Computerized Cognitive Training for Amelioration of Cognitive Late Effects among Childhood Cancer Survivors: A Randomized Controlled Trial

Conklin, et al

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COGTRN: COMPUTERIZED INTERVENTION FOR AMELIORATION OF COGNITIVE LATE EFFECTS AMONG CHILDHOOD CANCER SURVIVORS

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Protocol Summary

COGTRN - Computerized Intervention for Amelioration of Cognitive Late Effects among Childhood Cancer Survivors

Principal Investigator: Heather M. Conklin, PhD

IND Holder: Not Applicable

Brief Overview: Children treated for a brain tumor (BT) or acute lymphoblastic leukemia (ALL) show elevated rates of working memory impairment. Working memory (WM) is the ability to hold and manipulate information online; for example, when an individual mentally rehearses a phone number in order to dial it without writing it down. A computer-based working memory intervention has been successful in children diagnosed with ADHD and stroke survivors. Individuals participating in the intervention showed improvements on working memory measures as well as more complex problem solving skills. Neuroimaging (brain scans) conducted before and after training showed changes in brain activation suggestive of underlying changes in brain systems that support working memory.

The objective of this study is to investigate the benefits of this working memory intervention in a sample of childhood cancer survivors and look at brain-based changes that may occur as the result of working memory intervention. To achieve this goal, we plan to study childhood cancer survivors randomly assigned to the working memory intervention or a passive waitlist. Both groups will participate in cognitive testing pre-, post- and six months post-intervention. Intervention participants will also partake in neuroimaging exams before and after the intervention. The questions we will investigate are:

1. Will cancer survivors participating in the intervention demonstrate greater improvement in working memory, attention and problem solving than patients assigned to the waitlist?
2. Will improvements in working memory, attention and problem solving demonstrated at the end of the intervention be maintained six months later?
3. Will there be predictable changes in brain activity as measured by neuroimaging?

Findings from this study have direct potential to support a nonpharmaceutical cognitive intervention for cancer survivors that is a safe and effective alternative to stimulant medications with great promise for improving quality of life.

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Intervention: Cogmed Working Memory Training Program
Participants randomized to the intervention arm will complete the Cogmed RM working memory training program. Cogmed RM is a computer-based training program completed in the home. This program requires approximately 30 minutes every weekday for five weeks. The program software guides the child through eight rotating exercises each day, with increasing difficulty based on the child's level of performance. Exercises train both visuospatial and verbal WM using child-friendly activities. A research team member will serve as a coach who monitors weekly progress online and offers support through weekly phone calls with the study participants and their caregivers. This individual will not complete post-intervention assessments to maintain study blind. A home computer with internet connection and speakers is required. A laptop computer and/or wireless internet access will be provided to families whose only obstacle to participation is the lack of computer access or internet connectivity in the home setting. Families randomized to the WM intervention will complete a tutorial with study staff that provides instruction in using a computer, the internet and the WM training software.

Objectives:

- Primary Objective:
  - To assess the impact of a computer-based working memory intervention on the performance of childhood cancer survivors on measures of working memory, attention and executive functions.

Responsible Investigator: Heather M. Conklin
Estimated date for completion of data collection: 02/28/2013

- Secondary Objectives:
  - To evaluate the maintenance of improvements on measures of working memory, attention and executive functions six months following participation in the computer-based intervention program.

Responsible Investigator: Heather M. Conklin
Estimated date for completion of data collection: 6/30/2013

  - To use fMRI to examine the neural correlates of working memory before and immediately after intervention.

Responsible Investigator: Heather M. Conklin
Estimated date for completion of data collection: 12/31/2012

Hypotheses/Estimates:

1.a. Participants in the working memory intervention will demonstrate significantly greater improvement from pre- to immediate post-intervention on performance- and rater-based measures of working memory relative to childhood cancer survivors placed on an intervention waitlist.

1.b. Participants in the working memory intervention will demonstrate generalized cognitive benefits, as indicated by significantly greater improvement from pre- to immediate post-intervention on performance- and rater-based measures of attention and executive functions relative to waitlisted controls.

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2. Six months after intervention, intervention participants will perform significantly better than waitlisted controls on working memory, attention and executive function measures. 3. Participants in the working memory intervention will demonstrate increased brain activity in the prefrontal and parietal cortices after working memory training.
Criteria for Evaluation: Neurocognitive evaluations and functional MRI
Study Design: We will use a single-blind (psychological examiner), randomized, waitlist-controlled experimental design to test our hypotheses about behavioral and neuroanatomical changes associated with the Cogmed intervention in childhood cancer survivors. We will recruit patients who were treated for a BT or ALL with CNS-directed therapy. **Efforts will be made to insure that patients participate in either study screening/pre-intervention or follow-up assessment during routine visits to St. Jude for medical care.** fMRI studies will be conducted only with participants randomized to the Cogmed intervention, at the same visit as the study screening/pre-intervention assessment and post-intervention assessments. The time period between pre- and post-cognitive assessments will be approximately 10 weeks for both intervention and control groups to allow adequate time for completion of 25 training sessions by members of the intervention group. Both groups will be brought back six months after post-cognitive assessments to complete a second post-intervention cognitive assessment to evaluate maintenance of cognitive improvements. Waitlist controls will be offered the Cogmed intervention, after completion of their post-waitlist cognitive assessment. **Participants who choose to complete Cogmed training will be given the option to participate in a post-intervention cognitive assessment during their next routine visit to St. Jude.**
Study Population: Inclusion Criteria for Screening Phase 1) Received CNS-directed treatment (intrathecal chemotherapy or cranial irradiation) for a BT or ALL 2) Infratentorial tumor location (for the BT cohort) 3) Off treatment for at least one year with no evidence of recurrent or progressive disease 4) Age 8-16 years inclusive at the time of enrollment 5) English as the primary language 6) Research participant and one parent willing to participate and provide consent/assent according to institutional guidelines Exclusion Criteria for Screening Phase 1) Significant impairment in global intellectual functioning (estimated or full scale IQ < 70 based on standardized testing routinely conducted on primary treatment protocols) 2) History of CNS injury/disease predating or unrelated to cancer diagnosis 3) Documented ADHD predating cancer diagnosis 4) Treatment with psychostimulant or psychotropic medication within two weeks of

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study participation

5) Major sensory or motor impairment that would preclude valid cognitive testing secondary to inability to complete study procedures (e.g., blindness, paresis, poorly controlled seizures/photosensitive epilepsy, psychosis)

Inclusion Criteria for Intervention Phase

1) Signed screening consents and has undergone screening
2) Fully evaluable psychological testing results (including IQ $\geq$ 70)
3) Age-scaled score on Digit Span, Letter-Number Sequencing or Spatial Span < 7 **or** at least one standard deviation below IQ score
4) Training aide is available to participate in required sessions
5) Participant and training aide demonstrate computer proficiency
6) Participant has access to or will be provided a laptop or home computer with internet connection and speakers
7) Participant willing to participate in required aspects of Cogmed RM
8) Participant is able to take part in fMRI without sedation

Exclusion Criteria for Intervention Phase

1) Major psychological condition that would preclude completion of protocol intervention (e.g., significant oppositionality, autism spectrum disorder, severe anxiety or depressive symptoms)
2) Orthodontic appliances that cause MRI distortion or signal loss outside the mouth and sinus area

Amendment 3.0

Sample Size: Participants will be enrolled until 68 patients demonstrating WM problems are accrued to the intervention trial, with approximately 34 randomized to an intervention group and 34 to a waitlist control group. We expect to recruit and screen up to 150 patients to identify 68 eligible participants.

Randomization:

The randomization will be stratified based on gender, age (8-11, 12-16) and diagnosis (BT, ALL) in order to roughly balance the intervention and waitlist control groups on these three factors. The randomization will be performed using a program that implements the block-randomization scheme proposed by Zelen.[122] **Given a sample size of 68 and eight strata, a block size of 4 will be used to achieve balance on these factors.** The program resides on the Department of Biostatistics network and has been routinely used for randomization since 1992. The PI will be provided access to the program and will be responsible for randomizing patients. The system stores all required data for randomization in a secure Access database. Once a patient is randomized, all related data are frozen in the database and cannot be changed.

Data Analyses:

Planned Analyses for Primary Study Aim:

Primary Objective 1.1.1 To assess the impact of a computer-based WM intervention on the performance of childhood cancer survivors on measures of

WM, attention and executive functions.

For each patient in the two groups (intervention and control), WM scores will be taken at three time points: Visit 1 (pre-intervention), Visit 2 (immediate post-intervention), and Visit 3 (6 months post-intervention). As illustrated in Section 4.1, there are about 10 weeks between Visit 1 and Visit 2, and about 6 months between Visit 2 and Visit 3. The magnitude of pre- to post-intervention change in WM performance will be estimated for each group and will be compared between the two groups.

1.1.1 a. Participants in the WM intervention will demonstrate significantly greater improvement from pre- to immediate post-intervention on performance- and rater-based measures of WM relative to childhood cancer survivors placed on an intervention waitlist.

A t-test will be used to compare the magnitude of pre- to immediate post-intervention change (Visit 2 – Visit 1) between the intervention and control groups for both performance- and rater-based WM measures. Consistent with the Klingberg et al. study,[19] the primary performance-based WM outcome measure will be Spatial Span Backward from the WISC-IV Integrated. The primary rater-based WM outcome measure will be the BRIEF WM Index. Other performance- and rater-based WM measures described in sections 5.1 and 5.2 will also be investigated using similar but exploratory analyses. **If 10 or more participants initially randomized to the control group decide to complete intervention training after their 6 month post-waitlist assessment (Visit 3), and agree to an additional cognitive assessment, we will conduct paired t-tests to investigate changes in WM performance (Visit 4 – Visit 3) on these same measures to further explore intervention efficacy.**

Amendment 1.0

1.1.1 b. Participants in the WM intervention will demonstrate generalized cognitive benefits, as indicated by significantly greater improvement from pre- to immediate post-intervention on performance- and rater-based measures of attention and executive functions relative to waitlisted controls.

A t-test will be used to compare the magnitude of pre- to immediate post-intervention change (Visit 2 – Visit 1) between the intervention and control groups for both performance- and rater-based measures of attention and executive functions. To assess attention, Spatial Span Forward from the WISC-IV Integrated will serve as the primary performance-based measure and the Conners' III Parent Rating Scale-Inattention Scale as the primary rater-based measure. To assess executive function, DKEFS-Color-Word Inhibition will serve as the primary performance-based measure and the BRIEF Metacognition Index as the primary rater-based measure. Other attention and executive function measures described in sections 5.1 and 5.2 will be investigated using similar but exploratory analyses. **If 10 or more**

Amendment 1.0

participants initially randomized to the control group decide to complete intervention training after their 6 month post-waitlist assessment (Visit 3), and agree to an additional cognitive assessment, we will conduct paired t-tests to investigate changes in WM performance (Visit 4 – Visit 3) on these same measures to further explore intervention efficacy.

Planned Analyses for Secondary Aims:

Secondary Objective 1.2.1 To evaluate the maintenance of improvements on measures of WM, attention and executive functions six months following participation in the computer-based intervention program.

Both groups of participants will participate in cognitive assessments at three time points: pre-, post- and six months post-intervention. A mixed model with random coefficients will be used to estimate the average trajectory of cognitive performance over time for both groups on measures of WM, attention and executive functions. Given this trajectory may be better represented by a curve rather than a straight line, a second order polynomial (e.g., Y= a0 + a1*t + a2*t^2) will be used for model fitting, where "a" represents estimated parameters and "t" the time from pre-intervention assessment.

1.2.1 a. Six months after intervention, intervention participants will perform significantly better than waitlisted controls on WM, attention and executive function measures.

We will compare the cognitive performance of the intervention and control groups at six months post- intervention using three different analytic approaches. The first analysis will compare the mean scores of the two groups, on our primary WM, attention and executive function variables outlined above, at the six months post-intervention time point using a simple two group comparison (e.g., t-test). The second analysis will compare the change in scores of the two groups from the pre-intervention assessment to the six months post-intervention using a repeated measures ANOVA including only pre- and six months post-intervention data. In the third analysis, a mixed model will be fit that includes both groups and data from all three time points; a group status variable will be used to differentiate the two groups with respect to pre-intervention, as well as linear and curvature terms that estimate the longitudinal pattern of cognitive scores. With this model, the mean scores at six months post-intervention will also be compared across the two groups. The first two statistical approaches provide a cross-sectional analysis of performance at six months post- intervention and are robust with respect to modeling assumptions but are less powerful to detect group differences. In contrast, the third statistical approach gives a longitudinal analysis of scores across the three time points and is powerful to detect any differences in baseline scores, as well as linear and curvature

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patterns over time, provided the assumptions of the model are not violated.

Gender, age, and diagnosis are potential factors influencing the outcomes of WM, and thus will be roughly balanced in the randomization of patients into the two groups (intervention and control). The randomization will be performed using a program that implements the block-randomization scheme proposed by Zelen.[122] Gender (male, female), Age Group (8-11, 12-16), and Diagnosis (ALL, BT) will be the three stratification factors for the stratified block randomization. **Given a sample size of 68 and eight strata, a block size of 4 will be used to achieve balance on these factors.** The program resides on the Department of Biostatistics network and has been routinely used for randomization since 1992. The PI will be provided access to the program and will be responsible for randomizing patients. The system stores all required data for randomization in a secure Access database. Once a patient is randomized, all related data are frozen in the database and cannot be changed. In analysis, we will investigate the effects of stratification factors using the factor selection procedure to fit the mixed model, provided there are enough participants within each strata.

Amendment 2.0

Secondary Objective 1.2.2 To use fMRI to examine the neural correlates of working memory before and after intervention.

Amendment 2.0

The patients randomized to the intervention will participate in fMRI examinations before and after WM training. Neural correlates of WM performance will be measured by comparing activations during WM tasks with activations during alternating control tasks as described in section 5.3. Neural activations associated with WM task performance will be compared at pre- and post-intervention time points.

1.2.2 a. Participants in the working memory intervention will demonstrate increased brain activity in the prefrontal and parietal cortices after working memory training.

The primary goal of this objective is to identify brain areas where activity measured by fMRI changes significantly from pre- to post-intervention for cancer survivors. We will focus analyses on frontal and parietal brain areas identified in the Olesen et al. study as ROIs for detection of activation, thus improving sensitivity and reducing the number of multiple comparisons across voxels. Two WM paradigms will be used during fMRI examinations, each with parametrically varied difficulty level: 1) Olesen's spatial WM task[21]: control, 3- and 5-spatial locations and 2) N-back verbal: 0-, 1- and 2-back. Functional images will be analyzed with SPM software to generate activation maps via a fixed-effect model for each subject, as described in section 5.3. Contrast images from the fixed-effect analysis in each subject will then be used for second-level random-effect analyses to create group activation maps. A significance level of $\alpha = .05$ corrected for multiple comparisons at the cluster level

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will be used for our primary analyses. These analytical procedures are well established. The magnitude of fMRI signal change, volume of brain tissue activated and association between activation and WM demand will be evaluated for each cluster. Olesen et al. found increased neural activity in the middle frontal gyrus and superior and inferior parietal cortices after five weeks of Cogmed training for healthy adults.[21] Exploratory whole-brain analyses will also be conducted.

In addition, DTI will be used to conduct exploratory analyses that investigate white matter connections between areas of activation measured with fMRI. The set of diffusion-weighted images will be analyzed to determine an effective diffusion tensor for each volume element (voxel) imaged. The information in the full-diffusion tensor is represented by 2 derived quantities, the apparent diffusion coefficient (ADC) and fractional anisotropy (FA).[111] The ADC is expressed as mm^2/s and is a measure of the magnitude of diffusion displacement. FA is a dimensionless quantity that is a measure of the directional anisotropy of water diffusion. We will determine the associations between ADC and FA and parameters of activation measured with fMRI. We will use the Tract-Based Spatial Statistics methodology to characterize the white matter and evaluate the association between DTI parameters, fMRI and medical variables.

Primary Anticipated Completion Date: 2/28/2013

Anticipated Study Completion Date: 06/30/2013

Timeframe for Primary Outcome Measure: The primary outcomes (neurocognitive performance) will be measured at pre-intervention baseline, immediate post-intervention/waitlist (10 weeks) and six months post-intervention/waitlist.

Data Management: Data management and statistical analysis will be provided locally by the Department of Psychology, the Neuroimaging Division of Radiological Sciences and the Biostatistics Department at St. Jude Children's Research Hospital

Human Subjects:

There are no physical or medical risks from the intervention program. It is possible that a participant could become frustrated or fatigued by some of the tasks. We think it is unlikely that this will happen, as these same, or similar, tasks have been used in studies with children in the past. However, should a child become frustrated or fatigued, he/she may take a break at designated points. Aside from the possibility that some tasks might be mildly frustrating, there are no other risks to taking part in this study of which we are aware.

There are no known significant risks from fMRI/MRI exams. Some people feel skin warmth during the exam. Also, some people experience claustrophobia (fear of being in a small space) in the scanner. If this happens, or if a participant experiences any other discomfort or distress, we will stop testing and a psychologist will be available to answer any questions.

Participants may or may not receive benefit from taking part in this study. Some research

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indicates that this training program may help children with working memory problems. These same potential benefits will be available to patients in the waitlist control group once they have completed their follow-up cognitive assessments. Even if there are no direct benefits to participants from this study, the information we learn may help us develop future treatments for working memory problems in other patients treated for childhood cancer.

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1.0 OBJECTIVES

1.1 Primary Objective

1.1.1 To assess the impact of a computer-based working memory intervention on the performance of childhood cancer survivors on measures of working memory, attention and executive functions.

a. Participants in the working memory intervention will demonstrate significantly greater improvement from pre- to immediate post-intervention on performance- and rater-based measures of working memory relative to childhood cancer survivors placed on an intervention waitlist.

b. Participants in the working memory intervention will demonstrate generalized cognitive benefits, as indicated by significantly greater improvement from pre- to immediate post-intervention on performance- and rater-based measures of attention and executive functions relative to waitlisted controls.

1.2 Secondary Objectives

1.2.1 To evaluate the maintenance of improvements on measures of working memory, attention and executive functions six months following participation in the computer-based intervention program.

a. Six months after intervention, intervention participants will perform significantly better than waitlisted controls on working memory, attention and executive function measures.

1.2.2 To use fMRI to examine the neural correlates of working memory before and immediately after intervention.

a. Participants in the working memory intervention will demonstrate increased brain activity in the prefrontal and parietal cortices after working memory training.

2.0 BACKGROUND AND RATIONALE

<u>Neurocognitive Sequelae in Childhood Cancer Survivors</u>

Survivors of childhood cancer who received CNS-directed therapy are at significant risk for cognitive impairments secondary to their disease and treatment.[1-4] These impairments have been associated with academic failure, high unemployment rates and reduced

quality of life.[5-7] As survival rates of children treated for cancer rise,[23] efforts to improve long-term cognitive outcomes become imperative.

Despite differences in disease processes between malignant BTs and ALL, the types of cognitive problems that emerge subsequent to CNS-directed therapy are notably similar.[1-4] Longitudinal studies of survivors of childhood BTs or ALL have most consistently revealed declines on global cognitive measures, including intellectual functioning, as measured by IQ tests.[2-3,24] Progressive IQ loss most likely reflects a decreased rate of learning compared to that of peers rather than a loss of previously acquired knowledge.[25] Risk factors associated with IQ decline most reliably include younger age at treatment,[24,26] longer time since treatment,[27] female gender,[24,28] treatment intensity (e.g., radiation dose or volume)[24,29] and complicating medical factors (e.g., hydrocephalus, meningitis or endocrinopathies).[30]

Recently, researchers have identified specific areas of cognitive impairment in childhood cancer survivors including attention,[8] working memory (WM; online maintenance and manipulation of information)[9,10] and processing efficiency[11] that may be more proximal contributors to global IQ decline. These emerging areas of deficit are informative, as nearly half of age-related improvements in IQ can be attributed to developmental improvements in WM and processing speed.[12] WM may be particularly vulnerable to therapy effects as indicated by larger WM impairment than predicted based on reduced information processing speed.[10] Adequate attention is required but not sufficient for good WM performance, which requires additional mental manipulation.

The existing literature is significantly limited by an over-reliance on global cognitive outcomes (e.g., IQ and academic skills) that are not specific enough to facilitate the development of targeted cognitive interventions. The proposed study meaningfully augments the existing literature by proposing an intervention targeting a specific skill (WM) that is not only highly vulnerable in this population but also a demonstrated building block for a number of higher-order reasoning abilities.[31-34]

Neurodevelopmental Underpinnings of Neurocognitive Sequelae

CNS-directed cancer therapies are well-established causes of changes in cerebral white matter.[35] Accumulating evidence suggests that reduced cerebral white matter accounts for a significant proportion of the observed decline in IQ among survivors of childhood BTs and ALL. For example, Reddick and colleagues compared 15 patients with medulloblastoma treated with tumor resection and cranial irradiation to 15 age-matched patients with low-grade astrocytoma of the posterior fossa treated with surgery alone.[36] All radiation-treated patients demonstrated significantly reduced white matter volumes compared to patients treated with surgery alone. Patients with medulloblastoma also demonstrated significantly lower IQ scores, which had a statistically significant association with volumes of cerebral white matter.[37] Further, a longitudinal study of patients with medulloblastoma revealed a significant decrease in cerebral white matter volumes, in contrast to expected developmental maturation, with a more rapid decrease in patients receiving higher radiation doses.[15]

White matter changes associated with CNS-directed therapies provide a context for understanding factors that place children at greatest risk for cognitive impairment secondary to cancer treatment. Mulhern and colleagues examined neurocognitive outcomes in 42 patients treated for medulloblastoma with radiation therapy (with or without chemotherapy).[38] Young age at radiation treatment was significantly associated with worse performance on most neurocognitive tests. After statistically controlling for time since treatment, the volume of normal appearing white matter accounted for about 70% of the association between age at radiation therapy and IQ score. Therefore, deficient development of cerebral white matter provides a neuro-developmental explanation for the adverse effect of young age at treatment on cognitive outcomes.[38]

Reddick and colleagues have proposed an association between reduced volumes of white matter and attention and/or memory deficits that, in turn, contributes to declines in IQ and academic achievement.[39] They studied 40 long-term childhood BT survivors receiving radiation therapy (with or without chemotherapy) who participated in neurocognitive assessments and MRI scans. After statistically controlling for age at radiation and time from treatment, they found that attentional abilities, not memory, explained a significant proportion of the association between white matter volume and IQ. Furthermore, a model including white matter volume, attentional ability and IQ explained greater than 60% of the variance in academic performance. Similar findings of reduced white matter volumes have been demonstrated in ALL survivors. For example, Reddick and colleagues found that ALL survivors who receive chemotherapy alone have larger white matter volumes than ALL survivors who receive cranial irradiation, yet their white matter volumes remain significantly smaller than those of healthy sibling controls.[40] Also, smaller white matter volumes were associated with larger deficits in attention, IQ and academic achievement.[40] These findings demonstrate that a primary implication of reduced cerebral white matter volumes in children treated for BTs or ALL is compromised attentional abilities that lead to declines in IQ and academic achievement.[39] It is important to note that although attention is subserved by a more distributed network than WM, it is supported by frontal brain areas. This finding suggests that frontal areas may be particularly vulnerable to radiation effects. WM was not explicitly assessed in these studies.

Frontal Lobe Development and Vulnerability

Myelination (increase in cerebral white matter) begins during the third or fourth month of gestation and continues postnatally through the twenties.[41] The last brain areas to myelinate are the anterior portions of the frontal lobes. Axon myelination imparts increased speed and efficiency of neuronal transmission that facilitates communication among brain areas.[42] Myelination of brain areas appears to parallel their functional maturation, with cognitive abilities coming on-line as supporting brain areas myelinate.[43] It has been proposed that skills emerging at the time of brain injury (or in this case, time of cancer treatment) are most vulnerable to loss.[44-45]

Postmortem histologic findings have long suggested that frontal-subcortical pathways continue to develop into the third decade of life, as indicated by ongoing myelination and pruning.[13,14] Structural neuroimaging findings reveal this same protracted pattern of

frontal lobe development in vivo.[46-48] Furthermore, fMRI studies employing putative frontal lobe tasks have shown more diffuse frontal lobe activation in children than in adults.[41] Our previous work indicates that these maturational brain-based changes coincide with improved WM task performance by adolescents.[49,50]

Multiple aspects of frontal lobe architecture render this area susceptible to injury. Most notably, with respect to the pediatric oncology population, the frontal lobes are rich in myelin.[51] Given that changes in white matter have been demonstrated following CNS-directed therapy, the frontal lobes may be disproportionately vulnerable to treatment-related neurotoxicity. Vascularization of the frontal lobes also renders them vulnerable to injury, with frontal watershed areas particularly susceptible to hypoxic injury in the case of decreased blood flow to the brain.[52] Treatment-related CNS injury in cancer survivors has been hypothesized to include microvascular occlusion,[53,54] a hypothesis supported by animal models.[55] Vulnerability of the frontal lobes to damage secondary to vascular insult further supports WM as a target for intervention in cancer survivors.

Working Memory and the Prefrontal Cortex

An instrumental function supported by the frontal lobes is WM. WM is a limited-capacity system that facilitates online maintenance and manipulation of information used to guide cognition and behavior.[56-57] The most commonly provided example of WM is when someone mentally rehearses a phone number so as to successfully dial the number without writing it down. WM is an important function that subserves many complex cognitive and academic skills including language comprehension,[31] mathematical computation,[32] reading and writing.[33-34] WM is highly correlated with IQ in healthy children,[58] and a substantial portion of age-related improvements in IQ can be attributed to developmental improvements in WM.[12]

Baddeley and Hitch described a tripartite WM model that includes an attentional control system, the central executive, and two subordinate systems, the phonological loop and visuospatial sketchpad.[59] The phonological loop and visuospatial sketchpad maintain domain-specific information in WM, while the central executive mediates higher-order processing including strategic organization of information. Animal models, clinical cases of acquired lesions and neuroimaging studies all converge in identifying frontal-subcortical pathways as the primary neural substrates underlying WM processes.[60-62] Furthermore, recent neuroimaging findings have been consistent with the Baddeley and Hitch model, identifying distinct patterns of neural activation associated with the type of information held in WM (e.g., verbal or spatial) and the type of processing performed upon such information (e.g., rehearsal or simple storage).[62] The prefrontal cortex is consistently identified as the primary brain area supporting the WM central executive.

Empirically Validated Interventions in Childhood Cancer Survivors

Few systematic attempts have been made to develop interventions to remediate cognitive impairments emerging secondary to cancer treatment. Stimulant medications have been used for decades to successfully and safely treat children diagnosed with ADHD.[63-64] The most commonly prescribed medication for ADHD is methylphenidate (MPH), a

piperidine derivative that acts by releasing dopamine from presynaptic vesicles, reducing dopamine reuptake and inhibiting monoamine oxidase.[65] The first randomized, placebo-controlled trial of MPH in childhood cancer survivors was conducted by Thompson and colleagues.[66] Significant improvement was demonstrated on a continuous performance measure of sustained attention but not on measures of verbal memory or visual-auditory association. The same group of investigators later reported on 83 childhood cancer survivors who participated in a placebo-controlled, double-blind, cross-over study.[16] Parent and teacher ratings of attention and teacher ratings of social skills showed improvement during MPH treatment relative to placebo. We recently demonstrated that these benefits are maintained during a year long trial.[67]

As a group, childhood cancer survivors tolerate MPH well.[68] We found that the frequency and severity of side effects are similar to or less than those reported for children diagnosed with ADHD.[69-70] As previously observed by Mulhern and colleagues,[16] we also identified a subgroup of cancer survivors with decreased MPH tolerance who experience significant, and sometimes atypical, adverse side effects.[68] Although the rate of early termination due to side effects in ALL survivors paralleled that seen in patients with ADHD,[69,71] the rate among BT survivors was three times higher (18.52% vs. 6.12%). Female gender and lower IQ were also risk factors for higher rates of side effects.[68] Furthermore, we have found growth deceleration associated with MPH.[72] During a one year MPH trial, cancer survivors receiving MPH demonstrated a significant deceleration in weight and body mass index (BMI) relative to case-matched survivors not receiving MPH. Higher daily MPH dose and higher parent-reported medication side effects (e.g., loss of appetite) were associated with greater deceleration in BMI and weight.[72] Growth deceleration is of particular concern for the childhood cancer population, because they are already at risk for growth retardation secondary to disease- and treatment-related factors such as cancer burden in the CNS, concomitant endocrinopathies, chemotherapy and radiation therapy.[73-75]

It should be noted that children were precluded from participating in these MPH trials for a number of possible medical contraindications (e.g., uncontrolled seizures, uncorrected hypothyroidism or a history of Tourette syndrome). Furthermore, a significant proportion of evaluated children (36%) qualified for the trial, but their parents refused participation.[17] The most common reason cited by parents was concern about placing their child on a stimulant medication. Among children who were eligible for participation and adequately tolerated MPH during a three week trial, the response rate using a conservative, statistically derived criterion (Reliable Change Index) was 45.28%.[76] This rate is significantly lower than the 75% typically reported in the ADHD literature.[63] Taken together, findings from these MPH trials are encouraging, revealing an intervention that is safe and beneficial for nearly half of cancer survivors experiencing attention and learning problems. Yet, there remain a significant proportion of children for whom MPH is not a viable treatment option because of medical exclusions, parental refusal, medication intolerance or poor response. Based on these findings, the development of nonpharmaceutical interventions for cancer survivors is clearly a necessity.

The most systematic, nonpharmaceutical approaches to cognitive remediation in survivors of childhood cancer have been developed by Butler and Copeland.[77] These researchers developed a tripartite model, Cognitive Remediation Program (CRP), that uses techniques from brain injury rehabilitation, special education and clinical psychology.[78] CRP includes 20, two hour sessions, which are completed one-on-one with a child over four to five months. Butler and colleagues recently published a multi-center, randomized, controlled trial of CRP in 167 survivors of childhood cancer who ranged in age from 6 to 17, were at least one year off treatment and were experiencing attention problems.[79] CRP participants experienced a significant improvement in academic achievement, incorporated more metacognitive strategies in problem solving and showed improvements on a parent-rated measure of attention.[79] There were no significant differences between the group receiving CRP and controls on any measures of neurocognitive functioning, including attention, WM and episodic memory.[79] Effect sizes were small to medium (range, 0.1 to 0.5), but comparable to other brain injury rehabilitation programs and psychological interventions.[80-81] This study offers initial encouragement, particularly for improving academic skills in childhood cancer survivors; however, the personnel time and financial requirements are great, and the benefits modest. In addition, only individuals who live in close proximity to a center offering intensive intervention can benefit from this program. There is an obvious need for a less expensive, less time-intensive and portable cognitive intervention program with demonstrated efficacy.

Cogmed Working Memory Training Program

The current proposal includes Cogmed RM, a software program created for children 7 years of age or older. This software was developed by neuroscience researchers and game developers at the Karolinska Institute in Stockholm.[82] Cogmed training consists of a 30-minute session completed each weekday for five weeks. The child is guided through eight rotating exercises daily that train both visual-spatial and verbal WM. As ability improves, exercises become more difficult. Compliance and performance can be tracked over the Internet. Feedback is provided during weekly telephone coaching sessions to maintain motivation.

Cogmed has demonstrated efficacy for improving WM and executive functions in children diagnosed with ADHD.[18-19] Klingberg and colleagues conducted a multicenter randomized, controlled, double-blind study using Cogmed with 53 children, between the ages of 7 and 12, diagnosed with ADHD. Forty-four participants (83%) completed at least 20 sessions. For the main outcome measure, spatial span, there was greater improvement between baseline and post-intervention assessments in the treatment group compared to the control group [effect size (ES) = 0.93]; this effect was still significant at 3-month follow-up (ES = 0.92). There were significant positive treatment effects for all executive tasks (i.e., Stroop Interference Task, ES = 0.34; WISCIII Digit Span, ES = 0.59; and Raven's Colored Progressive Matrices, ES = 0.45), and benefits were maintained at similar levels three months post-intervention (ES = 0.25, 0.57 and 0.30, respectively). Parent ratings of ADHD symptoms also showed a significant reduction (ES = 1.21 at the end of intervention, and ES = 0.67 at three month follow-up). These effect sizes are similar to WM benefits found with stimulant medication.[83-84] WM scores often

normalized, with post intervention scores within 0 to 0.3 standard deviations of healthy peers.[19]

A recent study of healthy children demonstrating low WM skills also revealed normalization of WM abilities following Cogmed intervention, with maintenance of benefits six months after training.[115] All children were between the ages of 8 and 11 and scored at or below the fifteenth percentile on two measures of verbal WM (listening recall and digit span backwards). Twenty-two children were randomly assigned to the Cogmed intervention and 20 to a control condition. Immediately following intervention, children completing the Cogmed training demonstrated significant improvements on all WM measures with effect sizes ranging from 0.62 to 1.55. Six months following intervention, training gains in each WM domain remained significant with effect sizes ranging from .44 to 1.16.).[115] The maintenance of WM improvement six months following intervention is encouraging with respect to sustained cognitive benefits.

The Cogmed training program has demonstrated benefits in adults with acquired cognitive deficits secondary to experiencing a stroke. Westerberg and colleagues completed a randomized, placebo-controlled trial with 18 patients between the ages of 34 and 65 who were on average 20 months post stroke.[20] All patients exhibited deficits on a self-report measure of attention. Nine patients participated in the five week Cogmed training, and nine patients served as passive controls. The treatment group improved significantly more than controls on performance measures of WM and attention, as well as on a self-report attention scale.[20] These findings indicate cognitive deficits subsequent to acquired brain injury are amenable to WM training.

Functional neuroimaging conducted before and after WM training suggests neuroplasticity for supporting brain systems.[21-22] Olesen and colleagues investigated changes in brain activity associated with WM training.[21] Two experiments were conducted with healthy adults who participated in Cogmed WM training for five weeks. fMRI exams were conducted before, during and after training. Findings from both experiments converged in identifying increased brain activity in the middle frontal gyrus and superior and inferior parietal cortices related to improvement in WM performance.[21]

Although the brain areas identified in these experiments are consistent with earlier imaging studies investigating neural correlates of WM performance,[62] previous studies with non-WM tasks found practice-related decreases (rather than increases) in activity.[85-86] It can be argued that tasks used in non-WM studies allowed for automation of the core skill such that the task demands decreased with practice, and the task became less effortful. With WM tasks, unique trial stimuli and the requirement to keep information on line through active maintenance precludes automation.[87] In studies demonstrating decreased activation during imaging, changes occurred during a single scanning session. In the Olesen experiments, changes occurred over several weeks, which is more consistent with skill acquisition associated with cortical plasticity.[88] An alternative explanation to neuroplasticity is a change in strategy use. A follow-up study employing single-subject analyses revealed that task-related activity before and after training was very similar; it differed in intensity and size of activation rather than pattern, which is more consistent with plasticity than different strategy use.[22] Finally, change in strategy

was not typically reported by participants.[21] Taken together, fMRI findings are highly suggestive of cortical plasticity for WM brain regions secondary to Cogmed training.[21-22]

Synthesis and Study Significance

Clinical advances have significantly improved the survival rates of children diagnosed with cancer. Thus, it is imperative that research efforts are devoted to improving the quality of survival, and mitigating cognitive late effects is key to optimizing quality of life. There are very few empirically supported cognitive interventions for cancer survivors, with stimulant medications receiving the greatest research attention. While MPH is beneficial and safe for a subset of cancer survivors, there remain a significant proportion of children for whom MPH is not a viable treatment option based on medical exclusions, parental refusal, medication intolerance or poor response. CRP is the only nonpharmaceutical cognitive intervention validated for cancer survivors. Study findings offer initial encouragement, particularly with respect to improving academic skills. However, benefits are modest and do not generalize to measures of attention, WM or episodic memory. In addition, CRP requires highly trained personnel, as well as significant time and financial resources, and is offered at limited locations. Nonpharmaceutical interventions that are less expensive, less time intensive and portable are needed. WM is the ideal target for intervention in childhood cancer survivors because neurodevelopmentally it is highly vulnerable to CNS-directed therapy and it is a demonstrated building block for a number of higher order reasoning abilities, abilities shown to decline subsequent to cancer treatment. Behavioral and neuroimaging studies suggest that Cogmed is a promising therapeutic alternative.

Preliminary Studies

The proposed study represents a new line of investigation in a long-standing research program at St. Jude that focuses on characterizing the neurocognitive sequelae of cancer and cancer therapy and developing interventions that mitigate the impact of these sequelae on quality of life. The proposed study is novel in its focus on a nonpharmaceutical intervention that targets WM specifically and in its portability, which allows for remote administration. We present three preliminary studies that support our methodologic approach for investigating the Objectives of this proposal and our capabilities to conduct the proposed research. First, findings from three institutional protocols investigating neurocognitive outcomes in children treated with CNS-directed therapy reveal the extent and significance of WM problems in this population. Second, findings from fMRI studies conducted at St. Jude investigating attention and WM performance in childhood BT survivors demonstrate our ability to successfully isolate neural circuits of interest in this unique clinical population. Third, preliminary results from a small trial of Cogmed with cancer survivors suggest initial feasibility with respect to recruitment, study compliance and ability to conduct valid pre- to post-intervention assessments.

Working Memory Impairment in Childhood Cancer Survivors

We are currently assessing attention and WM abilities in survivors of ALL receiving treatment on an institutional protocol (TOTXV). Ninety-seven consecutively enrolled children (55 males and 42 females; age 8.22 ± 3.93 years at diagnosis) were assigned to low-risk (n = 48) and standard/high-risk (n = 49) groups based on comprehensive biological and clinical risk classification.[89] During consolidation therapy, the low-risk group received 2.5 gm/m^2 methotrexate intravenously and triple intrathecal therapy (methotrexate, cytarabine, hydrocortisone) every other week for four doses, whereas the standard/high-risk group received 5.0 gm/m^2 methotrexate intravenously with triple intrathecal therapy. Attention (Digit Span Forward) and WM (Digit Span Backward) were assessed with the age appropriate Wechsler scale at completion of therapy (two years post consolidation therapy). For patients in the standard/high-risk group, Digit Span Forward ($p < .003$), Digit Span Backward ($p < .001$), Total Digit Span ($p < .001$) and full scale IQ ($p < .02$) were statistically lower than the normative mean.[89] In the low-risk group, only Digit Span Backward ($p < .0001$) was statistically lower. Across all risk groups, a significantly higher percentage of patients performed below the average range (scale score < 7) on Digit Span Backward (66%) than Digit Span Forward (15%).[89] This also represents a substantially higher number of below average performers on this measure than expected in typically developing individuals (16%). Together, these findings suggest that WM is especially sensitive to treatment-related changes in children treated with chemotherapy for ALL, detecting difficulties potentially missed by global intelligence measures.

The St. Jude institutional protocol for treatment of newly diagnosed medulloblastoma, supratentorial primitive neuroectodermal tumor and atypical teratoid rhabdoid tumor (SJMB03) includes assessment of WM. Children receive risk-adapted therapy including six weeks of craniospinal irradiation, with a conformal boost to the primary tumor site, followed by four cycles of adjuvant chemotherapy consisting of high-dose cisplatin, cyclophosphamide and vincristine. Craniospinal irradiation is 23.4 Gy for average-risk patients (residual tumor < 1.5 cm^2 and no evidence of metastasis) and 36 to 39.6 Gy for high-risk patients (residual tumor ≥ 1.5 cm^2 or metastatic disease within the neuroaxis). The radiation boost consists of 55.8 Gy to the primary tumor site for both risk groups. Seventy-two patients have now completed the two year post treatment neurocognitive assessment (47 males and 25 females; age 9.99 ± 4.64 years at diagnosis). The high-risk group (n =16) is demonstrating significantly greater WM impairment relative to the average risk group (n = 56) on both performance based measures [Woodcock Johnson, Third Edition (WJIII)- WM Cluster Standard Score (higher score is better)- 90.57 ± 17.42 vs. 101.15 ± 16.28; $p < .05$] and a parent rater measure [WM Index T-Score from the Behavior Rating Inventory of Executive Function (BRIEF; higher score is worse)- 59.45 ± 9.55 vs. 51.28 ± 11.70; $p < .05$]. Further, the high-risk group exhibits significant deficits relative to the normative population on both WJIII- WM Cluster ($p < .10$) and the BRIEF WM Scale ($p < .01$), with 35.7% (WJIII- WM cluster) and 54.5% (BRIEF WM Scale) of the high-risk group performing in the clinically impaired range (unpublished data).

Our research group has completed the first year of funding to study WM performance after reduced-dose conformal radiation therapy (protocol RT-1) for localized CNS tumors

(ependymoma, craniopharyngioma and low-grade glioma). The primary study aim is to use laboratory measures of WM to identify specific cognitive processes underlying the previously observed decline on global cognitive measures. To assess this aim, the performance of BT survivors is compared to solid tumor (ST) survivors and healthy sibling controls. Thus far, 50 BT survivors (age 7.41 ± 3.41 years at treatment; 5.77 ± 2.27 years since treatment), 40 ST survivors (age 4.50 ± 4.18 years at treatment; 8.71 ± 3.94 years since treatment) and 40 siblings have been assessed. Groups are balanced by gender (all 50% male) and age at assessment (BT-13.18 ± 2.88, ST- 13.21 ± 3.46; Siblings-12.91 ± 2.62). Linear mixed models reveal significantly worse performance for BT survivors relative to both ST survivors and siblings on all WM measures (verbal and object self-ordered search tasks and Digit Span Backward, $p < .05$).[120] Further, comparison of the BT to the ST group indicates greater deficiency in WM (self-ordered search tasks) than recognition memory (forced choice recognition tasks; $p < .05$), suggestive of a specific area of cognitive vulnerability. Parents also endorsed significantly greater WM impairment for BT survivors compared to ST survivors and siblings (BRIEF-WM Index, $p < .001$).[120] Patients with infratentorial tumors performed significantly worse than patients with supratentorial tumors on the experimental WM measures ($p < .05$). Findings across these studies reveal prevalent and significantly elevated rates of WM impairment in children treated with intrathecal chemotherapy for ALL as well as children treated with radiation therapy for BTs, highlighting the vulnerability of this ability and the importance of this area for targeted cognitive intervention.

fMRI in Childhood Cancer Survivors during Attention and Working Memory Tasks

We have extensive experience conducting fMRI studies with St. Jude patients. We established that the basic signal mechanism used in most fMRI studies, the BOLD effect, is intact in survivors of childhood BT and ALL,[90] and spatial normalization procedures required for group analysis of fMRI data are effective in children who have been treated for a BT located in the posterior cranial fossa.[116] For the WM tasks in the proposed study, we will use the same general acquisition and analysis methods that we have used previously. Here we summarize results from two preliminary studies to demonstrate: 1) sensitivity of fMRI to altered patterns of brain activation in childhood cancer survivors and 2) successful implementation of the n-back WM task that we will use to characterize neural correlates of WM in the intervention group.

We used a continuous performance test (CPT) to investigate the neural correlates of attention in children who survived a posterior fossa BT. We first obtained images from 30 healthy adults to establish a priori regions of interest (ROIs) that would be evaluated in patients and sibling controls. Clusters of activation were located in the frontal, cingulate, parietal, temporal and occipital cortices and in the putamen, red nucleus and cerebellum (Fig. 1).[91] We performed the fMRI CPT experiment in 55 pediatric subjects, including 25 survivors of posterior fossa BT (mean age, 11.7 ± 3.4 years; range, 7 -17 years) and 30 age-similar healthy sibling controls (mean age, 12.7 ± 3.5 years; range, 6 - 17 years). Patients were diagnosed with cancer between 1.9 and 13.1 years of age and were more than one year past completion of all therapy (median 6.4 years). Thirteen subjects (25%, 7 patients and 6 controls) were excluded from analysis because of

excessive motion during fMRI scanning, distortion caused by orthodontic appliances or inability to complete the examination; one control was excluded because MRI examination revealed a pituitary abnormality. Thus, our analysis included 18 patients and 24 controls. In addition to random-effects analysis, activation was evaluated in eight ROIs based on preliminary study of healthy adults. Talairach coordinates[92] and search radius [x, y, z, (r)] for the ROIs were: right [50, 19, -8, (8)], left [-32, 23, -3, (8)] ventral frontal cortex; right [44, -72, -8, (16)], left [-44, -72, -2, (16)] ventral visual; anterior cingulate cortex [4, 8, 47, (14)]; and right inferior parietal lobule [55, -34, 26, (5)]. No ROIs were evaluated in the cerebellum, because all patients had posterior fossa lesions. ROIs were evaluated on the activation map generated from the fixed-effect analysis for each subject p=0.001 (uncorrected) and a cluster-size threshold of five voxels.

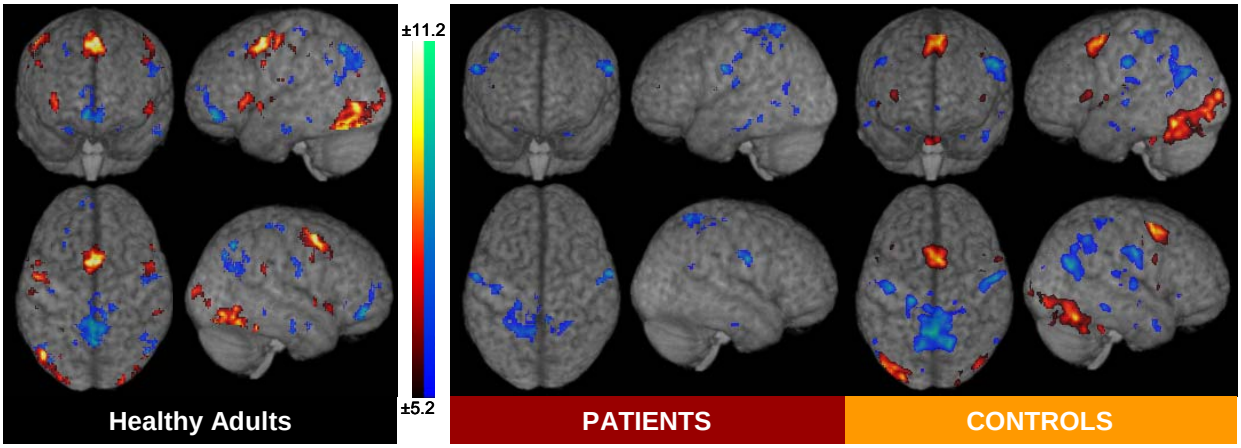


Fig. 1. Group activation maps for the CPT task. Red-based overlay indicates CPT > fixation; blue-based overlay indicates fixation > CPT. The pattern of activation in controls was very similar to that in healthy adults, but in patients, CPT activation was disproportionately reduced compared to healthy children and adults. Second-level random effects analysis: ROIs were identified a priori in healthy adults for subsequent evaluation in pediatric survivors and siblings (see Fig. 2). The brain template was created from the T1-weighted structural scans of the healthy controls. Renderings were created with MRIcro (www.mricro.com).

We found significant differences in behavioral performance and brain activation between the patients and controls. Full scale IQ was lower (p= .02) in patients (91 ± 15) than in controls (102 ± 11). Furthermore, the CPT experiment in children showed omission error rates were significantly higher (p= .03) in patients (median 3.1%) than in controls (median 0.9%). Despite modest differences in CPT performance, there were dramatic differences in the pattern of brain activation measured with fMRI during the CPT (Fig. 1). The activation map for the controls was essentially the same as that for healthy adults**,** both for areas that were more active during task (red overlay) and for the default mode network that was more active during rest (blue overlay). The range of the T-statistic over the whole map was -9.7 to 11.2 in adults and -8.9 to 9.4 in healthy children. The default mode network in patients was comparable to that in both controls and healthy adults. Remarkably, no task-induced activation was detected in the random-effects analysis of the patients. The range of the T-statistic for patients was -9.1 to 5.6. Failure to detect CPT activation is unlikely a true lack of neural activity, given performance was similar between groups. More likely explanations for the lack of CPT activation include altered BOLD coupling or functional network reorganization caused by disease- or treatment-induced brain injury. Indeed, ROI analysis based on the adult network showed CPT

activation was similar in most, but not all, regions for both subject groups, but the location of the peak activation within each region was more variable in patients than controls (Fig. 2).

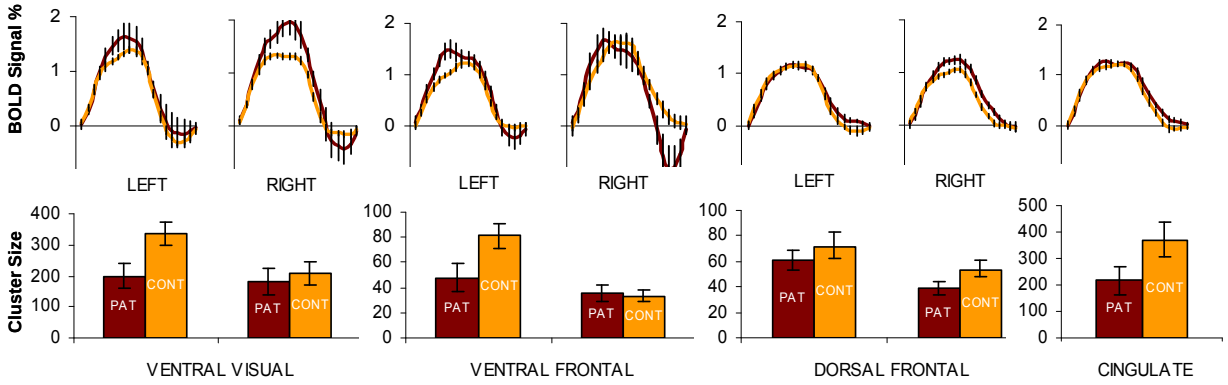


Fig. 2. ROI analysis in patients and controls. The BOLD signal was at least as great in patients as in controls. The volume of activation was generally lower, and the location of peak signal within each region was more variable in patients. The time course of the BOLD signal represents the average over blocks and subjects. Error bars indicate standard error of the mean.

We recently implemented the n-back task for fMRI (Fig. 3) and have studies underway in healthy young adults and survivors of ALL and BT. The n-back task is a prototypical WM measure that requires a participant to respond to a presented stimulus only when it is the same as the one presented on a trial a predetermined number (n) prior to the current trial.[117] For example, in the letter-based task, participants view a continuous stream of single, phonologically distinct, letters. 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) is used during which the same continuous stream of single letters is presented but the participant need only decide whether each letter matches a single target communicated at the start of the task (similar to the CPT).

2-Back Task

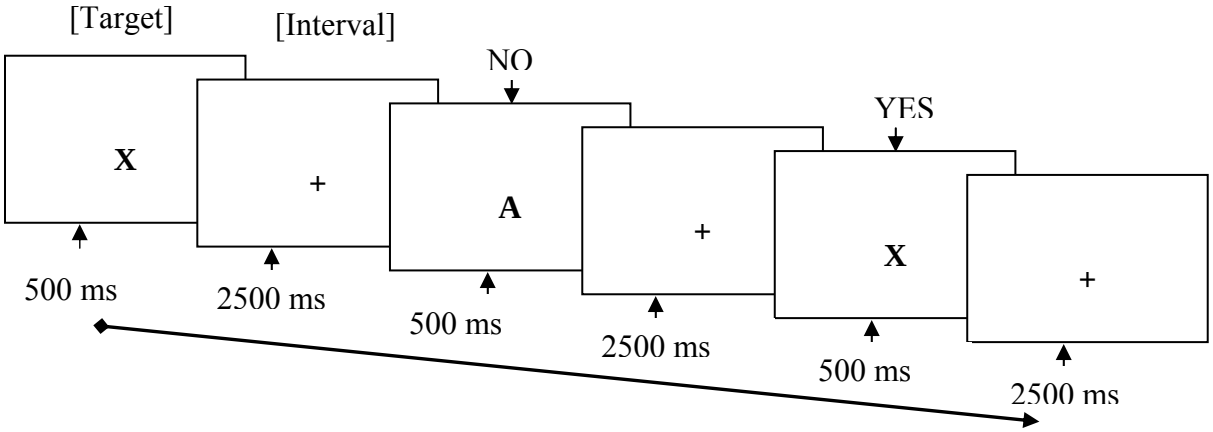


Fig. 3. For the verbal n-back, participants will view a continuous stream of single random stimuli from a set of phono-logically distinct letters. Each letter is presented for 500 ms, with an inter-stimulus interval of 2,500 ms.

So far we have performed the n-back experiment in 20 long-term survivors of ALL (mean age, 26.2 ± 3.0 years; range, 23 -38 years) and 25 age-similar healthy controls (mean age, 25.4 ± 3.7 years; range, 19 -31 years). Preliminary random effects group analysis has demonstrated activation in the typical network of brain regions that has been reported in fMRI studies of the n-back task (Fig. 4)[117] including anterior cingulate/medial frontal, dorsolateral prefrontal, ventrolateral prefrontal, frontal polar and parietal areas. Activation in right dorsolateral prefrontal and right parietal regions increased with increasing WM load, and bilateral activation in ventrolateral prefrontal areas was only detected in the 2-back condition. Analysis of group differences in activation and correlation of the imaging data with behavioral performance will not be conducted until enrollment in these ongoing pilot studies is completed.

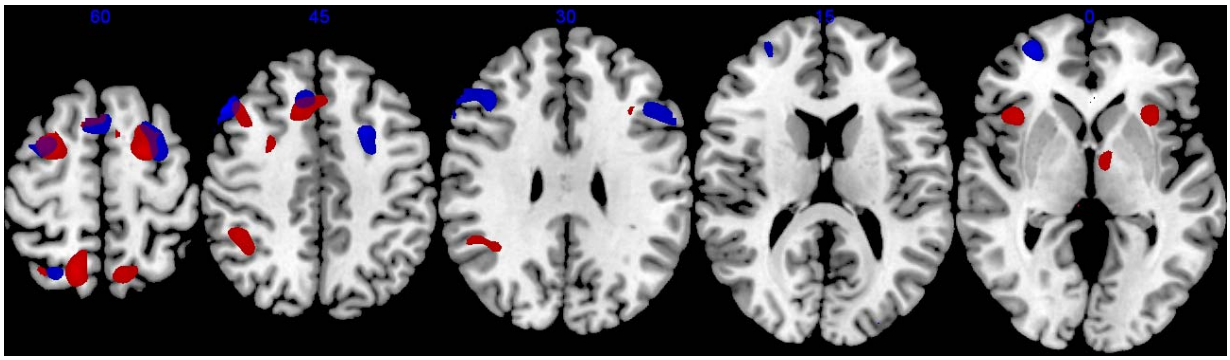


Fig. 4. Patterns of activation for the n-back task in long-term survivors of ALL. Random effects group analysis ($p < 0.05$, FEW corrected for multiple comparisons). Blue indicates the contrast 1-back > 0-back and red indicates the contrast 2-back > 1-back.

Cogmed Feasibility for Childhood Cancer Survivors

St. Jude has a long history of collaborating with Duke Medical Center on intervention trials for cancer survivors.[16,67,76] We have been consulting with our Duke collaborators regarding a feasibility trial they are conducting using Cogmed with cancer survivors. The primary aims of this study include assessing feasibility and acceptability of the intervention. Their sample size ($N = 24$; 12 randomized to the active intervention) is not powered to measure effects, nor are the Duke investigators using neuroimaging to assess brain-based changes associated with the intervention, both of which are unique aspects of the current study. So far, the acceptance rate for trial participation has been high. No one approached in-person has refused to be screened and no one who has qualified has refused the intervention. They have recruited 21 of the targeted 24 participants and 85% have completed training (others still in progress). Twelve of these 21 participants were randomized to the intervention group and 9 to the control group. Intervention and control groups are balanced by gender (50.0% male vs. 61.5% male), diagnosis (50.0% BT vs. 38.5% BT), age at diagnosis (6.9 ± 4.39 years vs. 4.4 ± 2.18 years), and time off treatment (5.5 ± 2.42 years vs. 2.9 ± 1.85 years). Most participants have completed all 25 training sessions with a mean completion rate of 24.3 sessions. Among children participating in the study, 57.1% reported they often or always enjoyed training sessions (only 7.1% reported they rarely or never enjoyed training) and 94.4% of parents reported they were somewhat or very satisfied with their child's participation. The researchers

have found internet monitoring allows them to adjust task difficulty based on performance so frustration can be avoided or alleviated. Though sample sizes are small and findings preliminary, initial outcomes are promising. They have found greater improvement between baseline and post-intervention WM assessments in the treatment group compared to the control group [Cohen's ES= .72 for the WM Index on the Wide Range Assessment of Memory and Learning (WRAML-II)].These findings are very encouraging for feasibility, acceptability and compliance for using Cogmed with childhood cancer survivors.

3.0 RESEARCH PARTICIPANT ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

3.1 Inclusion Criteria for Screening Phase

3.1.1 Received CNS-directed treatment (intrathecal chemotherapy or cranial irradiation) for a BT or ALL

3.1.2 Infratentorial tumor location (for the BT cohort)

3.1.3 Off treatment for at least one year with no evidence of recurrent or progressive disease

3.1.4 Age 8-16 years inclusive at the time of enrollment

3.1.5 English as the primary language

3.1.6 Research participant and one parent willing to participate and provide consent/assent according to institutional guidelines

3.2 Exclusion Criteria for Screening Phase

3.2.1 Significant impairment in global intellectual functioning (estimated or full scale IQ < 70 based on standardized testing routinely conducted on primary treatment protocols)

3.2.2 History of CNS injury/disease predating or unrelated to cancer diagnosis

3.2.3 Documented ADHD predating cancer diagnosis

3.2.4 Treatment with psychostimulant or psychotropic medication within two weeks of study participation

3.2.5 Major sensory or motor impairment that would preclude valid cognitive testing secondary to inability to complete study procedures (e.g., blindness, paresis, poorly controlled seizures/photosensitive epilepsy, psychosis)

3.3 Inclusion Criteria for Intervention Phase

3.3.1 Signed screening consents and has undergone screening

3.3.2 Fully evaluable psychological testing results (including IQ ≥ 70)

3.3.3 Age-scaled score on Digit Span, Letter-Number Sequencing or Spatial Span < 7 **or** at least one standard deviation below IQ score

3.3.4 Training aide is available to participate in required sessions

3.3.5 Participant and training aide demonstrate computer proficiency

3.3.6 Participant has access to or will be provided a laptop or home computer with internet connection and speakers

3.3.7 Participant willing to participate in required aspects of Cogmed RM

3.3.8 Participant is able to take part in fMRI without sedation

3.4 Exclusion Criteria for Intervention Phase

3.4.1 Major psychological condition that would preclude completion of protocol intervention (e.g., significant oppositionality, autism spectrum disorder, severe anxiety or depressive symptoms)

3.4.2 Orthodontic appliances that cause MRI distortion or signal loss outside the mouth and sinus area

3.5 Research Participant Recruitment and Screening

Survivors of childhood cancer between the ages of 8 and 16 will be recruited for study participation until 68 patients demonstrating WM problems are accrued to the intervention trial. Approximately 34 patients will be randomly assigned to the WM intervention group and 34 to a waitlist control group. The randomization will be stratified based on gender, age (8-11, 12-16) and diagnosis (BT, ALL) in order to roughly balance the intervention and waitlist control groups on these three factors.

Amendment 2.0

Approximately 389 patients will be eligible based on criteria for age at enrollment, time since treatment, IQ and clinical status. Of these 389 patients, 246 have been treated for ALL with triple intrathecal chemotherapy (e.g., TOTXIII, TOTXIV, TOTXV, TOTXVI, INFNT, ALLR17), 78 have been treated for a BT on SJMB03 with craniospinal radiation with a conformal boost and adjuvant chemotherapy, and 56 have been treated for a BT on RT-1 with

conformal radiation therapy. An additional 9 patients have been identified through referrals or clinic schedules as treated off protocol with CNS-directed therapy for a BT. Based on the rate of WM impairment on these studies, we anticipate at least 166 will meet study

Amendment 3.0

inclusion criteria. We expect to screen up to 150 patients to identify 68 eligible participants, including approximately 34 who successfully complete the investigational intervention. Patients will initially be contacted in order of their next appointment to remove selection bias.

3.6 Enrollment on Study

After confirmation of participant eligibility, as defined in Section 3.1 and 3.2, an eligibility checklist will be completed within the online Patient Protocol Manager (PPM) system of the Central Protocol and Data Monitoring Office (CPDMO). This system will then allow an authorized study team member to generate a research participant-specific consent form. This will be completed for both the screening and intervention phases of the study.

In the event of any problems with the PPM system, a completed eligibility checklist will be faxed to the CPDMO at (901) 595-6265. A phone call will follow to (901) 595-2568 to ensure that the fax has been received. Eligibility will be reviewed and entered into the institutional database, and a research participant-specific consent form will be generated. The consent, protocol and protocol standard order set will be delivered to the area designated on the Checklist.

Amendment 1.0

Using either method, the signed consent forms must be faxed **or emailed** to the CPDMO in order to complete the enrollment.

The CPDMO is staffed 7:30 am-5:00 pm CST, Monday through Friday. A staff member is available at (901) 413-8591 Saturday, Sunday, and holidays from 8:00 am to 5:00 pm.

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.

4.0 STUDY DESIGN AND METHODS

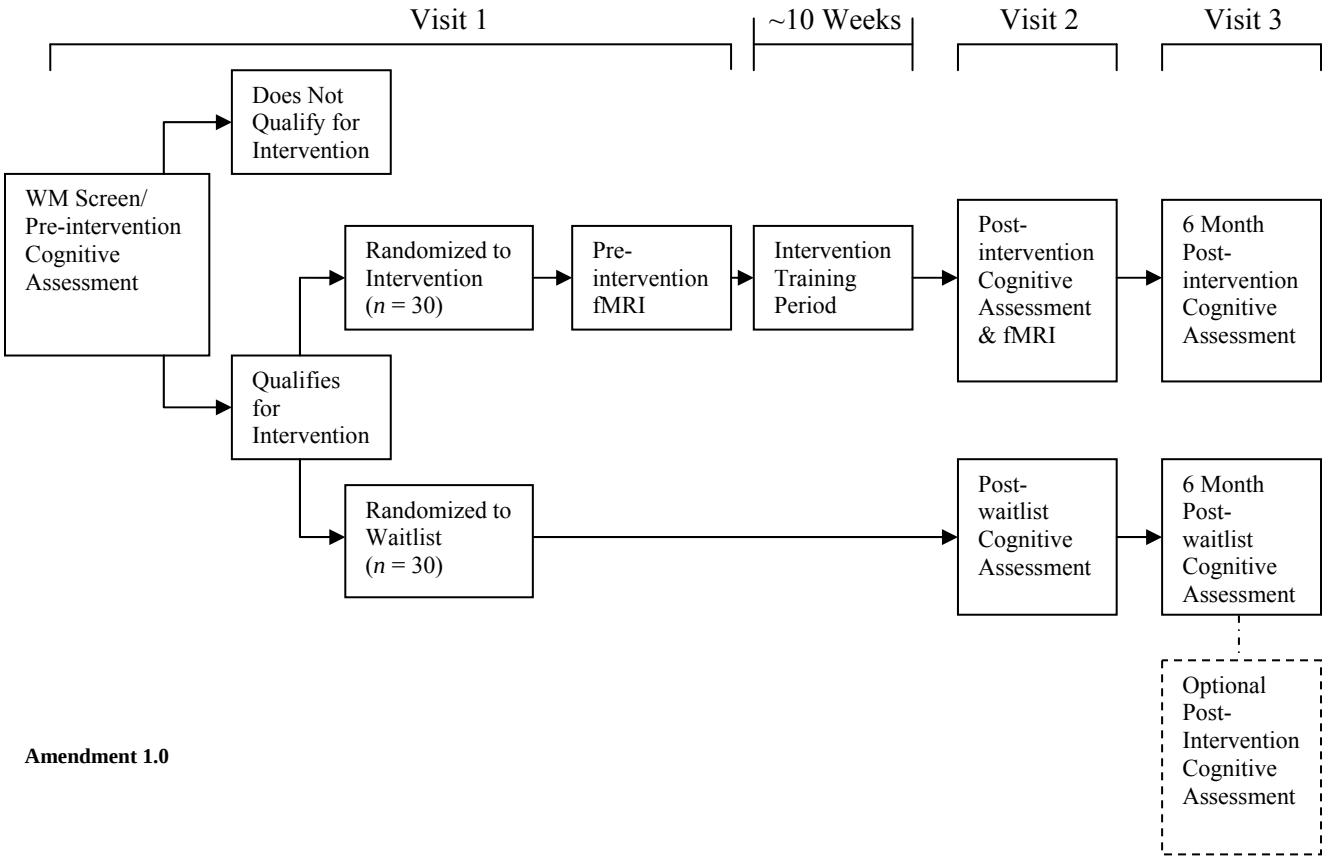
4.1 Study Design

We will use a single-blind (psychological examiner), randomized, waitlist-controlled experimental design to test our hypotheses about behavioral and neuroanatomical changes associated with the Cogmed intervention in childhood cancer survivors. We will recruit patients who were treated for a

Revision 0.1

BT or ALL with CNS-directed therapy. **Efforts will be made to insure that patients participate in either study screening/pre-intervention or follow-up assessment during routine visits to St. Jude for medical care.** fMRI studies will be conducted only with participants randomized to the Cogmed intervention, at the same visit as the study screening/pre-intervention assessment and post-intervention assessments. The time period between pre- and post-cognitive assessments will be approximately 10 weeks for both intervention and control groups to allow adequate time for completion of 25 training sessions by members of the intervention group. Both groups will be brought back six months after post-cognitive assessments to complete a second post-intervention cognitive assessment to evaluate maintenance of cognitive improvements. Waitlist controls will be offered the Cogmed intervention, after completion of their post-waitlist cognitive assessment. **Participants who choose to complete Cogmed training will be given the option to participate in a post-intervention cognitive assessment during their next routine visit to St. Jude.**

Amendment 1.0



Amendment 1.0

4.2 Methods

Screening Criteria

Only participants demonstrating WM problems will be randomized for

inclusion in the intervention trial to treat those patients in greatest need and reduce the chance of ceiling effects on outcome measures. The screening battery is contained within the pre-intervention assessment. For this study, WM impairment is defined as an age-scaled score on Digit Span, Letter-Number Sequencing or Spatial Span that is at least one standard deviation below the normative mean (i.e., < 7 where the normative mean = 10 ± 3) or at least one standard deviation below the participant's IQ score. Preliminary data indicate that, depending on risk factors for cognitive late effects (e.g., time since treatment and treatment intensity), 11% to 66% of BT and ALL survivors meet this criterion.

If during the screening assessment a psychological condition is identified that may significantly limit the likelihood of completion of the protocol intervention (i.e., oppositional behaviors, anxiety or depression), the child will not be randomized for inclusion in the intervention trial phase. This screening process is discussed below in 5.2.

Intervention

The WM training program used for the intervention trial will be the Cogmed RM program for children described above (page 6).[82] It is a computer-based training program completed in the home. This program requires approximately 30 minutes every weekday for five weeks. Completion of sessions on the weekend will be allowed. The program software guides the child through eight rotating exercises each day, with increasing difficulty based on the child's level of performance. Exercises train both visuospatial and verbal WM using child-friendly activities. A research team member will serve as a coach who monitors weekly progress online and offers support through weekly phone calls with the study participants and their caregivers. This individual will not complete post-intervention assessments to maintain study blind. A home computer with internet connection and speakers is required. A laptop computer and/or wireless internet access will be provided to families whose only obstacle to participation is the lack of computer access or internet connectivity in the home setting. Families randomized to the WM intervention will complete a tutorial with study staff that provides instruction in using a computer, the internet and the WM training software. Additional time and instruction will be provided to individuals exhibiting lower computer literacy.

Compensation

Incentives ($10 each for pre-, post- and 6 month follow-up assessments, as well as $10 after 9, 17 and 25 sessions during training) will be used to facilitate compliance. Groups will be provided equal incentives, so as not to introduce motivational differences between groups (resulting in payments to control participants at 2, 4 and 6 weeks between pre- and

post-assessments). Individuals who complete the screening assessment and do not qualify for the study will also be paid $10 for their time.

Amendment 2.0

Participants who complete the optional post-intervention cognitive assessment will also be paid $10 for their time.

5.0 REQUIRED EVALUATIONS, STUDY INTERVENTION, AND OBSERVATIONS

All participants will be assessed with a brief battery of neurocognitive measures at the outset of the study to identify individuals experiencing WM problems and to establish a baseline estimate of performance level. This same battery will be repeated with all participants after the 10-week training period to compare performance of patients participating in the intervention with the waitlist control group, and six months post-intervention to evaluate maintenance of cognitive improvements observed immediately after the intervention. The following is a list of measures to be included at all three assessment time periods, pre-, post- and six months post-intervention **(as well as a potential fourth assessment for waitlist control participants completing training after 6-month post assessment)**:

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5.1 Neurocognitive Measures

Wechsler Abbreviated Scale of Intelligence (WASI).[93] To obtain an IQ score for each participant, the Vocabulary and Matrix Reasoning subtests will be administered from the well-standardized WASI. From these subtest scores, an age standardized abbreviated IQ with a mean of 100 and standard deviation of 15 will be derived. This abbreviated IQ is highly correlated with full scale IQs ascertained from the Wechsler Scales (correlations with WISC-III[94] = .81 and WAIS-III[95] = .87). Internal consistency reliability for the WASI IQ estimate is high (r= .93). The WASI was chosen over other abbreviated IQ measures to reduce practice effects from Wechsler scales included in the treatment protocols. Administration time, 15 to 20 minutes.

Wechsler Intelligence Scale for Children, Fourth Edition Integrated (WISCIV-Integrated).[58] The WISCIV-Integrated Digit Span, Letter-Number Sequencing and Spatial Span tasks represent the core performance-based WM measures. Digit span will be administered to measure attention (Digit Span Forward) and WM (Digit Span Backward). For Digit Span Forward, the examiner verbally presents random sequences of digits that the participant is required to repeat back verbatim. For Digit Span Backward, the participant must repeat the digits in reverse order. Digit Span Backward, with the additional requirement of re-ordering stimuli on-line, is typically considered a measure of verbal WM. Internal consistency reliability for this subtest is high (r= .87). For Letter-Number Sequencing, the examiner verbally presents random sequences of numbers and letters after which the participant is required to repeat back the numbers in ascending order and the letters in alphabetical order. Internal

consistency reliability is high (r= .90). Digit Span and Letter-Number Sequencing comprise the WISCIV-Integrated WM Index. Spatial Span was created to be a visual analog of the Digit Span Task. During administration, the examiner taps specified sequences of blocks of random location using a board that consists of 10 blue blocks fastened to a white plastic board. The participant is required to repeat the block taps in the same order (Spatial Span Forward) or in reverse order (Spatial Span Backward). Internal consistency reliability for this subtest is high (r= .80). The Spatial Span Task will serve as a spatial counterpart to the Digit Span Task allowing for investigation of WM changes across verbal and spatial WM domains. This task will be the primary outcome measure for the WM intervention because it is a nontrained task in the spatial modality, similar to stimuli presentation in the training program. It is also the subtest used to assess Cogmed training effects in children with ADHD.[18,19] These well-standardized tasks provide age standardized scores with a mean of 10 and standard deviation of 3. Together, these tasks require less than 15 minutes to complete.

Conners' Continuous Performance Test, Second Edition (CPT-II).[98] The CPT-II is a computerized measure of sustained attention. Individual letters are presented on a computer screen for 250 ms each. Children are instructed to press the space bar as quickly and accurately as possible for any letter (targets) except the letter "X" (nontarget), which appears on 10% of the 360 trials. Interstimulus intervals vary by trial blocks with lengths of 1, 2 or 4 s. Test-retest reliability for the CPT, with a three month interval, ranges from .55 to .84 for primary indices.[98] Construct validity is indicated by performance differences between children with and without ADHD.[99] The CPT is used regularly to monitor response to medication in children with ADHD and has negligible practice effects for repeat administration.[100] The CPT program computes hit rates (correct response to a target), omission errors (failure to respond to a target), commission errors (response to the nontarget "X"), reaction time, sensitivity and response bias. This measure requires 14 minutes to complete.

Delis Kaplan Executive Function System (DKEFS).[103] The DKEFS is the first nationally standardized set of tests designed to assess the key components of executive functions believed to be mediated primarily by the frontal lobes.[103] Three subtests that assess core executive functions including fluency, cognitive flexibility, set shifting, monitoring and inhibition were chosen for this study. Verbal Fluency is composed of three 60 s conditions: letter fluency (examinee names items that begin with a specified letter), category fluency (examinee names words that belong to a specified category) and category switching (examinee alternates between saying words that belong to two specified categories). Test re-test reliability ranges from .53 to .70 across conditions. The Trail Making Test consists of five conditions. The primary executive function task is the

number-letter switching condition, which is a visual-motor sequencing procedure that assesses cognitive flexibility and set shifting. The other four conditions assess fundamental task components necessary for the switching condition including visual scanning, number sequencing, letter sequencing and motor speed. Internal consistency reliability for the number-letter switching condition ranges from .57 to .79. The Color-Word Interference Task is a variant of the classic Stroop procedure for assessing verbal inhibition. The task consists of 4 conditions: naming color squares, reading color names, inhibiting reading words to name the dissonant color ink in which they are printed (classic interference) and switching between reading words and naming the dissonant ink color in which they are printed. Internal consistency reliability for the switching condition ranges from .62 to .79. Participants will be asked about a history of color-blindness and data for participants for whom color blindness impacts performance will be removed from analysis for this subtest only. Together, these subtests require 15 to 20 minutes to complete.

Woodcock Johnson III Tests of Achievement (WJ-III).[121] The WJ-III is a comprehensive set of individually administered tests for measuring academic achievement. As a brief screen of academic skills, the Reading Fluency and Math Fluency subtests will be administered. Reading fluency requires the participant to read simple sentences, decide if the statement is true and circle Yes or No. Math Fluency requires the participant to solve simple addition, subtraction and multiplication problems. Both subtests measure the number of items correctly completed within a 3-minute time limit. Test retest reliabilities are high for the study age range (Reading Fluency- .90; Math Fluency- .89).

5.2 Parent and Child Report Measures

The Behavior Rating Inventory of Executive Function (BRIEF).[96] The BRIEF is a parent questionnaire designed to assess behavioral manifestations of executive functioning. Executive functions include goal-directed behaviors, such as the ability to plan, organize, sustain and change performance in response to feedback. The BRIEF questionnaire consists of 86 items from which eight clinical scales (Inhibit, Shift, Emotional Control, Initiate, WM, Plan/Organize, Organization of Materials and Monitor) are derived. Scores are age and gender standardized with a mean of 50 and a standard deviation of 10. Internal consistency reliabilities for all scales are high (r= .82 - .98). The WM Scale correlates moderately with the Behavior Assessment System for Children- Attention Problems Scale (r=. 69),[97] thereby providing evidence for construct validity. The BRIEF WM scale will be the primary rater-based measure compared to performance-based measures of WM described above. The measure requires 10 to 15 minutes to complete.

Conners' Rating Scales, Third Edition (CRS-III).[101] The Conners' Parent Rating Scale and Conners' Self-Report Scale assess symptoms and behaviors associated with ADHD. The long form consists of 110 items (parent) or 59 items (self-report) rated on a scale from 0 (not true at all) to 3 (very much true). From these items, multiple content scales (Hyperactivity/ Impulsivity, Learning Problems, Executive Functioning, Aggression, Peer Relations and Family Relations) and DSM_IV symptom scales (ADHD, Oppositional Defiant Disorder and Conduct Disorder) are derived. The measure also includes screener items for anxiety and depression. Scores elevated within the clinical range on the Oppositional Defiant Disorder scale, Conduct Disorder scale, anxiety screening items or depression screening items will prompt a diagnostic interview by a qualified clinician. If this interview reveals significant oppositional behavior, anxiety or depression that would interfere with the ability to complete the study intervention, patients will not be randomized for the intervention trial phase. In this situation, parents will be informed of the findings and will be assisted in gaining any necessary clinical services. All scale scores are age and gender standardized with a mean of 50 and standard deviation of 10. Internal consistency reliabilities for this measure range from .85 to .94 for the parent form and from .84 to .92 for the self-report form.[101] Evidence for criterion-oriented validity includes significant correlations with the Behavior Assessment System for Children, Second Edition (BASC-II)[102] (e.g., .72 between the BASC-II Attention Problems and CRS-III Inattention scales).[101] Children 8 to 18 years of age can complete the self-report form. The measure requires 15 to 20 minutes to complete.

Developmental and Demographic Questionnaire. A questionnaire created for a previous study investigating WM development in typically developing children will also be used in this study.[49,50] This structured questionnaire includes questions about general child characteristics and development (e.g., age, gender, ethnicity, acquisition of developmental milestones and past emotional or behavioral problems). There are additional questions about family demographic characteristics (e.g., parental education and income) that allow for derivation of an index of socioeconomic status (SES). SES is a powerful predictor of cognitive abilities such that it is important to make sure comparison groups are similar or that SES is accounted for statistically. This questionnaire requires 10 to15 minutes and will be completed pre-training (see Appendix).

Participant/Parent Satisfaction Questionnaire. A questionnaire was created for this study to assess participant satisfaction with the Cogmed intervention. This questionnaire includes items rated on a Likert scale by the parent and participant that pertain to benefits and burden associated with completing Cogmed tasks. Open ended questions are also provided. This questionnaire requires 5 minutes to complete and will be

administered to the participant and a parent mid-way through intervention and at completion (see Appendix).

Computer Skills Questionnaire. A questionnaire was created for this study to assess participant home computer status. This questionnaire includes items rated on a Likert scale by the parent and participant that pertain to basic computer skills necessary for completing Cogmed tasks. Specific questions are also provided to determine the level of computer access in the home. This questionnaire requires 5 minutes to complete and will be administered to the participant and a parent prior to randomization (see Appendix).

5.3 Neuroimaging Exam

Neuroimaging examinations (fMRI and Diffusion Tensor Imaging [DTI]) will be conducted once before and once immediately after training. Two types of WM tasks will be used: a grid-based spatial WM task used in fMRI studies by Olesen and colleagues[21] (page 7) and a classic n-back WM task previously used by our group (page 12). Both tasks will be administered as a block design alternating between WM and control trials. For statistical analysis, a general linear model (WM task vs. control) will be used to isolate WM activity for each participant, for each task.

The n-back task is reviewed on page 12. For the Olesen task (Fig. 5), each scan will consist of four sessions including six control and six WM trials; three WM trials will be high-load and three will be low-load, in random order. The WM task used will include three (low-load) or five (high-load) red circles presented sequentially in a 4 x 4 grid. Cue presentation will be followed by a blank grid indicating the response phase. Participants will then indicate the location and order of presented cues by clicking on a computer screen with an optic track-ball. In the control task, five green circles will be presented sequentially in the two uppermost rows. Circles stay on the grid during the response phase and participants click them in any random order.

Olesen et al. Task

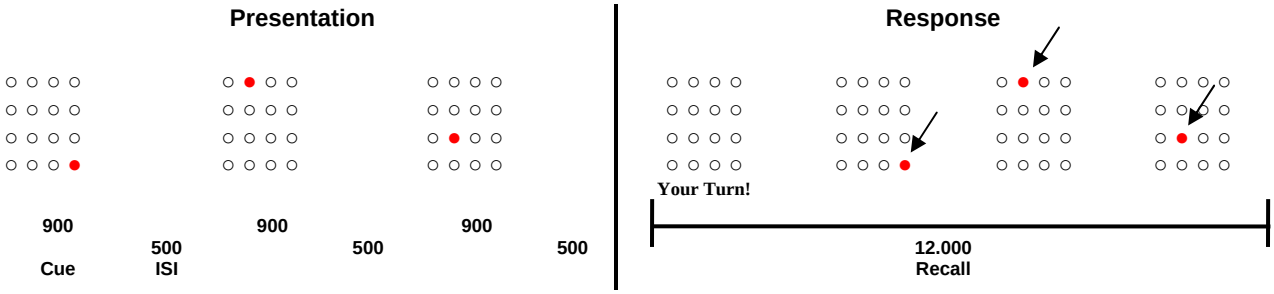

Fig. 5. A series of red circles will be presented sequentially on a 4x4 grid. Each cue will be presented for 900 ms with a 500 ms inter-stimulus interval (ISI). Cue presentation is followed by presentation of a vertical line and blank grid indicating the beginning of the recall phase, which lasts 12,000 ms. Participants indicate the location and order of the presented cues by clicking on a computer screen with an optic track-ball. Three low-load (a sequence of 3 circles) and three high-load (a sequence of 5 circles) trials will be presented in random order, each separated by a control task. The inter-trial interval will be 5,000 ms. In the control task, five green circles are presented sequentially in the two uppermost rows. Circles stay on the grid during the response phase and participants click them in random order. Figure adapted from Olesen et al., 2004.

The fMRI images will be acquired in planes parallel to the line connecting the anterior and posterior commissures. Pulse-sequence parameters will be similar to those used in studies previously conducted by our group. All participants will undergo conventional imaging to identify morphologic abnormalities, to facilitate spatial normalization of brain images and to visualize functional imaging results. Whole-brain functional images will be acquired with T2*-weighted EPI pulse sequences. Stimuli will be presented on a rear projection screen at the back of the magnet via an LCD projector and viewed by way of a mirror mounted to the head coil. Functional images will be analyzed with SPM via 2-level analysis. Images from each participant will be realigned to correct for interscan head motions,[104] normalized to a standard coordinate system (MNI standard brain)[105] and smoothed with a 6-mm, full-width at half-maximum Gaussian kernel. In the first-level analysis, data will be analyzed according to a fixed-effect general linear model with task-induced activity represented by a boxcar function convolved with the canonical hemodynamic response function.[106] After parameter estimation, the contrasts selecting the activation of interest will be set in the model, and the corresponding contrast image will be generated. The contrast image from each participant will then be used as a variable in second-level, random-effect analysis.[107] Regional activation will be summarized with the Activation Index (AI) of Wei and colleagues, which is defined as the sum of the Z scores of all activated voxels within a significant cluster or within an otherwise specified ROI.[108] Coordinates for the location of clusters of activation will be converted from MNI space to Talairach space using the nonlinear transformation posted at http://www.mrc-

cbu.cam.ac.uk/imaging/. The location of clusters will be checked by visual comparison with the atlas of Talairach et al.[92]

DTI will also be conducted to evaluate white matter connections among areas activated during fMRI. Normal brain function requires integration of activity among specialized cortical areas, therefore altered patterns of activity detected with fMRI may be associated with therapeutic injury to the white matter.[38] DTI provides unique information about tissue microstructure and organization, and it is widely used in basic neuroscience and clinical research.[118,119] DTI calculation will be performed with the DTI Toolkit under SPM. Data will be realigned before tensor calculation to correct for linear image drift caused by gradient-induced heating. Realignment parameters will be estimated for the baseline images of each acquisition and then applied to all of the diffusion-weighted images for the respective acquisition. Finally, the mean of the realigned image sets will be used for tensor calculation.

5.4 Staff Training and Integrity of Intervention

Training will only be required for study-specific procedures (i.e., Cogmed training and coaching, administration of neurocognitive measures). Those responsible for facilitating these procedures will include experienced clinical research assistants, post-doctoral fellows and advanced graduate students, all under the supervision of a licensed clinical neuropsychologist. Training will initially be conducted for the entire group at the onset of the study, followed by individual supervision as the study progresses. A two day training course specific to the study intervention (Cogmed RM) has been conducted for study staff by a Research Manager from Cogmed – Working Memory Training in Stockholm, Sweden. Cogmed research staff/technical support and Dr. Hardy (PI of the Duke feasibility study) remain available for consultation as the study proceeds.

6.0 CRITERIA FOR REMOVAL FROM PROTOCOL & OFF-STUDY CRITERIA

Amendment 1.0

Participation in the study will terminate **after the screening visit if the participant fails to meet inclusion/exclusion criteria for the Intervention phase of the study. For those participating in the Intervention phase, participation will terminate** upon completion of cognitive measures and questionnaires at the 6 month follow-up visit **(or after post training assessment for those waitlist participants choosing to complete intervention)**. We do not anticipate that there will be circumstances in which the investigators will withdraw a participant from the study without their consent. However, if research participants should become distressed, frustrated or uncooperative with the study tasks, the study intervention or the neuroimaging procedures, they may be taken off without completing all required assessments. It should be noted that, should participants become frustrated with particular aspects of the intervention, there is a level of flexibility regarding the exercises present in a given day's training. Data

from the Duke feasibility study (page 13) shows that removal or minimization of frustrating tasks has been successful in maintaining compliance without compromising intervention efficacy.

Additionally, participants will be removed from the study if they are found to have relapsed or progressive disease that requires new cancer-directed treatment, or if they begin a psychostimulant trial between the pre- and post- assessments. In each of these cases, which we anticipate to be infrequent, we will replace the study participant and will not use their data for analysis of stated study objectives. If a participant randomized to the intervention trial fails to complete a minimum of 20 training sessions but the family is willing to maintain study participation, we will continue to gain post-intervention assessments but will not use their data for analysis of stated objectives. While we expect noncompliance to be low based on the Duke feasibility trial, if there are more than 5 participants who fail to complete at least 20 sessions, we may complete statistical analyses to gain more information about noncompliance. These participants will also be replaced to maintain adequate power for investigating stated study objectives. In all cases, we will monitor these numbers to assist with data interpretation.

7.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

In addition to the required continuing review reports to the IRB, the principal investigator will report all serious or unexpected adverse events that might impact the safety of or risk to the study participants. Serious, unexpected events will be reported within 48 hours, and all others within 10 working days. Since this is a non-therapeutic study that involves only minimal risk, we believe the likelihood of serious adverse events is very low. As required, unexpected death will be reported to the IRB office immediately. Again, since the procedures entail minimal risk, we think this is extremely unlikely.

8.0 DATA COLLECTION, STUDY MONITORING AND CONFIDENTIALITY

This is a non-therapeutic study that involves only minimal risk to participants. A data safety and monitoring board is not required. The principal investigator and/or her designee will review completed questionnaires and data forms with the study staff to ensure completeness prior to computer database entry. Confidentiality of the data will be maintained by keeping all completed study materials in locked files within the Department of Psychology (questionnaires and cognitive data sheets) or the Department of Radiological Sciences (neuroimaging data), with access only to study staff, and as required by CPDMO monitors. Likewise, access to the study computer database will be limited to study staff, biostatisticians and CPDMO monitors. Additional monitoring will be conducted as required by the CPDMO. 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 protocol compliance, adverse event reporting, and data

completeness will be conducted according to recommended schedule for this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Design and Analysis for Primary Objectives

Primary Objective 1.1.1 To assess the impact of a computer-based WM intervention on the performance of childhood cancer survivors on measures of WM, attention and executive functions.

For each patient in the two groups (intervention and control), WM scores will be taken at three time points: Visit 1 (pre-intervention), Visit 2 (immediate post-intervention), and Visit 3 (6 months post-intervention). As illustrated in Section 4.1, there are about 10 weeks between Visit 1 and Visit 2, and about 6 months between Visit 2 and Visit 3. The magnitude of pre- to post-intervention change in WM performance will be estimated for each group and will be compared between the two groups.

1.1.1 a. Participants in the WM intervention will demonstrate significantly greater improvement from pre- to immediate post-intervention on performance- and rater-based measures of WM relative to childhood cancer survivors placed on an intervention waitlist.

A t-test will be used to compare the magnitude of pre- to immediate post-intervention change (Visit 2 – Visit 1) between the intervention and control groups for both performance- and rater-based WM measures. Consistent with the Klingberg et al. study,[19] the primary performance-based WM outcome measure will be Spatial Span Backward from the WISC-IV Integrated. The primary rater-based WM outcome measure will be the BRIEF WM Index. Other performance- and rater-based WM measures described in sections 5.1 and 5.2 will also be investigated using similar but exploratory analyses. **If 10 or more participants initially randomized to the control group decide to complete intervention training after their 6 month post-waitlist assessment (Visit 3), and agree to an additional cognitive assessment, we will conduct paired t-tests to investigate changes in WM performance (Visit 4 – Visit 3) on these same measures to further explore intervention efficacy.**

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1.1.1 b. Participants in the WM intervention will demonstrate generalized cognitive benefits, as indicated by significantly greater improvement from pre- to immediate post-intervention on performance- and rater-based measures of attention and executive functions relative to waitlisted controls.

A t-test will be used to compare the magnitude of pre- to immediate post-intervention change (Visit 2 – Visit 1) between the intervention and control groups for both performance- and rater-based measures of attention and executive functions. To assess attention, Spatial Span Forward from the WISC-IV

Integrated will serve as the primary performance-based measure and the Conners' III Parent Rating Scale-Inattention Scale as the primary rater-based measure. To assess executive function, DKEFS-Color-Word Inhibition will serve as the primary performance-based measure and the BRIEF Metacognition Index as the primary rater-based measure. Other attention and executive function measures described in sections 5.1 and 5.2 will be investigated using similar but exploratory analyses. **If 10 or more participants initially randomized to the control group decide to complete intervention training after their 6 month post-waitlist assessment (Visit 3), and agree to an additional cognitive assessment, we will conduct paired t-tests to investigate changes in WM performance (Visit 4 – Visit 3) on these same measures to further explore intervention efficacy.**

9.2 Statistical Design and Analysis for Secondary Objectives

Secondary Objective 1.2.1 To evaluate the maintenance of improvements on measures of WM, attention and executive functions six months following participation in the computer-based intervention program.

Both groups of participants will participate in cognitive assessments at three time points: pre-, post- and six months post-intervention. A mixed model with random coefficients will be used to estimate the average trajectory of cognitive performance over time for both groups on measures of WM, attention and executive functions. Given this trajectory may be better represented by a curve rather than a straight line, a second order polynomial (e.g., Y= a0 + a1*t + a2*t^2) will be used for model fitting, where "a" represents estimated parameters and "t" the time from pre-intervention assessment.

1.2.1 a. Six months after intervention, intervention participants will perform significantly better than waitlisted controls on WM, attention and executive function measures.

We will compare the cognitive performance of the intervention and control groups at six months post- intervention using three different analytic approaches. The first analysis will compare the mean scores of the two groups, on our primary WM, attention and executive function variables outlined above, at the six months post- intervention time point using a simple two group comparison (e.g., t-test). The second analysis will compare the change in scores of the two groups from the pre-intervention assessment to the six months post-intervention using a repeated measures ANOVA including only pre- and six months post-intervention data. In the third analysis, a mixed model will be fit that includes both groups and data from all three time points; a group status variable will be used to differentiate the two groups with respect to pre-intervention, as well as linear and curvature terms that estimate the longitudinal pattern of cognitive scores. With this model, the mean scores at six months post-intervention will also be compared across the two groups. The first two statistical approaches provide a cross-sectional analysis of performance at six months post- intervention and are robust with respect to modeling assumptions but are less powerful to detect group differences. In

contrast, the third statistical approach gives a longitudinal analysis of scores across the three time points and is powerful to detect any differences in baseline scores, as well as linear and curvature patterns over time, provided the assumptions of the model are not violated.

Gender, age, and diagnosis are potential factors influencing the outcomes of WM, and thus will be roughly balanced in the randomization of patients into the two groups (intervention and control). The randomization will be performed using a program that implements the block-randomization scheme proposed by Zelen.[122] Gender (male, female), Age Group (8-11, 12-16), and Diagnosis (ALL, BT) will be the three stratification factors for the stratified block randomization. **Given a**

Amendment 2.0

sample size of 68 and eight strata, a block size of 4 will be used to achieve balance on these factors. The program resides on the Department of Biostatistics network and has been routinely used for randomization since 1992. The PI will be provided access to the program and will be responsible for randomizing patients. The system stores all required data for randomization in a secure Access database. Once a patient is randomized, all related data are frozen in the database and cannot be changed. In analysis, we will investigate the effects of stratification factors using the factor selection procedure to fit the mixed model, provided there are enough participants within each strata.

Secondary Objective 1.2.2 To use fMRI to examine the neural correlates of working memory before and after intervention.

Amendment 2.0

The patients randomized to the intervention will participate in fMRI examinations before and after WM training. Neural correlates of WM performance will be measured by comparing activations during WM tasks with activations during alternating control tasks as described in section 5.3. Neural activations associated with WM task performance will be compared at pre- and post-intervention time points.

1.2.2 a. Participants in the working memory intervention will demonstrate increased brain activity in the prefrontal and parietal cortices after working memory training.

The primary goal of this objective is to identify brain areas where activity measured by fMRI changes significantly from pre- to post-intervention for cancer survivors. We will focus analyses on frontal and parietal brain areas identified in the Olesen et al. study as ROIs for detection of activation, thus improving sensitivity and reducing the number of multiple comparisons across voxels. Two WM paradigms will be used during fMRI examinations, each with parametrically varied difficulty level: 1) Olesen's spatial WM task[21]: control, 3- and 5-spatial locations and 2) N-back verbal: 0-, 1- and 2-back. Functional images will be analyzed with SPM software to generate activation maps via a fixed-effect model for each subject, as described in section 5.3. Contrast images from the fixed-effect analysis in each subject will then be used for second-level random-effect analyses to create group activation maps. A significance level of $\alpha = .05$ corrected for

multiple comparisons at the cluster level will be used for our primary analyses. These analytical procedures are well established. The magnitude of fMRI signal change, volume of brain tissue activated and association between activation and WM demand will be evaluated for each cluster. Olesen et al. found increased neural activity in the middle frontal gyrus and superior and inferior parietal cortices after five weeks of Cogmed training for healthy adults.[21] Exploratory whole-brain analyses will also be conducted.

In addition, DTI will be used to conduct exploratory analyses that investigate white matter connections between areas of activation measured with fMRI. The set of diffusion-weighted images will be analyzed to determine an effective diffusion tensor for each volume element (voxel) imaged. The information in the full-diffusion tensor is represented by 2 derived quantities, the apparent diffusion coefficient (ADC) and fractional anisotropy (FA).[111] The ADC is expressed as mm^2/s and is a measure of the magnitude of diffusion displacement. FA is a dimensionless quantity that is a measure of the directional anisotropy of water diffusion. We will determine the associations between ADC and FA and parameters of activation measured with fMRI. We will use the Tract-Based Spatial Statistics methodology to characterize the white matter and evaluate the association between DTI parameters, fMRI and medical variables.

9.3 Patient Enrollment and Sample Size

Amendment 2.0

For this study, participants will be enrolled until 68 patients demonstrating WM problems are accrued to the intervention trial, with approximately 34 randomized to an intervention group and 34 to a waitlist control group. Patient randomization will be stratified based on gender, age (8-11, 12-16) and diagnosis (BT, ALL), for which a block randomization scheme will be used. For stratification, age will be the age at study screening. With respect to Objectives 1.1.1 a and b, findings from the randomized clinical trial by Klingberg et al. revealed an effect size of .96 on the primary WM measure for the ADHD group participating in the Cogmed intervention, whereas the effect size on the same measure was .29 for the control group.[19] The control group in that study, unlike the proposed study, received a lower-level WM intervention such that we anticipate less of a change in our waitlist control group. In the Duke feasibility trial, a difference of .72 in ES was estimated between the intervention and control groups on their WM outcome measure (page 13-14). With a sample size of 30 each for our groups, a difference of .65 between group ES can be detected by a one-sided test with a significance level of .05 and 80% power for any of the WM measures specified above. With respect to Objective 1.2.2, a sample size of 30 for the intervention group participating in fMRI is consistent with a set of fMRI methodological studies using a WM task that found a sample size of 12 was required to achieve 80% power at the single-voxel level for typical activations with a liberal threshold of $p < .05$.[112] By more than doubling this suggested sample size, we maintain this level of power at more realistic thresholds that approach those used after correcting for multiple comparisons.[112]

In the fMRI study reviewed above (page 10), 25% of childhood cancer survivors were excluded from analysis because of excessive motion during scanning, distortion caused by orthodontic appliances or inability to complete the examination. To reduce this rate of unusable data, we will exclude children with orthodontic appliances from study participation and all children will participate in a video-based orientation and training program before the fMRI experiment. The material will familiarize the participants with the sights, sounds and activities that they will experience during the fMRI session. A high rate of success has been achieved using this approach in previous fMRI studies.[90] By incorporating these strategies, we anticipate less than 10% of the data will be excluded, and we will replace participants whose data exceed this percentage.

10.0 OBTAINING INFORMED CONSENT

Parental consent and research participant assent will be obtained from all participants. We will recruit patients primarily from outpatient clinics with methods similar to those used by faculty within the Department of Psychology in the past. The list of patients that have received CNS-directed therapy developed through a Milli search will be reviewed by study staff who will identify potentially eligible research participants. Given the time demands of our procedures, potentially eligible patients will be contacted (generally by telephone) a few days to a few weeks prior to their scheduled clinic appointments, to briefly describe the proposed study, and assess their level of interest. For those expressing interest, an appointment for study procedures will be made in the Milli system in conjunction with clinical appointments**, as appropriate**. At that appointment, a detailed discussion of the study will take place. Only study staff who have completed human subjects protection training and have been appropriately trained in the procedures for obtaining consent will be used to approach parents and patients about the study. Study staff will describe the planned study procedures in detail. Patients and parents will be encouraged to ask questions, and if they choose, can examine the study questionnaires and view the laboratory setup prior to making their decision about participating. In addition to the specifics of the research procedures, study staff will highlight the voluntary nature of study participation, the potential direct benefits to the participants in this study, that we believe the risks are minimal, and that they can choose to discontinue their participation at any time.

Revision 0.1

Written consent forms will be completed for both screening and intervention phases of the study and all consent procedures will be documented according to standard hospital operating procedures. In cases where patients initially show interest and agree to an appointment, but subsequently decline participation, the consent conference will be documented along with any reasons for refusal (if stated).

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APPENDIX I: Schedule of Evaluations

Evaluation	Baseline Pre-Intervention/Waitlist	Immediate Post-Intervention/Waitlist	6 Months Post-Intervention/Waitlist	Subsequent Visit to SJ
Informed Consent	X			
Neurocognitive Assessment	X	X	X	X[2]
fMRI[1]	X	X		

[1]fMRI studies will be conducted only with participants randomized to the Cogmed intervention.
[2]Optional assessment for Waitlist Control subjects who complete Cogmed training after 6 month post-waitlist assessment

APPENDIX II: TESTS PERFORMED FOR GOOD CLINICAL CARE

*None of the specified evaluations are considered standard of care services.

APPENDIX III

RESEARCH TESTS

Research Test	Baseline Pre-Intervention/Waitlist	Immediate Post-Intervention/Waitlist	6 Months Post-Intervention/Waitlist	
Neurocognitive Assessment	X	X	X	Required
fMRI[1]	X	X		Required

[1]fMRI studies will be conducted only with participants randomized to the Cogmed intervention.

APPENDIX IV: **Special Instructions for Collecting, Shipping, and Receiving of Samples from Collaborating Sites**

**Not Applicable*

APPENDIX V: Study Questionnaires

Developmental and Demographic Questionnaire

Relationship to Child: Mom ___ Dad ___ Other ___

Child's Grade in School: _____

Child's Ethnicity: [1-Caucasian, 2- African American, 3- Hispanic, 4- Asian/Pacific Islander, 5- Native American, 6- Other (please specify)] _____

Is your child right-handed or left-handed? _____

If left-handed or ambidextrous, is anyone else in the family left-handed? _____ **Who?** _____

How many people live in your home at the present time? _____

What is the primary language spoken in your home? _____

Are there other languages spoken in your home? ____ If yes, what are these? _____

What is your marital status? [1-single, never been married, 2- married to child's parent, 3- divorced, not remarried, 4-divorced, remarried, 5- widowed, 6- other (please specify)]
_____

Please complete the following information for the child's mother and father:

Mother	**Father**
Occupation: _____	**Occupation: _____**
Highest Level of Education: _____ (e.g., high school graduate, GED, technical school, B.A./B.S., M.A./M.S., M.D., J.D., Ph.D.)	**Highest Level of Education: _____**
Number of years of Education: _____	**Number of Years of Education: _____**
Ethnic Background: _____ *Please use above code for this item	**Ethnic Background: _____**
Native Language: _____	**Native Language: _____**

What is the total average income in your home (round to the nearest 5,000)? _____

Does your family live in an urban, suburban or rural area? _____

Was your child born prematurely? _____

If you answered yes: How many weeks premature was your child? ____ Did your child stay in the neonatal intensive care unit (NICU)? ____ How many days? ____

How much did your child weigh at birth? _____ (lbs & ozs)

At what age did your child meet each of the following developmental milestones?:

Sat alone _____ **Walked alone _____**

Spoke first word _____ **Put 2 and 3 words together _____**

Toilet-trained during the day _____ **Toilet-trained throughout the night _____**
*If uncertain of age, but you believe within normal age limits, please write, WNL

Were there concerns about delays in achieving any of these milestones? _____

If yes, please describe: _____

_____

Prior to cancer diagnosis, has your child ever had an injury or accident requiring medical attention? _____ If you answered yes: What was the nature of the injury and the required treatment?

_____

_____

Has your child ever had a head/brain injury? _____

If you answered yes: Did (s)he lose consciousness? _____ For how long? _____ What treatment was provided? _____ Did (s)he spend the night in the hospital? _____

Has your child ever been unconscious due to another injury or illness? _____

If you answered yes: For how long? _____ What was the cause? _____

What treatment was provided? _____ Did (s)he spend the night in the Hospital? _____

Prior to cancer diagnosis, has your child ever had a seizure? _____

If you answered yes: How many times? _____ At what ages? _____

Did any seizures occur outside a time of illness with a high fever? _____ What treatment was

sought? _____ Was your child diagnosed with epilepsy? _____

Prior to cancer diagnosis, has your child ever been seen by a neurologist? _____

If you answered yes: For what symptoms? _____

What diagnosis (if any) was given? _____

Prior to cancer diagnosis, has your child ever been admitted to a hospital overnight? _____

If you answered yes: Please report the age and reason for each hospitalization:

Age	**Reason**
_____	_____
_____	_____
_____	_____

Please indicate whether your child has had any of the following (prior to cancer diagnosis):

Arthritis	**Y**	**N**
Asthma	**Y**	**N**
Chronic or recurrent lung disease	**Y**	**N**
Birth defects, such as spina bifida or cleft lip	**Y**	**N**
Blood disease, such as sickle cell anemia or hemophilia	**Y**	**N**
Bowel disease, such as inflammatory bowel disease	**Y**	**N**
Congenital heart disease	**Y**	**N**
Cystic fibrosis	**Y**	**N**
Diabetes	**Y**	**N**
HIV infection or AIDS	**Y**	**N**
Kidney disease	**Y**	**N**
Leukemia or other cancer	**Y**	**N**

Nerve problems	**Y**	**N**
Tics/twitching	**Y**	**N**
Brain injury or disorder	**Y**	**N**
Muscle problems, including cerebral palsy or muscular dystrophy	**Y**	**N**
Bone Disease	**Y**	**N**
Endocrine problems (e.g., thyroid, pancreas, hormonal problems)	**Y**	**N**
Recurrent ear infection	**Y**	**N**
Recurrent urinary infections	**Y**	**N**
Severe allergies	**Y**	**N**
Lead Poisoning	**Y**	**N**
Special nutritional needs	**Y**	**N**
Any surgeries	**Y**	**N**
Other chronic illness (please specify) _____	**Y**	**N**
Any medical problems not listed above (please specify) _____	**Y**	**N**

If you answered yes to any of the above illnesses, please provide relevant details (e.g., age of diagnosis, treatments undertaken and current status): _____

_____

_____

Prior to cancer diagnosis, has your child had any disorders or problems with:

Learning	**Y**	**N**
Hearing	**Y**	**N**
Vision	**Y**	**N**

If you answered yes to any of the above problems, please provide relevant details:

_____

Prior to cancer diagnosis, did your child have an Individualized Education Plan (IEP)? _____

If you answered yes, what was the IEP for? _____

Prior to cancer diagnosis, did your child receive any specialized school services? _____

If you answered yes, please specify the types of services: _____

_____

Prior to cancer diagnosis, has your child ever seen a counselor, doctor, pastor or someone else for emotional or behavioral problems? _____

If you answered yes: How old was your child? _____ What was the nature of the problem? _____

_____

Was a diagnosis provided? _____(If yes, which) _____

Has your child ever taken medications for emotional or behavioral problems? _____

If you answered yes: How old was your child? _____ Which medication ? _____

Has your child ever received treatment for drugs or alcohol? _____

If yes, please specify (e.g., age at treatment, nature of treatment, outcome) _____

_____

Treatment Satisfaction Questionnaire
(Parent Version)

Subject ID: _____ Date: _____ Session: 12 25

Respondent: Mother Father Other Caregiver _____

The CogMed computer program worked each time it was used.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

The instructions provided to me were helpful and easy to understand.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

The weekly telephone calls accurately addressed any difficulty my child was having.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

The weekly telephone calls provided useful tips to improve my child's performance.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

I think sending my child's progress weekly is a good idea.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Scheduling time for my child to complete the daily sessions was easy.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

My child was agreeable to completing the sessions.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

How did you typically respond to your child if he/she resisted completing the sessions?

_____

_____

My child enjoyed this training program.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

My child enjoyed this as much as other video games he/she usually plays.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

My child was not easily bored during the sessions.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

My child did not get frustrated during the sessions.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

My child was able to complete the sessions independently.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

My child looked forward to playing the racing game at the end of the session.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

The gift card provided motivation for my child to complete the activities.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Please rank the following in order of preference, with "1" indicating the reward that would provide the <u>most</u> incentive for your child.

_____ More money on the gift cards
_____ More frequent rewards
_____ Fewer required sessions
_____ Shorter sessions

I was able to upload the information to the internet each week.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

I noticed a change in my child during this study.

1	2	3	4	5

Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Other people (e.g., teachers) noticed a change in my child during this study.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

My child's grades improved during this study.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

My child benefitted directly from this study.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

The best thing about this study was: _____

_____

I would recommend this study to other parents.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

I wish I could have changed: _____

_____

Comments/Suggestions: _____

_____

_____

Treatment Satisfaction Questionnaire
(Participant Version)

Subject ID: _____ Date: _____ Session: 12 25

My age is: _____

I understood the rules of the games.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

It was easy to find time to complete my daily sessions.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

I rarely complained when completing the sessions.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

How did you feel about completing the sessions? _____

_____

I enjoyed these games.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

I enjoyed these games as much as other video games I usually play.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

The sessions kept my attention.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

I was able to complete the sessions without help from my parent.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

I looked forward to playing the racing game at the end of the session.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

The gift card motivated me to complete the activities.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

Which of the following might make you more likely to complete these games? Write "1" next to the reward you would most like to receive and continue ranking your 2nd, 3rd, and 4th choices.

_____ More money on the gift cards
_____ More frequent rewards
_____ Fewer sessions
_____ Shorter sessions

These games helped me do better work at school.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

I think other children my age would like being in this study.

1	2	3	4	5
Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree

I think the program would be better if:_____

_____

Comments/Suggestions: _____

_____

_____

Computer Skills Questionnaire

Do you own a computer? ____Yes ____No

If Yes, ____ PC ____ Mac

Do you have home Internet access? ____ Yes ____ No

If Yes, Provider Name_____
Speed: Dial-up / Cable / DSL / Other _____

If No, do you have convenient local access to a computer and the Internet?
_____Work _____Public Library _____Friend/Family Member _____Other

How many hours per week do you spend on your computer?

____ 0 to 5 hours
____ 6 to 10 hours
____ 11 to 20 hours
____ More than 20 hours

Which of the following activities do you perform on your computer?

____ E-mail/Social networking
____ Work Documents/School Homework
____ Playing games
____ Listening to music/Watching movies
____ Other _____

Do you have someone you can ask for help if you have questions regarding your home computer? ____Yes ____No

Please rate the following activities in terms of how comfortable you are with them:

General use of a computer

1	2	3	4	5
Not at All Comfortable	Not Very Comfortable	Neutral	Somewhat Comfortable	Very Comfortable

Turn on and safely turn off the computer

1	2	3	4	5
Not at All Comfortable	Not Very Comfortable	Neutral	Somewhat Comfortable	Very Comfortable

Use of the mouse

1	2	3	4	5
Not at All Comfortable	Not Very Comfortable	Neutral	Somewhat Comfortable	Very Comfortable

Use of the keyboard

1	2	3	4	5
Not at All Comfortable	Not Very Comfortable	Neutral	Somewhat Comfortable	Very Comfortable

Use of Windows operating system (Folders, Menus, MS Office programs…)

1	2	3	4	5
Not at All Comfortable	Not Very Comfortable	Neutral	Somewhat Comfortable	Very Comfortable

Save data to the hard drive or portable media (disk, flash drive, etc)

1	2	3	4	5
Not at All Comfortable	Not Very Comfortable	Neutral	Somewhat Comfortable	Very Comfortable

Install software program to the computer

1	2	3	4	5
Not at All Comfortable	Not Very Comfortable	Neutral	Somewhat Comfortable	Very Comfortable

Start a software application and close it

1	2	3	4	5
Not at All Comfortable	Not Very Comfortable	Neutral	Somewhat Comfortable	Very Comfortable

Connect to the Internet

1	2	3	4	5
Not at All Comfortable	Not Very Comfortable	Neutral	Somewhat Comfortable	Very Comfortable

Use e-mail to open and read a message

1	2	3	4	5
Not at All Comfortable	Not Very Comfortable	Neutral	Somewhat Comfortable	Very Comfortable

Use e-mail to create and send a message

1	2	3	4	5
Not at All Comfortable	Not Very Comfortable	Neutral	Somewhat Comfortable	Very Comfortable

Upload files to the Internet or into a software program

1	2	3	4	5
Not at All	Not Very	Neutral	Somewhat	Very Comfortable

Comfortable	Comfortable	Comfortable