in points lost and images A and C resulted in no loss of points. Critically, participants received either 2 mA cathodal tDCS (n=7) or sham stimulation (n=8) targeting left dorsolateral prefrontal cortex (DLPFC) for 20 minutes starting at the beginning of reversal and continuing throughout. After meeting reversal criterion participants completed a test phase in which they saw previously presented stimuli pairs (A/B and C/D) in never seen Context 4. Participants were asked to select the image they preferred most. In order to test generalization of previous learning and effects of tDCS on generalization of reversal learning, no accuracy feedback was provided during this test phase.

Results
Although there were no differences between groups in the total amount of points lost or the number of trials needed to reach criterion (p>0.05), in the context-dependent reversal condition, participants who received active tDCS made more errors (38.2%) than those who received sham (26%), p=0.04. A direction of effects examination suggests that while the sham group did not show a strong preference to any image in generalization Context 4 during the test phase, participants who received active tDCS continued to avoid the image that resulted in loss of points during reversal and instead selected the image that resulted in losses during initial learning.

Conclusions
Although these data are preliminary, patterns of responses suggest that cathodal tDCS to the DLPFC during reversal might facilitate generalization of updated stimulus-outcome contingencies to novel contexts. In doing so, tDCS might promote overriding of initially learned avoidance behavior and its generalization to novel contexts.

Funding
Brown Institute for Brain Science/Norman Prince Neuroscience Institute New Frontiers Award to M.vtW-F and R.B.
Testing the necessity of the rostrolateral prefrontal cortex for sequence monitoring with continuous theta burst stimulation (cTBS)

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Keywords: transcranial magnetic stimulation, prefrontal cortex, sequential control, executive function, monitoring

Background
We perform abstract sequences every day. For example, the goal of making coffee combines both motor actions (pour ad stir) and abstract sequential sub-goals (add water and coffee prior to brewing). Previously, we demonstrated with fMRI and single pulse transcranial magnetic stimulation (TMS) that the rostrolateral prefrontal cortex is increasingly activated ("ramps") and necessary, during sequences of abstract categorization tasks [1]. These results dissociated RLPFC from two other control regions, rostromedial prefrontal cortex (RMPFC) and predorsal premotor (pre-PMD). To better isolate the computations underlying sequential control, we developed a sequence monitoring task that removed categorization decisions (based on [2]). FMRI showed that activity in the RLPFC also ramps during monitoring alone [3], but left open whether its role was still causal. To determine whether the RLPFC is also necessary for sequence monitoring, we tested whether continuous theta burst stimulation (cTBS) to RLPFC changed task performance in comparison to RMPFC or sham stimulation.

Methods
Participants monitored a repeated series of four stimuli. On each trial, participants pressed a button to indicate whether the image was in (InSeq) or out of a pre-instructed order (OutSeq). There were two trials types: 1) all stimuli were visible (Vis) and 2) all but the last stimulus in the block was "occluded" by an irrelevant, placeholder image (Occ), requiring participants to monitor the sequence without external cues. To limit potential response slips, participants could change their responses within the response time window. Visual feedback was given at the end of each block of sequential stimuli. Participants performed one task run (baseline) pre-stimulation, underwent cTBS, and performed the task again post-stimulation. CTBS [600 pulses, 40 s, triplets of 50 Hz repeated every 200ms (5 Hz overall)] was delivered at 80% of the participant’s active motor threshold [4]. Using a within-subjects design, order of stimulation was counterbalanced across three brain regions, left RLPFC, RMPFC, and sham targeted on right RLPFC. Each participant completed three separate sessions (≥ 24 hours between sessions). A prospective, randomized, double-blinded, active sham-controlled design combined weekly sessions of rTMS and standard PE at a Veterans Administration Hospital. Eight adult patients received a full course of protocol-driven PE therapy and were randomly assigned to receive either rTMS or sham rTMS. rTMS was delivered to the right or left prefrontal cortex with a figure-eight solid core coil at 120% motor threshold, 10 Hz, 5s train duration, 10s intertrain interval for 30 minutes (6000 pulses) weekly for 5 weeks (30,000 stimuli).

Results
Preliminary data supported a causal role of RLPFC in sequence monitoring. Participants (n=9) monitored the sequence of four images as a sequence. Elevated reaction times (RTs) at the first position evidenced sequence initiation costs (Pos1>Pos2,3,4, F1,8 = 20.79, p=0.002), replicating previous results [3]. We found that cTBS stimulation changed the proportion of trials on which participants “corrected” their responses, i.e. changed an initial incorrect response to a correct response. This change in corrections was evident in OutSeq items, relative to InSeq items, in the Occ condition (F1,8 = 5.40, p=0.048). Specifically, cTBS to RLPFC increased the proportion of corrected responses, whereas stimulation to RMPFC decreased this proportion. This change was not apparent in the Vis condition (t= 1.41, p=0.195). Further, we observed a trend that the effects of RLPFC stimulation varied across sequence position (F1,8 = 5.57, p=0.056).

Conclusions
These results suggest that cTBS stimulation to the RLPFC disrupts participants’ capabilities to accurately detect and respond to errors in monitored sequential information, potentially by limiting their ability to inhibit a pre-potent response and/or monitor position within a sequence.

References

Funding
Supported by NIGMS CoBRE P20GM103645 (TMD), NINDS R01NS065046 (DB), James S. McDonnell Foundation (DB), Brown University Department of Neuroscience Connors Fellowship (THM), and the Carney Institute for Brain Science (Innovation Award & TMS equipment).
Interacting Effects of Transcranial Alternating Current Stimulation (tACS) and Addiction History on Habitual Responding

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Keywords: transcranial alternating current stimulation, addiction, habitual, goal-directed, substance abuse

Background
Addiction is a chronic disorder that affects 20.7 million people [1] and poses a large societal burden. Despite our current understanding of the neurobiological mechanisms of executive dysfunction in addiction, new avenues for therapeutic discovery are needed. One possibility is the development of novel brain stimulation techniques to modify executive function. The current study goal was to combine transcranial alternating current stimulation (tACS) with our previous research showing that individuals with a history of addiction transition to habit-based response strategies more rapidly than do healthy controls [2]. To test whether tACS could shift behavior between goal-directed or habit-based action selection, we applied 10 Hz-tACs (alpha) bilaterally to the dorsolateral prefrontal cortex (DLPFC) of adults with or without an SUD history.

Methods
Participants with (N=17; SUD) and without (N=20; Control) an addiction history completed three study sessions in a randomized, double-blind within-subjects design. Control and SUD groups were matched on age, education, socioeconomic status, estimated IQ, gender and ethnicity. During the initial session, participants completed questionnaires and trained on a computerized stimulus-response (S-R) learning task (Hidden Association between Images Task; HABIT [2]). Participants returned to the lab for two tACS sessions to test the effects of stimulation versus sham on habitual responding. Participants underwent head measurement according to the international 10-20 system to place two DLPFC electrodes and a reference electrode at the vertex; impedance was kept below 5 kΩ. Stimulation methods for tACS followed those in [3]. Briefly, sham stimulation was applied at 2mA peak-to-peak with a 10Hz sine-wave flanked by 10 second linear ramps in and out for a duration of 5 minutes and 20 seconds. True stimulation used the same parameters but lasted 30 minutes. Stimulation was administered while participants performed the task.

Results
To quantify the degree to which responses were habitual, we calculated the percentage of perseverative relative to total errors following an S-R contingency change in the HABIT. There was a trend for a significant interaction between stimulation condition and group (F₁,33=3.58, p=0.067, η²=0.03), with true stimulation increasing habitual responding only in Controls. A partial correlation, controlling for age, baseline (sham session) habitual responding, and stimulation order, revealed a strong inverse relationship between habitual responding during true alpha stimulation and years of substance abuse (Pearson r=-0.8, p=0.001), indicating that a longer duration of substance abuse reduced sensitivity to the habitual responding promotion of 10 Hz-tACS observed among controls.

Conclusions
Among adults with no history of addiction, we found that true 10 Hz-tACS stimulation increased habit-based action-selection. In contrast, among adults with a history of addiction, this effect varied inversely with years of drug abuse, demonstrating the importance of incorporating individual variability metrics when analyzing stimulation results. Moreover, it raises the possibility that 10Hz-tACS stimulation effects depend on individual alpha frequency. These findings provide proof of principle that tACS can alter action selection strategy and lay a foundation for future studies to test stimulation specificity within the DLPFC.

References

Funding
This research is supported by a King Research Excellence Award and Dashielii Dissertation Startup Award (UNC Dept. of Psychology) and the National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, through Grant Award Number 1UL1TR001111 (NC Tracs 2KR561406) to THM, and NIAAA P60AA011605.
Effects of social experience on the neuromodulation of the escape circuit: empirical and computational analysis

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Keywords: social experience, neuromodulation, dopamine, Mauthner cell, neurocomputational model

Background
Understanding how social factors influence nervous system function is of great importance. Using zebrafish as a model system, we demonstrate how social relationship affects the neuromodulation of escape and swim circuits in zebrafish. Social interactions between adult male zebrafish (Danio rerio) consist of aggressive encounters that ultimately lead to the formation of stable relationships of either socially dominant or subordinate animals. Our current understanding of how identified brain circuits are modulated by social relationships in vertebrate model systems is limited. Dopamine is a neuromodulator implicated in social regulation: aggression, depression, motivation, and motor activity. We will investigate the effects of social relationships on the dopaminergic pathway using the Mauthner escape circuit through empirical and neurocomputational methods.

Methods
Wild type AB zebrafish strain were housed communally with mixed sex. Males were randomly selected from communal tanks and physically and visually isolated from conspecifics for one week in isolation tanks. Following isolation, animals were randomly paired with a conspecific continuously for two weeks in a novel tank of equal dimension to the isolation tanks. These paired animals quickly formed stable dominance relationships by the third day of interactions and remained stable [1]. Then, we conducted a series of empirical experiments to test the role of dopaminergic pathway in regulating escape in dominant and subordinate animals. We also constructed a neurocomputational model of the M-cell escape circuit to investigate how the interplay among social status and dopaminergic pathways affects the M-cell escape response.

Results
Injection of D1 receptor (D1R) antagonist leads to an increase in sensitivity of the startle response in dominants while there was no change in sensitivity in subordinates. On the other hand, injection of D1R agonist leads to no significant change in sensitivity of the startle response in both dominants and subordinates. Injection of D3R agonist leads to a significant increase in sensitivity of the startle response in dominants while it leads to a decrease in subordinates. Injection of GABA antagonist leads to no significant change in sensitivity of the startle response in dominants. However, GABA receptors in subordinates leads to a significant decrease in startle response. Injection of Glycine antagonist leads to a significant increase in sensitivity of the startle response in dominants while there was no change in subordinates. Our neurocomputational model replicates the empirical results and suggests the possible locations of dopamine receptors. Moreover, it suggests the relationship between GABA and Glycine in the Mauthner escape circuit.

Conclusions
Male zebrafish form stable social relationships consisting of dominant and subordinate animals, where subordinates' startle response is significantly more enhanced than dominants. Dopamine modifies escape behavior in a social status-dependent manner through inhibitory interneurons. Based on a review by Korn and Faber [2], GABAergic neurons influence the Mauthner neurons through the lateral dendrite. Blocking GABA showed a significant decrease in subordinate sensitivity while blocking Glycine increased the dominant sensitivity.

References

Funding
Interdisciplinary grant from ECU Research Division to F.A.I.
tDCS accelerates learning of laparoscopic surgical skills in a pre-registered, double-blind, randomized control design

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Keywords: transcranial direct current stimulation, laparoscopic surgery, learning

Background
Laparoscopic surgery involves complex visual-motor coordination skills that are carried out through indirect video guidance of movement. Mastery of these skills is required for board certification and therefore trainees undergo extensive deliberate practice prior to qualification testing. Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation approach that delivers constant, low voltage current via electrodes on the scalp to modify neuronal excitability in the underlying cortex. tDCS has been reported to enhance performance across domains including memory, perception, emotion and psychiatric health, with particularly strong empirical support when used to modulate motor function [1]. Because of the relative ease of use, low cost, and potential benefit there is an important need to test if tDCS has the potential to accelerate the development of laparoscopic technical skills.

Methods
This study was a double-blinded, randomized, and controlled study, pre-registered with ClinicalTrials.gov under protocol #NCT03083483. Here, 2mA of active tDCS was applied over bilateral M1 in 20 participants and over supplementary motor area (SMA) in 20 others, while sham tDCS was used in 20 control subjects (10 in each configuration, 30 second ramp on and ramp off). Within a 7-day period, training included 6, 20-minute sessions of the Fundamentals of Laparoscopic Surgery (FLS) peg-transfer task. Pre- and post-testing was completed using a timed repetition of the task. Videos of performance were recorded and scored to determine the number of correct object transfers performed in each session. Deductions were made for bad transfers (1 object) and dropping the object outside the field of view (3 objects). Linear mixed effects models were tested comparing each active to the combined sham performance.

Results
Results demonstrated a significant main effect of session, with all groups showing learning over the course of practice, and significant interactions between training group and session, with both the bilateral M1 and SMA groups exhibiting significantly greater learning than the sham group (ps<0.01). Moreover, while bilateral M1 stimulation produced less variability, both active tDCS groups obtained performance improvements nearly double that of sham stimulation and reached the final level of sham condition improvement in roughly ½ the number of training sessions. No differences were seen as a function of gender and only minimal adverse events were observed (e.g., lightheadedness).

Conclusions
Laparoscopic skill training was enhanced by active relative to sham tDCS for both bilateral M1 and SMA stimulation. This observation illustrates the accrued benefit of sustained electrical stimulation over a short timeframe and may suggest that longer training sessions with active stimulation could be of particular benefit for motor skill learning. Moreover, these findings the potential promise of accelerating laparoscopic technical training using this light-weight, low-cost, portable neuromodulatory approach.

References

Funding
This study was supported internally at our institution. MLC supported by a NIH T32 Training Grant: T32HL069749.
Online Paired-Pulse Transcranial Magnetic Stimulation (TMS) and Motion Perception in an Individually-Titrated Motion Discrimination Task

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Keywords: transcranial magnetic stimulation, visual perception, motion-sensitive cortex

Background
The capacity for transcranial magnetic stimulation (TMS) to modulate visual perception provides a well-characterized avenue for studying state dependency in the brain, defined here as the impact of ongoing brain activation during cortical stimulation¹. TMS effects arising from stimulation of motion sensitive visual cortex, however, have led to diverse findings, in part due to variability in the strength of motion perception produced by visual stimuli, and in part from differing methods to target visual cortex². The present study reflects a controlled attempt to better understand how these elements impact TMS effects.

Methods
Online TMS was applied to motion-sensitive cortex at 120% of resting motor threshold to test whether paired-pulse, long-interval cortical inhibition (LICI) stimulation impacted performance on a motion direction discrimination task as compared to sham TMS, and whether these effects are modulated by both task difficulty and targeting approaches. Participants (N=15) determined on each trial if a cluster of dots in the right periphery was moving coherently to the left or right. Difficulty was manipulated by altering dot coherence through a staircase procedure on day one. Three individualized coherence levels were selected to achieve desired performance levels of 60, 75, and 90% accuracy. On day two, participants performed the task while receiving TMS targeted to motion-sensitive visual cortex in two different ways. Target stimulation was defined either by scalp measurements (3 cm dorsal, 5 cm lateral to inion) or as the peak activation in the NeuroSynth meta-analytic database, and was applied 50 ms prior to motion onset.

Results
Analyses showed no significant active-versus-sham effect of TMS when LICI was delivered to the Neurosynth-defined target (p=0.15) nor at the scalp coordinates (p=0.17), which were separated by 58 mm on average. Additionally, there was no significant effect observed for the interaction between TMS at the Neurosynth-defined target or the 3-5 scalp measurement and task difficulty level (p=0.12 and p=0.33, respectively).

Conclusions
These findings do not support the hypothesis that LICI affects sensitivity to motion direction when applied to motion-sensitive cortex. While this type of paired-pulse TMS has led to cortical inhibition as a result of increased GABA receptor-mediated inhibition in motor cortex², applying similar TMS parameters to motion-sensitive cortex did not impact online motion perception using either targeting approach. Future studies can build upon these findings to further explore how the relative timing of stimulation and stimulus presentation influence motion perception.

References

Funding:
BRAIN Initiative Award: RF1MH114253
Investigating the Potential Safety and Efficacy of Brainstem Modulation Therapy for the Management of Parkinson’s Disease

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Keywords: caloric vestibular stimulation, Parkinson’s disease, noninvasive, brainstem modulator

Background
Caloric vestibular stimulation (CVS) introduces thermal energy to the external ear canal which modulates the firing rate of the vestibular nerves. This stimulus activates brainstem centers and elicits compensatory responses across cortical and sub-cortical structures. Although CVS is conventionally used to diagnose balance disorders and brainstem dysfunction, we recently demonstrated in a single case-study of a subject with Parkinson’s disease (PD) material reduction in motor and non-motor symptoms after 8 weeks of daily CVS therapy \([1]\) delivered via a solid-state, computer-controlled ThermoNeuroModulation (TNM\(^\text{TM}\)) device (limited by Federal law to investigational use), developed by Scion NeuroStim. Unlike conventional air and water irrigators, CVS via the TNM device can be self-administered at home with a high degree of dose control \([2]\). Here, we sought to replicate these original results in a blinded, placebo-controlled group to further evaluate the potential safety and efficacy of TNM therapy for the treatment of non-motor and motor symptoms in PD.

Methods
Eligible and consenting participants were randomly allocated 1:1 to a placebo or active arm. After a 4-week baseline period, participants self-administered 18 minutes of active or placebo treatment twice daily in the home for 8 weeks. Participants were followed during the baseline and treatment periods and at 5 and 24 weeks post-treatment. Motor and non-motor symptoms were monitored during participants’ on-states using standardized clinical measures including the MDS-UPDRS, Non-Motor Symptoms Scale, Montreal Cognitive Assessment and the PDQ-39. All participants were stably treated with dopamine replacement therapy throughout the study.

Results
In the per protocol group, active-arm participants (n = 16) exhibited significantly greater improvements in both motor and non-motor symptoms as well as activities of daily living at the end of treatment relative to placebo-arm participants (n = 17). Notably, gains were still evident in full at the 5-week follow-up and in part at the 24-week follow up. Outcomes were obtained with excellent treatment blinding and high treatment adherence/participant satisfaction.

Conclusions
Daily TNM\(^\text{TM}\) therapy was associated with significant reductions in both motor and nonmotor symptom burden and minimal adverse events. A fully-powered, multicenter effectiveness study should be undertaken to replicate the effect and further assess durability of gains. Parallel mechanistic studies are needed to isolate physiological effect and optimize dose.

References

Funding
This study was internally funded by University of Kent and partially supported by Scion NeuroStim.
The effect of transcranial direct current stimulation on food cravings in overweight and obese women

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Keywords: transcranial direct current stimulation, food cravings, obesity, overweight, brain stimulation

Background

Obesity is a major health issue and only a limited amount of interventions have been shown to result in sustained weight loss. Obesity has been linked to an enhanced hedonic response to food cues. Neuromodulation, and specifically transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases self-reported ability to resist food in adults, but no studies have yet measured the long term behavioral and cognitive effects of tDCS on hedonic eating.¹ Our aim was to test the effect of tDCS vs sham stimulation on food cravings, weight, and eating behaviors in obese and overweight women with high hedonic eating scores.

Methods

This is a pilot for an ongoing double-blind trial. Overweight/obese women were randomly assigned to receive tDCS vs sham stimulation to the right dorsolateral prefrontal cortex (dIPFC) during 8 daily 20-min sessions while completing a computerized Go-no-Go task. Demographic data and hedonic eating questionnaires (Three Factor Eating Questionnaire (TFEQ), Yale Food Addiction Scale (YFAS), General Food Cravings State Questionnaire (GFCQS) were obtained before and after completing the intervention. Data is presented as means and ranges. T-tests were used to explore differences before and after intervention.

Results

Eight overweight/obese women have been recruited so far, ages 18-48, BMI 31.3 (27.5 – 34.5) kg/m². After intervention, BMI was 30.4 (27.1 – 35.1) kg/m² (baseline vs. after intervention, p = 0.007). The tDCS group (n=3) had a mean BMI of 29.0 (27.4 - 30.9) kg/m² at baseline and a mean BMI of 27.9 (26.9 – 29.7) kg/m² after the intervention, while the sham stimulation group (n=5) had a mean BMI of 32.6 (29.8 - 34.5) kg/m² at baseline and a mean BMI of 31.8 (28.2-35.1) kg/m² after the intervention. Intervention in general, resulted in significant decreases in hedonic eating measures of cognitive restraint (CR) (CR before: 2.28 (1.67 – 2.89) vs. after: 2.59 (2.16 – 2.83) p=0.045) and food addiction scores (YFAS-SC before: 4.63 (3-7) vs. after: 2.75 (1 - 5), p=0.026), while no changes were seen so far in uncontrolled (UE) and emotional (EE) eating (UE before: 2.86 (1.9 – 3.4) vs. after: 2.43 (1.9 – 3.1) p=0.058; EE before 2.85 (2.2 – 3.6) vs. after 2.48 (1.7 – 2.8) p= 0.121), or in the GFCQS (before 53.63 (34 - 72) vs. after 46.38 (31-67), p=0.137).

Conclusions:

Our results show that our intervention, in general, resulted in significantly decreased food addiction scores and improved cognitive restraint. We have not yet analyzed the differential effect of tDCS vs sham stimulation, due to ongoing recruitment and small sample size so far. However there is a trend for significant weight loss after tDCS compared to sham stimulation. More participants will be recruited and their results analyzed in the next few months.

References

[1] Goldman et al., Prefrontal cortex transcranial direct current stimulation (tDCS) temporarily reduces food cravings and increases the self-reported ability to resist food in adults with frequent food craving. Appetite. 2011; 56: 741-746

Funding

2015 Oppenheimer TENS Pilot Research Award
An acoustic model of transcranial magnetic stimulation coils: optimizing the coil structure for reduced noise

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Keywords: transcranial magnetic stimulation, acoustics, coil click, coil noise

Background
Transcranial magnetic stimulation (TMS) is a versatile tool for both basic brain research and clinical applications. It induces currents in the brain through a strong sub-millisecond magnetic pulse. Such pulses require surge currents of several thousand amperes in the stimulation coil, which result in loud impulse sounds, often referred to as coil click, of up to 140 dB. For typical TMS devices, the characteristic frequency of the magnetic pulse is about 3 kHz [1], and the coil click has its peak acoustic power between 5–10 kHz [2]. Thus, the coil click is in the sensitive hearing range of humans. The loud sound poses a risk of hearing loss for both stimulation subjects and TMS operators. In addition, the coil click can evoke unwanted auditory activation resulting in auditory evoked potentials which are phase-locked with the stimulus and thus cannot be readily separated from other TMS-evoked potentials in electroencephalographic data.

Methods
We developed an acoustic model for a conventional TMS coil with simple internal mechanical structure. To facilitate optimization, we describe the coil geometry with a limited set of parameters. First, we compute the required coil current in a spherical head geometry using an analytical closed-form solution [3]. Subsequently, the finite element method (FEM) provides the magnetic field distribution within the coil, which further allows deriving the internal Lorentz forces. These forces are fed as body loads to a FEM-based structural-mechanics solver in the time domain to obtain the mechanical vibrations of the exterior surfaces of the coil. Finally, we calculate the near-field sound pressures based on the resulting surface velocities. We implemented the first part in Mathworks MATLAB R2018a and the others in COMSOL Multiphysics 5.3a.

Results
We computed the relationship between coil geometry and sound pressure of the coil click at physiologically matched stimulation intensity with the described pipeline. For coil geometries of existing commercial TMS coils, the pipeline yields reasonable sound-pressure levels that are in agreement with the literature. With this pipeline, we optimized the geometry for a figure-of-eight TMS coil with simple internal mechanical construction, including the inner and outer radii of the windings, the wire dimensions, and the thickness of the surrounding plastic casing.

Conclusions
We built a preliminary acoustic model for TMS coils. The model allows us to optimize the acoustic properties of coils. The model could be further refined by inserting more accurate material parameters, especially for the damping properties in the relevant frequency range.

References

Funding
This study was supported by the NIH under grant No. R01MH111865.
A Wearable, Wireless, and Dynamically Controllable Ultrasonic Neural Stimulator for Freely Behaving Small Animals

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Keywords: ultrasonic neural stimulator, wearable, CMUT

Background
Focused ultrasound (FUS) has been used to study brain function in neuroscience with a promise of being minimally invasive and safe, while achieving a high spatial and temporal resolution [1]. However, most of the ultrasound transducers used for neural stimulation are bulky so that the experimental animals need to be fixed to a frame and anesthetized. Such physical restraints and the use of anesthesia can possibly affect the response of the animal to stimulation. Moreover, the current FUS methods mostly tend to use single transducers that have limited capabilities in focusing and steering, thereby requiring mechanical translation of a transducer for targeting different regions. Therefore, it is highly desirable to implement a wearable, wireless, and dynamically controllable ultrasonic neural stimulator for freely behaving small animals [Fig 1. (a)].

Methods
The developed miniature stimulator consists of a 16-channel 1D transducer array, a custom front-end integrated circuit (IC) [2], a power management unit (PMU), and a Bluetooth Low Energy enabled microcontroller [Fig 1. (a)]. Capacitive micromachined ultrasonic transducers (CMUTs) fabricated in our lab were used for the transducer array, which offer ease of fabricating large arrays and integration with electronics. The custom IC generates excitation signals with programmable phase delays and amplitudes; therefore, the ultrasonic beam can be dynamically focused at the target depth and steered in the desired direction. The stimulator was validated with a bench-top acoustic measurement setup, which was wirelessly controlled by a PC. The transducer array was immersed in vegetable oil and excited with 5-MHz, 13.5-V pulse trains duty cycled with 10-Hz pulse repetition frequency (PRF).

Results
The focused beam at a depth of 5 mm achieved a peak-to-peak pressure level of 554 kPa\textsubscript{pp}, which corresponds to the spatial-peak pulse-average intensity (\textit{I\textsubscript{SPPA}}) of 2.9 W/cm\textsuperscript{2} [Fig. 1(b)]. The measured 3-dB beamwidth was 0.4 mm. We also steered the beam to ±2 mm in X-direction, corresponding to ±30° steering angle for a focal depth of 3.5 mm in Z-axis [Fig. 1(c)].

Conclusions
In this work, we presented an untethered ultrasound neural stimulator for small awake/behaving animals. With a hydrophone-based measurement setup, we demonstrated the beamforming and beamsteering capabilities of the system. Our future efforts will focus on further smart partitioning of the system towards a truly wearable device for small freely moving animals.

References

Funding
This work is supported by the National Institutes of Health under Grant EY028456.

Figure 1. (a) Envisioned wearable ultrasonic neural stimulator and the schematic diagram of a prototype (bottom right). (b) Measured 2D beam patterns and beam profiles with a beam unfocused/focused. (c) Measured 2D beam pattern with a beam steered in ±30°.
Effects of online repetitive transcranial magnetic stimulation on cognitive processes: a meta-analysis

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Keywords: online rTMS, cognition, meta-analysis

Background
Repetitive transcranial magnetic stimulation (rTMS) has become a widely used approach to investigate neural bases underlying cognitive functions including various aspects of attention, memory, language, perception, and more. When applied while subjects are performing a task, online rTMS generates neural noise interfering with ongoing cognitive processing. This rTMS-induced “virtual lesion” has been used to causally investigate brain-behavior relationships with a better insight into the timing of neural processing involved in a task. However, recent studies have shown that online rTMS can also induce paradoxical enhancement, or state-dependent effects. Given the rapid proliferation of online rTMS studies, it is crucial to develop a better understanding of whether online rTMS has a disruptive or facilitatory effect on cognitive performance, and which are the optimal parameters to achieved the desired effect.

Methods
We performed the meta-analysis according to the recommendations of the Cochrane group, involving selection of eligible articles according to inclusion and exclusion criteria, quality assessment of these studies, data extraction of outcomes and quantitative synthesis. The search protocol for this meta-analysis has been registered on the International Prospective register for systematic review with the number 42016038981. PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, Web of Science, Scopus, and PsycInfo databases were reviewed to identify and compile all English-language studies that explored the effects of placebo-controlled, online rTMS on cognitive process, which yielded 9134 articles. After title, abstract and full-text screen by independent investigators, we extracted data regarding study design, population characteristics, cognitive domains, intent when applying rTMS, targeted brain regions, and type of sham method. We also extracted stimulation parameters such as intensity and frequency of stimulation, number of TMS pulses applied on each trial and timing of these pulses relative to the trial. We extracted the principal outcomes measures: reaction time and accuracy, and their respective standard errors. Using the Mantel-Haenszel approach, we fitted random-effects models to each outcome to synthesize a pooled odds ratio with 95% confidence intervals. We performed subgroup analyses by cognitive domains and rTMS frequency. Study heterogeneity was assessed using the Cochrane's Q and I\(^2\) statistics.

Results
The final meta-analytic dataset included 143 studies published between 1998 and 2016. Results showed that rTMS at 10Hz and 20Hz have a disruptive effect on accuracy for attention, executive, language, memory, motor, and perception domains, while no effect were found with 1Hz or 5Hz. 10Hz and 20Hz rTMS also slows down reaction time in attention, language, and perception tasks. Curiously, during memory tasks, 5Hz rTMS quickens reaction time without accuracy tradeoff.

Conclusions
In agreement with the “virtual lesion” concept, this meta-analysis confirmed that rTMS mainly disrupt cognitive performance. However, this is true only for rTMS applied at 10 and 20Hz; when applied at 5 Hz, rTMS seem to enhance performance in memory tasks.

Funding
This research was funded in part by grant support from the National Institute of Aging grant # U01 AG050618. Z.-D. Deng is support by the National Institute of Mental Health Intramural Research Program.
Structural Brain Network Modal Controllability Predicts Antidepressant Treatment Response with rTMS

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Keywords: transcranial magnetic stimulation, depression, DTI, controllability

Background
Repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (dLPPFC) is an FDA-approved treatment for depression. Increasing evidence indicates that depression is accompanied by altered structural connectivity in the white matter. A recent article by Gu et al. [1] proposed to characterize brain networks using a dynamical system measure of controllability, calculated from structural brain connectome derived from diffusion tensor imaging data. We investigate the relationship between controllability of structural brain networks and rTMS treatment response.

Methods
The Institutional Review Board of Weill Cornell Medical College approved this study. 25 currently treatment-resistant depressed patients (age 21–68) received daily 10-Hz rTMS over dLPPFC 5 days/week for 5 weeks. Treatment response was assessed using the 24-item Hamilton Rating Scale for Depression (HAM-D-24). Diffusion tensor images were acquired within 7 days prior to the rTMS treatment course. Global tractography was performed using a spherical convolution model in MRtrix 3. A weighted connectivity matrix was computed based on number of streamlines traversing between 408 subparcellated cortical and subcortical brain areas in the Harvard–Oxford atlas. We computed modal controllability, which characterizes ability of a brain region to drive the network into difficult-to-reach states.

Results
At the dLPPFC, anterior cingulate cortex, and right lateral frontoparietal regions, higher baseline modal controllability is associated with higher depression severity (p < .01, FDR corrected). At dLPPFC, modal controllability at baseline was positively correlated with the change in HAM-D-24 from before to after rTMS (Pearson correlation r = 0.61, p < .01). Modal controllability at baseline was negatively correlated with the change in HAM-D-24 (r = -0.67, p < .001) at the dLPPFC and right superior parietal regions. Receiver operating characteristics constructed using parietal modal controllability for discriminating treatment responders and nonresponders had an area under the curve of 0.88.

Conclusions
Higher modal controllability indicates higher input energy is required to steer the brain to remote states. The association between modal controllability and depression severity implies that the depressive brain state is difficult to perturb. At the treatment target of dLPPFC, higher modal controllability is correlated with better treatment response with rTMS, which is consistent with the clinical observations that severity of depression can predict remission rates using rTMS. Perhaps the more surprising result is that lower controllability at the right superior parietal region is correlated with better treatment outcome. Not only can the controllability measure serve as a useful biomarker of rTMS treatment response, but may also be considered a potential target for driving brain state transitions in depression.

References
The list of references should be identified by natural numbers with a bracket in the text [1]. We encourage to use ‘Vancouver’ style for the references.


Funding
Z.-D. Deng is supported by the NIMH Intramural Research Program.