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NEUROSTIMULATION IN ADULT SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

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Protocol MNEMONIC and Title: NEUROSTIM NEUROSTIMULATION IN ADULT SURVIVORS OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)
Principal Investigators: Tara Brinkman, PhD & Kevin Krull, PhD
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Brief Overview: Long-term survivors of ALL are at-risk for neurocognitive impairment, particularly in the area of executive functioning. Relatively limited research has focused on interventions for improving neurocognitive outcomes in long-term survivors of ALL. A promising technique for cognitive enhancement is Transcranial Direct Current Stimulation (tDCS) which differs from conventional cognitive remediation approaches in that it directly stimulates specific brain regions responsible for cognitive processes and activates functional networks similar to those activated during cognitive training.
Intervention: Eligible participants will be randomized to receive 1 mA direct current stimulation over the left dorsolateral prefrontal cortex or placebo/sham for 20 minutes. All participants will receive home-based computerized cognitive training. Participants will complete tDCS paired with cognitive training at least 2 times per week for 6-months.
Study Design: Double-blind randomized placebo-controlled trial
Sample Size: Approximately 104 research participants
Data Management: Data management for this study will be supervised by the Neuropsychology Research Team and Clinical and Survey Research Center in the Department of Epidemiology and Cancer Control. Statistical analysis will be provided locally by the Biostatistics Department at St. Jude Children's Research Hospital.
Human Subjects: There is low risk to participants related to active tDCS. Potential side effects include redness and slight tingling at the site of stimulation, and all side effects are reversible. Recent meta-analyses show side effects to occur no more frequently than placebo conditions. Our pilot data show comparable side effects among adult survivors of ALL treated with active tDCS vs. sham. The study will involve direct assessment using standard clinical neurocognitive measures and MRI. Both modalities are non-invasive and routinely used for assessment of patients with cancer and survivors of childhood cancer. Adverse events will be monitored, reported, and treated accordingly.

TABLE OF CONTENTS

1.0 OBJECTIVES 1
2.0 BACKGROUND AND RATIONALE 3
3.0 RESEARCH PARTICIPANT ELIGIBILITY CRITERIA AND STUDY ENROLLMENT 10
3.1 Inclusion Criteria 11
3.2 Exclusion Criteria 11
3.3 Research Participant Recruitment and Screening 12
3.4 Enrollment on Study at St. Jude 12
3.5 Procedures for Identifying and Randomizing Research Participants 12
4.0 DESIGN AND METHODS 13
5.0 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS 20
6.0 CRITERIA FOR REMOVAL FROM PROTOCOL 21
7.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS 22
8.0 DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY 24
9.0 STATISTICAL CONSIDERATIONS: 26
10.0 OBTAINING INFORMED CONSENT 30
11.0 EMERGENCY UNBLINDING 31
APPENDICES 32
12.0 REFERENCES 33

1.0 OBJECTIVES

Adult survivors of childhood acute lymphoblastic leukemia (ALL) treated with cranial radiation, intrathecal methotrexate (MTX), or high dose intravenous MTX and/or cytarabine are at risk for neurocognitive morbidities, particularly in the domain of executive function. Deficits in executive function have been associated with reduced educational attainment, employment, and emotional functioning. We have recently identified that higher treatment intensity, as reflected through serum concentration of MTX, is associated with worse executive functioning, increased brain activation in dorsolateral prefrontal regions based on functional MRI, and decreased myelin integrity in frontostriatal tracts based on diffusion tensor imaging. This suggests that frontal brain regions may be less efficient in survivors treated with more intense therapies than those treated with less intensive therapy. Therefore, interventions designed to target the dorsolateral region and focus on remediation of executive functioning skills may be particularly beneficial for survivors. Importantly, because long-term survivors have lived with neurocognitive deficits for many years, environmental and psychological adaptation may occur. Therefore, it is critical to consider both direct testing and patient-reported symptoms of executive dysfunction. Because most long-term survivors do not reside in close proximity to their primary cancer treatment center, the need for interventions that can be repeatedly delivered remotely is critical. We recently conducted a pilot trial of remote transcranial direct current stimulation (tDCS) to the dorsolateral prefrontal cortex paired with cognitive training for the treatment of executive dysfunction in a randomly selected sample of 30 adult survivors of childhood ALL (mean age 33 years, SD 7.5 years). Among the 27 survivors eligible for remote stimulation, 25 (93%) completed at least 50% of the home-based sessions, and 22 (81%) completed all prescribed sessions. These data support the safety, acceptability, and short-term feasibility of tDCS among long- term survivors. Among the survivors who completed the intervention, we observed significant improvements on direct testing of executive functioning (working memory: 0.5 SD increase) and patient-reported emotional regulation (0.7 SD increase). Now, we propose a randomized placebo-controlled study to examine the efficacy of tDCS paired with remote cognitive training vs. placebo (sham) paired with remote cognitive training on symptoms of executive dysfunction in long-term survivors of ALL. We will examine neuroimaging correlates associated with intervention outcomes to assess impact on underlying neural networks. Ultimately, this work has the potential to significantly impact current standard of care as few efficacious interventions are available for these relatively common symptoms of executive dysfunction in long-term survivors of childhood cancer.

1.1. Primary Objective

1.1.1. To evaluate the efficacy of home-based transcranial direct current stimulation (tDCS) paired with remote cognitive training on direct testing of executive function in survivors of ALL.

Hypothesis: Survivors randomized to active tDCS + cognitive training will demonstrate greater improvement on direct testing of executive function compared to survivors randomized to sham + cognitive training.

1.2. Secondary Objectives

1.2.1. To evaluate the efficacy of home-based transcranial direct current stimulation (tDCS) paired with remote cognitive training on patient-reported symptoms of executive dysfunction in survivors of ALL.

Hypothesis: Survivors randomized to active tDCS + cognitive training will demonstrate greater improvement on patient-reported symptoms of executive dysfunction compared with survivors randomized to sham + cognitive training.

1.2.2. To examine the effects of home-based tDCS paired with remote cognitive training on patterns and excitation levels of regional brain activation as measured by functional magnetic resonance imaging and magnetic resonance spectroscopy, respectively.

Hypothesis: 1.2.2.a. Survivors randomized to active tDCS + cognitive training will demonstrate increased efficiency in dorsolateral prefrontal regions during a working memory task compared to survivors randomized to sham + cognitive training.

Hypothesis 1.2.2.b. Survivors randomized to active tDCS + cognitive training will demonstrate altered glutamatergic (excitatory) and GABAergic (inhibitory) activity in the dorsolateral prefrontal regions engaged during the working memory task compared to survivors randomized to sham + cognitive training.

1.2.3 To examine the effects of home-based tDCS paired with remote cognitive training on white matter integrity and structure as measured by diffusion tensor imaging.

Hypothesis: Survivors randomized to active tDCS + cognitive training will demonstrate improved white matter integrity (as reflected by increased fractional anisotropy and decreased diffusivity) in the dorsolateral prefrontal cortex compared to survivors randomized to sham + cognitive training.

1.3. Exploratory Objectives

1.3.1. To examine the effects of tDCS on patient-reported symptoms of depression, anxiety, fatigue, pain, and sleep.

1.3.2. To examine the prevalence, type, and frequency of side effects/adverse events associated with sham/active tDCS treatment.

2.0 BACKGROUND AND RATIONALE

2.1. Background

Childhood acute lymphoblastic leukemia (ALL) is the most common form of pediatric cancer and over 85% of children diagnosed survive >5 years.[1] These survivors comprise a substantial proportion of the growing population of adult survivors of childhood cancer, estimated to exceed 500,000 by the year 2020. Treatment for ALL has included cranial radiation, intrathecal methotrexate, and high dose intravenous methotrexate, all of which are risk factors for neurocognitive morbidities, particularly in executive functions (e.g., working memory, flexibility, fluency, initiation, inhibition, emotional control).[2] This is critical because deficits in executive functions are associated with reduced educational attainment, employment, health behaviors, and quality of life.[3,4]

In a cohort of roughly 800 adult survivors of childhood ALL, we identified 59% to be impaired on at least one direct test of executive function and 30% self-reported symptoms of executive dysfunction, including emotional regulation.[5] Importantly, because long-term survivors have lived with neurocognitive deficits for many years, environmental and psychological adaptation may occur. Therefore, it is critical to consider both direct testing and patient-reported symptoms of executive dysfunction in survivors.

Our research demonstrates that executive function deficits increase with time from diagnosis and are associated with treatments beyond cranial radiation. Among survivors treated on a contemporary chemotherapy-only protocol, we identified higher serum concentration of methotrexate was associated with worse executive functioning and higher functional MRI brain activation in dorsolateral and medial prefrontal regions during working memory tasks (Figures 1 and 2 at right).[6] Survivors also demonstrated poor myelin integrity in frontostriatal tracts based on diffusion tensor imaging. This suggests that frontal brain regions may be less efficient in survivors treated on contemporary chemotherapy protocols. Similarly, among adolescent survivors of ALL, reduced

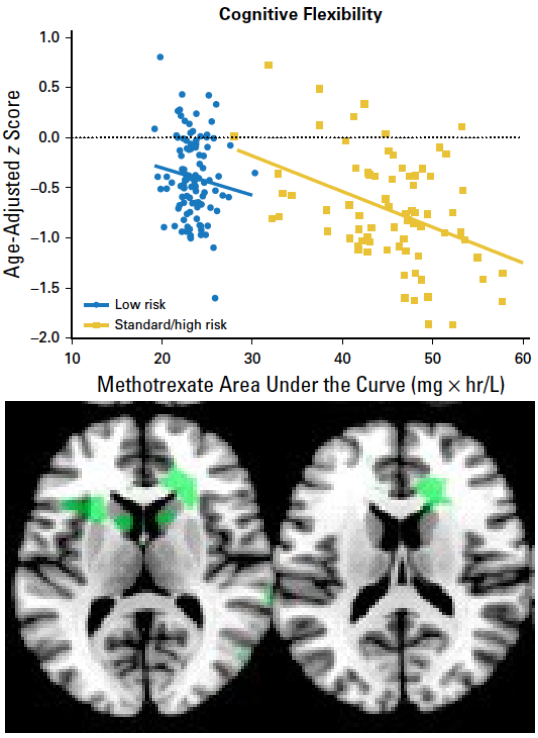
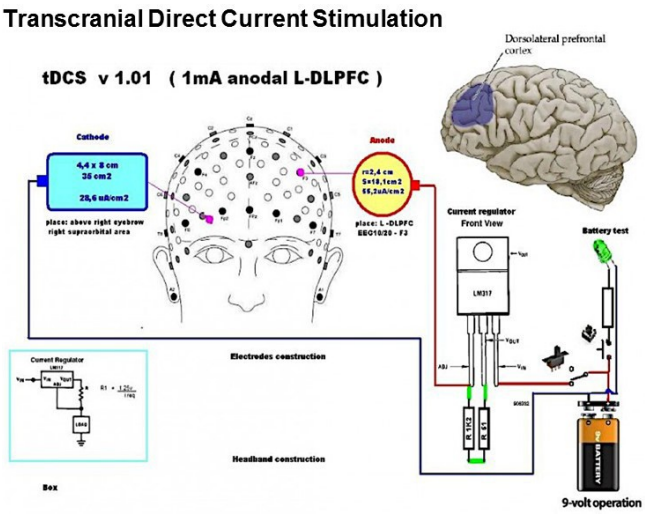


Figure 1 & 2: Top-Lower flexibility correlated with higher serum methotrexate; Bottom-Group average (n=176) fMRI higher activity (green) correlated with higher serum methotrexate during an N-Back task.

frontal white matter volume has been associated with poor response inhibition and in adult survivors,[7] smaller surface areas in prefrontal cortical regions has been associated with poor emotional control and self-monitoring.[8] Therefore, interventions designed to target the prefrontal cortex and focus on remediation of executive functioning skills may be particularly beneficial for ALL survivors.



Relatively limited research has focused on interventions for improving outcomes in long-term survivors of ALL.[9-13] A promising technique for cognitive enhancement is transcranial Direct Current Stimulation (tDCS),[14-17] which differs from conventional interventions in that it directly stimulates specific brain regions responsible for cognitive processes and activates functional networks similar to those activated during cognitive training.[17] tDCS involves modulation of cerebral cortex excitability by direct application of low-level electric current to an anode electrode site, the current travels to a cathode electrode site stimulating brain regions that lie in the path of current flow. The impact of tDCS on improving working memory has been previously studied among healthy volunteers and neuropsychiatric patients.[17] Anodal tDCS of the left dorsolateral prefrontal cortex has been shown to improve working memory,[18] interference inhibition,[18][18] and inhibitory control[19] as well as increased functional brain connectivity in the prefrontal cortex in individuals with ADHD.[20] Importantly, survivors of ALL have similar profiles of executive dysfunction as individuals with ADHD suggesting that similar treatment effects may be observed. We propose to use tDCS to enhance cognitive training of executive functioning skills in survivors. Therefore, we expect to observe a greater effect than what has been observed following tDCS alone. Moreover, past studies have not required the presence of specific executive function deficits prior to treatment with tDCS. By enrolling survivors with known deficits, we will be more likely to observe positive treatment responses.

Brain regions implicated in executive functions underlie the ability to employ emotion and mood regulation strategies.[21-23] The dorsolateral prefrontal cortex plays a critical role in emotional processing, particularly the down-regulation of negative emotions.[24,25] Frontal subcortical circuits are involved in the organization of information to facilitate a behavioral response (dorsolateral prefrontal circuit), motivate a behavioral response (anterior cingulate circuit),

and integrate emotional information into a response (orbitofrontal circuit).[26] Because of the closely linked neurocircuitry underlying executive functionsand emotional regulation, interventions that effectively treat executive dysfunction in survivors may also have positive consequences for control of emotions. In addition, tDCS over the dorsolateral prefrontal cortex has shown positive effects on emotional regulation, depression,[27] and fatigue[28,29] in a number of studies. The efficacy of tDCS in improving symptoms of executive dysfunction inlong-term adult survivors of childhood cancer has not been evaluated. Because these adults developed neurocognitive impairments when they were treated as children, the potential benefit to them may differ from those with active disease processes.

2.2. Rationale

Compared to studies characterizing neurocognitive outcomes, limited research has focused on developing interventions for improving late-effects in cancer survivors,[9-13] and no such studies could be identified in adult survivors of childhood cancer. Stimulant medications are relatively easy to administer, and have shown partial efficacy, though survivors report excessive adverse events (likely due to their past chemotherapy exposures).[30] tDCS does not have the negative side effects of many of the pharmaceutical approaches commonly used for symptoms of neurocognitive dysfunction. This is critical because survivors are at known risk of polypharmacy,[31] a practice that makes them vulnerable to adverse drug events, financial toxicity, poor adherence, and drug-drug interactions. Treatment of executive dysfunction with a nonpharmacological approach may help to minimize such risks. Several non-pharmaceutical interventions for improving cognitive functions have been conducted in the general and aging populations, as well as in patients with neuropsychiatric diseases. These include cognitive training[32] and physical exercise.[33,34] Physical exercise promotes a general increase in cerebral blood flow and brain volume for gray matter and white matter, which has been associated with improved general brain health[35-37] but often requires intensive oversight and monitoring and is difficult to implement long-term. Cognitive training is intended to strengthen neural networks through repeated co-activation, with the goal of improving efficiency;[32] however, our pilot data suggest limited efficacy in isolation in the adult survivors of childhood cancer. Most potentially efficacious cognitive interventions are limited by problems of feasibility (i.e. high dropout rates, limited disseminability) and resource requirements (i.e. time intensive, on-site supervision). Therefore, we propose an intervention that is portable, safe, and has low burden to the cancer survivor. Moreover, the intervention uses complementary home-based treatment modalities (cognitive training and neurostimulation) to target a highly prevalent late effect (executive dysfunction) in childhood cancer survivors.

The **scientific premise** of the current study is that treatment for childhood ALL impacts the function and integrity of the prefrontal cortex, resulting in executive

dysfunction in survivors, and that interventions targeting this brain region and specific cognitive skills will result in improved executive function in survivors. Specifically, we hypothesize that tDCS paired with cognitive training will improve executive functioning in adult survivors of childhood ALL who experience executive dysfunction. For the proposed study, we will examine efficacy of tDCS, which will inform development of larger trials designed to examine treatment intensity (dose) and duration and dissemination and implementation. Ultimately, this work has the potential to significantly improve clinical practice, particularly as it relates to the treatment of executive dysfunction in adult survivors of childhood cancer. If tDCS paired with cognitive training is efficacious and improves executive function, we will have identified a treatment that can be made readily available to health care providers and survivors. Because these treatments are portable, they can be easily disseminated to survivors who do not reside near their primary cancer treatment centers.

The potential impact of identifying efficacious treatment for neurocognitive impairment is substantial, as it addresses serious health outcomes in survivors of childhood cancer, a population that is expected to exceed 500,000 by the year 2020. Neurocognitive impairment is highly prevalent and is associated with reduced educational attainment and unemployment,[38] which have a substantial impact on the individual survivor and society at large. Moreover, neurocognitive impairment is associated with increased health care costs and burden on healthcare delivery systems (i.e. rehabilitation, long-term supportive care).[39] Identification of interventions that reduce this risk will have substantial benefit to individuals and society. Ultimately, results may generalize to survivors of other childhood cancers and survivors of adult onset cancers with similar neurocognitive morbidities. Executive dysfunction is prevalent among survivors of pediatric brain tumors as well as survivors of breast cancer, though the impact of tDCS has not, to our knowledge, been examined in these populations.

2.3. Background and Rationale for Ancillary and Exploratory Studies

Clinical trial experience. We recently completed a 6-month double-blind randomized placebo-controlled clinical trial of an insomnia intervention for adult survivors of leukemia, brain tumors, and solid tumors (n>500). Similar to the proposed study, we enrolled participants in separate cohorts based on the presence/absence of symptoms and randomly allocated participants within each cohort to receive the intervention (i.e. melatonin) or placebo. Participants were required to complete baseline and 6-month post-intervention evaluations (neurocognitive and sleep) on campus at St. Jude Children's Research Hospital. 402 completed the 6-month intervention over a 5-year interval, which demonstrates our ability to recruit, enroll, and engage a large number of participants in a 6-month clinical trial requiring on campus follow-up (Brinkman, manuscript in development). Importantly, participants randomized to the placebo in the melatonin trial did not receive a potentially efficacious intervention whereas in the proposed study participants in the sham/placebo

group will receive cognitive training. Therefore, we expect the sham/placebo group to receive some clinical benefit (albeit significantly less than the active tDCS group) and anticipate less attrition over the 6-month study.

Neuroimaging. Over the past seven years, we have completed over 1000 quantitative and functional brain magnetic resonance imaging (MRI) procedures (i.e. volumetric analysis, diffusion tensor imaging, functional magnetic resonance imaging, susceptibility weighted imaging) in long-term survivors of childhood cancer enrolled in the St. Jude Lifetime Cohort study (i.e. the cohort from which participants for the proposed study will be recruited). We recently completed pre- and post-intervention MRI's in a subset of the survivors enrolled in the insomnia clinical trial discussed above. 94% of the survivors selected for this subset returned to campus for the post-intervention MRI scan. One particular imaging study laid the initial foundation for the currently posed clinical trial. This study involved neurocognitive assessment and multimodal brain imaging (DTI and fMRI) in long-term survivors of childhood ALL. Results of this investigation (R01 MH085849 to KR Krull) demonstrated executive function to be the most commonly impaired domain. Furthermore, functional connectivity analyses demonstrated that those with impairment as a group had a poorer executive/attention network compared to though without neurocognitive impairment (Figure 3 at right; Kesler et al, 2018).

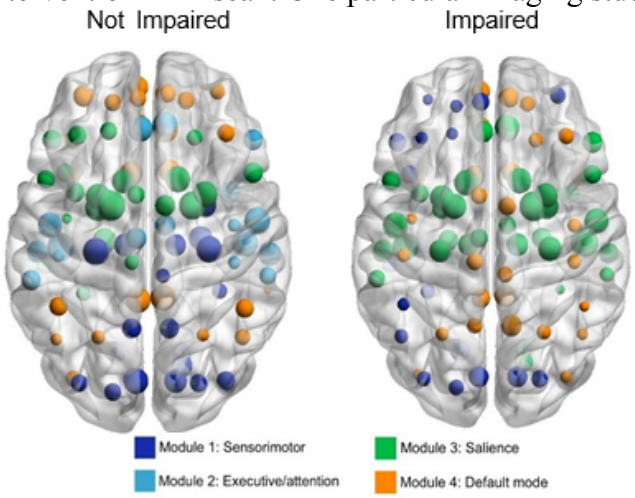


Figure 3: Group average connectivity maps showing disrupted executive/attention network (light blue) in the group of survivors with neurocognitive impairment (right).

Remote cognitive training.

Cognitive training improves cognitive function. We completed a pilot study to investigate feasibility and preliminary effectiveness of portable cognitive training in adult survivors of childhood cancer. Thirty-three adult survivors with attention and/or memory deficits were recruited to participate in a cognitive intervention using Nintendo DS brain training games. Prescribed training included 20 minutes of game play per day, five days a week, over a 6-month period. Biweekly telephone calls were conducted to record self-reported adherence. Neurocognitive assessments were completed at baseline and post-intervention. Nineteen age- and sex-matched survivors with attention and/or memory deficits underwent repeat neurocognitive assessment without intervention and served as comparisons. Intervention and practice effects were

analyzed through a 2x2 repeated-measures ANOVA. The majority of survivors completed 80% of sessions over the 6-month training. Compared to the control group, survivors who completed cognitive training demonstrated improvement on a measure of cognitive flexibility ($F(1, 37)=6.07$, $P=0.02$), but not working memory ($F(1, 37)=1.17$, $P=0.29$). We concluded that portable cognitive training over a 6-month duration was a feasible approach and may improve select cognitive processes (Krull, unpublished data).

We randomized 41 chemotherapy treated breast cancer survivors (age 56 +/- 6 years) who were at least 18 months off-therapy to Lumosity training or waitlist. Target enrollment was met within 2 months. Adherence was defined as completing all assigned training sessions and demonstrating a positive performance slope on all training tasks (no participants demonstrated flat or negative performance slopes). Adherence was 95%. Compared to controls, the training group demonstrated significantly improved performance on the primary outcome, the Wisconsin Card Sorting Test (WCST, effect size = 0.78), a measure of executive function. Secondary outcomes included HVLT-R Total Recall for memory and BRIEF for self-rated executive function, which were also improved[40] (Figure 4). There were no adverse effects of the intervention.

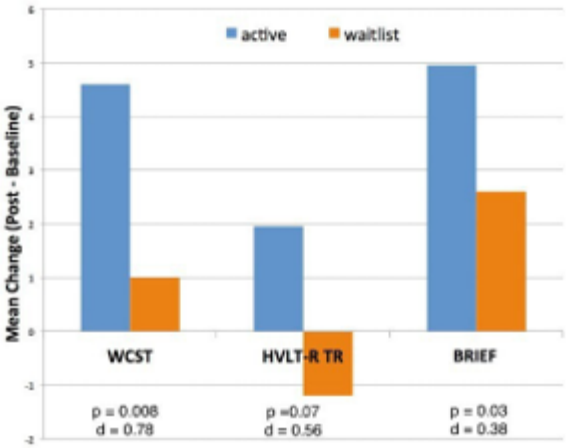


Figure 4: Compared to waitlist controls, breast cancer survivors randomized to cognitive training demonstrated significant improvements in cognitive function.

Cognitive training increases brain network resilience in healthy adults.

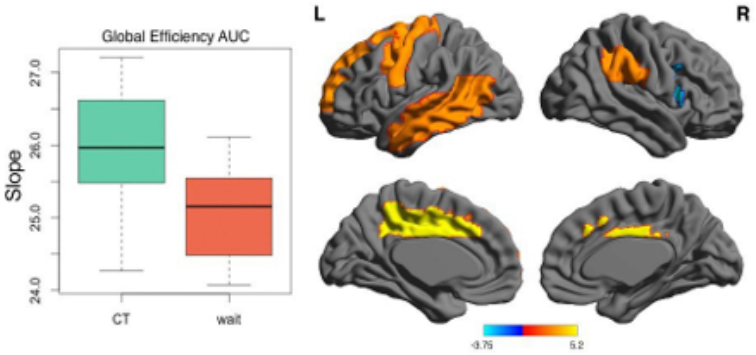


Figure 5: Left - Healthy adults randomized to training showed significantly improved structural brain network global efficiency following simulated neurodegeneration compared to waitlist controls. Right – Training induced changes in brain connectivity (color bar indicates T score). AUC: area under the curve.

Participants were 35 healthy adults (mean age = 40 +/- 3.1 years) randomized to Lumosity cognitive training or a waitlist control. We used diffusion tensor imaging (DTI) to evaluate the structural brain network's resilience to simulated neurodegeneration. Specifically, we conducted targeted attack analysis on the structural connectome of each participant as described in our previous studies.[41,42] The impact of these attacks was measured by global efficiency area under the curve across simulated attacks.[41,43] This area under the curve indicates how quickly the brain network's efficiency declines across neurodegenerative attacks. Training adherence, as defined above, was 94%. Compared to controls, the training group demonstrated significantly increased global efficiency area under the curve ($p = 0.006$, $d = 1.61$), indicating greater resilience to simulated neurodegeneration (Figure 5). Regional analyses demonstrated training-related alterations in prefrontal-striatal-parietal and medial temporal white matter connectivity. The CT group also demonstrated improved executive function performance compared to controls as measured using a composite of WCST, Delis-Kaplan Executive Function System and Spatial Addition tests ($p = 0.016$, $d = 0.70$). There were no adverse effects of the intervention (Kesler, unpublished data).

Cognitive training improves functional brain network efficiency in patients with breast cancer. We conducted a single arm feasibility study with 12 chemotherapy treated breast cancer survivors (mean age = 57 +/- 5 years) who were at least 18 months off-therapy with self-rated cognitive impairment of 3 or higher out of 10. Targeted enrollment was met within 2 days of opening the study. Adherence was defined as above, in addition to compensatory strategy use by self- rating as 4 or higher on a scale of 0-8 where 4 was defined as "often". All 12 participants (100%) completed all Lumosity training sessions and demonstrated significant improvement on task performance ($p < 0.0001$) indicating adequate effort. Participants demonstrated significant improvement on the primary outcome measure,

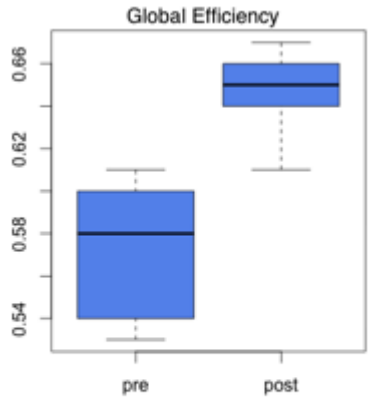


Figure 6: Functional brain network global efficiency was improved following cognitive training.

TMT Part B, a measure of executive function ($p = 0.035$, $d = 1.65$). Improvements were also noted in secondary outcomes including our Mobile Cognitive Assessment Battery (MCAB) Switching test ($p = 0.041$, $d = 0.78$), a measure of executive function, MCAB Cognition Index, a self-rating measure of executive function and memory ($p = 0.032$, $d = 1.7$). We also measured functional brain network global efficiency using resting state functional magnetic resonance imaging (rsfMRI) as we have previously described.[44,45] The training program was associated with increased functional network efficiency ($p < 0.0001$, $d = 1.8$, Figure 6). Improvement in brain network global efficiency was moderately associated with improvement in TMT B score ($r = 0.575$, $p = 0.064$) and significantly associated with improvement in the MCAB Cognition Index ($r = 0.740$, $p = 0.009$). Improved TMT B score was associated with improved MCAB Cognition Index ($r = 0.703$, $p = 0.011$) at Time 2 (3 months). Participants were also asked to rate how helpful the training program was with improving cognitive problems in everyday life on a scale of 0-8. The average rating was 6.2 +/- 1.3, range 4-8, corresponding to "helpful". There were no adverse effects of the intervention (Kesler, unpublished data).

These data highlight our ability to conduct remote cognitive training with Lumosity (the proposed training program for the current study) as well as the efficacy of this approach in remediating executive functioning deficits. Importantly, we observed considerably larger effect sizes in survivors of adult onset breast cancer compared to adult survivors of childhood cancer. This likely reflects the chronic nature of cognitive impairment in childhood cancer survivors compared with breast cancer survivors. Because adult survivors of childhood cancer have often had neurocognitive impairments for several decades, cognitive training alone may not be sufficient to remediate these deficits. We, therefore, propose to pair cognitive training with transcranial direct current stimulation to stimulate specific brain regions responsible for executive functioning and targeted by cognitive training to enhance training effects in long-term survivors.

Transcranial direct current stimulation. We completed a pilot trial of tDCS to the dorsolateral prefrontal cortex paired with cognitive training (Lumosity) for the treatment of executive dysfunction in a randomly selected sample of 30 adult survivors of childhood ALL (mean age 37 years, time from diagnosis 30 years). Survivors were trained to self-administer tDCS while on campus and then took a remote stimulation device home. They completed remote neurocognitive testing via Skype and completed tDCS at home (two sessions per week for two months, also observed via Skype). Among 27 survivors eligible for remote stimulation, 25 (93%) completed at least 50% of the sessions, and 22 (81%) completed all prescribed sessions. The most common adverse effects included itching/tingling and headaches, and 93% of reported adverse effects were indicated as tolerable. These data support the short-term feasibility of remote tDCS among long-term survivors and support the safety of tDCS in survivors of ALL. Among the 25 survivors who completed the intervention, we observed significant improvements on direct testing of executive functioning (working memory: 0.5 SD increase) and on patient-reported symptoms of executive

function (emotional regulation: 0.7 SD increase). However, the pilot study did not include a placebo (sham condition). Therefore, these data lead us to propose a more robust randomized placebo-controlled study to examine the efficacy of tDCS paired with cognitive training and delivered over a six-month duration.

3.0 RESEARCH PARTICIPANT ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

According to institutional and NIH policy, the study will accession research participants regardless of gender and ethnic background. Institutional experience confirms broad representation in this regard.

3.1 Inclusion Criteria

3.1.1 Completed treatment for acute lymphoblastic leukemia (ALL) at SJCRH < 21 years at diagnosis

3.1.2 Enrolled on St. Jude Lifetime Cohort Study

3.1.3 ≥5 years post-diagnosis of ALL

3.1.4 ≥2 years post-treatment completion deemed to impact the central nervous system

3.1.5 Currently between 18 and 39.99 years of age at the time of enrollment

3.1.6 English language proficiency

3.1.7 Executive dysfunction defined as having an age-adjusted standard score <16th percentile on Trail Making Test Part B (campus visit), Controlled Oral Word Association Test, Digit Span Backward, Shifting Attention Test , or Stroop Test or patient-reported executive dysfunction defined as a standard score >84th percentile on the Childhood Cancer Survivor Study Neurocognitive Questionnaire (NCQ) or the Behavior Rating Inventory of Executive Function.

3.2 Exclusion Criteria

3.2.1 Estimated intelligence score <80

3.2.2 Currently receiving cancer directed therapy

3.2.3 Currently taking medication intended to treat neurocognitive impairment (e.g. stimulants)

3.2.4 Participated in a past trial of neurostimulation

3.2.5 Female who is pregnant or breastfeeding [campus visit, for MRI safety screen]

3.2.6 Seizure within the past year

3.2.7 Implanted medical devices or metal in the head

3.2.8 Major psychiatric condition

3.2.9 Alcohol or drug abuse in the past year (AUDIT >=13/women and >=15/men or DAST-10≥3)

Per exclusion criteria 3.2.8., The Alcohol Use Disorders Identification Test (AUDIT) will be used to screen for individuals who have active alcohol use disorders and the Drug Abuse Screen Test (DAST-10) will be used to screen for individuals with active drug abuse. Both questionnaires include 10 items and are well-validated.

3.2.10 History of head injury or a neurodevelopmental disorder (i.e. genetic disorder, hypoxic-ischemic encephalopathy) associated with neurocognitive impairment and unrelated to cancer treatment

3.3 Research Participant Recruitment and Screening

We propose to utilize the SJLIFE alumnus dataset to identify evaluable long-term ALL survivors. Participant eligibility will be identified through hospital admission records and consultations with the SJLIFE study team prior to the patient's SJLIFE clinic visit or prior to recruitment by study team members. Individuals potentially eligible for this study will be mailed a letter or electronic (e-) communication to introduce the study and inform him or her that they may be eligible for enrollment. The letter/e- communication will state that a member for the SJLIFE study team will be contacting them within two weeks to discuss the study and inquire about their desire to participate. A second letter/e-communication and a second phone call will be attempted two to four weeks after the original letter if no initial response is received.

A requirement of NEUROSTIM eligibility is to be a participant in the SJLIFE study. Patients will be assessed for the capacity to consent as part of SJLIFE recruitment. If a participant is assessed to be competent to consent for SJLIFE, they will be competent to consent for NEUROSTIM.

If the SJLIFE participant expresses interest, they will be e-mailed, faxed, or mailed/FedExed a copy of the consent form if they agree to consent conference via phone; the consent conference will occur via phone and e-mail or facsimile will be used to document informed consent. Once the consent signature page is received the participant is enrolled on study as described in Section 3.4. Participants may provide signed consent via secure e-signature.

3.4 Enrollment on Study at St. Jude

A member of the study team will confirm potential participant eligibility as defined in Section 3.1-3.2, complete and sign the 'Participant Eligibility Checklist'. The signed consent/assent form must be faxed to the Clinical Trials Operations (CTO) at 595-6265 or emailed to protocoleligibilityoffice@stjude.org . Participants will be enrolled in accordance with policy Clinical Trials Administration – SOP - 39 Participant Eligibility Checklist and Verification Process.

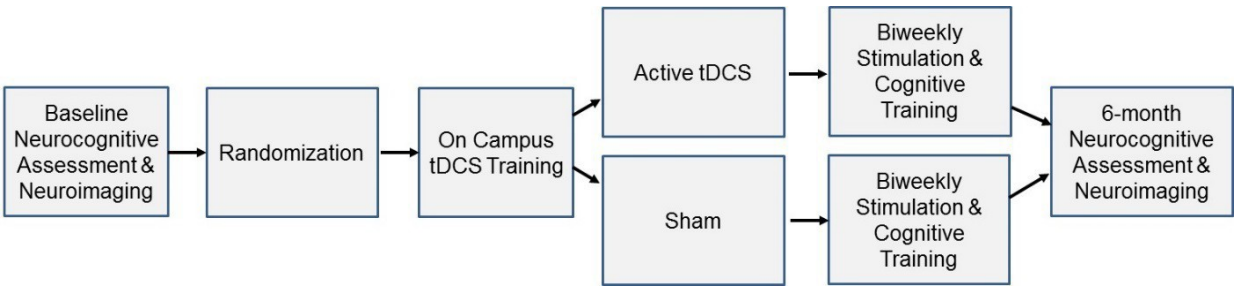
3.5 Procedures for Identifying and Randomizing Research Participants

This is a double-blind study in which neither the participant, interventionist, or outcomes assessor will know the treatment assignment. Participants will be randomized 1:1 to receive active tDCS or sham for 6 months. The randomization to treatment/placebo arms will be done using a program written in C++. Randomization will occur in blocks of 4 and be stratified by sex and cranial radiation therapy (yes/no). This program resides in the Department of Biostatistics and has been routinely used for randomization since 1992. The system stores all required data for randomization into a secure Access database. Once a participant is randomized all related data are frozen in the database and cannot be changed. Blinding of group assignment will be maintained until the study is complete or in the case of an adverse event for which removal of the blind is necessary to allow for appropriate patient care.

4.0 DESIGN AND METHODS

4.1. Design and Study Overview

The proposed study is a double-blind, randomized placebo-controlled trial of remotely delivered tDCS paired with cognitive training. Survivors with identified executive function impairment will be randomized to receive active tDCS + cognitive training or sham tDCS + cognitive training two days per week for a 6-month intervention period. Side effects will be monitored at each treatment. Neurocognitive and neuroimaging assessments will occur pre- and post-intervention for campus participants. Remote participants will follow similar procedures, but all neurocognitive assessments will be performed remotely and participants will not complete neuroimaging at baseline or 6-month assessments.



4.2. Study Procedures / Intervention / Observations:

Transcranial Direct Current Stimulation (tDCS) – Mobile System: For remotely supervised tDCS stimulation, we will employ a procedure consistent with recently published professional guidelines, on which Dr. Krull was a co-author.[46][46] The mobile tDCS system is manufactured by Soterix Medical and consists of a rechargeable lithium battery pack, control unit and a self-positioning headband with electrodes. Anodal electrodes will be placed over bilateral dorsolateral prefrontal cortices (equivalent to F3 and F4 electrode sites [10-20 electrode system]), with a cathode reference electrode placed at FPz. The electrodes are single-use and snap into fixed locations of a flexible headband that is individualized for each participant. Participants will be given the device after completing on-site training that includes how to connect the electrodes, make sure the skin areas are clean and dry, place the headband, and operate the device or will be trained remotely to use the device. If completing sessions remotely, participants will be asked to try on their headband prior to their first training session. A study team member will assist to ensure appropriate fit. If the headband is found to be ill-fitting, a new headband will be sent to the participant before any training sessions occur. As part of this training, participants will complete a single session of tDCS treatment. Those randomized to active stimulation will receive an active trial and those randomized to sham stimulation will receive a sham trial. During the remote tDCS intervention, participants will complete at least two stimulation sessions in their homes each week for 24 weeks. The active sessions will provide 1 mA DC for 20 minutes. The sham sessions will ramp up to 1mA DC flow over a 5 second interval and will then return to no current flow for the remainder of the session. In our experience with the pilot trial, participants perceived the ramp up sensation as active stimulation during the sham trial. Participants will be supplied electronic devices for the cognitive training, and the electronic device will be used to monitor correct tDCS usage. The tDCS unit requires a unique code for each stimulation session. Study staff will use video conferencing to confirm correct electrode placement, then provide the code to initiate treatment. Each session will be monitored for adherence and to assess potential adverse events. This methodology is consistent with the approach successfully utilized in our pilot study.

Following completion of up to four complete sessions without errors, participants will be transferred to independent use of the ElectraRx interactive web-based system. A team member will assist the participant with log-in to ElectraRX and completion of the tDCS session. The participant will be required to complete the adverse event log (modified PRISE) weekly prior to receiving the code to initiate the session on that day. The ElectraRX website provides the Principal Investigators real-time access to participant log-in history, including duration of stimulation session.

Cognitive Training: All participants randomized to either active or sham stimulation will complete online cognitive training within one hour of every at-home tDCS session. Consistent with procedures in our pilot study, the cognitive training program utilized will be Lumosity and involves training of executive function skills using computer-based cognitive tasks. Participants will be asked

to engage in training for 20 minutes a day, for each day they receive stimulation. Five cognitive tasks focused on specific executive functioning skills will be presented during each training session. The Lumosity website available to researchers records the day and time of each training session, as well as performance on the training activities for each participant. This will provide a measurement of adherence that can be linked to the tDCS session. The number of completed sessions and improvement over time for each participant will be recorded and available for analyses with neurocognitive outcomes.

Adverse Event Monitoring: Patient reports of adverse events will be monitored. Adverse events will be surveyed weekly, with symptoms reported for the two prior weekly stimulation sessions. Adverse event information will be collected by participant reporting and direct questioning using the patient report of incidence of side effects (PRISE). [47] The PRISE form assesses the presence of side effects for a variety of biological systems. For each organ/function systems (skin, nervous, eyes/ears, sleep, other), the participant indicates the presence of a side effect, and if present, the tolerability of the side effect (tolerable or distressing). We have modified the PRISE to include most commonly reported side effects of tDCS: tingling, itching sensation, burning sensation, pain, headache, fatigue, difficulty concentrating, nervousness[48]; there is also a slight risk of experiencing a flash of light called phosphenes; this is a harmless side effect that occurs when the current runs across the optic nerves and is less likely to occur with correct placement of the electrodes and headstrap.[49] In rare instances, a first-degree burn could occur at the electrode site (similar to a mild sunburn). The study team will follow-up on items endorsed on the PRISE to determine the severity of the adverse event.

Problem Solving: Adherence to 100% of prescribed sessions was 81% in our pilot study. Participants who do not demonstrate at least 80% adherence to the prescribed intervention (tDCS or cognitive training), determined on a biweekly basis (i.e. missing more than one session over a rolling two-week interval), will be contacted to participate in a problem-solving exercise. Dr. Brinkman or a member of the study team will monitor participant adherence throughout the intervention trial and will contact participants who demonstrate poor adherence behaviors to problem-solve potential barriers to adherence, as well as identify and discuss possible solutions. The standardized problem-solving model employed in our clinical trial with over 500 participants (see preliminary study section above) will be utilized for this process. The participant will select one solution that he/she is willing to implement over the next month and this solution will be operationalized. Participants will not be removed from the intervention trial due to poor adherence. Adherence will be examined as a covariate in assessment of intervention efficacy.

Participant compensation: As incentive and compensation for time off work, all participants in SJLIFE are reimbursed at $150/day. This standard reimbursement is provided by the institution for the baseline study visits. We will provide similar reimbursement of $150/day for participants to return to

campus for the 6-month post-intervention evaluation. All travel and room and board for campus participants (at baseline and 6-months) is covered through SJLIFE by the institution. Reimbursement will be given based on attendance and not completion of protocol related tasks. Participants will also receive a $50 electronic gift card at approximately the end of Week 6 and Week 18 of participation as well as a $100 electronic gift card at the mid-point of the study (approximately at Month 3) to thank them for participating in the research study. If a participant takes part remotely, they will be compensated $150.00 for baseline and $150.00 for 6-month follow up in addition to the electronic gift cards.

4.3. Study Measures

Direct Testing of Executive Function:

Working Memory: Digit Span Backward: Digit Span Backward (DSB), from the Digit Span subtest on the WAIS-IV,[50] is a measure of working memory. The examiner reads aloud numbers and the participant is required to repeat the numbers backwards. The number of digits recalled in the longest span is converted to a standard score using age-based norms. Considered a process score on the WAIS-IV DSB is found to have acceptable reliability and validity parameters.

Cognitive Flexibility: Trail Making Test Part B (Trails B) (campus assessment):[51] This is a timed task that requires a participant to shift his/her attention adaptively and flexibly. Specifically, participants are asked to draw a line from a number to a letter in ascending order as quickly as possible. Considered a measure of cognitive flexibility, Trails B is found to have adequate psychometric properties. Shifting Attention Test (SAT) and Stroop Test (ST) (remote or campus assessment; CNS Vital Signs): The number of correct responses (SAT) and errors (SAT; ST) are measures of cognitive flexibility. [52]

Verbal Fluency: Controlled Oral Word Association (COWA):[53] This is a task of cognitive/verbal fluency. Participants are given a letter and must say as many words that start with that letter within 60 seconds. There are two versions of the test, one using the letters FAS and the other using CFL, to control for practice effects.

Patient-Reported Executive Functioning:

Patient reported symptoms of executive dysfunction will be evaluated via the Childhood Cancer Survivor Study Neurocognitive Questionnaire (CCSS-NCQ) – Revised. Dr. Krull (co- Principal Investigator) is the principal architect of the CCSS-NCQ.[54] The CCSS- NCQ is a 32 item self-report questionnaire evaluating 4 domains of neurocognitive function: (1) memory; (2) task efficiency; (3)

organization; (4) emotional regulation. The CCSS-NCQ was developed specifically to address neurocognitive concerns of adult survivors of childhood cancer. It has been administered to over 12,000 non-brain tumor survivors within the CCSS cohort, and age- and sex-adjusted normative data are available from over 3,000 siblings of childhood cancer survivors. Extensive psychometric analysis of the CCSS- NCQ has been conducted, with the most recent involving Item Response Theory analysis and validation with traditional neuropsychological testing.[55] In addition, we will use the Behavior Rating Inventory of Executive Function (BRIEF) as a secondary measure of executive dysfunction as the BRIEF also provides comparable national normative data. These questionnaires will be completed as part of the neurocognitive evaluation at baseline, midpoint (approximately Week 12), and 6 months and will provide primary endpoint data for Specific Objective 2.

Patient-Reported Symptoms: We will examine the effects of tDCS on patient-reported symptoms of fatigue (PROMIS Fatigue; Fatigue Severity Scale,[56] depression (Patient Health Questionnaire [PHQ-8],[57] anxiety (Generalized Anxiety Disorder-7 [GAD-7],[58] pain (visual analog scale; PROMIS Pain Interference), and sleep (PROMIS Sleep Disturbance)[59]; these surveys are collectively referred to as SYMPTOMS survey. Because these symptoms may present and/or remit over a shorter duration of time than symptoms of executive dysfunction we will measure these symptoms at baseline, midpoint (approximately Week 12), and 6-month visit during the study. Completion of the questionnaires should take approximately 10 minutes.

Resting State fMRI (RsMRI) (campus assessment). RsMRI provides a measure of spontaneous, intrinsic brain function that can be used to assess the organization and connectivity of multiple brain networks.[60] Resting state networks are believed to modulate allocation of neural resources towards goal-oriented activities.[61] Compared to task-based approaches, the simplicity of rsfMRI makes it feasible for a wider range of participants. Additionally, task-related changes in brain metabolism tend to be quite small compared to the brain's large resting state energy consumption.[62] RsfMRI therefore provides assessment of neural processing that represents a greater proportion of the brain's resources and may therefore be a more robust source of disease-related signal changes.[60,62] Accordingly, our group as well as others have shown that rsfMRI is significantly more sensitive to cognitive impairment in patients with cancer compared to task- based fMRI.[45,61,63-65] Several studies including our own have also shown rsfMRI to be highly sensitive to cognitive training effects.[66-69]

Preprocessing: rsfMRI preprocessing will include realignment, coregistration to the segmented volumetric MRI scan, spatial normalization to a standard space template and smoothing at 8 mm FWHM as detailed in our previous publications[70,71] RsfMRI will be corrected for additional artifacts[72] and band pass filtered to 0.008–0.09 Hz as we have described previously.[45,61,63,73,74] Motion artifacts will be further corrected using a wavelet despike denoising strategy.[75]

Connectome Measurement: As we have previously described,[42,45,73,76-78] rsfMRI data will be used to construct functional connectomes for each participant at each time point. A connectome is a model of the brain network as a system of nodes (regions) and edges (connections between regions) that provides insight regarding the brain's organization, error tolerance and capacity for information processing, among other characteristics. We will measure several common connectome properties including global and local efficiency. Functional global efficiency will be used as a secondary outcome for our specific aims, based on our preliminary studies (section C.1). Global efficiency is the inverse of the average shortest path between nodes and is high when nodes are able to interact directly. It is thus an indicator of the brain network's integration and capacity for parallel information processing.[79] Measures of network efficiency are considered directly related to error tolerance, highly biologically relevant because they describe information flow and are less sensitive to disconnected and weakly connected nodes.[79] Connectome modularity, degree distribution and hub characteristics will also be measured as in our previous studies.[42,80,81] Modularity analysis involves decomposing the brain network into non- overlapping modules that correspond to distinct functional subnetworks.[82,83] Hubs are highly connected regions and will be identified based on degree distribution and then classified as provincial or connector type from module participation coefficient per previously established criteria.[84,85] These analyses will allow us to examine intervention-related changes in specific functional networks such as default mode and executive-attention networks. We will also measure the efficiencies of these subnetworks for comparison between treatment arms to address Specific Aim 3. Other connectome metrics such as small-worldness index, clustering coefficient, path length, and regional connectivity will be evaluated as exploratory outcomes.

N-Back Task (campus assessment). N-Back tasks are prototypical working memory measures used in neuroimaging studies. These tasks require a participant to respond to a presented stimulus only when it is the same as one presented on a trial at a predetermined number (N) prior to the current trial. Thus, this task requires constant online maintenance and monitoring of stimuli presentation in order to identify those recurring at the specified interval. For this study, we plan to use 1-back and 2-back trials. All stimuli will be presented on a computer monitor. Participants will view a continuous stream of single random stimuli from a set of phonologically distinct letters. Each letter is presented for 500ms, with an inter-stimulus interval of 2,500ms. For each letter, participants need to hit a response button when the letter is identical to the letter presented one or two back in sequence for the 1-back and 2-back trials respectively. A control condition (0-back trial) will be used during which the same continuous stream of single letters is presented but the participant need only decide whether each letter matches a single letter target communicated at the beginning of the task. These tasks should involve the same perceptual and response processes and differ only in the degree of working memory required to maintain the sequence of letters presented. Therefore, statistical comparison of the activations

associated with the control task with activations associated with the 1-back and 2-back tasks should yield the circuitry supporting working memory processes.

Structural Brain Connectivity (campus assessment): DTI data and 3D T1-weighted anatomic imaging data will be transferred from the PACS to a secure offline Diagnostic Imaging server and stored on the Hartwell Center File Cluster for processing and analysis. The analysis of the structural connectome is based on the recently published method of van den Heuvel and Sporns.[86] The cortex is parcelated into anatomical regions based on the high-resolution T1-weighted imaging using the FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/) and cortical thickness is assessed. The DTI is processed with voxel-wise tensor calculations performed with the DTI toolkit under the FMRIB Software Library (FSL) (http://fsl.fmrib.ox.ac.uk/fsl/). Probabilistic fiber tracking will be performed for individual seed points within the gray matter / white matter surface for each parcelated cortical region to evaluate strength of the connectivity between each individual region and every other region using FSL. The current project will focus analyses on the frontostriatal connections from the DLPFC to the striatum.

Significance of ^{1}H magnetic resonance spectroscopy: The development of sensitive methods for repeated and non-invasive measurement of tissue metabolic activity during treatment needs to be attempted to optimize and individualize the treatment. In recent years, a number of proton magnetic resonance spectroscopic (^{1}H MRS) studies provided insight into the in vivo neurochemistry of neurocognitive decline in dementia and neurological disorders. Metabolites including glutamate (Glu), N-acetyl aspartate (NAA), glutamine, creatine, phosphocreatine, m-inositol, γ-amino butyric acid (GABA), taurine, phosphocholine, and glycerophosphocholine are frequently observed in ^{1}H MRS spectra of human brain. Several reports indicate a possible correlation between the neurocognitive decline and cerebral neurotransmitter levels (PMID: 16860440, 27330972). NAA is a well-established biomarker of neuronal health (PMID: 11595395). Elevation of m-inositol is a useful marker of inflammation in brain (PMID: 23666436). We will perform single voxel ^{1}H MRS (SVS) in dorsolateral prefrontal cortex and other related regions in the patients to measure the a) neurotransmitter (Glu and GABA), b) NAA, and c) m-inositol levels.

Approach: Patients will undergo MRS scans using a PRISMA 3T scanner with a standard quadrature 32-channel head coil. MRI studies will be performed according to this imaging protocol. MRI sequences will include T1-weighted spin echo (TR/TE = 450/13 ms, FOV = 22 × 22 cm, matrix = 256 × 192, 50 slices, slice thickness = 3 mm, no gap), T2-weighted fast spin echo (TR/TE = 3400/95 ms, FOV = 22 × 22 cm, matrix = 256 × 192, 53 slices, slice thickness = 3 mm, no gap). SVS will be obtained using a point-resolved spectroscopic (PRESS) (PMID: 3326459) or semi-localized by adiabatic selective refocusing (sLASER) (PMID: 21413056) sequences with automated shimming and water suppression (TR/TE = 1500/30, number of averages = 128, voxel size 16-108 mm^3). Voxels will be prescribed graphically on an axial T1/T2-weighted image

in the dlPFC, basal ganglia, parietal cortex. Voxel size will be varied according to the size of the tissue. Acquisition time for each voxel will be ~5 min.

MRS data processing: ^{1}H MRS data will be fitted using LCModel software (v.6.3) (PMID: 8139448), a widely applied MRS analysis tool that employs a least-squares-based prior-knowledge fitting program. A basis set incorporating the following resonances: alanine, aspartic acid, creatine, phosphocreatine, GABA, glucose, glutamine, glutamate, glycerophosphocholine, phosphocholine, glutathione, myo-inositol, NAA, NAA + Glu, and taurine, with lipid resonances at 0.9, 1.3 and 2.0 ppm and macromolecule resonances at 0.9, 1.2, 1.4, 1.7 and 2.0 ppm.

5.0 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

5.1. Pre-Study & End-of-Study Evaluations

Neurocognitive Evaluation: Participants will complete a comprehensive neurocognitive evaluation at baseline and post-intervention. If a participant decides to withdraw prior to the end of the study intervention, a final comprehensive neurocognitive evaluation will also be offered. The campus neurocognitive evaluation is part of the standard SJLIFE evaluation. Participants will undergo a single neurocognitive evaluation that will serve to screen/identify eligible participants and as the baseline (pre-intervention) assessment. The campus evaluations take place in one of four designated testing rooms in the Cognitive Neuroscience Laboratory run by Dr. Krull. Tests will be administered by certified masters-level examiners under the supervision of a licensed neuropsychologist (Dr. Banerjee, Co-Investigator). Examiners will be blinded to tDCS intervention status. Testing will occur within a single morning or afternoon session and scheduled such that participants are not fasting or subjected to procedures that may interfere with sensory acuity (e.g. pupil dilation for ophthalmology testing). Examiners will complete a "Testing Evaluation Form" to systematically rate arousal, cooperation, motivation, concentration, and pace of session. This form will also be used to record spurious events that may have distracted the patients, as well as the number of hours the patient slept the night before and the time and content of their last meal. Testing order will be fixed for all survivors and set in a manner to reduce interference effects (e.g. no verbal tasks during the delay interval for long-term verbal memory task). The primary neurocognitive eligibility criteria include performance on three direct measures of executive functioning: Trail Making Test Part B/ Stroop Test/ Shifting Attention Test (cognitive flexibility),[51,52] Controlled Oral Word Association Test (cognitive/verbal fluency),[53] and Digit Span Backward (working memory).[50] All measures are standardized with national normative data provided. Remote participants will complete a modified version of the neurocognitive evaluation via a HIPAA-compliant video conferencing platform. The campus and remote assessment measures are detailed in the table below.

A direct measure of executive function will be obtained among participants using an electronically administered assessment (CNS Vital Signs Shifting Attention Test and Stroop Test).[52] This assessment is PC or laptop-based and self-administered, presents minimal risk to participants and enables them to complete the evaluation from their home. Participants will be invited to complete the assessment via e-mail. Each potential participant will receive a unique URL and keycode to access the CNS Vital Signs instrument via their personal computer or laptop. The CNS Vital Signs instrument provides audio instructions to the participant before beginning to describe the series of tests to be administered. Written instructions appear on the screen before beginning each test. The tests evaluate cognition through evaluation of memory, attention, non-verbal reasoning, and response time. The total administration time is roughly 10 minutes.

Domain	Measure	Time	Visit type
Intelligence	WASI - II	20 mins	both
Attention	Conner's Continuous Performance Test 3rd Ed.	20 mins	campus
	Trail Making Test Part A	5 mins	campus
	Digit Span Forward	5 mins	both
Memory	California Verbal Learning Test 2nd Ed.	20 mins	both
Processing Speed	Coding / Digit Symbol	3 mins	campus
	Grooved Pegboard	5 mins	campus
Executive Functions	Trail Making Test Part B	5 mins	campus
	Controlled Oral Word Association Test	3 mins	both
	Digit Span Backward	5 mins	both
	CNS Vital Signs Shifting Attention Test	5 min	remote or campus
	CNS Vital Signs Stroop Test	5 min	remote or campus
Visuospatial	Rey Complex Figure Copy	10 mins	campus
Patient-Reported Executive Functioning	CCSS Neurocognitive Questionnaire - Revised	5 mins	both
	Behavior Rating Inventory of Executive Function	10 mins	both

Neuroimaging (campus assessment): Participants will complete functional and structural neuroimaging at baseline and 6 months post-intervention. Resting state fMRI will be obtained during ten minutes of eyes open rest on a 3T scanner (Siemens Prisma; Siemens, Malvern, PA) using an accelerated multiband EPI pulse sequence (TR = 0.8s, TE = 30ms, FOV = 208mm, 2.5mm isotropic). The same imaging parameters will be applied during completion of the N-Back Task. Neuroimaging will be acquired at the same time points as the cognitive testing battery by trained MR technologists. All data will be inspected for quality visually and with the aid of in-house artifact detection software. Structural image data will be acquired to cover the whole brain with 108 oblique axial planes parallel to the line connecting the anterior and posterior commissures (AC-PC line). The structural connectome network will be estimated from diffusion tensor imaging (DTI) data and 3D T1-weighted anatomic imaging data. Whole brain diffusion tensor imaging (DTI) will be acquired with an accelerated multi-band, multi-shell sequence with high spatial and angular resolution (1.8 mm isotropic, 3 acq @ b=0; 1 acq of 12 dir @ b=1000; 1 acq of 64 dir @ b=1500; 1 acq of 64 dir @ b=2000; ~12 minutes total). 3D T1-weighted anatomic imaging will be acquired according to standard clinical parameters (1 mm isotropic voxels). All imaging will be conducted on a Siemens 3T imager.

Functional	Resting State	10 mins
	N-Back Task	6 mins
Structural	Diffusion Tensor Imaging	12 mins
	3DT1	6 mins

Appendix 1 provides a schedule of pre-intervention, on intervention, and post-intervention evaluations.

6.0 CRITERIA FOR REMOVAL FROM PROTOCOL

6.1. Off Study Criteria

- All protocol interventions are complete
- Death
- Lost to follow-up
- Request of the Patient/Parent
- Discretion of the Study PI, such as the following:
  - The researcher decides that continuing in the study would be harmful
  - A treatment is needed that is not allowed on this study
  - The participant's condition gets worse
  - New information is learned that a better treatment is available, or that the study is not in the participant's best interest

7.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

7.1. Reporting Adverse Experiences and Deaths to St. Jude IRB

Adverse events will be surveyed weekly. Event information will be collected using a modified version of patient report of incidence of side effects (PRISE; see description above).

Only "unanticipated problems involving risks to participants or others" referred to hereafter as "unanticipated problems" are required to be reported to the St. Jude IRB promptly, but in no event later than 10 working days after the investigator first learns of the unanticipated problem. Regardless of whether the event is internal or external (for example, an IND safety report by the sponsor pursuant to 21 CFR 312.32), only adverse events that constitute unanticipated problems are reportable to the St. Jude IRB. As further described in the definition of unanticipated problem, this includes any event that in the PI's opinion was:

- Unexpected (in terms of nature, severity, or frequency) given (1) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, as well as other relevant information available about the research; (2) the observed rate of occurrence (compared to a credible baseline for comparison); and (3) the characteristics of the subject population being studied; and

- Related or possibly related to participation in the research; and

- Serious; or if not serious suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unrelated, expected deaths do not require reporting to the IRB. Though death is "serious", the event must meet the other two requirements of "related or possibly related" and "unexpected/unanticipated" to be considered reportable.

Deaths meeting reporting requirements are to be reported immediately to the St. Jude IRB, but in no event later than 48 hours after the investigator first learns of the death.

The following definitions apply with respect to reporting adverse experiences:

Serious Adverse Event: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include: any substantial disruption of the ability to conduct normal life functions, allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse), a congenital anomaly/birth defect, secondary or concurrent cancer, medication overdose, or is any medical event which requires treatment to prevent any of the medical outcomes previously listed.

Unexpected Adverse Event:

- Any adverse event for which the specificity or severity is not consistent with the protocol-related documents, including the applicable investigator brochure, IRB approved consent form, Investigational New Drug (IND) or Investigational Device Exemption (IDE) application, or other relevant sources of information, such as product labeling and package inserts; or if it does appear in such documents, an event in which the specificity, severity or duration is not consistent with the risk information included therein; or
- The observed rate of occurrence is a clinically significant increase in the expected rate (based on a credible baseline rate for comparison); or
- The occurrence is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the

subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

Internal Events: Events experienced by a research participant enrolled at a site under the jurisdiction of St. Jude IRB for either multicenter or single-center research projects.

External Events: Events experienced by participants enrolled at a site external to the jurisdiction of the St. Jude Institutional Review Board (IRB) or in a study for which St. Jude is not the coordinating center or the IRB of record.

Unanticipated Problem Involving Risks to Subjects or Others: An unanticipated problem involving risks to subjects or others is an event which was not expected to occur and which increases the degree of risk posed to research participants. Such events, in general, meet all of the following criteria:

- unexpected;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. An unanticipated problem involving risk to subjects or others may exist even when actual harm does not occur to any participant.

Consistent with FDA and OHRP guidance on reporting unanticipated problems and adverse events to IRBs, the St. Jude IRB does not require the submission of external events, for example IND safety reports, nor is a summary of such events/reports required; however, if an event giving rise to an IND safety or other external event report constitutes an "unanticipated problem involving risks to subjects or others" it must be reported in accordance with this policy. In general, to be reportable external events need to have implications for the conduct of the study (for example, requiring a significant and usually safety-related change in the protocol and/or informed consent form).

Although some adverse events will qualify as unanticipated problems involving risks to subjects or others, some will not; and there may be other unanticipated problems that go beyond the definitions of serious and/or unexpected adverse events. Examples of unanticipated problems involving risks to subjects or others include:

- Improperly staging a participant's tumor resulting in the participant being assigned to an incorrect arm of the research study;
- The theft of a research computer containing confidential subject information (breach of confidentiality); and
- The contamination of a study drug. Unanticipated problems generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

8.0 DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY

8.1. Data Collection

Data from the neurocognitive evaluations will be recorded by study personnel by participant identification number on optical recognition forms and downloaded daily on to a computer server with restricted access to the research team. The CNS Vital Signs assessment is PC or laptop-based and self-administered. Participants will be invited to complete the assessment via e-mail. Each potential participant will receive a unique url and keycode to access the CNS Vital Signs instrument via computer or laptop. Baseline, midpoint, and 6-month follow-up questionnaires will be completed either on campus with a team member or by secure link sent via Encrypted email. The side effects survey (modified PRISE) will be completed via secure link.

The medical records are abstracted, and the data are recorded using an established database. All files will be password protected. Identifying information will be stored separately and the files will be linked by identification number. Any paper forms will be stored in a locked file cabinet. Biological samples will be labeled with only the participant identification number and sample number. Data will be evaluated without identifiers for safety monitoring, process evaluation and outcomes analysis, and linked to the identifying information only if necessary for participant safety.

Source document verification of eligibility for all SJCRH cases will be performed within two weeks of completion of enrollment. This will include verification of appropriate documentation of consent. Monitoring of timeliness of adverse and serious adverse event reporting will be done as events are reported. Monitoring of modified NCI Clinical Data Update System elements, adverse event reporting, and compliance with the conduct of the protocol will be conducted according to recommended schedule for this study.

8.2. Study Monitoring

This study is considered low risk for monitoring purposes. The Principal Investigator (PI) and study team are responsible for ensuring participant eligibility and protocol compliance. The study team will hold meetings as needed to review case histories or quality summaries on participants and will generate minutes which are signed by the PI.

A quality review for form completeness will be performed on the informed consent forms of 100% of St. Jude participants by Clinical Trials Operations (CTO) personnel.

CTO will review up to 10% of the study participants annually for life status, status on study, and the appropriateness of the informed consent and eligibility processes. The monitor will annually verify regulatory documentation pertinent to the study, all Serious Adverse Event reports, and Age of Majority consenting on all study

participants. St. Jude affiliates and domestic collaborating study sites will be monitored remotely annually by the St. Jude Monitor. The plan for monitoring may be revised over time, to adapt monitoring frequency and/ or intensity to a changing environment when appropriate (for example: new safety signals; positive history of compliance; all participants are in long term follow-up; or the enrollment period has ended). The Monitor will generate a formal report which is shared with the Principal Investigator, study team, and the Internal Monitoring Committee (IMC).

Protocol continuing reviews by the Institutional Review Board (IRB) and Scientific Review Committee (CT-SRC) will occur at least annually. In addition, Unanticipated Problems and/or Serious Adverse Event reports are reviewed by the IRB.

8.3. Confidentiality

Confidentiality will be maintained. Data forms will be kept in locked file cabinets, in locked office space, accessed only by study staff on an "as needed" hierarchical basis. Data files will be de-identified, linked by a participant identification number to a separate secure database. Data files downloaded for statistical analyses will not contain personal identifiers.

9.0 STATISTICAL CONSIDERATIONS:

9.1. Statistical Analysis and Power

We are proposing a double-blind, randomized, placebo-controlled trial of home-based tDCS paired with remote cognitive training. The sample size justification is based on evaluating the efficacy of tDCS + remote cognitive training vs. sham/placebo + remote cognitive training on directly assessed executive dysfunction in survivors of ALL. The primary study outcome is the digit span backward working memory subtest from the WAIS IV. We observed an improvement of 0.5 SD in working memory on the digit span backward subtest in our pilot study and will use this same outcome in our study. Let $\mu^{I}_{diff} = \mu^{I}_{baseline} - \mu^{I}_{6-month}$ and $\mu^{S}_{diff} = \mu^{S}_{baseline} - \mu^{S}_{6-month}$ denote the means of the differences in working memory z-scores from baseline to 6-month evaluation for the two groups; intervention and sham, respectively. We are interested in testing $H_0 : \mu^{I}_{diff} = \mu^{S}_{diff}$ vs. $H_1 : \mu^{I}_{diff} \neq \mu^{S}_{diff}$. With a sample size of 41 per intervention group (n=82) we will be able to detect a between group difference of 0.5 with 80% power using a one-sided two-sample t-test and a type 1 error of, assuming the correlation between the two time points is 0.6 or higher. Because both groups will receive cognitive training we expect to observe improvement in both treatment arms; however, irrespective of treatment gain from the cognitive intervention alone, we will be powered to detect a 0.5 SD difference between the intervention and sham groups.

Schema of the intervention:

Intervention	Measurement at T1 (Baseline)	Measurement at T2 (Six months)
Sham + Cognitive training	Y1	Y2
tDCS + Cognitive training	X1	X2

We expect that cognitive training will yield an improvement in EF of δ units, i.e. we expect that for the sham + cognitive training arm we will have,

$$\text{Let } E(Z1) = E(Y2 - Y1) = \delta$$

Further, we expect that the intervention arm will show a much larger improvement, i.e. we expect for the tDCS + cognitive training arm we will have,

$$\text{Let } E(Z2) = E(X2 - X1) = \delta + \theta$$

By comparing the two differences Z2 and Z1, we can estimate the improvement due to tDCS, i.e.

$$E(Z2) - E(Z1) = \theta$$

and we test this difference using a two-sample t-test. The sample size justification was based on having a sufficient number of survivors enrolled on the study to detect a clinically meaningful difference of 0.5 SD or larger, i.e. we wanted to detect a value of θ to be greater than 0.5 SD. We understand that this is an optimistic effect size because the combined effect of tDCS + cognitive training was approximately 0.5 SD in our pilot study. However, it should be noted that the objective of the pilot study was to assess feasibility and obtain a rough estimate of the effect size that would make the consideration of future investigation of the tDCS intervention justified. However, because our intervention will be for six months as compared to 8 weeks a larger effect size (greater improvement) would be expected and therefore we feel that assessing a difference of 0.5 SD between the two arms is justifiable. In the process, we also assume that the effects of the cognitive training alone will be small at best, i.e. δ to be small or negligible.

For the second objective, our pilot study demonstrated an improvement of 0.7 SD in patient-reported emotional regulation. With the proposed sample size, we should be able to detect a 0.7 SD difference with roughly >90% power with one-sided two-sample t-test with $\alpha = 0.05$. In order to account for roughly 20% attrition we will increase recruitment to 104 in order to have 82 evaluable survivors for the primary objective. Potential imbalances between study arms with regard to confounding factors (e.g. sex) will be evaluated between study arms and if necessary, adjusted comparisons will be carried out using linear regression. Otherwise, standard t-tests will be used. Because this is randomized trial, we expect analyses to be simple and directed towards ascertaining controlled and generalizable intervention effects. In addition, improvement in

executive functioning within each treatment arm and between two treatments will be compared using longitudinal methods and considering patient-reported symptoms of fatigue, depression, and pain using PROC MIXED or PROCGEE in SAS 9.3.

Dr. Kelser (consultant) will conduct fMRI analyses. She will be blinded to treatment assignment and study outcomes. Preparation and conditioning of fMRI data will be accomplished as described above. Specific to Aim 3, the groups will be compared to see if those randomized to the active stimulation condition demonstrate improved efficiency compared to those randomized to the sham stimulation condition. Improved efficiency will be defined as reduced activation in dorsolateral prefrontal cortex during performance on the N-Back task during the fMRI. We will require behavioral performance to be maintained at a minimum of 80% accuracy during the fMRI task. Using Statistical Parametric Mapping software (SPM12, Wellcome Trust Centre for Neuroimaging, London), contrast-images from the fixed-effect analysis in each subject will be used for second level random-effect analysis to create group activation maps. These contrasts include pre- *v.* post-intervention imaging during the N-back task. Participants assigned to active stimulation will then be contrasted to those assigned to sham stimulation. Effects will be evaluated with α=0.05 and appropriate multiple comparison cluster-wise correction. Voxels will be considered active for $p < .05$, corrected for multiple comparisons and with a minimum cluster size of 5 voxels (T threshold=6.4). Additional cluster-level analysis will be conducted with threshold $p < .0001$ (uncorrected for multiple comparisons) and minimum cluster size of 5 voxels. Clusters will be reported for which the cluster size statistic is corrected $p < .05$. Coordinates for the location of clusters of activation will be converted from MNI space to Talairach space by using the transformation method developed by the MRC Cognition and Brain Sciences Unit (Cambridge, UK, available online at http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtm). The anatomical name and Brodmann area (BA) reported for each cluster of activation will be determined with the Talairach demon, and the location of clusters will be carefully cross-checked by visual comparison with the Talairach atlas.

Connectome properties were calculated using graph theoretical analysis defined as previously described.[82,87,88] Thresholding connectomes is necessary for removing false positive edges and facilitating between group comparisons but can remove potentially valid information regarding differences in network topology.[89,90] Therefore, as in our previous studies,[91,92] we will compare connectome properties across multiple densities using the area under the curve (AUC).[93,94] Specifically, we will measure connectome properties at each density from minimum connection density to the last density associated with a small-world organization [88,95] up to a maximum density of 0.5.[96] We will then measure the AUC across this entire range and compare them longitudinally between groups using nonparametric permutation testing[88] with 5000 iterations and two-tailed p values. Regional connectome differences will be determined using the Network-Based Statistic (NBS). This method identifies connected substructures, or components, within the larger network. Permutation testing with 5000

permutations will be used to determine group differences in components controlling for multiple comparisons using family-wise error (FWE).[97] Relevant covariates as described above will be included in these models.

Our fourth aim is to examine the effects of home-based tDCS paired with remote cognitive training on patterns of regional brain connectivity as measured by diffusion tensor imaging. Dr. Reddick (Co-Investigator) will oversee DTI analyses. He will be blinded to treatment status and outcomes. We hypothesize that survivors randomized to active tDCS plus cognitive training will demonstrate increased fractional anisotropy in frontal brain regions. With a sample size of 82 in [41 randomized to tDCS, 41 randomized to sham/placebo] we will have 80% power to detect an effect size as small as 0.6 SD (with type 1 error control α=0.05). This effect size is reasonable based on our previously published data in long-term survivors of childhood ALL, which demonstrated that measures of fractional anisotropy differ between ALL survivors with and without executive function impairment with a mean (SD) of 0.38 (0.03) and 0.40 (0.03), respectively.[6]

Our exploratory objective is to examine the effects of tDCS on patient-reported symptoms of depression, anxiety, fatigue, pain, and sleep. These analyses will be conducted in a manner similar to that for Specific Aim 1, though with comparing performance change over six time-points. Linear or quadratic functions will be selected based on the distribution of the data over time. We also will descriptively examine the prevalence, type, and severity of side effects and compare them across sham and active tDCS treatment groups.

9.2. Anticipated Completion Dates

Anticipated Primary Completion Date: **April 1, 2023**
Projected Date of Completion: **October 1, 2023**
Anticipated Study Completion Date: **April 1, 2024**
Anticipated date of reporting: **April 1, 2025**

9.3. Summary of Primary and SecondaryObjectives

Primary and Secondary Summary of Objectives

Objective #	Objective Type	Analysis #	Resp Party	Stat	Safety	Analysis Measure	Analysis Title	Data Collection Time Frame	# of Participants	projected date of completion	Date of reporting
1.1	P	1	TB/KK	KS	N	Executive Function	Compare Directly Assessed Executive Function Pre- and Post-Intervention: Sham vs. Active tDCS	Baseline, 6 months	82	10/1/2023	4/1/2025
2.1	S	1	TB/KK	KS	N	Executive Function	Compare Patient Reported Executive Function Pre- and Post-Intervention: Sham vs. Active tDCS	Baseline, 6 months	82	10/1/2023	4/1/2025
2.2	S	1	NS/KK/SK	SK	N	Brain Activation	Compare Patterns of Regional Brain Activation Pre- and Post-Intervention: Sham vs. Active tDCS	Baseline, 6 months	82	10/1/2023	4/1/2025
2.2	S	1	NS/KK/KS	KS	N	Brain Activation & Executive Function	Examine Associations between Patterns of Regional Brain Activation and Directly Assessed Executive Function	Baseline, 6 months	82	10/1/2023	4/1/2025
2.3	S	1	GR/KK	KS	N	White Matter Integrity	Compare Indices of White Matter Integrity Pre- and Post-Intervention: Sham vs. Active tDCS	Baseline, 6 months	82	10/1/2023	4/1/2025
2.3	S	1	GR/KK	KS	N	White Matter Integrity & Executive Function	Examine Associations between Patterns of Regional Brain Activation and Directly Assessed Executive Function	Baseline, 6 months	82	10/1/2023	4/1/2025
3.1	S	1	TB/KK	KS	N	Patient Symptoms	Compare Patient Reported Symptoms Pre- and Post-Intervention: Sham vs. Active tDCS	Baseline, 6 months	82	10/1/2023	4/1/2025

3.2	S	1	TB/KK	KS	Y	Adverse Events	Examine Prevalence, Type, and Severity of Side Effects/Adverse Events	Biweekly for 6 months	104	10/1/2023	4/1/2025

Column Key

1. Objective # - Column corresponds to the number assigned to the primary and secondary objectives identified in the protocol, Section 1.0, Objectives.
2. Objective Type - Objectives are either primary or secondary. Enter either a P or S.
3. Analysis # - Identifies the number of analyses associated with each objective. For objectives that include multiple time points and measures, multiple analyses may be required.
4. Responsible Party - Identifies the responsible party. This will be either the Principal or Sub-Investigator. Enter their initials.
5. Statistician - Identifies the bio-statistician responsible for the objective. Enter their initials.
6. Safety - Identify whether the objective evaluates intervention safety. Enter either Y or N.
7. Analysis Measure - Identifies what is being measured. Not how. Outcome measures include the name of the specific measure (e.g., Systolic Blood Pressure) and a description of the metric that will be used to characterize the measure (e.g., Change in Systolic Blood Pressure)
8. Analysis Title - This is the measure title. Titles should be brief and succinct and identify what is to be measured and when. Examples could include: Number of participants with adverse events, area under the plasma concentration versus time curve (AUC) of drug XXX, and peak plasma concentration (Cmax) of drug XXX.
9. Data Collection Time Frame – Identifies when the objective will be measured. “At follow-up” and “end-of-study” are not viewed as adequate time frames. If the time frame includes multiple measurement points, the intervals need to be specified.
10. Patients – Number of patients expected to evaluate the objective. Patients for secondary objectives could be less than those required for the primary.

10.0 OBTAINING INFORMED CONSENT

10.1. Informed Consent Prior to Research Evaluations

Participants will be informed that all study procedures and evaluations are for research purposes and no clinical evaluations will be completed as a part of the study.

10.2. Consent at Age of Majority

The age of majority is the state of Tennessee is 18 years old. All participants will be ≥18 years of age at the time of initial study consent.

10.3. Informed Consent When English is the Primary Language

Participants will be introduced to the study during the consent process for SJLIFE or by e-mail and phone if scheduled for SJLIFE or NEUROSTIM but has not yet arrived on campus. The consent conference for remote participation will be completed by phone. A member of the study team will explain the study and review the potential risks and benefits.

If the SJLIFE participant expresses interest, they will be e-mailed, faxed, or mailed/FedExed a copy of the consent form if they agree to consent conference via phone; the consent conference will occur via phone and e-mail, facsimile, or e-signature will be used to document informed consent. Once the consent signature page is received the participant is enrolled on study as described in Section 3.4

For campus-based participation, the formal informed consent process will take place at St. Jude Children's Research Hospital on the first day of the participant's NEUROSTIM or SJLIFE visit, at which time the study nurse or member of the study team will explain the assessments involved in the study and review the potential risks. If the consent conference was previously conducted by phone, the study team member will re- review the consent document and/or reconsent the participant on the current version of the protocol as needed. Once the research staff is confident that the potential participant understands the research study, and if the individual agrees to participate, the consent form will be signed by the subject, and the informant. If an individual has diminished cognitive abilities such that a legal guardian or medical power of attorney has been assigned, we will obtain informed consent from the appointed individual.

10.4. Consent When English is Not the Primary Language

Not applicable in the current study.

In the case of a medical emergency or in the event of a serious medical condition, when knowledge of the investigational product is essential for the clinical management or welfare of the participant, an investigator or other physician managing the participant may decide to unblind that participant's treatment code.

The physician managing the medical emergency or serious condition should attempt to contact the principal investigator to discuss options prior to unblinding, and the principal investigator should approve the unblinding, when applicable. However, ensuring patient safety is the primary objective when the decision to unblind the treatment assignment is made.

The principal investigator or designated study personnel will request to unblind the participant's treatment arm. The principal investigator or treating clinician will contact Dr. Krull to receive the unblinding information.

All occurrences of emergency unblinding will be reported to the IRB according to the criteria established in protocol section 9.0, and the FDA, when applicable. In a majority of cases, emergency unblinding will occur while managing a serious adverse event (SAE), and will therefore be reported with the SAE. If the unblinding event is not directly associated with an SAE, the same timeline and mechanism for reporting SAEs will be used to notify the IRB of the event (section 9.1).

APPENDICES

APPENDIX I

Event	Screen	Baseline	On Treatment: Study Month						6-month Evaluation
			1	2	3	4	5	6	
Informed Consent	X								
History and Physical (campus only)	X								
Pregnancy Test (campus)	X								X
Neurocognitive Evaluation		X							X
Neuroimaging Evaluation (campus)		X							X
Home-based stimulation sessions (at least twice per week)		X	X	X	X	X	X	X	X
Home-based Lumosity sessions (at least twice per week)		X	X	X	X	X	X	X	X
Side Effects Rating (weekly)			X	X	X	X	X	X	
Symptoms (depression, anxiety, pain, fatigue, sleep)		X			X				X

St. Jude Children's Research Hospital
IRB NUMBER: 19-0053
IRB APPROVAL DATE: 03/01/2022

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