Table 1
Treatment effect sizes with and without correction for average self-report of subjective discomfort during each session. Effects in **bold** = larger and *italic* = smaller with discomfort.

Measure[a]	Effect without discomfort		Effect with discomfort	
	η^2	d	η^2	d^b
DS Forward	0.12	0.73	0.12	0.73
DS Back	0.43	1.74	0.36	*1.49*
Sequencing	0.55	2.22	0.63	**2.59**
Learning	0.16	0.88	0.11	*0.71*
Memory	0.62	2.58	0.56	*2.26*
Recognition	0.21	1.02	0.11	*0.72*
Trails A	0.81	4.12	0.84	**4.62**
Trails B	0.15	0.84	0.19	**0.97**
Pegs Dom	0.12	0.75	0.14	**0.80**
Peg Nondom	0.16	0.89	0.09	*0.61*
PAOF	0.36	1.50	0.26	*1.19*
CESD	0.22	1.07	0.07	**2.98**

[a]DS Forward = Digit Span Forward; DS Back = Digit Span Backwards; Sequencing = Digit Span Sequencing; Learning = Hopkins Verbal Learning Test—Revised total recall; Memory = Hopkins Verbal Learning Test—Revised delayed recall; Recognition = Hopkins Verbal Learning Test—Revised recognition memory; Trails A, Trails B = Trail Making Test, Parts A and B; Pegs Dom, Pegs Nondom = Grooved Pegboard, Dominant and Nondominant Hands Times; PAOF = Patient Assessment of Own Functioning total; CESD = Center for Epidemiological Studies Depression Scale.

Over the next two weeks, participants then completed six 20-minute training sessions. After completing all training sessions, participants completed the same battery of neuropsychological tests and self-report measures. They also completed a final interview during which they were asked what group they believed they had been assigned to and their overall impression of the training program.

Blinding

tDCS was delivered in a single-blind design in which the operator was aware of treatment group assignment. All assessments, including neuropsychological test administration and final interview, were completed by an assessor blind to participants' treatment assignment. Ratings of mental ability, mood, and discomfort were collected at the end of each treatment session by asking the participants to respond to Likert-type ratings by tapping on a computer screen with the operator out of the room.
All participants in this study had expressed oral consent for screening procedures and written informed consent prior to other study procedures. The protocol under which this study was carried out was approved by the Nova Southeastern University IRB. This study was registered at ClinicalTrials.gov (NCT02647645).

4. Results

Eleven participants completed all study procedures; their mean age was 51.5 years, two were women and two were white, with the others African American. Two participants withdrew prior to randomization as they believed our training site was too distant from their home after they completed eligibility determination. The other participant withdrew because of hospitalization for a health condition not related to study participation. All participants stated that they believed that they had been assigned to the active tDCS condition.
Covariate corrected statistical models showed that 13 of 14 effect sizes favored active tDCS, with sizes ranging from moderate to large (i.e., d = 0.73 to -2.66; results reported elsewhere). Covariate corrected analyses of self-report of discomfort over treatment sessions suggested the presence of group differences (see Figure). We then evaluated the impact of including subjective discomfort on treatment effect size by including participants' average report of discomfort in the same models (see Table 1).
Results for a measure of verbal learning (Hopkins Verbal Learning Test—Revised Total) are illustrated in the Figure. Most participants stated the training was valuable; the two participants who did not had been assigned to the sham condition. All indicated they would participate in a similar study in the future.

5. Discussion and Conclusion

Results suggest that tDCS with cognitive training via computer gaming can improve cognitive function in older persons with HIV and mild neurocognitive disorder. Results also suggest that perceived discomfort during tDCS did not have a significant effect on effect size. The results may suggest that the sham method used in this study has appropriate blinding efficacy to the subjects. Further study on tDCS as an intervention for HIV related cognitive dysfunction is warranted.

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PROCEEDINGS #7. TRANSCRANIAL DIRECT CURRENT STIMULATION EFFECTS ON PREFRONTAL CORTEX IN MAJOR DEPRESSIVE DISORDER (MDD) MEASURED BY *IN VIVO* PROTON MAGNETIC RESONANCE SPECTROSCOPY (^{1}H MRS)

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1. Abstract and Introduction

Depression is the most common mood disorder and the second cause of disability worldwide with individual and societal costs exceeding $100 billion annually. Although pharmacological and psychological interventions are effective for some patients, over 30% fail to respond to such interventions alone. Alternative approaches that target other mechanisms in depression such as brain plasticity are essential to prevent or arrest the progression of the disease, thwart relapse, and restore function. Transcranial direct current stimulation (tDCS) is a novel, noninvasive, and painless neuromodulation method, involving the application of weak direct currents (1–2 mA) through electrodes on the scalp. A growing number of studies suggest that tDCS over prefrontal cortical regions holds promise for the treatment of unipolar depression and can have long-lasting benefits. However, despite its advantageous characteristics such as safety, low cost, and ease of use, tDCS treatment has not progressed from such proof-of-concept investigations to routine clinical practice. This shortcoming is largely due to the small sample sizes, the scarcity of data on dose-response effects, and substantial variability in methodology across these studies—limitations exacerbated by a lack of knowledge on the precise effects of tDCS on the brain. Specifically, tDCS-induced changes in brain chemistry remain poorly understood. Here, we used proton magnetic resonance spectroscopy (^{1}H MRS) to quantify local concentrations of neurotransmitters in MDD before and after tDCS.

2. Methods

A single-voxel, short echo semi-LASER ^{1}H MRS sequence (TE = 35 ms; [1]) optimized for excellent spatial localization was used to measure MR spectra from voxels very close to the skull from 8 MDD patients (4 undergoing active and 4 sham tDCS over left dorsolateral prefrontal cortex). Measurements were taken prior to and after 20 minutes of active or sham tDCS. Due to possible ambiguity of quantification of Glu vs. Gln in unedited spectra, we modified our TE-averaged semi-LASER sequence to add TE-averaging for robust selective glutamate detection. We note that although a

more direct approach would be a glutamine-selective sequence, this was not feasible because of the relatively low Gln concentration.

3. Results

Using LCModel quantification, we found higher Gln concentrations following stimulation after active ($p = 0.05$, $n = 4$), but not sham treatment ($p = 0.67$, $n = 4$). Glx (Gln + Glu) also appeared to increase following active ($p = 0.09$, $n = 4$), but not sham ($p = 0.44$, $n = 4$) stimulation. Glutamate concentrations were not different between pre and post tDCS (active $p = 0.8$, $n = 4$; sham $p = 0.41$, $n = 4$).

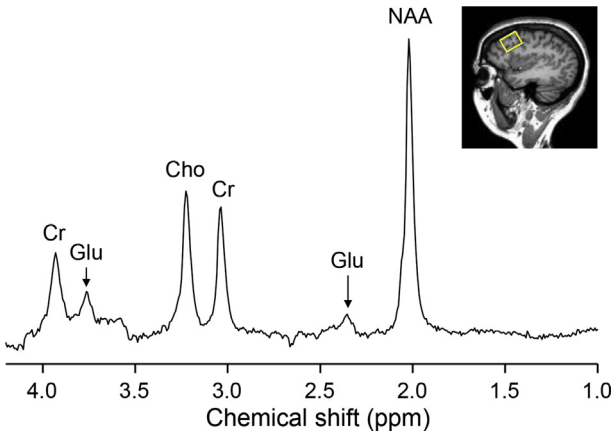

Fig. 1. A representative spectrum acquired from a human dorsolateral prefrontal cortex voxel ($2.5 \times 2.5 \times 2.5$ cm^3,) using the semi-LASER based TE-averaged sequence optimized for reliable glutamate detection (TR = 2000 ms and TE = 35-346ms, 32 steps with 10 ms increment, 256 total acquisitions). Arrows indicate the clear detection of glutamate signals. These results confirm ability to obtain optimal MRS signal without subcutaneous lipid signals contamination that can often introduce significant variability in MRS quantification.

4. Discussion and Conclusion

Our results suggest that tDCS affects brain biochemistry in vivo by increasing glutamine and Glx at the stimulation site. This result indicates elevated glutamate associated with tDCS, as glutamate is rapidly converted to glutamine in the astrocytes, an effect demonstrated previously following ketamine challenge [2].

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PROCEEDINGS #8. TACS BURSTS SLOWS YOUR PERCEPTION: INCREASED RT IN A SPEED OF CHANGE DETECTION TASK

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1. Abstract

Synchronization in the gamma frequency band (30-100Hz) has been observed in a large body of cognitive functions and thus, proposed as a neural mechanism necessary for behavior. Current studies however present correlative evidences, where observed behavior is associated to an increase of gamma oscillations. Here, we propose a stimulation to perturb the ongoing oscillations while subjects conduct a classical cognitive task known to induce gamma oscillatory activity. With this we will test whether the perturbation of the ongoing oscillation by tACS modulate behavior in a causal way.

2. Introduction

Gamma oscillations are associated to a variety of cognitive and executive functions, from sensory processing in early sensory cortices to distributed processes such as working memory, attention and consciousness access [1]. However, these associations have been largely established through correlative analysis, where changes in gamma have been associated to a quantifiable behavioral response in a non-causal manner. Transcranial alternating electrical stimulation (tACS) in this context becomes a promising tool to perturb in a controlled manner the brain while processing information. However, little is known about the precise neural mechanism by which tACS affects the human cortex. Current hypotheses suggest that tACS can either directly entrain brain oscillations and/or induce synaptic plasticity. Entrainment has been reported in studies in-vitro that required invasive interventions, while its presence in non-invasive human studies is still under debate [4,5].
This study aims to bring these two worlds together. Entrainment of brain activity due to tACS can be studied when stimulating at the oscillatory frequency that has is functionally relevant for the network. In parallel, if the neural system is entrained by tACS, perturbation of its ongoing oscillatory frequency shall be altered due to tACS. Here, we present a cognitive task that entrains the visual system at gamma frequency and perturb it with tACS, analyzing its impact on the behavioral response.

3. Methods

Thirty healthy subjects participated in a randomized, sham-controlled crossover study and were required to respond with a keypress to the change of speed of the inward-moving visual stimulus (visual change-detection task) in a reaction time visual task paradigm.

Stimulus and behavioral task

Each trial started with a fixation point (Gaussian of diameter 0.5°). In the designed trial sequence, after 1 to 1.5 seconds (interval randomly chosen from a uniform distribution of 1-1.5 s) the fixation point is replaced by a moving grating (sine wave of 5° located at the fovea contracting towards the fixation point at a spatial frequency of 4 cycles/°, contrast 100%). After 6 to 8 seconds, its velocity increases to 2.2 deg/sec until response is reported or 0.8 seconds have passed (CH onset, see Fig. 1A). Subjects were instructed to report the velocity increase with a right-hand button press on a keyboard, which made the moving grating disappear. Feedback was provided to participants as OK/KO signs that appear after response. A response earlier than 0.2 seconds after CH onset was considered KO. Stimulus was displayed on an LCD screen located at 60cm of the subject, with a vertical refresh rate of 60Hz. A total of 240 trials were recorded organized in 4 blocks of 60 trials each, where subjects could rest. Participants signed an informed consent form and were informed about the content and risks associated to the experiments before start. The experimental campaign was conducted at Hospital Clinic and approved by their ethics research committee before start.

Stimulation protocol

tACS (*Starstim*, Neuroelectrics) was applied in 5-second bursts of either alpha (10Hz), gamma (70Hz) frequencies or sham using a multi-electrode optimized montage (*Stimweaver*, Ruffini et al., 2014) with 1.2mA intensity and no DC offset (normal electric field distribution shown in Fig. 1 B). Bursts were delivered to the occipital cortex at the onset of visual stimulation (see Fig. 1A), with the objective of interfering with the specific dominant gamma frequency [3].