Reducing Breast Cancer-related Fatigue and Improving Cognition with Transcranial Direct Current Stimulation (tDCS)

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Protocol Chair

Tracy D. Vannorsdall, Ph.D.
Johns Hopkins Hospital
600 N. Wolfe Street, Meyer 218
Baltimore, MD 21287
Office: 410-955-3268
Fax: 410-955-0504
Email: tvannor1@jhmi.edu

Protocol Co-Chair

Karen Smith, M.D., M.P.H.
Kimmel Cancer Center at Sibley Memorial Hospital
Building B, 1st Floor
5255 Loughboro Rd NW
Washington, DC 20016
Office: 202-660-6500
Fax: 202-660-6501
Email: ksmith60@jhmi.edu

Co-Investigator

Antonio Wolff, M.D.
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Statistician

Chiung-Yu Huang, PhD
Division of Oncology Biostatistics & Bioinformatics
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Supporters

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1. SUMMARY

Fatigue and cognitive dysfunction are commonly reported symptoms associated with impaired quality of life and productivity in breast cancer survivors. Working memory, the brain's system for temporarily storing and manipulating information required to carry out more complex cognitive tasks, is particularly affected by cancer and its treatment.

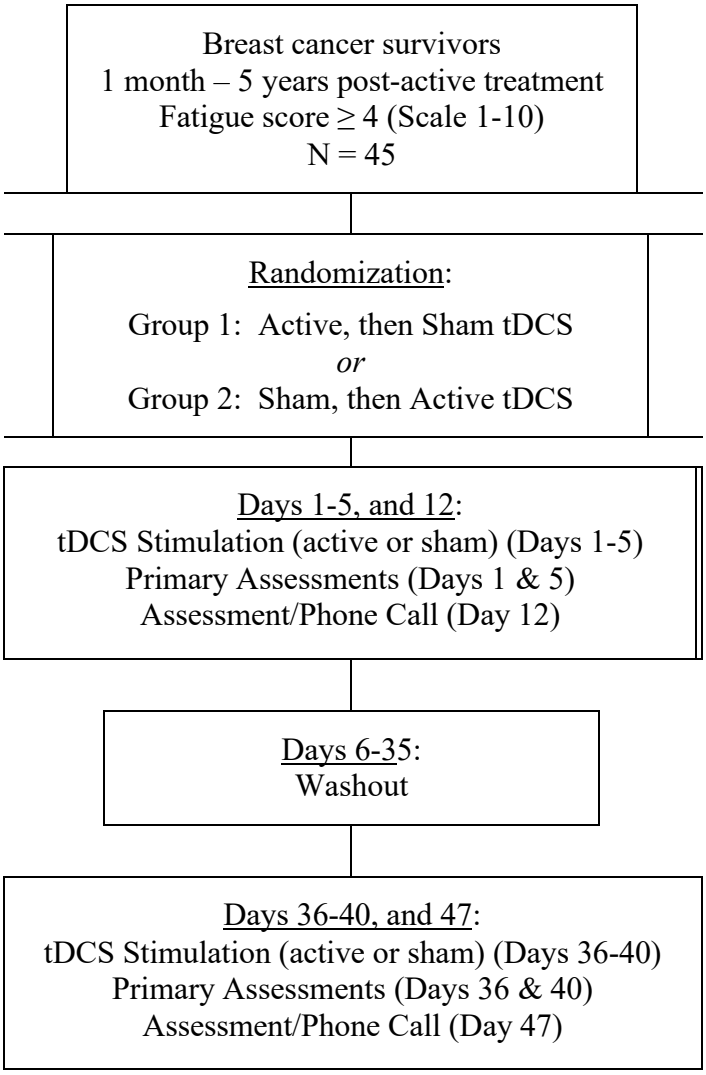
In women who have undergone chemotherapy for breast cancer, neuroimaging studies show structural brain changes as well as functional inefficiencies in a region critical for working memory, the left dorsolateral prefrontal cortex (DLPFC). Fatigue appears to play a critical role in the recruitment of the DLPFC during cognitive tasks.

Transcranial direct current stimulation (tDCS) is a safe, portable, non-invasive form of electrical brain stimulation that enhances neuronal transmission beneath the scalp electrodes. Active treatment consists of a mild electrical current (2mA) administered via saline-soaked sponge electrodes placed along the intact scalp for 30 minutes a day for five days. Used as a control in the proposed trial, sham stimulation involves the brief delivery of current in a manner that does not result in changes in neuronal firing patterns, but is perceived as active treatment by participants. Our group and others have shown that when applied to the left DLPFC, active tDCS improves cognition in healthy adults and energy in patients with fatiguing medical conditions.

The proposed investigation consists of a randomized, sham-controlled, double-blind, cross-over experiment. Women who have finished treatment of breast cancer and who report persistent fatigue ($\geq$ 4 on a scale of 1 to 10) will complete measures of fatigue and cognition before and after five consecutive days of active or sham tDCS applied to the left DLPFC. Following a four-week washout, participants will return to complete the opposing stimulation condition (active/sham) over another five consecutive days. About one week after each session participants will receive/complete a brief study phone call with the study staff, with a total time on study of about 47 days ($\pm$ 5 days).

The primary endpoint is change in objectively measured working memory performance (Paced Auditory Serial Attention Test; PASAT) before and after five consecutive days of active or sham tDCS. Secondary endpoints are changes in subjective fatigue (Multidimensional Fatigue Symptom Inventory 30-item short form; MFSI-SF) and subjective cognitive functioning (Functional Assessment of Cancer Therapy Cognitive Scale; FACT-Cog) before and after five consecutive days of active or sham tDCS. Exploratory objectives include assessing the effect of tDCS in other objectively assessed cognitive skills as described below, identifying disease-, treatment-, and person-related predictors of response to tDCS intervention, and describing side effects in this population. With 45 patients and a two-sided type I error rate of 5%, we have at least 80% power to detect a medium effect size (Cohen's d) of 0.43 or greater.

2. SCHEMA


Breast cancer survivors
1 month – 5 years post-active treatment
Fatigue score ≥ 4 (Scale 1-10)
N = 45
Randomization:
Group 1: Active, then Sham tDCS
or
Group 2: Sham, then Active tDCS
Days 1-5, and 12:
tDCS Stimulation (active or sham) (Days 1-5)
Primary Assessments (Days 1 & 5)
Assessment/Phone Call (Day 12)
Days 6-35:
Washout
Days 36-40, and 47:
tDCS Stimulation (active or sham) (Days 36-40)
Primary Assessments (Days 36 & 40)
Assessment/Phone Call (Day 47)

3. OBJECTIVES

3.1 Primary

3.1.1 To determine the efficacy of five consecutive days of tDCS in improving objectively assessed working memory in breast cancer survivors with persistent fatigue.

The Paced Auditory Serial Attention Test (PASAT)[1,2] will serve as the primary measurement tool for the objective assessment of working memory.

3.1.2 Secondary

3.1.2 To determine the efficacy of five consecutive days of tDCS in improving subjective cognition in breast cancer survivors with persistent fatigue.

The primary measurement endpoint for subjective cognition will be scores on the Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog), a self-report measure addressing cognitive functioning, functional interference, quality of life and overall cognitive complaints over the past week.

3.1.3 To determine the efficacy of five consecutive days of tDCS for the treatment of subjective fatigue in breast cancer survivors with persistent fatigue.

The primary measurement tool for subjective fatigue will be the Multidimensional Fatigue Symptom Inventory 30-item short form (MFSI-SF), which assesses participants' subjective ratings of general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor over the past week.

3.1.4 To determine whether the effects of tDCS on subjective cognition and fatigue persist at approximately seven days following the last day of stimulation in breast cancer survivors.

Secondary endpoints will be ratings on the MFSI-SF and FACT-Cog obtained via phone seven days after the fifth tDCS session of each study wave.

3.2 Exploratory

To assess the effect of five consecutive days of tDCS in improving other objectively assessed cognitive skills in breast cancer survivors with persistent fatigue.

Exploratory endpoints will include changes in performance on objective tests of cognitive functioning including measures of learning and memory (Hopkins Verbal Learning Test-Revised, HVLT-R[3] and Brief Visuospatial Memory Test-Revised, BVMT-R[4]), auditory attention (WAIS-IV Digit Span subtest[5]), psychomotor speed and executive functioning (Trail Making Test Parts A and B [6]), speeded lexical fluency (Calibrated Ideational Fluency Assessment[7]), and manual speed (Grooved Pegboard[8]).

3.2.1 To evaluate disease-, treatment- and person-related predictors of improvements in cognitive function and fatigue in response to the tDCS intervention.

3.2.2 To describe the side effects of tDCS

4. HYPOTHESES

4.1 Primary

4.1.1 Five days of active tDCS will result in greater improvements in objectively assessed working memory (PASAT) relative to sham tDCS.

4.2 Secondary

4.2.1 Five days of active tDCS will result in greater improvements in subjective cognition relative to sham tDCS.

4.2.2 Five days of active tDCS will result in greater improvements in subjective fatigue relative to sham tDCS.

4.2.3 Five days of active tDCS will result in greater improvements in subjective fatigue and cognition one week following active stimulation relative to sham stimulation.

4.3 Exploratory

4.3.1 Five days of active tDCS will result in greater improvements (relative to sham tDCS) in selected cognitive skills (e.g. attention, processing speed) that are also heavily reliant on the functioning of the left DLPFC whereas active tDCS will not alter other cognitive abilities (e.g. many language skills, visual perception) that are less reliant on the DLPFC.

4.3.2 Patient factors such as baseline fatigue, depression, and anxiety will predict response to tDCS.

4.3.3 Participants will report only mild side effects of tDCS intervention such as tingling under the electrode.

5. BACKGROUND AND RATIONALE

5.1 Cancer-related Fatigue and Cognitive Dysfunction

The American Society of Clinical Oncology defines cancer-related fatigue as distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer and/or its treatment such that it is disproportional to recent activity and interferes with usual functioning [9]. A majority of women with breast cancer (56-95%) report persistent fatigue following treatment with adjuvant chemotherapy [10]. Cognitive dysfunction is also reported at high rates, with approximately one third of women experiencing subjective cognitive declines following treatment [11]. These subjective cognitive complaints are closely linked to objective cognitive impairments on formal neuropsychological testing [12]. Cognitive deficits most commonly occur in the areas of working memory and vigilance, processing speed, memory, and other higher cognitive functions [12,13]. Both fatigue and cognitive dysfunction are associated with reduced quality of life and productivity [14]. There are currently no effective treatments for either the enduring fatigue or cognitive dysfunction experienced following treatment for breast cancer [10].

The DLPFC region is involved in cognitive skills other than working memory, such as executive functioning, attention and processing speed. Other cognitive abilities are generally less reliant on DLPFC functioning. For example, many language skills and visual perception are driven by more posterior or distributed brain regions.

Among healthy adults, functional neuroimaging studies have documented relatively consistent patterns of brain activation during working memory tasks involving the left prefrontal and premotor regions [15]. When completing tests of higher order cognition, breast cancer survivors fail to recruit these left frontal regions at a level seen in their non-affected peers, which may account for their poorer performance on cognitive testing [16,17]. Functional MRI-derived measures of neural activity in networks supporting attention and working memory are strong predictors of post-treatment cognition and fatigue in breast cancer survivors [18]. Importantly, fatigue has been shown to mediate the relationship between DLPFC activation and cognitive performance in breast cancer patients [17].

5.2 Transcranial Direct Current Stimulation (tDCS)

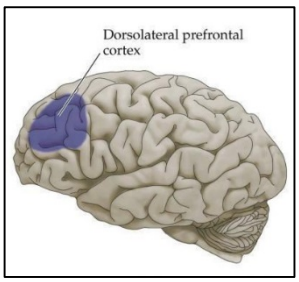
A rapidly growing body of evidence demonstrates that transcranial direct current stimulation (tDCS) can induce changes in physical and cognitive functioning [19], and it may represent an effective way of resuscitating higher cognitive functions and reducing fatigue in patient populations. The technique involves passing weak direct electrical current through the scalp to produce a relatively localized, polarity-dependent alteration of the electrical potential in cortical tissue beneath the scalp electrode [20,21], which appears to alter the excitability of underlying cortical neurons and to modulate their firing rates, as measured by single-unit recordings in animals or evoked potential measures in animals and in humans [22]. The effects of these alterations can be excitatory (with anodal stimulation) or inhibitory (with cathodal stimulation).

As it has been previously used, tDCS is administered to the scalp via 25-35 cm^2 saline-soaked sponges. A weak (1-2 mA) direct current is applied through the electrodes for up to 40 minutes at a time. Under these conditions, the technique has been shown repeatedly to be safe in healthy

individuals from childhood to older adulthood as well as in a variety of patient populations such as those with stroke, epilepsy and mental illness[23-25]. TDCS is also generally unobtrusive. Many subjects do not perceive the current being applied. Some subjects report a tingling sensation under the electrode during tDCS, although increasing the current can eliminate this perception.

The prefrontal cortex, and the DLPFC in particular, is an attractive neuroanatomic target to address cognitive dysfunction and fatigue via tDCS in breast cancer survivors. See Figure 1. Numerous prior investigations have demonstrated that tDCS applied to the left DLPFC can improve working memory in both healthy adults and patient groups [26,27]. Early work by Fregni and colleagues [28] demonstrated the specificity of anodal stimulation to the left DLPFC in improving working memory, as indexed by an n-back task performance, in healthy adults. These results were specific to anodal stimulation of the left DLPFC, as working memory performance remained unchanged in response to both cathodal stimulation of the left DLPFC and anodal stimulation of the left primary motor cortex. Similar improvements in working memory have been seen after tDCS in patients with stroke [29], Parkinson's disease [30], and major depression [31]. In a case study of a single breast cancer survivor, tDCS was found to be safe and tolerable while resulting in improvements in cognitive functioning for approximately two weeks [32]. In multiple sclerosis, tDCS applied to the DLFPC has also repeatedly been shown to be safe and tolerable resulting in reduced fatigue ratings, with effects lasting up to three weeks following active stimulation[33-35].

Figure 1.



Studies of tDCS provide evidence to suggest that sustained and repeated stimulation paradigms can prove effective in generating prolonged treatment effects. Depending upon the duration of stimulation, and the experimental situation, effects of tDCS have been found to persist for minutes, hours, or up to a month [36,37]. For example, a single 13-minute session of motor cortex stimulation has yielded up to 90 minutes of altered cortical excitability [24], and consecutive daily sessions of tDCS were associated with a significant behavioral improvement lasting up to two weeks post-treatment in individuals experiencing post-stroke motor dysfunction [36]. With respect to cognitive enhancement, it has been demonstrated that repeated daily anodal tDCS applied to the DLPFC results in improvements in working memory that last up to a week or longer in adults with major depression [38], and these cognitive enhancements are independent of tDCS-induced changes in mood functioning. In multiple sclerosis, repeated daily stimulation aimed at reducing neuropathic pain yielded significantly diminished pain ratings three weeks following the termination of stimulation and was not associated with any adverse reactions [37]. Similarly, improvements in subjective fatigue ratings have been demonstrated to persist for up to three weeks following tDCS in multiple sclerosis [33] and two weeks in a participant with breast cancer[32].

5.2.1 Preliminary tDCS Data at Johns Hopkins

Our lab has demonstrated the ability of a single tDCS session to improve higher cognitive functions in adults [39]. We have also shown that tDCS alters resting brain network connectivity associated with working memory performance [40]. Most relevant to the current proposal are our pilot data for five patients with multiple sclerosis which, like breast cancer, more commonly affects women and is associated with persistent fatigue and cognitive deficits. TDCS was both safe and tolerable in these patients. We observed a relative reduction in fatigue ratings and improvement in working memory test performance (PASAT, N-back) over five days of active stimulation as compared to increased fatigue and modest cognitive practice effects observed in response to sham stimulation. See Figure 2. Depression scores remained unchanged and were unlikely to have contributed to the observed improvements in fatigue and cognition [41].

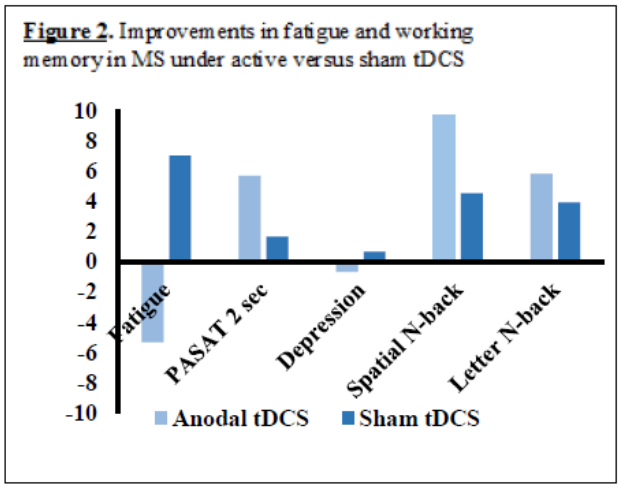


Figure 2. Improvements in fatigue and working memory in MS under active versus sham tDCS

Despite the evidence documenting the safety and utility of tDCS as a means of enhancing working memory and reducing subjective fatigue in patient populations whose deficits are characterized by inefficient prefrontal network activity, working memory deficits, and fatigue (e.g., multiple sclerosis, depression [27,34,38,41]), it has yet to be thoroughly investigated as a means of reducing fatigue and enhancing cognitive functioning in breast cancer survivors. Demonstrating efficacy in improving cognitive function and fatigue in breast cancer survivors with this short-term tDCS intervention is a first step in evaluating this intervention as a possible technique for longer-term management of fatigue and cognitive dysfunction in this population.

6. PARTICIPANT SELECTION

6.1 Inclusion Criteria

6.1.1 Women, 18 years of age or older

6.1.2 Stage I-III breast cancer

Treatment Status: At least 1 month and no more than 5 years after the conclusion of active breast cancer therapy, including surgery, radiation therapy and (neo)adjuvant chemotherapy, if administered.

NOTE: Adjuvant HER2-targeted therapy and endocrine therapy may be ongoing at the time of study enrollment. Those who require endocrine therapy must have been on their current endocrine regimen for at least four weeks prior to study enrollment and must not have plans to change or initiate endocrine regimens during the study period.

6.1.3 Fatigue: Reports moderate fatigue on most days within the past week (i.e., at least 4 out of the last 7 days), rated as ≥ 4 on a 0 (no fatigue) to 10 (worst fatigue) scale.

6.1.4 Able and willing to complete study tasks as evidenced by at least the following: fluent English speaker; hearing and language comprehension; and, sufficient literacy to complete study forms and questionnaires

6.1.5 Patient understands the study regimen, its requirements, risks, and discomforts, and is able and willing to sign an informed consent form.

6.2 Exclusion Criteria

6.2.1 Evidence of recurrent breast cancer at the time of enrollment.

6.2.2 Dementia as assessed by a MMSE score < 24 on initial screening.

6.2.3 Known pregnancy or nursing.

6.2.4 Any of the following: diagnosis of schizophrenia or bipolar disorder made by a physician, seizure disorder, pacemaker, hearing aids, any metal implanted in the head, or the presence of other known current untreated causes of fatigue such as anemia (defined as Hgb < 10 g/dL within 3 months of study enrollment) or untreated hypothyroidism.

6.2.5 Use of the following medications for seven days prior to and during study participation:

i. Stimulant medications
ii. Sleep medications
iii. Carbamazepine/Tegratol
i. Cough/cold medicines (e.g. Dextromethorphan, Triaminic, Robitussin, Vics Formula 44)
ii. Flunarizine/Sibelium
iii. Propnolol/Inderal

iv. Sulpiride
v. Pergolide
vi. Rivastigmine/Exelon
vii. Carbidopa/levodopa or levodopa
viii. Ropinirole/Requip
ix. Nicotine patch

6.2.6 Use of narcotic pain medication, benzodiazepines, or illicit drugs for seven days prior to and during study participation.

6.2.7 Self-reported consumption of > 14 alcoholic drinks per week or positive screening on the CAGE questionnaire in relation to the past year. NOTE: A single, standard alcoholic drink is defined as 10 grams of alcohol, which is equivalent to 285 mL of beer, 530 mL of light beer, 100 mL of wine or 30 mL of liquor.

6.2.8 Skin conditions involving open sores on the scalp that would prevent proper application of the electrodes.

6.2.9 Hairstyles that obstruct placement of the electrodes including cornrows, dreadlocks, braids or other hair accessories that cannot be removed.

6.2.10 Other medical or other condition(s) that in the opinion of the investigators might compromise the objectives of the study

6.3 Inclusion of Women and Minorities

Individuals of all races and ethnic groups are eligible for this trial. Breast cancer is predominantly a disease of women and we anticipate that the majority of participants will be women.

7. STUDY DESIGN AND TREATMENT PLAN

7.1 Summary

We propose a straightforward randomized sham-controlled double-blind crossover trial of active tDCS versus sham tDCS.

Participants will complete two five-day study waves separated by a four-week washout period. During each wave, participants will complete a brief cognitive battery and study questionnaires on the first and last day of the study wave (i.e., Monday and Friday). On all five days of each wave, participants will engage in cognitive tasks while receiving stimulation (either active or sham) in order to maximize stimulation effects [27]. In order to assess for duration of subjective effects, participants will complete self-report measures of subjective fatigue, mood, and cognition by phone approximately seven days after the final day of the first study wave. After a washout period of four weeks, participants will repeat a second study wave wherein they engage in the same study procedures while receiving the opposite stimulation condition (active/sham); again followed by a phone call for subjective ratings of fatigue, mood, and cognition.

Basic Study Schedule*				
Days 1 – 5	**Day 12**	**Days 6 – 35**	**Days 36 – 40**	**Day 47**
Wave 1		Washout	Wave 2	Follow-up
5 consecutive daily study visits (Monday-Friday)	15-minute study phone call	No study activities	5 consecutive daily study visits (Monday-Friday)	15-minute study phone call

* See Study Calendar, Section 8, for detailed schedule and scheduling windows/allowances.

7.2 Recruitment

Patients will be recruited through referrals from their Oncologists, including, but not limited to those at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. Additionally, interested participants may contact the study team directly through study fliers distributed to physician offices and patient support groups.

Potential participants may be identified during chart review in advance of a routine clinic visit or during a routine clinic visit with a provider. Individuals will be approached by the provider or study team to determine willingness to learn more about a study for which they may be eligible. Discussions regarding study participation will take place privately and individuals will be provided with the IRB approved consent form.

In addition, potential participants may contact the study team directly. This contact may be in the form of telephone, email, etc. Initial discussions regarding study participation may take place by phone, email, etc., and individuals may be provided with the IRB approved consent form and other IRB reviewed and approved materials (e.g., Patient Handout), as applicable.

In all cases, as much time as is needed to consider study participation will be allowed to possible participants; resulting in multiple phone calls, visits, emails, or other communication, as necessary. For individuals who choose to take part, informed consent will happen as per the consent process.

7.3 Determination of Eligibility

Preliminary eligibility for participation will be reviewed by a member of the study staff via a telephone screening process (Appendix). For patients who reach the study team without referral of their treating provider, a member of the patient's oncology care team will be consulted to confirm that s/he believes that the participant is appropriate for protocol participation. Patients who appear to be eligible after the telephone screening will be invited to meet with the study team. At this time, consent will be obtained and eligibility then confirmed including the completion of the screening assessments detailed in section 7.6.1.

Upon confirmation of eligibility, patients will be registered into the study, at which time a study-specific subject ID/number will be assigned. Patients who are found not to be eligible will be considered screen failures. PHI will be retained to justify screen failures, and will be stored under the same secure conditions as all study-related data for the length of the trial.

Randomization will occur after study registration.

Study intervention cannot begin until the patient has provided consent, is confirmed eligible, and is successfully registered and randomized.

7.4 Randomization and Blinding

Upon eligibility confirmation and study registration, participants will be randomized to receive active or sham tDCS during the first five-day study wave (to be followed by the opposing condition in the second five-day study wave). This is a double-blind study. Both the participant and study team members will remain blinded to the application of active or sham tDCS throughout the course of an individual's study participation.

The tDCS device (NeuroConn DC Stimulator Plus Model 0021) comes with a list of pre-programed five-digit numeric codes that are manually entered into the stimulator by the study team member at the time of an individual's study participation. These codes cause the device to deliver either active or "pseudo stimulation" (i.e., sham stimulation). Pairs of two codes (one active, one sham) for each participant will be aggregated by a study statistician who will then provide these pairs, and their order of administration, to a member of the study team in a way that the stimulation condition is not known (i.e., only the numeric codes and administration order will be relayed, not the key linking the codes to the stimulation condition).

All participants will be asked whether they thought that they received active or sham stimulation during each wave. This will take place at the end of the fifth day of the final study wave as part of the side effects questionnaire.

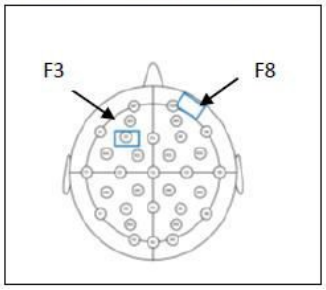
7.5 Methods and Intervention

7.5.1 tDCS

TDCS will be administered to relatively localized brain regions using the international 10-20 classification system to apply electrodes to the head. See Figure 3.Current will be administered via 25-100 cm^2 saline-soaked sponge electrodes. To affect the left prefrontal region, the active electrode will be placed over the left prefrontal region (F3) and adhered via an adjustable

rubberized head strap. The indifferent (reference) electrode will be placed over the right supraorbital region (F8) and will also be affixed via an adjustable rubberized head strap.

Figure 3. Electrode montage



7.5.1.1 Active Stimulation

Under the active stimulation condition, 30 minutes of 2mA stimulation will be applied to the left DLPFC (F3) daily over the course of five consecutive days (Monday-Friday). The rationale for this approach is based on prior studies exploring left DLPFC stimulation to enhance cognition [27-30,38] and reduce fatigue [33-35], as well as Ohn's work [26] documenting greater effects of tDCS on working memory following longer stimulation periods and Fregni's work [38] documenting persistence of effects when stimulation is administered over multiple occasions. This approach has also proven useful in treatment of fatigue in medical patients[33-35].

7.5.1.2 Sham Stimulation

Under the sham stimulation condition, participants will wear the electrodes in the same manner as active stimulation (F3, F8) for 30 minutes.

During sham stimulation, a small current pulses every 550 ms (110 μA over 15 ms) rather than delivering constant current as is done in the active stimulation condition. This brief period of stimulation causes a slight itching or tingling sensation similar to that experienced during the initial period of active stimulation. During active stimulation, participants usually habituate to the physical sensations within 30-60 seconds[42]; which is the characteristic that is thought to allow sham stimulation to be effective without delivering enough current to modulate neural networks.

All other study activities including self-report measures and cognitive training will remain identical across active and sham stimulation sessions.

7.5.1.3 Dose and Application

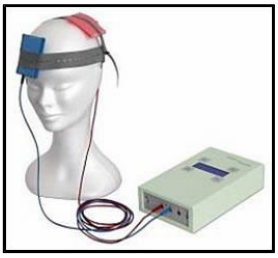
The dose and duration of stimulation administered under the active and sham conditions will remain identical for all participants. Under the active condition, 2mA of current will be delivered for 30 minutes. Under the sham condition, only brief pulses will be administered during the 30-minute session.

1. On each study day just prior to the application of electrodes, a participant's head will be measured in order to identify their F3 location.
2. The sponge electrodes will be moistened with saline prior to insertion of the rubber electrode and placement on a participant's head.
3. Electrodes will be affixed via adjustable rubberized straps.
4. The numerical condition code will be entered into the NeuroConn DC Stimulator Plus device, which will then administer 30 minutes of either active or sham stimulation.

7.5.2 NeuroConn DC Stimulator Plus

tDCS has been established as a valid and reliable tool for at least temporarily affecting brain and behavior with minimal risks (for review, see [22] and [43]). Stimulation will be delivered by a NeuroConn DC Stimulator Plus (Model 0021), which is a battery-driven constant current stimulator. See Figure 4. The NeuroConn stimulator is certified as an active medical device (class IIa) by the European Union Notified Body 0118, and has been safely used in scores of published tDCS studies around the world.

Figure 4.



The stimulator is not connected to a mainline power source and cannot produce more than 4.5 mA of current. The current density, as indexed by stimulation strength (A)/electrode size, is a relevant parameter for inducing neuronal damage [44]. We will be remaining within the recommended current density safety guidelines of 40 μC/cm2 *ph [44]. We also reviewed the safety notes in the operator manuals provided by the manufacturer of the device. The stimulation parameters in the planned investigation do not exceed the stimulation limits or violate the safety directives specified in the operator manual.

The active constant current and sham current settings both enable an impedance control that reliably detects any electrode disconnection. In the event of an electrode disconnection, the experimenter is alerted and the device automatically stops delivering current. The 30-minute dose delivery session is paused briefly while the electrode is quickly reaffixed to the head, reinitiating the electrical circuit. The 30-minute stimulation session is promptly resumed.

We will use non-metallic, conductive rubber electrodes covered by saline-soaked sponges to minimize the potential for chemical reactions at the interface of the scalp or skin and the electrodes.

Following IRB approval, the NeuroConn DC Stimulator Plus device will undergo evaluation by Johns Hopkins Clinical Engineering. Both active and sham tDCS will be administered by a trained study team member.

7.5.3 Cognitive tasks during stimulation

During each stimulation session under both active and sham tDCS conditions, participants will engage in a computerized working memory n-back task that continuously adapts to the performance of the individual, remaining equally engaging and demanding over the course of training and across individuals of varying working memory ability [45,46].

7.6 Study Assessments

Participants are expected to spend no longer than two hours completing cognitive testing and questionnaires on any given study day. This battery of cognitive tools and questionnaires consists of instruments that are routinely used in the clinical setting with medically frail and elderly patients. Their completion is not expected to result in increased fatigue in study participants. Nonetheless, breaks will be taken as necessary and appropriate in order to facilitate participant comfort and engagement.

7.6.1 Screening Instruments
Screening instruments will be administered at study entry and will take approximately 12 minutes to complete.

7.6.1.1 Mini Mental State Exam (MMSE; [47]). Participants will complete the MMSE, a brief cognitive screening measure that assesses orientation, attention, learning/memory, language functioning, and visuoconstruction skills. Administration requires approximately five minutes and will be used to ensure that all participants meet our stated inclusion criteria (i.e., non-demented as defined by a MMSE score ≥24).

7.6.1.2 CAGE [51]. The CAGE questionnaire is a widely used 4-item screening instrument for problem drinking. Each item is scored 0 (absent) or 1 (present). Scores ≥ 2 are considered clinically significant. Scores on the CAGE along with the patient's report of the number of alcoholic drinks consumed per week will be used to ensure that all participants meet our stated inclusion criteria with respect to alcohol consumption. Included within Appendix P.

7.6.1.3 Quantitative Fatigue Assessment. Potential participants will be asked to rate their fatigue on a 0 (no fatigue) to 10 (worst fatigue imaginable) scale in order to ensure that the study enrollment is limited to those with reports of at least moderate fatigue, as stated in our inclusion criteria. Consistent with ASCO guidelines for assessment of fatigue in cancer [52], scores of ≥ 4 will be considered indicative of at least moderate fatigue.

7.6.2 Tools to Assess Primary and Secondary Endpoints
The primary and secondary endpoints will be assessed at the beginning and end of each five-day study wave in-person (i.e., subjective cognition and fatigue), and approximately seven days after the last stimulation session by phone (i.e., subjective cognition and fatigue). In-person testing will take approximately 20 minutes; whereas, testing via phone will take approximately 10 minutes.

7.6.2.1 Paced Auditory Serial Attention Test (PASAT) [1,2]. The primary measurement tool for assessing objective cognitive functioning will be performance on the PASAT.

The PASAT is working memory task that has been well-validated medical populations including breast cancer[53]. Test administration involves the aural presentation of single digits via computer in order to ensure a standardized rate of stimulus presentation. Stimuli are presented every three seconds (trial 1) or every two seconds (trial 2). Participants add each new digit to the one immediately prior as the test continues to

present stimuli. The test score reflects the total number of correct sums given (out of 60 possible) in each trial.

Two equivalent, alternative PASAT forms will be used to minimize practice effects. The test takes approximately 10 minutes to complete. It will be completed prior to and following both five-day active anodal and sham stimulation conditions (i.e. on four occasions). Available data indicates that prior to adjuvant treatment, breast cancer patients with stage I-III disease score an average of 46.6 ± 11.2 on the PASAT trial 1 (3 second administration) and an average of 34.3 ± 10.1 on trial 2 (2 second administration)[54].

7.6.2.2 Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog version 3)[55]. The measurement endpoint for subjective cognition will be scores on the FACT-Cog, a 37-item self-report measure addressing cognitive difficulties and their effect on patient quality of life. The measure addresses six cognitive domains (memory, concentration, mental acuity, verbal fluency, functional interference, and multitasking). The questionnaire is easy to use and appropriate for individuals with a history of cancer of varying age groups and backgrounds.

Responses are provided on 5-point Likert scales addressing the frequency with which each type of cognitive difficulty occurred from 0, "never" to 4, "several times a day" over the prior seven days. Two additional subscales address "noticeability" or comments from others regarding cognition and "effect of perceived cognitive impairment on quality of life." These are rated on 5-point Likert scales ranging from 0, "not at all" to 4, "very much." The total FACT-Cog score is obtained by summing the individual subscale scores and ranges from 0 to 148. Breast cancer patients produce a mean FACT-Cog total score of 119.0 ± 23.3.[56]

The FACT-Cog takes approximately 5 minutes to complete. It will be completed prior to and following both five-day active anodal and sham stimulation conditions (i.e. on four occasions). It will also be completed by phone (taking approximately 5 minutes) seven days (± three days) after the final (fifth) stimulation session of each study wave in order to assess for persistence of stimulation effects.

7.6.2.3 Multidimensional Fatigue Symptom Inventory 30-item short form (MFSI-SF)[57]. The primary measurement tool for subjective fatigue will be the MFSI-SF, which assesses participants' subjective ratings across five empirically derived subscales (general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor). Responses are provided on 5-point Likert scales addressing the extent to which each symptom was experienced during the preceding week (0, not at all to 4, extremely). The five subscale scores are obtained by summing scores within each subscale. The MFSI-SF total score is obtained by subtracting the vigor subscale score from the sum of the four fatigue subscales. Scores range from -36 to 144.

The MFSI-SF is well validated in breast cancer patients[58,59]. Breast cancer patients with fatigue produce an average score of 14.7 ± 15.2[60].

The MSFI-SF takes approximately 5 minutes to complete. It will be completed by all study participants prior to and following both five-day active anodal and sham stimulation conditions (i.e. in person on four occasions). It will also be completed by phone (taking approximately 5 minutes) approximately seven days (± three days) after the final (fifth) stimulation session of each study wave in order to assess for persistence of stimulation effects.

7.6.3 Tools to Assess Exploratory Endpoints

In order to determine which domains of cognition are improved by five consecutive days of tDCS, other objectively assessed cognitive skills will be assessed at the beginning and end of each study wave. Testing will take approximately 40 minutes and will include the following outcomes:

7.6.3.1 Hopkins Verbal Learning Test- Revised (HVLT-R)[3]. The HVLT-R is designed to evaluate verbal learning and memory. The task takes approximately 8 minutes to complete. Participants attempt to memorize a list of 12 items presented aloud over 3 consecutive learning trials (learning score). After a 20-25 minute delay (during which time other cognitive tests are administered) they are asked to recall as many words as possible (recall score) and to identify word list items from a list of targets and distractors (recognition score). Scores on the learning trial range from 0 – 36, the recall trial from 0 to 12, and the recognition trial from -12 to 12. The HVLT-R has six alternate forms. Scoring and interpretation are simple and outlined in a professional manual. Normative data are available in the form of demographically-adjusted T-scores[4].

The reliability and validity of the HVLT-R as a measure of new learning and memory has been demonstrated in a variety of patient populations and healthy controls [61]. Clinical trials have repeatedly shown it to be sensitive to the impact of cancer and treatment-related neurotoxicities[62-65]. It was also recommended for inclusion in a core set of neurocognitive tests by the International Cognition and Cancer Task Force (ICCTF)[11]. Breast cancer survivors have been shown to produce a mean HVLT-R learning z-score of -0.44 ± 1.23[63].

7.6.3.2 Brief Visuospatial memory Test (BVMT-R[4]). The BVMT-R serves as the nonverbal analogue to the HVLT-R. Here, participants are presented with six figures on a page for ten seconds. The stimuli are removed and participants are asked to reproduce the figures from memory. As with the HVLT-R, there are three learning trials (learning score). After a 20-25 minute delay (during which time other cognitive tests are completed) they are asked to reproduce the stimuli (recall score) and identify the figures from an array of targets and distractors (recognition score). Scores on the learning trial range from 0 – 36, the recall trial from 0 to 12, and the recognition trial from -6 to 6. The task takes approximately 8 minutes to complete. The BVMT-R has six alternate forms. Scoring and interpretation are simple and outlined in a professional manual. Normative data are available in the form of demographically-adjusted T-scores [4].

7.6.3.3 Trail Making Test (TMT). The Trail Making Test is composed of two parts (A and B).

Part A is designed to evaluate visual motor scanning and processing speed, while part B is designed to evaluate executive functioning [66]. These tests require patients to connect circles in numerical (part A) or alternating numerical and alphabetical sequence (part B) as quickly as possible. Results are reported as the number of seconds required to complete each part, with higher scores reflecting higher degrees of impairment (range 0 – 300 seconds per trial). Normative data are available in the form of demographically adjusted T-scores[67,68]. The entire task takes approximately five minutes to complete.

The Trail Making Test[23] is a well-established neuropsychological measure with solid psychometric properties [69]. Clinical trials have repeatedly shown it to be sensitive to the impact of cancer and treatment-related neurotoxicities[62-65]. It was also recommended for inclusion in a core set of neurocognitive tests by the ICCTF[11]. Breast cancer survivors have been shown to produce z-scores of 0.56 ± 1.29 on part A and 0.15 ± 1.22 on part B.[63]

7.6.3.4 Calibrated Ideational Fluency Assessment (CIFA)[7]. The CIFA verbal fluency trials are designed to evaluate verbal fluency and executive functioning. The task requires patients to name as many words as possible beginning with two different letters (letter fluency) and that belong to two different categories (category fluency) over four separate one-minute trials. The task takes approximately five minutes to complete. Scoring is based on the number of correct words produced over the course of the four trials, with greater values reflecting better performance. Normative data are available in the form of demographically adjusted T-scores [7].

Tests of verbal fluency are reliable and well-validated tests of cognitive processing[69,70]. Clinical trials have repeatedly shown verbal fluency performance to be sensitive to the impact of cancer and treatment-related neurotoxicities[62-65]. This type of task was also recommended for inclusion in a core set of neurocognitive tests by the ICCTF[11].

7.6.3.5 Wechsler Adult Intelligence Scale-Fourth edition (WAIS-IV) Digit Span subtest[5] . The Digit Span subtest assesses simple attention and working memory. Participants are read aloud increasingly lengthy strings of digits and are asked to repeat these strings in forward and backward sequences. The number of digit strings correctly completed forward, backward, and overall serve as outcome measures. The test takes approximately five minutes to complete. Normative data in the form of demographically adjusted scaled scores are available in a professional manual [71].

The Digit Span subtest of the Wechsler scales has excellent psychometric properties and is an extremely well-validated measure of simple attention and working memory[71]. It has repeatedly been shown to be sensitive to cancer and treatment-related neurotoxicity[72-74]. Normative data are available in the form of demographically adjusted scaled scores. Breast cancer survivors have been shown to produce scaled scores of 10.04 ± 2.67 on the Digit Span test.[63]

7.6.3.6 Grooved Pegboard Test[8]. The grooved pegboard test is a well-validated test of manual speed and dexterity that has been shown to be sensitive to treatment-related neurotoxicity in breast cancer patients[75]. The test involves placing grooved pegs into

variously oriented holds in a small board as quickly as possible. Participants complete the task with the dominant hand followed by the non-dominant hand. The test takes approximately five minutes to complete. The test is scored according to the number of seconds required to complete the board using each hand (range 0 – 300 seconds per hand). Published normative data are available in the form of demographically-adjusted T-scores.[68]

7.6.4 Patient Reported Outcomes to be assessed at the Beginning and End of each five-day Study Wave

Symptoms of anxiety, depression, sleep quality, and quality of life will be administered prior to and following each five-day study wave (i.e. on four occasions). Testing will take approximately 15 minutes.

7.6.4.1 Hospital Anxiety and Depression Scale (HADS)[48]. Depression and anxiety are common in breast cancer survivors [49,50] and can negatively affect cognitive functioning including working memory and processing speed[69] as well as functioning of the DLPFC[76]. In order to determine whether changes in mood or anxiety are contributing to changes in the primary outcome variables, participants will complete the HADS[48], a brief, well-validated[77] self-report questionnaire addressing symptoms of anxiety and depression experienced over the previous seven days. In addition to being administered prior to and following each five-day study wave, it will also be administered at both study phone calls (i.e. study days 12 and 47). It takes approximately five minutes to complete.

7.6.4.2 Pittsburgh Sleep Quality Index. In order to control for any differences in sleep quality that may affect fatigue ratings, participants will complete the Pittsburgh Sleep Quality Index prior to and following both five-day active anodal and sham stimulation conditions (i.e. on four occasions) [78]. This questionnaire assesses sleep quality and disturbances over the prior month. It takes approximately 5 minutes to complete.

7.6.4.3 EORTC Quality of Life Questionnaire (QLQ-C30). Quality of life is frequently diminished in breast cancer survivors and is associated with greater rates and severity of fatigue [79] and depression[80]. In order to control for any differences in quality of life that may affect self-reported fatigue and mood, participants will complete the EORTC Quality of Life Questionnaire (QLQ-C30). This self-report measure assesses health-related quality of life in cancer patients participating in clinical trials. Via five functional scales, three symptom scales, and a global health status measure, the QLQ-C30 addresses physical, role, emotional, cognitive and social functioning as well as symptoms of fatigue, pain, insomnia and others in a 30-item questionnaire. This questionnaire takes approximately 5 minutes to complete.

7.6.5 Additional Assessments

Prior to receiving the first session of active tDCS stimulation or sham stimulation (i.e., at baseline), all participants will spend approximately 30 minutes completing several questionnaires and brief cognitive tests to provide the information necessary to describe our sample characteristics fully and to adjust for participant characteristics in our statistical analyses.

7.6.5.1 History Form. Other characteristics with known associations with performance on tests

of higher-order cognition include illiteracy, English as a second language, educational attainment, occupation, history of learning disabilities, substance abuse and health behaviors that impact cerebral vasculature, other cerebrovascular risk factors, psychiatric and systemic illness and their treatment, traumatic brain injury, family history of several of the above-mentioned variables, and use of disease-modifying drugs and cognitively enhancing drugs such as psychostimulants or caffeine. Conditions associated with fatigue include anemia, thyroid dysfunction and cardiac dysfunction. As such, we will ask participants to complete a history form addressing these issues at the start of their participation. The questionnaire takes approximately five minutes to complete.

7.6.5.2 Hopkins Adult Reading Test (HART)[81]. Verbal intelligence has been demonstrated to hold moderate correlations with various cognitive abilities. Premorbid IQ is also an important predictor of baseline cognitive dysfunction in cancer patients [82]. To estimate verbal intelligence, participants will complete the HART at baseline. This test requires participants to read aloud a list of 35 irregularly spelled words. The HART takes approximately 2 minutes to complete. Scoring is based on the number of items correctly pronounced, which is then converted into a standard score based on published normative data[68].

7.6.5.3 Edinburgh Inventory[83]. A history of left-handedness places one at greater probability of being right hemisphere dominant for language or for being of mixed dominance. Because this investigation seeks to alter some verbally-mediated cognitive abilities, knowledge of one's probability of being left hemisphere dominant for language will be an important consideration. The Edinburgh Inventory specifically assesses handedness and takes approximately 3 minutes to complete.

7.6.5.4 UCLA Loneliness Scale[84]. Loneliness is associated with subjective cognitive difficulties in breast cancer survivors[85]. As such, at the beginning of study participation participants will complete the UCLA Loneliness Scale, which addresses one's perceived social isolation and loneliness. This questionnaire takes approximately 5 minutes to complete.

7.6.5.5 NEO Five Factor Inventory- 3rd edition (NEO-FFI 3)[86]. Personality characteristics are related to fatigue and other factors in cancer patients, as well as with a tendency to respond to exhibit a placebo effect[87]. At baseline all participants will complete the NEO-FFI 3 in order to assess their standing on the five primary personality factors of openness, neuroticism, extroversion, agreeableness and conscientiousness. This questionnaire takes approximately 10 minutes to complete. Scores for each of the five factors are presented as T-scores.

7.6.5.6 TDCS Side Effects. Participants will also complete a brief questionnaire to assess physical sensations and mood experienced prior to and following each stimulation session (i.e. twice during all ten sessions) to document the presence and severity of any tDCS-related side effects. Participants will be asked to rate the severity of these experiences and to report any other sensations they were not asked about directly. At the end of the study each participant will also be asked whether they believed they were receiving active or sham tDCS during each of the two study waves, and they will rate

their degree of confidence with respect to those judgments. This task takes less than five minutes to complete.

NOTE: Please see questionnaires and cognitive tests in Appendices A through U.

7.7 Concomitant and Supportive Therapy

Participation in this study will not disrupt any current care of therapy. The concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, with the exception of the following:

The use of concurrent medications for fatigue, alertness or sleep will be assessed at the beginning of each study wave and will not be allowed as outlined in the exclusion criteria (above, Section 6.2).

7.8 Discontinuation and Withdrawal of Subjects

All patients who initiate protocol intervention will be included in the overall evaluation of response (intent-to-treat analysis). All reasons for discontinuation of intervention will be documented clearly in the record.

In the event that the intervention is stopped early and unless the subject refuses, follow-up will continue for the planned duration of the study to collect data for the study endpoints.

7.8.1 Discontinuation of Intervention

The reasons for discontinuation of protocol intervention include:

- Unacceptable major toxicity or inability to tolerate the tDCS procedures.
- Intercurrent illness or condition that would, in the judgment of the treating investigator, affect assessment of clinical status to a significant degree or require discontinuation of study intervention.
- Becoming pregnant or starting to nurse.
- Initiating the use of a prohibited medications that may interfere with the efficacy of tDCS.
- At subject's own request. Note: The reason for discontinuation from the study must be documented. The patients will be included in the overall evaluation of response (intent-to-treat analysis) if any protocol intervention was administered prior to withdrawal.
- Study is closed or cancelled for any reason.

7.8.2 Withdrawal from Study

The reasons for withdrawal from the study include:

- Subject withdraws consent for follow-up.
- Subject is lost to follow-up.
- Study is terminated for any reason.

7.9 Additional Information

All participants will be reimbursed for their direct participation, including time spent completing the consent and screening process and time spent completing study interventions, at the rate of $15.00 per hour or any fraction thereof. In addition, vouchers will be provided for parking in the event the participant is seen at a clinic where she must pay for parking. Reimbursement will be mailed by check at the end of the study (i.e., after both 5 day tDCS/sham sessions; preferred, if acceptable to the subject). If a subject chooses to terminate the testing session early or signs the consent but is ultimately deemed ineligible, she will still be reimbursed for the number of hours she has participated. Reimbursement will not be provided for the time spent during the follow-up telephone calls.

Participants will be involved in a study design that involves several test sessions, across a number of days. To encourage participants to finish the study, there will be an incentive of $50 at the completion of the final test session (by phone). Of course, as noted before, if a subject should choose not to complete the whole study, she will be paid for the portion(s) completed.

8. STUDY CALENDAR

Procedure	Screening	Intervention							End of Study
		Day(s)							
		1	2-4	5	12[b]	36	37-39	40	47[b]
Approximate Duration of Participation (minutes)	*12*	*140*	*45*	*115*	*10*	*115*	*45*	*115*	*10*
Consent, Demographics, Medical and Cancer History	X								
Concomitant Medication and Supplement Use	X					X			
Mini Mental State Exam	X								
CAGE	X								
Quantitative Fatigue Assessment	X								
Transcranial Direct Current Stimulation (active/sham)		X	X	X		X	X	X	
Computerized Working Memory Task[a]		X	X	X		X	X	X	
Paced Auditory Serial Attention Test		X		X		X		X	
Functional Assessment of Cancer Therapy Cognitive Scale		X		X	X	X		X	X
Multi-dimensional Fatigue Symptom Inventory		X		X	X	X		X	X
Hopkins Verbal Learning Test-Revised		X		X		X		X	
Brief Visuospatial Memory Test-Revised		X		X		X		X	
Trail Making Test Parts A and B		X		X		X		X	
Calibrated Ideational Fluency Assessment		X		X		X		X	
WAIS-IV Digit Span Subtest		X		X		X		X	
Grooved Pegboard Test		X		X		X		X	
Hospital Anxiety and Depression Scale		X		X	X	X		X	X
Pittsburgh Sleep Quality Index		X		X		X		X	
EORTC Quality of Life Questionnaire		X		X		X		X	
History Form		X							
Hopkins Adult Reading Test		X							
Edinburgh Inventory		X							
UCLA Loneliness Scale		X							
NEO-Five Factor Inventory - 3		X							
Side Effect Questionnaire[c]		X	X	X		X	X	X	

a. Computerized working memory task is administered during transcranial direct current stimulation
b. Day 12 and Day 47 assessments will be performed by phone -1/+3 days of days 12 and 47.
c. The side effect questionnaire will be completed before and after each transcranial direct current stimulation session (a total of 20 times). On days 5 and 40, participants will be asked if they believed they were receiving active or sham tDCS during the wave they have just completed and to rate their degree of confidence with respect to these judgments.

NOTE: If there is a greater than 21-day period between the screening procedures/determination of eligibility and the initiation of the study intervention, participants will be re-screened during an appointment reminder phone call approximately one week prior to the study intervention. We will permit a between-wave washout period of five rather than four weeks, in which case the second

wave and end of study will be delayed by seven days. The schedule should be followed as closely as is realistically possible; however, the schedule may be modified due to problems such as scheduling delays or conflicts (e.g., clinic closure, poor weather conditions, vacations, etc.) with the guidance of the Principal Investigator/designee, as appropriate, and will not be reportable as a deviation unless the endpoints of the study are affected.

9. ADVERSE EVENTS

In previous studies, a serious adverse event related to tDCS has been defined as that which is caused by tDCS and/or aggravated by tDCS and which results in: irreversible damage to brain tissue, persistent disability or incapacity, unexpected inpatient hospitalization, death or is life-threatening, or medical or surgical intervention to preclude impairment of a bodily function due to tDCS [43]. Bikson and colleagues recently reviewed the literature on over 33,000 tDCS sessions and 1,000 participants who underwent repeated tDCS sessions [43]. They found no reports of serious adverse effects or irreversible injury. Similarly, in our experience running over 125 healthy adults and patients through tDCS trials, we have not observed any serious adverse events. There have been a handful of patients who reported mild temporary skin irritation. Adverse events will be assessed through the tDCS Side Effects Questionnaire, which is administered before and after each stimulation session.

It has been demonstrated that tDCS does not: (1) cause heating under the electrodes; (2) result in harmful changes on MRI; or (3) alter levels of serum neuron-specific enolase, a sensitive marker of neuronal damage [24,88]. Many subjects (up to 71%) perceive a tingling sensation under the electrode during tDCS, although "ramping up" the current can eliminate this perception. Stimulation will be administered via saline-soaked sponge-covered rubber electrodes in order to minimize potentially unpleasant cutaneous sensations during both active and sham stimulation (itching, tingling, etc.). During tDCS, the most common partially adverse effects include mild tingling (71%), moderate fatigue (35%), and light itching under the electrode (30%). Following tDCS, the most common reported adverse effects are headache (12%), nausea (3%), and insomnia (<1%).[25] Taken together, all available research suggests that prolonged application should not pose a risk of brain damage when applied according to safety guidelines. There have been rare cases of temporary skin burns related to tDCS; these have all resolved. High electrical impedance at the site of electrode contact could theoretically have been the cause of such burns. The NeuroConn Stimulator Plus monitors electrical impedance and, as a safety precaution, the device terminates current flow if impedance exceeds 55kΩ. The completion of the side effects questionnaire will help determine whether participants experience any negative consequences of the stimulation and will add to the growing literature on tDCS safety and side effects.

9.1 General

In the case that adverse events related to the study intervention are reported, these will be recorded per the descriptions and grading scales found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for adverse event reporting that can be found at http://ctep.cancer.gov/reporting/ctc.html.

Information about all intervention-related adverse events, including those volunteered by the subject verbally or reported by the patient on the tCDS side effect questionnaire, discovered by investigator/study personnel questioning, or detected through other means, will be collected, followed, and reported appropriately.

Only adverse events thought to be related to tDCS will be collected, tracked and reported (as per section 9.2.4 on attribution). The adverse events related to any ongoing treatment for the patients' other medical conditions, including breast cancer, will not be collected.

All adverse events experienced by subjects will be collected from the time of first administration of tDCS (active or sham), throughout the study and until the final study visit. Subjects continuing to experience toxicity believed to be related to tDCS after discontinuation of the study may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

9.2 Definitions

9.2.1 Adverse event (AE): An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to the study.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol).

Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy.

9.2.2 Serious adverse event (SAE): A serious adverse event is an untoward sign, symptom, or medical condition which:

- results in death;
- is immediately life-threatening;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- jeopardizes the subject and requires medical or surgical intervention to prevent; or one of the outcomes listed above.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

A hospitalization planned before the start of study participation) and/or for a preexisting condition that has not worsened does not constitute a serious adverse event. A hospitalization for a social reason in the absence of an adverse event also does not meet the criteria for a serious adverse event.

The following events will also require expedited reporting for this protocol, similar to those events meeting the definition of SAE above:

- a female subject becomes pregnant while receiving investigational therapy, the pregnancy must be reported; follow-up to obtain the outcome of the pregnancy should also occur;
- abortion, whether accidental, therapeutic, or spontaneous, should additionally always be classified as serious, and expeditiously reported;
- exposure of a baby during lactation to study treatment

9.2.3 Expectedness

- Unexpected adverse event: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk

- Expected (known) adverse event: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current device manual or is included in the informed consent document as a potential risk.

9.2.4 Attribution

The relationship of all adverse events and serious adverse events to the study intervention will be assessed by an investigator and assigned as follows:

- Definite: The AE is clearly related to the study treatment. An adverse event which has a timely relationship to the administration of the investigational intervention, follows a known pattern of response, for which no alternative cause is present.
- Probable: The AE is likely related to the study treatment. An adverse event, which has a timely relationship to the administration of the investigational intervention, follows a known pattern of response, but for which a potential alternative cause may be present.
- Possible: The AE may be related to the study treatment An adverse event, which has a timely relationship to the administration of the investigational intervention, follows no

known pattern of response, but a potential alternative cause does not exist.

- Unlikely: The AE is doubtfully related to the study treatment. An adverse event which does not have a timely relationship to the administration of the investigational intervention, follows no known pattern of response, does not reappear or worsen after re-administration of the investigational intervention (if applicable), and for which there is evidence that it is related to a cause other than the investigational agent.
- Unrelated: The AE is clearly NOT related to the study treatment. An adverse event, for which there is evidence that it is definitely related to a cause other than the investigational intervention. In general, there is no timely relationship to the administration of the investigational intervention, or if there is a timely relationship, the event does not follow a known pattern of response, and there is an alternative cause.

Only adverse events which are definitely, probably or possibly related to tDCS will be tracked, recorded and reported for this study.

9.3 Reporting Procedures

9.3.1 General

All adverse events will be captured on the appropriate study-specific case report forms (CRFs).

9.3.2 Serious Adverse Events

All serious adverse events, regardless of causality to study intervention, will be reported to the Principal Investigator.

9.3.3 Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as is possible.

10. DATA AND SAFETY MONITORING

10.1 Data Management

All information will be collected on study-specific case report forms by the study staff. In the event that an electronic database is used, the following procedures will apply:

- The database will be password protected; only authorized staff may enter and view study data.
- Passwords and system IDs will not be shared.
- Physical security of the workstations/files will be maintained.
- Staff is trained on the data entry system and importance of security procedures.
- Workstations with the database open will not be left unattended.

All study data will be reviewed for completeness and accuracy by the Principal Investigator. The study data may also be periodically reviewed by the Sidney Kimmel Comprehensive Cancer Center Clinical Research Office.

10.2 Meetings

The study staff will schedule meetings, as needed, depending on the rate of accrual, and will include the Protocol Chair, Co-Chair, and the following study team members as appropriate: study coordinators, data managers, research nurses, sub-investigators, collaborators (if applicable), and statistician.

During these meetings matters related to the following will be discussed: enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), validity and integrity of the data, safety data, analysis of samples, and progress of data for objectives.

10.3 Monitoring

This is a Level I study under the SKCCC Data Safety Monitoring Plan. The principal investigator is responsible for internally monitoring the study and establishing additional external data and safety monitoring oversight, as required. The principal investigator will also monitor the progress of the trial, review safety reports, and confirm that the safety outcomes and response assessments favor continuation of the study.

The study involves a device, NeuroConn DC Stimulator Plus Model 0021, that meets the criteria for non-significant risk (NSR) for which an IDE from the FDA is not required for the clinical trial outlined [89].

This study will be monitored per the SKCCC Data Safety Monitoring Plan. The Clinical Research Office QA Group will perform an audit as the specified intervals. All trial monitoring and reporting will be reviewed at least annually by the SKCCC Safety Monitoring Committee.

11. ADMINISTRATIVE PROCEDURES

11.1 Protocol Amendments

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB before implementation. The Principal Investigator (or her designee) is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating centers.

11.2 Informed Consent

Those members of the research team (principal investigator, co-investigator, research staff) who consent patients have been trained in informed consent procedures, are familiar with the protocol, and are listed as a consenter in the application document. Patients are given adequate time and privacy to consider the research study. Before the patient signs the consent, the consenter must be satisfied that the participant understands the information provided, has had an opportunity to discuss the information and ask questions, and is aware that he/she may withdraw from the study at any time.

The investigator (or her designee, as appropriate) will explain to each subject the nature of the study, its purpose, procedures involved, expected duration, potential risks and benefits. Each subject will be informed that participation in the study is voluntary and that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment. This informed consent will be given by means of a standard written statement and will be submitted for IRB approval prior to use. No patient will enter the study before her informed consent has been obtained.

In accordance with the Health Insurance Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

11.3 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations)
- Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996)

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice.

12. STATISTICAL CONSIDERATIONS

12.1 Overall

12.1.1 The primary outcome measure will be performance on the PASAT. Specifically, our primary hypothesis is that anodal tDCS will result in greater offline (i.e. post-versus pre-stimulation) improvement in objective cognitive test scores after multiple days than does sham stimulation. Our primary outcome variable reflects the difference between pre- and post-anodal stimulation compared to pre- and post-sham stimulation, or [(score before anodal minus score after anodal)-(score before sham minus score after sham)].

12.1.2 Our secondary outcome measures will be subjectively rated fatigue and cognitive functioning as indexed by scores on the MFSI-SF and FACT-Cog. Specifically, our primary hypothesis is that anodal tDCS will result in greater offline (i.e. post-versus pre-stimulation) improvement in subjective fatigue and cognition after multiple days than does sham stimulation. Our secondary outcome variables reflects the difference between pre- and post-anodal stimulation compared to pre- and post-sham stimulation, or [(score before anodal minus score after anodal)-(score before sham minus score after sham)].

12.1.3 Exploratory outcome measures will include scores on other objective cognitive tests; disease-, treatment- and person-related predictors of response to tDCS intervention; and side effects of active and sham tDCS intervention as outlined above.

12.2 Sample Size and Accrual

The proposed study is a randomized, sham-controlled, double-blind, cross-over experiment. Each participant will receive five consecutive days of active tDCS and five consecutive days of sham stimulation in a random order, with a 4 to 5-week washout period in between. The primary endpoint is the difference in PASAT score before and after active/sham tDCS. The effect of tDCS in working memory performance will be evaluated by comparing the change in PASAT score before and after tDCS with that before and after sham stimulation. The null hypothesis is that tDCS usage will yield the same mean change in PASAT score as the sham stimulation.

Our accrual goal is to have 45 patients complete the crossover experiments with both active and sham tDCS. In the multiple sclerosis literature studies with a similar design have reported an attrition rate of approximately 10%[33-35]. Hence, to achieve the target accrual, we expect to enroll 50 breast cancer patients, with the expectation that 5 may not complete the crossover experiments. This sample size (n=45) will yield at least 80% power to detect a medium effect size (Cohen's d) of 0.43 or greater at a two-sided type I error rate of 5% using paired t-test.

12.3 Analysis Plan

The comparison between active tDCS and shame stimulation in change in PASAT score will be performed using a two-sided paired t-test based on data from participants who complete the crossover experiments. We will also use a linear mixed effects model to evaluate the effect of tDCS in the change in PASAT score by including data from all participants who complete at least one study wave.

For secondary and exploratory endpoints, pre- and post-stimulation scores, including scores on the PASAT, FACT-Cog, and MFSI-SF, and the corresponding changes in scores (post-pre) after five consecutive days of stimulation will be summarized using descriptive statistics and displayed graphically for each stimulation condition. Data may be transformed as appropriate to reduce skewness and improve symmetry. To account for correlation among multiple measurements within the same patient, linear mixed effects models will be used to evaluate the effect of tDCS, where the outcome is the change in scores (post-pre stimulation) and the covariates will include the indicator of the stimulation condition. Other covariates in the exploratory analyses may include but not be limited to the order of the experiments (for assessing carryover effects), number of days receiving active/sham stimulations, baseline fatigue, depression, anxiety, loneliness, handedness, cancer stage, and cancer treatment. The change in MFSI-SF and FACT-Cog score obtained (via phone) seven days after each study wave will be analyzed using the same approach. Exploratory sensitivity analyses will be carried out to examine if dropout/missingness is informative.

Data analyses will be performed by the study statistician, Dr. Chiung-Yu Huang.

12.4 Reporting and Exclusions

Subjects who sign a consent form, but do not initiate protocol intervention for any reason (e.g., subjects who are screen failures), will be replaced and will not count towards our accrual goal.

APPENDICES

A Medications and Supplements
B Hospital Anxiety and Depression Scale
C Mini Mental State Exam
D Quantified Fatigue Assessment
E Paced Auditory Serial Attention Test
F Functional Assessment of Cancer Therapy Cognitive Scale
G Multi-Dimensional Fatigue Symptom Inventory
H Hopkins Verbal Learning Test- Revised
I Brief Visuospatial Memory Test- Revised
J Trail Making Tests Part A and B
K Calibrated Ideational Fluency Assessment
L WAIS-IV Digit Span subtest
M Grooved Pegboard Tests
N Pittsburgh Sleep Quality Index
O EORTC Quality of Life Scale
P History Form
Q Hopkins Adult Reading Test
R Edinburgh Handedness Inventory
S UCLA Loneliness Scale
T NEO-Five Factor Inventory-3
U Side Effects Questionnaire
V Stimulation Detection

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