Nova Southeastern University
Institutional Review Board for Research with Human Subjects (IRB)
New Protocol Submission

Center Rep:	**To be completed by IRB Office**
Date Sent to IRB:	**Protocol Number:**

Instructions: In order to comply with federal regulations and with the university's IRB guidelines, the Principal Investigator (PI) is required to complete all of the following items. After completing, submit this document and all consent forms and research instruments (questionnaires, interviews, etc.) to the appropriate IRB College/Center Representative. You can find your college/center representatives using the following link: http://www.nova.edu/irb/membership.html.

- If your study qualifies for center level exemption from further review, the Center Representative will exempt your study, provide you with a memo to that regard, and give you copies of the stamped, approved consent/assent form(s), if applicable. The Center Representative will log your study into the IRB database and forward a copy of the complete submission to the IRB office.
- If your study appears to qualify for expedited review, then once the Center Representative believes the submission is complete, the Center Representative will log your study into the IRB database and forward **ONE** complete submission packet to the IRB office for review.
- If full review is required, the Center Representative will log the study into the IRB database and will provide the PI with instructions for submitting 2 stapled or rubber banded copies (AND 1 unstapled original) of the submission and all supporting materials (research protocol, consent/assent forms, letters of authorization, etc.) to IRB. Please note: ONLY ONE copy of all research instruments (tests instruments, interview protocols, etc.) needs to be submitted. The completed package must be received by the IRB by the last business day of the month prior to the next scheduled IRB meeting. Because mail, including express delivery, takes at least a day to be delivered within the university, please make allowance for this in your planning. Incomplete submissions will delay review by the IRB. The IRB reserves the right to postpone review of protocols at convened meetings due to needed revisions.

Use a word processor to complete this form. You do not need to be concerned about where page breaks fall. You are to complete all **BLUE** sections. Be sure that all pages, including any appendices or attachments, except for consent/assent forms and advertisements, are numbered sequentially. For further information, refer to http://www.nova.edu/irb/manual/policies.html and http://www.nova.edu/irb/process.html

Do **not** approach subjects about being in the research study until you have received NSU IRB approval.

Form Version: August 1, 2013

1. General Information

1.A. Research Project Title:

Cognitive Training with and without tDCS to Improve Cognition in HIV

1.B. Insert Principal Investigator's (PI) Last Name and Date of Submission in the footer.

1.C. Brief Overview (Max 250 Words):

The purpose of the proposed study is to develop pilot data on the potential efficacy of computer-based cognitive training or the combination of computer-based cognitive training with transcranial direct current stimulation (tDCS) in improving cognitive function in persons with HIV-related mild neurocognitive disorder (MND). tDCS is a noninvasive brain stimulation technique in which a small direct current (1-2 mA) is applied to the scalp during a cognitive or motor activity, inducing a very small current that affects specific neural circuits related to the site at which

electrodes are placed. tDCS has been judged safe and has shown significant treatment effects in studies with other populations, but has not been extensively studied in individuals with HIV infection. tDCS has been shown to facilitate learning in a number of studies, suggesting that it may improve or enhance learning in those with cognitive problems. As HIV infection is associated with decrements in a number of cognitive skills, including working memory, executive functions, and psychomotor speed that are related to individuals' functional status and medication adherence, the demonstration of a technique to enhance the effects of cognitive training in this population would have substantial clinical benefits as well as scientific value.

1.D. Principal Investigator (PI) Information			
Name	Raymond L Ownby, MD, PhD, MBA	Relationship to NSU	
Mailing Address (for Students)			
Interoffice Mail Code (for Faculty/Staff)	COM	Student	
Daytime Phone	2-1804	Faculty	X
Alternate Phone	Cell: 954-608-4846	Staff	
NSU Email Address	Ro71@nova.edu	NSU Center/College/Dept	
Alternate Email Address	R_ownby@bellsouth.net	COM	
Degree/Academic Information	MD, PhD, MBA	PI CITI Completion Date*	
		8/19/13	

Please briefly describe your applicable professional, educational, employment, professional licensure, and research experience. Do NOT attach your vitae.

Dr. Ownby is Professor and Chair of Psychiatry and Behavioral Medicine in the College of Medicine at NSU. He is board certified in adult psychiatry with subspecialty certifications in psychosomatic medicine and behavioral neurology/neuropsychiatry. In addition, Dr. Ownby trained as a clinical neuropsychologist and is board certified in this psychological specialty. He holds licenses for independent practice of both medicine/psychiatry and psychology. Dr. Ownby has extensive experience in research and clinical practice in the neurocognitive aspects of HIV/AIDS, including previous NIH support for a research study in the area as well as a number of related research publications based on this and other research projects.

Specifically with respect to the use of tDCS for this research study, in preparation Dr. Ownby has completed two workshops, both two days in length, on the use of tDCS in neuropsychiatric disorders. The first completed at Harvard Center for Non-invasive Brain Stimulation at Beth Israel Deaconess Hospital in March 2014, included didactic instruction and supervised practice in safety issues related to tDCS as well as electrode placement, treatment protocols, and electrical stimulation devices. This workshop included supervised use of the FDA-approved Chattanooga Ionto electrophoresis device that will be used in this study. A second workshop completed in September 2014 at the University of Florida similarly included didactic instruction combined with supervised practice in safety issues, electrode placement, and treatment protocols (certificate of completion included with this submission).

1.E. Co-Investigators (Co-I) Information (including faculty advisers)			
	Co-Investigator 1	Co-Investigator 2	Co-Investigator 3
Name			
Mailing Address			
Contact Phone Number			
Email Address			
Degree/Academic Information:			

CITI Completion Date*			
Please briefly describe applicable professional, educational, employment, professional licensure, and/or research experience for all co-investigators. Do NOT attach vitae.			

1.F. Research Assistant Information (if applicable)			
	Research Assistant 1	Research Assistant 2	Research Assistant 3
Name	Rosemary Davenport, RN, ARNP		
Mailing Address			
Phone Number	2-1804		
Email Address	Rd667@nova.edu		
CITI Completion Date*	8/31/2012		

*NOTE: CITI must have been completed within the last 3 years. If a member of the research team is affiliated with another institution, please include a copy of that individual's training certification.

1.G. Funding Information			
Funding status	Unfunded	Funding Applied For	Funded
			X

If you indicated "Funded" or "Funding Applied For," complete the following.				
Source of Funding	Principal Investigator's Research Incentive account			
Project Title (if different from above)	N/A			
Principal Investigator (if different from above)	N/A			
Type of Application	Grant	Subcontract	Contract	Fellowship
Award Amount:	Funds sufficient to provide participant compensation as described below are available.			

1.H. Management of Conflict of Interest

Read the financial conflict of interest policy at http://www.nova.edu/irb/manual/forms/significant-financial-interest.pdf

I certify that I, as PI, have read this policy, and have verified that my co-investigators and research assistants also have read this policy. PI Initials

For studies that are funded by a governmental agency (any federal, state or local governmental entity that has promulgated regulations or policies requiring investigator financial disclosure or requiring institutional conflict of interest policies relating to award of grants or contracts) read the Office of Sponsored Program's Financial Conflicts of Interest in Sponsored Programs policy.

I certify that I, as PI, have read these guidelines, and have verified that my co-investigators and research assistants also have read these guidelines.

PI Initials

Do any investigators have a significant financial interest, as defined in the above referenced policy, in relation to this study? Yes ☐ No ☐

If yes, please describe the nature of the conflict of interest below

If you answered yes, please be sure to include the following statement, or a similar statement, within the description section of the consent forms: "The principal investigator and/or co-investigator(s) of this research study have a significant financial interest as it relates to this study." Continue, describing the conflict in the consent/assent documents.

1.I. Dates and Phases of Study

Proposed Start Date			
Shortly after IRB approval	☐	Other (list date)	

Proposed Duration of Research (including analysis of the results)	
One year or less X	Other (describe, please note minimum annual continuing review required)

Is this a multi-part study?

Yes	No
	X

If "Yes," please note that procedures used in later phases may affect the review status of this study. Briefly describe the later stages.

1.J. Multiple Site Information

Will the study be conducted at an NSU location?

Yes	No
X	

If "Yes," provide the location within NSU, e.g. department or clinic.

The study will be completed in Dr. Ownby's research offices located in Suite 3542 of University Park Plaza.

Will the study involve any NSU faculty, staff or students as subjects?

Yes	No
	X

Will the study be conducted at a non-NSU location?

Yes	No
	X

Will any of the activities be done online or via telephone (e.g., completion of surveys, delivery of instructional content)?

Initial participant contact and screening may be completed by telephone.

Yes	No
X	

If "Yes", for the Internet based activities, will these be done via a secure site?

No Internet activities.

Yes	No

If "Yes," please complete the following for the non-NSU sites.
Include these sites on the consent form in the "site information" section.

	Site 1	Site 2	Site 3
Site Name			
Address			
Phone Number			

You will need documentation of permission to conduct the research at non-NSU sites. Attach the permission letter(s) or IRB approvals to this document.

1.K. Cooperative Research

Cooperative research projects are those that involve more than one institution or when an investigator is employed at or is an agent of an institution other than NSU, (For more information, see **http://www.hhs.gov/ohrp/humansubjects/guidance/engage08.html**). Each participating institution is responsible for safeguarding the rights and welfare of human subjects and for complying with all regulations.

Does this research involve cooperative research?	Yes	No
		X

Has this proposal been submitted or will the proposal be submitted to another Institutional Review Board (or authorizing individual, entity, or ethics review board) for review?	Yes	No
		X

If "Yes," please complete for each site. Please attach documentation of approval. (Copy the section of the table and add if there are multiple sites.)

Name of Institution	N/A

IRB/Administrative Decision (check applicable)

Approved	Submitted (not yet approved)	Not yet submitted	NSU IRB approval required prior to submission

Date of Review	Contact Person / Phone Number	Level of Review (if IRB Reviewed)		
		Exempt	Expedited	Full

2. Subject/Participant Information

2.A. Overview of Proposed Subjects/Participants

(complete **all** that apply and provide maximum number proposed within each category):

Subject Group	Fetus in Utero/ non-viable fetuses/ abortuses	Newborns or Infants	Children (aged 2-6)	Children (age 7-12)	Adolescents (aged 13-17)	Adults (18+)	Pregnant Women	Adults with Guardians
Mark X for each proposed subject type						X		
# of Proposed Subjects*						32		

Please briefly describe your potential subjects:

Participants will be HIV-infected individuals 18 years of age and older with HIV-associated Mild Neurocognitive Disorder (MND) as determined by their scores on neuropsychological tests and self-report of cognitive problems. Standard diagnostic criteria known as Frascati criteria have been developed and will be followed (Antinori et al., 2007) in selecting participants. These criteria require that the patient have memory complaints and below average performance on several neuropsychological measures. The degree of cognitive impairment this represents is not sufficient to impair potential participants' ability to understand procedures, potential risks and benefits, and to provide informed consent.

*By proposed subjects, the IRB means subjects who will consent to be in the study and begin the study activities.

2.B. Subject Vulnerability

Do any subjects have limited decision-making autonomy, have communication problems that would limit ability to dissent to study procedures, belong to a group that is vulnerable to coercion, or belong to a group defined by regulation as requiring greater care?	Yes	No
		X

If you indicated "Yes", please mark with an X next to each applicable category in the

column to the right and complete the remainder of this section	
Prisoners	
Pregnant Women	
Cognitive impairment or emotional problems that potentially limit decision making	
Communication impairments that may preclude communicating a decision to discontinue participation or refuse participation	
Students of the investigator or investigator's department	
Employees of the investigator or investigator's department	
Children (minors)	
Terminally ill	

Other (specify):

If you indicated any of the above, please justify your rationale for including these subjects.

If you are using potentially vulnerable subjects as described above (infants, children, pregnant women/fetuses, terminally ill, decision-impaired, communication-impaired, students/employees, or prisoners), does the research create greater than minimal risk? Yes ☐ No ☐

If your subjects have a vulnerability that arises from their being students in your class or department, you will be asked for more information in Section 3.G. If the subjects have one of the other vulnerabilities, please describe proposed safeguards to protect vulnerable subjects.

If not evident from the researcher qualification information in 1.D. or 1.E., please describe the researcher(s) qualifications for working with vulnerable subjects

2.C. Study Design and Methodology

Part 1 – Purpose

Please briefly describe the **purpose** of your study. Note: Examples of study purposes are "to determine if a new reading intervention program improves 4th graders' reading scores" or "to survey patients on their perception of physical therapy services".

The primary purpose of this study is to develop pilot data that will be used to demonstrate the feasibility of a larger study for which we will plan to seek external funding. We will compare the performance of study participants' on several neuropsychological measures as well as their rate of learning on a computer-delivered working memory task in groups randomly assigned to receive either sham or true tDCS.

Part 2 – Goals and Justification

Briefly elaborate on the main **goals and justification** for the study. Summarize the background, rationale, nature, and significance of the proposed research. Include a brief overview of your prior research in the area, or literature that supports the need for this study. This section should be a brief overview, and typically is not more than a few paragraphs in length. You will be asked about procedures and instruments later in the submission.

Survival Has Improved but Cognitive Deficits Persist in Those with HIV. Although advances in antiretroviral treatment have resulted in significant improvements in the longevity of patients with HIV infection, studies show that cognitive problems continue to develop in these individuals, even with successful suppression of viral replication (Heaton et al., 2010; Heaton et al., 2011). Characteristics of the cognitive problems associated with HIV infection include deficits in psychomotor speed, working memory, learning, and executive function.

Cognitive Training May Improve Cognitive Deficits. Studies with normal elders and those with memory impairments show that cognitive skills such as attention, perceptual speed, working memory, and executive functions can be improved with training (Ball, Edwards, & Ross, 2007; Loewenstein, Acevedo, Czaja, & Duara, 2004), that training effects persist (Willis et al., 2006), and that training can generalize to related but different tasks (transfer) such as activities of daily living or other complex behaviors (Ball et al., 2007). Similar studies in laboratories and with neurologically impaired patients also show training and transfer effects (Cicerone, Levin, Malec, Stuss, & Whyte, 2006; Jaeggi, Buschkuehl, Jonides, & Shah, 2011). A small study and case reports suggest that cognitive training has positive effects on cognition and instrumental activities of daily living in persons treated for HIV infection (Rourke, 2011; Vance, 2010; Ackerman, Vance, Fazeli, & Ross, 2010).

Transcranial Direct Current Stimulation (tDCS) May Improve Cognition in Impaired Individuals. Studies have shown that the individuals performing some cognitive tasks may learn more rapidly and perform at higher levels of proficiency after exposure to tDCS during the task. Coffman et al.(Clark et al., 2012; Coffman et al., 2012), for example, in a study financed by the US Department of Defense, showed that individuals given tDCS significantly improved in threat detection in a computer-based combat simulation task. Fregni et al. (Fregni et al., 2005) showed that normal young individuals showed improvements in working memory after even brief exposure to tDCS. Boggio et al. (Boggio et al., 2006) showed that patients with Parkinson's disease also showed improvements in working memory performance after brief exposure to tDCS; this finding is important in relation to HIV since the cognitive deficits that occur in HIV infection are often linked to the same fronto-striatal circuitry affected in Parkinson's. No readily available trial has examined the effects of tDCS on working memory in persons with HIV infection, although Vance et al has argued that it may be an effective treatment and other authors have noted that depressed patients treated with tDCS may show improvements in cognition as well as mood (Loo & Martin, 2012). Further, Martin & Loo have shown in healthy participants that the use of tDCS during cognitive training (but not before) enhanced learning (Martin et al., 2013), and a similar effect of tDCS on working memory performance is also reported by Ohn et al. (Ohn et al., 2008). Cognitive training with tDCS is thus a promising treatment in those with HIV-related cognitive problems.

Given the Very Tiny Current, How Does tDCS Work? A reasonable question about tDCS is why such a tiny current delivered to the outside of the head can have an influence on neural activity. The current used in tDCS studies is 1-2 mA; by contrast, the current used in electroconvulsive therapy, an approved treatment for depression, is much larger (800 – 900 mA). Both computer modeling (Bikson,

Rahman, & Datta, 2012) and animal studies (Bikson et al., 2004; Rahman et al., 2013) have shown that the effects of tDCS may result from subtle changes in neuronal membrane polarization that can affect cells' probability of firing. This effect can be modified pharmacologically (Nitsche et al., 2003), with dopamine agonists such as L-dopa increasing the effect (Kuo, Paulus, & Nitsche, 2008) while dopamine antagonists (sulpiride) reduce it. The effects of tDCS on motor learning may be mediated by its impact on brain-derived neurotrophic growth factor (Fritsch et al., 2010).

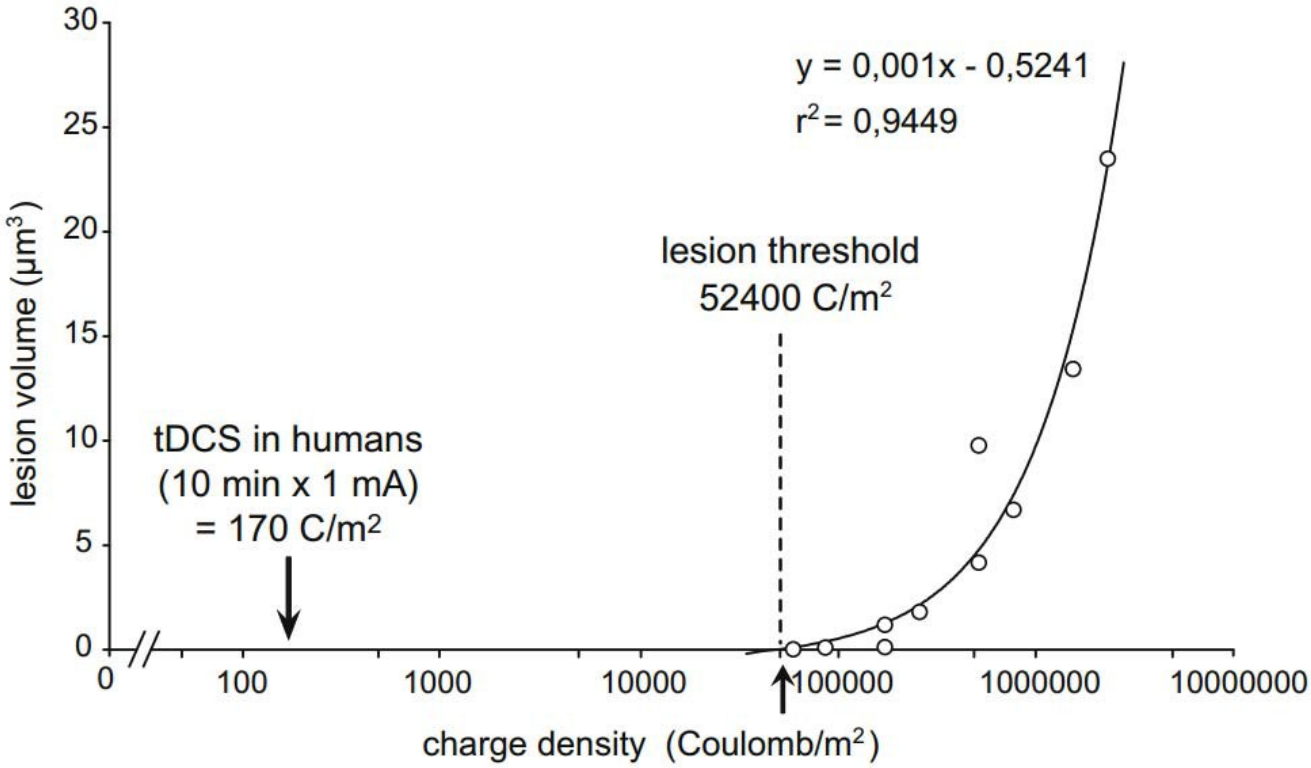
Safety of tDCS. tDCS is generally considered safe, based on data from multiple studies (Bikson, Datta, & Elwassif, 2009). A recent systematic review completed by the FDA of the safety of iontophoresis devices found 25 studies using iontophoresis devices for a variety of indications (available for download on the FDA website). The FDA staff review concluded that while incidence of adverse events varied widely among studies, "most adverse events were mild and did not require treatment. These studies support the safety of iontophoresis devices for these indications." [pg. 37]. Another review of adverse events during multiple studies of tDCS with 102 patients and 567 tDCS sessions (Poreisz, Boros, Antal, & Paulus, 2007) showed that the most common effects of tDCS were "tingling," "itching sensation," "burning sensation," "pain," "headache," and "fatigue." The frequency of these effects varied widely across studies reviewed but no serious events, such as burns, were reported.

A recent study of tDCS for depression (Brunoni et al., 2013) that used the same device to be used in the proposed study (Chattanooga Ionto), reports safety data for 103 patients. In this study, only the adverse effect of skin redness was more common in the active treatment group than in the sham tDCS group. No change in cognitive function was seen across groups, but several patients developed hypomania and 2 manic episodes occurred (there were similar occurrences of hypomania or mania across treatment groups of sertraline, tDCS, or their combination).

Animal data also indicate that tDCS is likely to be safe at the doses currently used in studies of cognition and mood. Liebetanz et al. (2009) systematically studied the effects of varying doses of tDCS on brain lesions in rodents. Data show that the dose of tDCS that resulted in lesions was two orders of magnitude greater than that used in most human tDCS studies (see figure, below).

Finally, the current for tDCS to be used in the proposed study can be compared to that used in electroconvulsive therapy (ECT), a widely-accepted noninvasive electrical treatment for depression. The current used by FDA-approved ECT devices is typically 800 to 900 mA, again much larger than the 1.5 mA current to be used in the proposed study.

These studies as well as those showing the relation of pharmacologic interventions inform the inclusion and exclusion criteria for the proposed study. The procedures to be followed in this study conform to the safety guidelines discussed by Bikson et al., 2009.



Evaluation of tDCS dosage vs. histologically-confirmed brain lesions in rats showing relation of dose causing lesion to tDCS dosing in humans.
From: Liebetanz, D et al. (2009). Clin Neurophysiol 120 (1161-1167).

Part 3 – Steps in the Research Study

In the box below, please outline in detail the **steps in the research study** in order as they will occur after consent has been secured. If there are different requirements for different groups/types of subjects within the study, please separate out the steps per group. Indicate how long the subject spends completing the different steps/procedures. Be specific about the tests given and/or treatments used, when they will occur, and their frequency.

1) Potentially eligible participants will be identified based on their cognitive testing results and self-report of memory problems during our previous study ("Improving Health Literacy about HIV Infection: Phase I & II;" NSU IRB Protocol No. 06120904Exp). Participants will be contacted by telephone to determine their interest in the study (participants provided permission to recontact about future studies at the time of their participation in the earlier study).

2) During the telephone contact, participants will be informed of the nature of the study, the need for a screening visit to determine eligibility, the study's length, the possibility of being randomly assigned to receive mild electrical stimulation to the head, the use of computer-based

cognitive training, and the extent of compensation. The interviewer will request verbal consent to ask the participant about possible cognitive problems, and the potential participant's response will be recorded.

Those who indicate a willingness to respond on this issue will then be screened for the presence subjective cognitive impairment using three questions evaluating possible difficulties with memory, cognitive speed, and attention as recommended by the European AIDS Clinical Society (listed in telephone screening script in Appendix). If potential participants respond negatively to all three questions, they will not be eligible for the study as self-report of cognitive difficulties is a key part of the diagnostic criteria for HIV-related Mild Neurocognitive Disorder (MND) (Antinori et al., 2007). They will be thanked for their time, asked if they have any questions, and the phone call will be ended.

Persons who answer yes to any of the three questions and continue to indicate an interest in participating will be informed that that may be eligible for the study, and verbal consent to ask additional questions about medical history and medication use will be requested (see telephone screening script). If the person meets preliminary evaluation of inclusion and exclusion criteria, they will then be informed that they may be eligible for the study but that a final determination will require additional screening during an in-person visit with cognitive tests. If the potential participant continues to indicate an interest in participating, he or she will be scheduled for the **eligibility visit.**

3) At the eligibility visit, potential participants will be reminded of the study characteristics as noted above and the need for them to meet study entry criteria on cognitive and symptom measures will again be stated (see eligibility visit flow sheet in Appendix). Verbal consent for screening procedures will be requested; participants' response will be recorded (see eligibility visit flow sheet in the appendix).

Participants who continue to meet all study criteria with respect to medical history and medication use (see flow sheet) will complete four brief neuropsychological measures (Hopkins Verbal Learning Test; Trail Making Test Parts A and B; Wechsler Adult Intelligence Scale Digit Span subtest; Grooved Pegboard; all listed below) as well as complete the Center for Epidemiological Studies Depression and the Patient's Own Assessment of Functioning Scale. These will take approximately 45 minutes to complete. After completing these measures, they will be provided with a break (approximately 5-10 minutes) while the researcher scores the measures and determines the potential participant's eligibility given the evidence of both subjective cognitive complaints and objectively below average (at least 1 standard deviation below normative performance) on at least two of the measures. If participants are not eligible based on their cognitive performance, they will be thanked for their attendance, asked if they have any questions, and provided compensation.

Participants who show evidence of below average cognitive performance in two areas assessed will be informed that they are eligible to participate in the study. Their continued interest in participation will again be elicited, and if they continue to state they would like to participate, the investigator will review the written informed consent form with the potential participant, answer questions about the study, and provide the potential participant with sufficient time to review the written informed consent form. The investigator will then ask the participant to briefly recount the purpose of the study as well as its risks and benefits using a previously validated procedure

(Palmer et al., 2005). If participants cannot provide adequate answers to these questions, the person obtaining informed consent will review the material until they achieve a satisfactory performance defined as a score of 4 out of a possible 6 on the three questions (see visit flow sheet for questions and scoring criteria).

We will encourage the potential participants to view the computer training room, observe the training tasks, and we will plan to show them the tDCS device, electrodes, and headband. If the potential participant continues to indicate an interest in the study, at this point he or she will be asked to sign the informed consent form. After the form is signed, the participant will be asked to complete the computer-administered measures (questions about mental functioning and mood as well as the CES-D depression scale and the Patient's Own Assessment of Functioning). The participant will then be scheduled for the first study visit, provided compensation and allowed to return home.

4) At the first study visit, participants will be randomly assigned to one of two treatment conditions, computer-based working memory training with true tDCS or sham tDCS. (Randomization will be accomplished using randomized permuted blocks of four). All participants will be fitted with saline-soaked 25 cm^2 sponge electrodes placed at F3 (in the International 10-20 EEG electrode system; this is about half of the distance of a line drawn between the eye and ear, and somewhat above this midpoint) and above the right orbit. This electrode placement is believed to allow for stimulation of the left dorsolateral prefrontal cortex known to be a key structure in verbal working memory, and has been used in previous studies of tDCS for cognitive enhancement. Computer software allows for a simulation of likely current flow using this electrode array (see color picture in Appendix); a black and white picture illustrates electrode placement (also in Appendix).

Participants receiving **active tDCS** will then receive 1.5 mA tDCS delivered by the Chattanooga Ionto electrophoresis device for 20 minutes while completing working memory training with the Brain Workshop software (example computer screens are included in the Appendix). The device provides an initial 30 s ramp-up of current so as to minimize discomfort and is designed to deliver a constant current even in the face of possible fluctuations in impedance due to changes in electrode or skin characteristics (e.g., increased resistance as the electrode dries). It includes circuitry that continuously monitors impedance so that if it changes beyond safety parameters the device immediately shut off with an audio alarm. This provision reduces risk of participant discomfort or other negative effects. The device also is controlled with a timer that guarantees a specific dose tDCS; it automatically ramps down the current and shuts off at the end of the session (20 minutes).

Participants receiving **sham tDCS** will be treated in the same fashion (fitted with the electrodes and headband) but current will be provided only for the 30 sec ramp up period and five seconds after that, when the current will ramp down. This provides no tDCS-related effect but provides the participant with a stimulus that is discernible by most persons. Since many persons only perceive the current at the beginning of a stimulation session (even when it continues for 20 minutes) this is believed to be an adequate control and is a strategy has been used in multiple other studies.

As the device does not provide for double-blinding in the delivery of tDCS (i.e., the operator must program it and will know if the person receives active or sham stimulation), Dr. Ownby will plan

to sit to one side and behind the participant in order to monitor the participant, encourage his work on the cognitive training task, provide tutoring on the task and interacting with the computer as needed. The study is thus single blind, and we will assess the success of blinding by asking participants which group they were in as part of the final study visit.

Cognitive Training. During the study visit, both groups will be asked to work with the n-back training program Brain Workshop. The phrase "n-back" refers to the task's requirement to monitor a series of discrete events (either blue blocks flashing on the screen in one of 9 positions or a series of letter heard over audio) and remember one that occurred a specific number prior to the current one. The number of prior events monitored is the "n." The participant is asked to press a letter on a keyboard when the current stimulus matches one delivered "n" times previously. For example, for a 2-back task using the letter series "a – d – g – d," the participant would respond with a key press when hearing the second letter "d" as it matches a letter presented two instances before the current one.

As this task can be challenging for those with cognitive impairments and we have previous experience in using it with older persons, the task's difficulty is tailored to individuals' abilities and can be increased as the participant shows greater levels of performance over time. Participants' performance is tracked automatically by the software and will be recorded only with the participant's research number.

At the conclusion of this visit and all subsequent visits, participants will provide brief ratings of their cognitive function, mood, and level of discomfort (see Appendix for questions).

Randomization: Participants will be randomized to treatment condition in permuted blocks of four, with a plan to recruit six blocks of four (total participants 24) based on power analyses that suggest a sample size of 12 in each group provides a power of 0.80 to detect between group differences. As we wish to obtain a final sample size of 12 in each group, however, depending on drop outs or persons otherwise lost to follow-up, we will plan to recruit two additional blocks of 4 up to a total number of 32 participants. The planned enrollment table in section 2A of this protocol thus indicates a possible total enrollment of 32.

5) Subsequent study visits. Participants will complete a total of six 20-minute training sessions with sham or true tDCS and working memory training. Participants will be asked to complete three sessions per week, and must complete all training sessions within three weeks.

6) Final study visit. At the final study visit, participants will complete the same brief neuropsychological battery done at the screening visit, the depression rating scale (CES-D), the Patient's Own Assessment of Functioning Scale, and be asked to state whether they were in the active or sham experimental groups. Final open-ended questions will elicit participants' experience with the study and whether they found it useful (see final visit flow sheet in Appendix).

Part 4 – Sources of Data Information

Are you using questionnaires, tests, instruments, or forms?

Yes	No
X	

If "Yes", list them below and include a copy of each as appendices.

Telephone screening script
Eligibility visit flow sheet with script and data recording sheet
Trail Making Test
Hopkins Verbal Learning Test
Grooved Pegboard
Wechsler Adult Intelligence Scale Digit Span recording sheet
Center for Epidemiological Studies – Depression scale (CES-D)
Patient's Own Assessment of Functioning (POAF)
Participant study visit log (documents date and time of visit)
Final visit flow sheet

Do you plan to use any data from records or archives?

Yes	No
X	

If "Yes", please describe (such as data originally created for non-research purposes or data created as a result of a previous study).

HIV RNA viral load and CD4 count from patient's personal records; potential eligibility for participants from a previous study will be evaluated using self-report of cognitive difficulties and performance on cognitive measures ("Improving Health Literacy about HIV Infection: Phase I & II;" NSU IRB Protocol No. 06120904Exp).

Do you plan to use any de-identified data?

Yes	No
	X

If "Yes", please describe the data and how it will be de-identified.

N/A

3. Additional Study Information

3.A. Clinical Testing

Food and Drug Administration
Investigational Drugs and Devices

	Yes	No
Does the study involve the use of an investigational drug?		X
If "Yes", has an Investigational New Drug application been submitted for the drug?		X
Does the study involve the use of an investigational device?		X
If "Yes", has an Investigational Device Exemption (IDE) been, or will be, secured prior to the start of		

	Yes	No
the study?		X
Does the study use any device (either as a part of the experiment or to collect data) that has not received FDA approved for clinical/medical use or is being used in a manner not consistent with its cleared/marketing status?	X	

If "Yes", please describe the device and how its use differs from its approved status by the FDA.

The Chattanooga Ionto electrophoresis device is approved for the delivery of direct current for the purpose of enhancing the delivery of drugs transdermally. In this study, the device's ability to deliver a small direct current while having continuous monitoring of impedance and safety will be capitalized upon for the purpose of delivering a small current transcranially that may enhance participants' cognitive function.

Clinical Procedures

	Yes	No
Does the study involve the use of any procedure that is not used in routine clinical practice?		X

If "Yes", please list the procedures.

3.B. Sensitive Information

	Yes	No
Are you asking questions about sensitive issues, such as illegal activity, sexual history, or anything else that, if made public, could jeopardize a person's reputation, employability, safety, or quality of life?		X

If "Yes", please describe the information.

	Yes	No
Does the study involve the collection of data from voice, video, digital, or image recordings made for research purposes?		X

If "Yes", please describe the procedures associated with these recordings.

3.C. Non-English Speaking Participants

	Yes	No
Will the study involve non-English speaking participants?		X
Will the study require translation of consent forms?		X

If you answered "Yes," please specify the language(s) that the consent forms will be translated in to:

If you are including non-English speaking participants, when you complete section III.H., please discuss how you will ensure that the participants understand the study, including the use of a qualified translator to provide oral consent information.

3.D. Subject Compensation

Will your subjects receive any payments, incentives, or gifts?

Yes	No
X	

If "Yes," please indicate the types of compensation. Otherwise move on to section E.

Monetary Payment	Gift	Extra credit (Students) or Workplace Incentive (Employees)
X		

Other incentive

Please describe:

Participants will receive compensation for each study visit. For the first (eligibility visit) they will be provided with $40, while for each of the briefer study visits they will be provided with $20 cash. They will be compensated $40 for the final study visit. The differences in compensation are based on the length of the visits; the first and last visits will require about twice as much time as the study training visits.

Describe the payment(s)/gift(s)/incentive(s), and if it is a gift, estimate its monetary value. Indicate whether all participants are given the payment/gift/incentive, or if only some are eligible. (Note: the value of the payment/gift/incentive should not be so significant that it might compromise the subject's good judgment.)

All participants who complete study procedures will be compensated for their time. In addition to the time spent in study activities, many of our participants in previous studies have taken time from their schedules or used public transportation to participate.

Describe when the subject will receive the payment/gift/incentive, and whether the amount differs depending upon whether different portions of the study are completed or is limited if the subject discontinues participation during the study.

Participants will be compensated on a pro-rated basis determined by the amount of time estimated for each study visit and the planned payment. If a person were to decide to discontinue participation after completing one half of the first or final study visit, for example, they would be compensated at the rate of ½ of $40, or $20. If they should discontinue other study visits they would be compensated in a similar fashion.

3.E. Inclusion / Exclusion Criteria for Subjects

Describe the inclusion and exclusion criteria for the proposed subjects. Please list the criteria in bullet or outline format rather than narrative. If the study limits participation based on gender, age or race, please justify the exclusion criteria. (Subject protection and appropriate study design may require specific inclusion or exclusion criteria, but the IRB does not permit subject selection that is not equitable or prevents a subpopulation from benefiting from the scientific discoveries of the study.)

Inclusion Criteria

1) Age 18 years or older
2) Diagnosed with HIV infection and on antiretroviral therapy for at least one month
3) Able to meaningfully participate in the informed consent process as determined by clinical observation and responses to questions about the study
4) Right handed
5) Self-report of cognitive difficulties in at least one of the areas of memory, mental slowing, or attention
6) Score one standard deviation or lower on two of four neuropsychological measures (NB: criteria 5 and 6 establish a diagnosis of Mild Neurocognitive Disorder (MND) in combination with exclusion criteria below).
7) Willingness to participate in multiple study visits
8) Able to provide recent laboratory measures of HIV-RNA (viral load) and CD4 cell counts.

Exclusion Criteria

1) Cognitive or psychiatric difficulties so severe as to make the person unable to meaningfully participate in the informed consent process as judged during telephone screening and clinical interview;
2) Unclosed skull defect
3) Metal plate in the skull
4) Any other metal in the head (e.g., bullet or shrapnel)
5) History of or current treatment for any seizures
6) History of adverse reaction to tDCS
7) Sensitive scalp by self-report, or use of products such as shampoo for sensitive scalp
8) Recent history (with the past 12 months) of brain injury with loss of consciousness or that resulted in any seizure
9)) Recent history (with the past 12 months) of neurosurgery involving the brain
10) Current use of medications that affect dopamine or serotonin reuptake (most commonly, antidepressants), dopamine release (e.g., medications for attention deficit/hyperactivity disorder), dopamine receptor activity (e.g., antipsychotics, also used as augmenting agents in the treatment of depression and as mood stabilizers in bipolar disorder) or GABA function (e.g., benzodiazepines, but use of short-acting non-benzodiazepine sleep medications such as zolpidem [e.g., Ambien] will be allowed).
11) Current treatment with any anticonvulsants (carbamazepine (Tegretol), oxcarbazepine (Trileptal) lamotrigine (Lamictal), divalproex (Depakote), topiramate (Topamax), levtiracetam (Keppra)) or with lithium (lithium or Eskalith).
12) Current use of bupropion (Wellbutrin SR or XL; Zyban).
13) History of bipolar disorder or history of mania or hypomania of any type.
14) Has a pacemaker.

3.F. Subject Recruitment

How will you recruit subjects (approach/invite/or ask people to be in your study)?

In our previous study ("Improving Health Literacy about HIV Infection: Phase I & II;" NSU IRB Protocol No. 06120904Exp), participants provided consent to being recontacted about future studies. In this study as well, participants completed a self-report of a questionnaire about HIV-related problems (including memory and thinking) and a battery of neuropsychological measures. Their reports on the questionnaire and their performance on the neuropsychological measures will allow us to assess whether they meet Frascati criteria for minor neurocognitive disorder (MND) related to HIV infection. Persons meeting these criteria will be contacted about possible participation. Preliminary review of data from the previous study show that approximately 50 persons from this study will be eligible for the new study. We anticipate that many of these persons will be interested in participating, but that we may not be able to contact all of these persons and all may not be study criteria. Based on our previous work, we anticipate that a number of persons will learn of the study by word of mouth and contact us about it. We think it is likely that we will be able to complete needed recruitment in this manner.

Recruitment Advertisements, Fliers, and Letters

	Yes	No
Are you using any letters, fliers, or advertisements?		X

If you answered yes, please list the type(s) below and attach a copy of the proposed materials as an appendix (do not copy and paste the flyer into this form).
(Note: Materials should list "Nova Southeastern University".)

3.G. Potential for Coercion in Subject Recruitment

	Yes	No
Are any of the subjects a student or advisee of the PI or a Co-I?		X
Does the PI or a Co-I serve in any capacity (e.g., administrative, therapeutic) that might affect a subject's willingness to participate?		X

If "Yes" to either of the above, then describe the relationship of the subjects and investigator.

If you answered yes, please read the NSU policy about use of students in research.
http://www.nova.edu/irb/manual/forms/research_students_subjects.pdf

	Yes	No
Are any of the subjects employees of, or report to, the PI or a Co-I?		X
Are any of the subjects a patient of the PI or a Co-I?		

	Yes	No
		X
Are any of the subjects a patient within a PI or a Co-I's clinical practice?		X
Are any of the subjects informed about the study by their doctor / clinician?		X

If you answered "yes" to any of the questions in this section (3.G.), please describe how you will ensure that the subjects will feel free to decline participation without fear of reprisal. If the subjects are patients, how will you prevent "therapeutic misconception" (the mistaken belief that when a care provider provides information about a study, it means that the provider thinks that study participation will benefit the patient).

N/A

If you are providing any incentive to the student/employee subjects, discuss whether there is a mechanism for students / employees to receive the incentive by doing something other than participating in the research project (see http://www.nova.edu/irb/manual/forms/research_students_subjects.pdf).

N/A

3.H. Informed Consent

Part 1 – Consent Process

Informed consent is a process that begins with advertising or telling potential subjects about your study, continues as the investigator or staff provides details to potential subjects via dialog, and is formalized by the signing of the consent.

Note: Minors must have consent of their parents or guardians before you can approach the minor about participating in the study.
Note: Allow as much time as possible and feasible for the subject to think about whether to enroll in the study. Generally, the greater the study risks, the longer the decision period.

Please overview the steps in the consent process in your research study. If there is more than one group of subjects, separately describe the process for each group.

In this study, the informed consent process will begin with initial contact with potential participants, most commonly via telephone. We will contact potential participants based on their scores on cognitive measures and self-report of cognitive problems during our previous study and their previous consent to being recontacted for future studies. During initial contact, participants will be informed of the availability of the study and asked whether they are interested in becoming a participant. If they indicate that they are interested, the phone interviewer will provide details of the study such as the inclusion and exclusion criteria, the nature of the intervention, time required to complete the study (time and number of study visits), need to

provide results of HIV viral load and CD4 cell count, potential risks, and compensation. If the potential participant continues to indicate an interest in participating, their verbal assent to ask questions about their thinking and memory will be asked (see telephone script in appendix). If the potential participant gives verbal permission, their response will be recorded and then the three screening questions (see script) will be asked. If the potential participants responds no to all questions, they will be thanked for their willingness to talk and their time, and informed that they are not eligible for the study. They will be asked if they have any questions and if so they will be answered. If not, they will be thanked and the interview will be ended.

If the participant answers yes to any of the questions (indicating that they experience symptoms of cognitive dysfunction), they will be informed that they may be eligible for the study and that the interviewer would like to ask more questions about their medical history and treatment. The interviewer will request verbal assent for these questions as well. He or she will then review study exclusion criteria (see questions and checklist in the telephone screening script). If the person continues to be eligible, the interviewer will inform the potential participant of this fact and state that final eligibility determination depends on additional in-person evaluation. They will be informed that the in-person screening will involve the administration of a 30-45-minute battery of neuropsychological measures of memory, attention, and executive function and questions about their mood and mental functioning. They will be informed that they will be paid $40 for the visit even if they do not qualify for the study (and that their compensation will be pro-rated if they choose to leave before the completion of the visit) and that they will be informed of their eligibility during the visit.

The informed consent process will continue at the eligibility visit. Scheduled participants will again be reminded of the nature of the research study and the requirements of the study. If they continue to indicate an interest in participating, their verbal permission to complete the brief battery of neuropsychological measures will be solicited, after the measures and time required is again stated. Their response will be recorded, and if they assent to the assessment, the brief battery of measures will be administered. After administration, the potential participant will be offered a break with refreshments (coffee, tea, soda, snacks) while the researcher scores the measures to assess the potential participant's eligibility. If the potential participant does not score in the range to make them eligible for the study, they will be informed of this fact, thanked, for their interest and participation, and provided compensation.

If the participant scores at levels that make them eligible for the study, they will be informed of this and asked if they continue to be interested in participating. If they continue to indicate an interest in participating, they will be asked if they are available to complete additional informed consent procedures, including review of the written informed consent form. If they indicate that they are available for this additional activity, the informed consent form will be given to the participant and encouraged to read it. The researcher will review the form with the potential participant as well, and the potential participant will be asked if she or he has any questions about the study. The potential participant will then be asked the three questions developed by Palmer et al. and validated against the longer MacArthur Assessment of Competence—Clinical Research (Palmer et al., 2005). If the potential participant does not achieve an adequate score on the three questions (each can be scored as 0, 1 or 2 based on the person's demonstrated understanding of the study's purpose, risks, and benefits for a total of 6) the person obtaining written informed consent will review the relevant information and again ask the person to explain the issue in which he or she did not demonstrate adequate understanding. The potential

participant's final score must be 4 of 6 to be eligible for the study as this indicates a clear understanding of at least one area and at least partial understanding of several others. In the Palmer et al study, this score had a high degree of sensitivity in detecting those with inadequate understanding of clinical research on a longer measure.

After this discussion, the participant will be asked if he or she is ready to sign the form; if so, they will sign the form, but if not, they will be encouraged to review the form and the investigator will answer any questions. If the participant declines to sign the form, the study visit will be concluded and the potential participant will be compensated for their time in the eligibility portion in the study.

After providing written informed consent, participants will be asked to complete several questionnaires (the depression questionnaire (CES-D) and the Patient's Own Assessment of Functioning as well as ratings of cognitive functioning and mood). The visit will conclude with scheduling the first study visit and providing the participant with compensation.

The informed consent process will continue during the active or sham treatment sessions during which the participant's reactions and concerns about the study procedures will be actively elicited by the investigator. During each study session, the participant will be asked if she or he has any questions or concerns about the previous session; these will be recorded and responded to. Participants will be reminded that their participation is completely voluntary and that they can discontinue the study at any time without loss of any benefits to which they might be entitled.

Part 2 – Consent Process and Document Waiver/Alteration Information

In most cases, subjects need to participate in a meaningful consent process and receive a consent/assent form that documents agreement to participate in research. However, in a few cases the subject's confidentiality is protected by waiving/altering consent procedures or the requirement for signed consent forms. Please read the IRB's policy on informed consent for explanations, including what the IRB must demonstrate to permit waiver or alteration (http://www.nova.edu/irb/manual/forms/informed_consent.pdf). Please note, however, that while your study may qualify for waiver or alteration, that determination is at the discretion of the IRB.

One case where a signed informed consent form is NOT used is when a researcher is only reviewing existing/archival data that were collected for non-research purposes. If the data are obtained from the records by someone with authorization, and the data are de-identified, then it may be appropriate not to ask subjects (those whose data you are collecting) to provide consent, because the research involves no more than minimal risk, the waiver or alteration will not adversely affect the rights or welfare of subjects, the research could not practicably be carried out without the waiver or alteration, and, when appropriate, the subject will be provided pertinent information about participation. (NOTE: If your study has other procedures that require interaction with subjects or prospective collection of data, it is unlikely that waiver or alteration of consent procedures or the signing of consent forms would be appropriate.) If this describes your study, then you may request

a waiver of the requirement for informed consent and the documentation of signed consent.

If you think this applies in your study, please describe your rationale.

Another situation involving waiver or alteration of the requirement to obtain a signed consent form is when the research only entails conducting anonymous surveys that are not intrusive. If there is no way that the subjects' responses could be linked to them, then waiving the requirement for a signed consent form would minimize a risk to their confidentiality and privacy because the only record linking the subject and the research would be the consent form. If the principal risk would be potential harm resulting from a breach of confidentiality and the research presents no more than minimal risk to subjects and involves no procedures for which written consent is normally required outside of the research context, then the elements of informed consent are put into the survey itself. The person indicates his/her voluntary participation by completing the survey after being advised about the study and voluntary nature of his/her participation.

If you think this applies in your study, please describe your rationale.

There may be other cases where you would wish to ask for a waiver or alteration of informed consent or signed consent documentation.

If you are seeking a waiver or alteration, please describe your rationale.

Part 3 – Consent and Assent Document Information

Typically, you are asked to use the NSU format consent and assent forms. However, if this is cooperative research, or sponsored research that requires the use of a different template or model, you may use their format.

I will use NSU format consent/assent forms	X
I will be using another institution's format for consent/assent forms (NOTE: Please review the other institution's consent forms and the NSU requirements to be sure that all of the NSU requirements are present. You may also want to discuss the consent forms with your college/center representative)	
As noted above, I am requesting a waiver/alteration of consent and/or signed consent form requirements	

If you have different procedures for different groups of subjects, you will need a separate consent and/or assent form for each group. If the reading level of different groups of subjects differs, this may also require you to have different consent and/or assent forms (e.g. young children vs. adolescents). If your subjects are children, you will also need parental consent.

What is the total number of consent/assent form types that you plan to use?

1

If using more than one consent form, create a list below that describes the different forms that you

will be using (e.g. 1. Teacher consent form, 2. Parent consent form, 3. Assent form for children age 7-12, 4. Assent form for adolescents).

Include copies of the consent / assent forms. When you attach the consent forms, put them in this order. Please note that the IRB prefers that the consent document be written using the simplest language possible, and strongly recommends the question and answer format (see Document Model #1 for Adult/General Consent Form [Readability Score: Grade 6]).

3.I. Protected Health Information Use

	Yes	No
Are you obtaining any data from the subject's medical record?		X
Are you asking the subject about his or her health information, and doing so in a clinic or entity that would normally be subject to HIPAA regulations on protected health information?		X

If you answered "Yes" to either question, continue. Otherwise go on to section 3.J.

Please review the NSU HIPAA research policies available at (http://www.nova.edu/irb/manual/policies.html for more information.

Please note that effective 12/10/2009 the NSU IRB no longer reviews separate HIPAA authorizations for research. It is the principal investigator's responsibility to use the correct HIPAA authorization as outlined in the aforementioned policy. In instances where the HIPAA authorization must be a part of the informed consent form for research, the NSU IRB will review the compound consent.

Specify the exact data to be gathered (e.g., weight, blood pressure, IQ score, diagnosis, depression rating, number of treatments, etc.).

Participants will be required to provide recent (within 3 months) results of HIV RNA (viral load) and CD4 counts as part of initial assessment for participation in the study.

Which procedure are you proposing to use? (Check)

I will obtain the subject's authorization to obtain the protected health information via the NSU Authorization for Use and Disclosure of Protected Health Information in Research (research activities will be occurring at an NSU clinic).	
I will obtain the subject's authorization to obtain the protected health information via the authorization for use and disclosure of protected health information in research provided by the non-NSU covered entity.	
The protected health information data are a fully de-identified data set (data obtained without recording any patient information, with the data accessed by an employee of the institution).	
The data are part of a limited data set agreement as defined by the Office of Human Research Protections. (Attach a copy of the agreement.)	

If part of a limited data set agreement, what is the justification that confidentiality is protected?

I have a waiver provided by a duly constituted privacy board. (Attach a copy of the waiver.)	

HIPAA Research Authorization

If the research is to be conducted at an NSU clinic, have you created a HIPAA authorization form as outlined in the HIPAA Research Policy No. 1 (http://www.nova.edu/irb/manual/policies.html) and in keeping with the Instructions for Preparing the Authorization For Use and Disclosure of Protected Health Information in Research Form and the model form provided (http://www.nova.edu/irb/manual/forms.html)?

Yes	No
	X

Please note, do NOT submit a copy of the HIPAA authorization form if you are following the model noted in the aforementioned policy.

If the research is to be conducted at a non-NSU covered entity, have you reviewed the HIPAA Research Policy No. 6: Guidance on Research at Outside Entities (http://www.nova.edu/irb/manual/policies.html)?

Yes	No
X	

Researchers are advised to discuss the proposed research with the applicable HIPAA privacy officer at the non-NSU covered entity.

Does the researcher sponsor or cooperating agency require the incorporation of the HIPAA authorization within the consent document (Compound Consent)?

Yes	No
	X

If yes, please briefly indicate who requires that this be in the informed consent document.

Please note, consent forms that include the HIPAA authorization may need approval from the university Office of Corporate Compliance.

3.J. Student/Academic Information Use

Are you obtaining any data from the subject's academic records?

Yes	No
	X

If you answered "Yes", continue. Otherwise go on to section K.

Specify the exact data to be gathered (e.g., GPA, standardized test score, IQ score, medical/psychological information stored in academic files, attendance records, disciplinary records, etc.).

Specify how you will obtain the data.

Which procedure are you proposing to use? (Check all that apply)

I will obtain the subject's consent to obtain the academic information. ☐

The academic information will be a part of a fully de-identified data set (data obtained without recording any subject information, and provided to you in keeping with the institution's policies and the Federal Educational Rights and Privacy Act [FERPA]). ☐

3.K. Risks, Discomforts, & Inconveniences

In this section, discuss all potential risks (physical, economic/financial, legal, psychological, social, etc.), discomforts, or inconveniences to the subjects.

- All studies using identifiable subject information must address the issue of possible loss of subject confidentiality
- Some possible risks include physical, psychological or emotional harm, breach of confidentiality, and invasion of privacy.
- Discomfort includes anticipated risk for mild physical or emotional pain.
- Study inconveniences include loss of time or pay.

Each risk, discomfort and inconvenience should be addressed individually in the following format (use the tables provided and copy if the study presents more than 3).

- List each risk individually
- Discuss likelihood: How likely is it that this risk/discomfort or inconvenience will occur? This is usually classified as minimal, moderate, or high.
- Discuss magnitude/duration: How dire is the risk/inconvenience/discomfort, and if it occurs, how long do you expect that the subject will be affected?
- Discuss risk minimization: Describe the procedures undertaken to minimize the risk that this specific risk/discomfort/inconvenience will occur.

Risk/Discomfort	Discomfort, tingling, itching, or redness at tDCS electrode sites
Likelihood	High (greater than 20% based on data from Poreisz et al., 2007)
Magnitude/Duration	Mild/throughout the study
Risk Minimization	Participants will be closely monitored during treatment sessions. If impedance changes during treatment, the tDCS device will automatically stop current delivery. Participants will be encouraged to report any discomfort, and should the discomfort increase substantially the tDCS delivery will be stopped. If the person experiences vesicles or evidence of skin irritation that does not resolve promptly (i.e., within 20 minutes) after discontinuation of the tDCS, he or she will be dropped from the study.

Risk/Discomfort	Burn at electrode site
Likelihood	Very low (less than 1%)
Magnitude/Duration	Moderate/throughout the study
Risk Minimization	Participants will be closely monitored during treatment sessions. If impedance changes during treatment, the tDCS device will automatically stop current delivery. Dr. Ownby or Ms. Davenport will be in the office at all times during study visits, and will be able to monitor the participant. Participants will be encouraged to report any discomfort, and should the discomfort increase substantially the tDCS delivery will be stopped. A recent FDA advisory panel reviewed adverse effect data from studies using electrophoresis devices and concluded that risks of burns are low (see discussion of safety, above).

Risk/Discomfort	Fatigue
Likelihood	High (35% based on data from Poreisz et al., 2007)

Magnitude/Duration	Moderate/throughout the study
Risk Minimization	Participants will be closely monitored during all study visits; each visits will begin with a review of any problems that occur between visits and each will end with a review of discomfort and an open-ended discussion of any problems of concerns so that participants can readily communicate any issue they experience.

Risk/Discomfort	Difficulties in concentrating
Likelihood	Moderate (4-10% based on data from Poreisz et al., 2007)
Magnitude/Duration	Moderate/throughout the study
Risk Minimization	Participants will be closely monitored during all study visits; each visits will begin with a review of any problems that occur between visits and each will end with a review of discomfort and an open-ended discussion of any problems of concerns so that participants can readily communicate any issue they experience.

Risk/Discomfort	Manic or hypomanic episode
Likelihood	Low
Magnitude/Duration	Moderate/throughout the study
Risk Minimization	Several participants in previous studies of tDCS for depression developed manic or hypomanic episodes. In the largest and best controlled study (Brunoni et al., 2013), the occurrence of these episodes was similar in groups receiving only antidepressant medication and in those receiving antidepressant medication plus tDCS. Since some persons who appear to have unipolar depression may actually have unrecognized bipolar disorder, the significance of this finding for risk in studies of tDCS for cognitive problems is not clear. In order to minimize this risk, however, we will screen persons for a history of mania or hypomania as well as for a personal or family history of bipolar disorder. We will also exclude anyone taking mood stabilizing medication (anticonvulsants or lithium; see list in exclusion criteria) as patients are sometimes given mood stabilizers for possible mood disorders without a clear understanding of the purpose of these medications.

Risk/Discomfort	Distress, frustration, or fatigue from the difficulty of the computer-delivered cognitive training task
Likelihood	Low
Magnitude/Duration	Mild/throughout the study
Risk Minimization	Participants will be closely monitored during training sessions and provided ongoing coaching and encouragement to help them become proficient at the memory and attention task and to not become excessively frustrated. The task itself is designed to begin with a low level of difficulty and progress so as to continuously challenge the participant without becoming excessively difficult. We have already completed preliminary acceptability testing of the cognitive training activity with a group of HIV+ participants who are similar to those to be enrolled in the proposed study (“Usability of Revised Educational and Cognitive Training Interventions for HIV,” Protocol No. 05251228Exp)

	and found a high level of acceptance for it.

Risk/Discomfort	Inadvertent disclosure of HIV status or other information that might be embarrassing to the participant.
Likelihood	Low.
Magnitude/Duration	Large/throughout the study
Risk Minimization	All data recording will either be done on coded paper sheets or in electronic format with the participant only identified by a number. The record of the relation of participant number to participant identifying information will be kept separate from study files in a locked file cabinet in an office that is also locked outside of normal business hours. The office is in the researchers' suite of offices, which are themselves locked at all times.

Risk/Discomfort	Upset from discussions of cognitive difficulties or review of mood symptoms
Likelihood	Low
Magnitude/Duration	Potentially serious/throughout the study
Risk Minimization	Based on our previous experience, many participants are already aware that HIV infection may result in cognitive or mood symptoms. Discussion and assessment activities (e.g., completing a depression rating scale) can increase this awareness and may result in upset. The researchers are acutely aware of this possibility and will monitor participants' reaction to screening questions, determination of eligibility, and study participation. Only one participant (of a total of 124) in our previous study became upset when learning about the implications of HIV infection. When this occurred, it was possible for Dr. Ownby to meet with the participant, debrief him or her, and determine the need for additional counseling or treatment. In this study we will debrief participants after each study visit with respect to their reactions to the study measures and procedures. They will be provided with brief counseling when needed and will be referred to community resources if further treatment is required.

One way in which confidentiality is partially protected is to destroy study documents containing identifiable information when they are no longer needed. The IRB requires that study materials be kept for a minimum of three years from the end of the study to permit study auditing; you may elect to keep them for a longer period of time and study sponsors may have their own data retention requirements. Please indicate when and how you plan to destroy data that contains identifiable subject information, such as consent forms, lists that link subject identity to data coding, or raw data containing subject names.

Data will be retained for a minimum of three years after the conclusion of the study. Paper records will be destroyed through secure document destruction services, while electronic data will be destroyed by overwriting relevant portions of computer hard drives with software that overwrites memory areas with irrelevant data on multiple occasions.

3.L. Benefits to Subjects

In this section, discuss all direct benefits of the study to participants. This does not include "helping research" or other generalities, nor does it include compensation for participation. Some examples of benefits include receiving free treatment, receiving a list of reputable local services, or obtaining tutoring. The value of any such benefits should be listed as well. If there are no direct benefits to the participants, this should be indicated.

Are there any direct benefits to the research participants?

There are no direct benefits to study participants	This study provides benefit to, or is likely to benefit, the participants
X	

List/describe each benefit

3.M. Data Analysis Plan

Please describe preliminarily proposed data analysis procedures.

Study outcomes will be evaluated through analysis of group differences on neuropsychological measures after correction for baseline differences in age, disease status (CD4 count), mood, and baseline performance. Additional outcomes will include the rate of learning in the computer-delivered memory and attention task between groups. Individual and group slopes for the task will be plotted and visually inspected as well as tested using parametric statistics.

3.N. Scientific Benefit

Briefly discuss how generalization of the information obtained from this study will be scientifically useful, or useful to your research site.

The demonstration that tDCS has a positive impact on cognitive training in persons with HIV-related MND would have significant implications for the development of strategies to enhance cognitive functions in persons with MND. As these cognitive functions have been related to functional status and medication adherence in persons with HIV, improving cognition have important effects on clinical outcomes and, since adherence is related to viral suppression which is in turn related to infectivity, the study may have important implications for public health.

Results of this study may demonstrate the feasibility of tDCS studies at NSU and provide preliminary data that will be used in applications for additional NIH funding.

3.O. Risk/Benefit Ratio

To be approved, a study needs to have greater benefits than risks. Why do you believe this study has a positive benefits-to-risks ratio?

The benefits of the study are the demonstration of a potentially useful strategy for improving cognitive function in persons with HIV-related cognitive function. Previous studies of computer-based cognitive training have shown that it can be accomplished with very little likelihood of adverse events. Similarly, multiple studies of tDCS have shown that it can be used to enhance cognition and mood in healthy individuals and those with a variety of neurocognitive and pain disorders. These studies as well as a recent review of the safety of iontophoresis devices for an FDA advisory panel show that these devices for delivery small electrical currents are safe. The potential benefits of the knowledge to be achieved are thus substantial while the potential risks are very small, resulting in a positive benefits to risk ratio.

3.P. Safety Monitoring Plans

All researchers are required to report adverse events and unanticipated problems in keeping with the NSU IRB policy (http://www.nova.edu/irb/manual/forms/adverse_events.pdf).

Studies that entail significant risk to subjects, such as randomized controlled drug trials, may warrant safety monitoring by an outside safety board. Does your study utilize a Data Safety Monitoring plan?

Yes	No
X	

If "Yes," please describe the safety monitoring plans. Please specify if the study will be monitored by the investigators, sponsors (if applicable), or a Data Safety Monitoring Board (DSMB). Sponsored studies may reference an attached Investigator Brochure.

For this study, we do not intend to empanel as DSMB but will provide close and ongoing monitoring of each participant during study procedures. An investigator will be present at all times during study sessions including those that involve sham tDCS, and all participants will be debriefed at the conclusion of each study session. This verbal debriefing will include questions about discomfort, fatigue, and frustration. Participants will also complete brief ratings of mood, mental functioning, and discomfort (see appendix) at the end of each session to allow additional monitoring of participant reactions to the study.

3.Q. Other Information

If there is other information about this study that is required in order for those reviewing the study to fully understand the study, its risks and benefits, please describe below.

3.R. Principal Investigator Assurance and Obligations

I certify that all information provided in this submission (including any supporting documents) is a complete and accurate description of the proposed study. I agree to the following:

This study will be conducted in the manner described in this submission and will not be implemented (including subject recruitment or consenting) until all applicable IRBs have granted permission to conduct the research. No changes to this study will be implemented until an amendment form has been submitted and approved by the IRB.

PI Initials ☐

If the IRB approves this study via expedited or full procedure, I will submit for continuing review as stipulated in the approval letter. If the study or data analysis will exceed the approval period, I will submit a Submission Form for Continuing Review of IRB Approved Studies in a timely manner (well in advance of the renewal date). I understand that study activities may not continue past an approval period.

PI Initials ☐

I will provide a copy of the signed consent form to the subject or patient, if applicable.

PI Initials ☐

I will retain all signed informed consent documents and study-related records for a minimum of three (3) years (or longer as stipulated by funding agencies) from the date the study is concluded.

PI Initials ☐

I will report in writing any serious adverse events to the IRB within 24 hours and all other adverse events and unanticipated problems within 5 working days.

PI Initials ☐

I will provide participants with any significant new information obtained during the course of the study and submit reports of new information to the IRB as a Study Amendment.

PI Initials ☐

If my study has been approved at the Expedited or Full Review levels, I will report to the IRB when this study has closed (no further data collection or analysis). This report will be provided no later than 30 days after the end of the study via the IRB Closing Report Form.

PI Initials ☐

Principal Investigator's Signature: _____ Date: _____

3.S. Co-Investigator Assurance and Obligations (for Student PIs)

If this study is for the completion of a degree requirement, the thesis adviser or dissertation chair must sign the attestation below.

- All departmental approvals by the student's committee (if applicable) and chair or thesis adviser have been completed.
- I accept that the University and IRB consider the faculty advisor's responsibility to be equal to that of the student in regard to
  - The quality of the research design AND the accuracy of the protocol
  - The appropriateness of the recruitment methods, the design of the process for informing the subjects about the nature of the study, and the process of obtaining informed consent
  - The readability, accuracy, and format of the informed consent/assent document(s) and the explanation of all informed consent procedures.

My signature below attests that I have read this submission in its entirety and believe that it is accurate, complete, appropriate, and adheres to the principles of the Belmont report and that all departmental approvals by the student's committee have been completed.

Chair/Adviser's Signature: _____ Date: _____

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