Pediatric Survivors of Severe Malaria: Academic Performance Following a Cognitive Intervention in Uganda

By

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ABSTRACT

Background: Severe malarial infection manifests in sub-Saharan pediatric populations in two ways – severe malaria anemia and cerebral malaria. Both cause damage to brain physiology, causing deficits in cognitive functions such as memory, attention, problem solving, and motor control. Malaria mortality has decreased due to increased pharmaceutical availability, but damage is often already done prior to accessing treatment. Consistently high rates of malaria have resulted in malaria becoming a leading cause of cognitive impairment in sub-Saharan Africa. Though efforts must be made in illness prevention, it is necessary for effective tertiary therapies to exist until prevention is more effective. Computerized cognitive rehabilitation therapy (CCRT) offers promising, low-cost, acceptable cognitive benefits for children surviving severe malaria, but validation for real world impact is lacking.

Objectives: The objectives of this research are to evaluate the desirability and functional impact of CCRT among pediatric survivors of severe malaria. The hypothesis driving this objective is that CCRT-based cognitive improvements evident in children, will lead to improved performance in the academic setting. Evidence of academic improvements resulting from exposure to CCRT would indicate that translational effects of such an intervention are valid in regards to a measure of everyday functioning (school work). This information has the potential to provide a rationale for the continued use of cognitive training to improve long-term outcomes.

Methods: Three studies were conducted to address the objectives. First, a qualitative analysis of the Ugandan perspective of CCRT. Ugandan professionals familiar with CCRT were interviewed regarding facilitators and barriers to CCRT and its implementation. Second, a descriptive study of academic performance differences between healthy children and survivors of severe malaria. Third, an analysis of change in academic performance over one year, following training with CCRT. All analyses take into account moderating variables that may influence CCRT's functional impact (i.e., socio-economic status, home environment, age, and gender). The second and third studies were a post hoc analysis of school reports collected from participants enrolled in a randomized controlled trial in Uganda.

Results: The qualitative analysis identified potential facilitators and barriers that may be encountered regarding CCRT implementation. Ugandan professionals demonstrated the hope and opportunity for the implementation while acknowledging that challenges, such as geography and resource availability, must be considered. The baseline study found no statistically significant difference between healthy children and survivors of severe malaria in academic domains of Arithmetic, English, Reading, Writing, and Luganda. The final study also found no statistically significant differences in academic performance over time following training with CCRT.

Conclusion: Ugandan teachers, researchers, and health providers see great potential and desirability for implementing CCRT in the academic setting. Their unique areas of expertise can inform future endeavors of dissemination through identifying barriers, such as resource availability, and facilitators, such as perceived value. Stakeholders place value on this intervention, however, the second study was not able to identify differences in academic performance between survivors of severe malaria and healthy children. The lack of differences may indicate the impact of malaria on cognitive outcomes is not as severe as previously thought,

but it may also indicate the limitations of the measure. Finally, evidence of academic change over time was lacking in the third study. These results may indicate CCRT has no direct influence upon academic performance, or as noted before, may result from limitation of the measure of academic performance.

INTRODUCTION

Specific Aims

Malaria is an ever present affliction among individuals in sub-Saharan Africa. There are between 300-500 million new cases of malaria in sub-Saharan Africa every year (Njama, Dorsey, Guwatudde, Kigonya, Greenhouse, Musisi & Kamya, 2003). Children are specifically vulnerable to the disease, often experiencing severe episodes that can end in death and are occurring at a rate of approximately 1 million per year for children under the age of 5 (Njama et al, 2003). According to a World Health Organization (WHO) report published in 2014, severe malaria (SM) is diagnosed when one or more of the following are observed with no other identifiable cause: impaired consciousness, acidosis, hypoglycemia, anemia, acute kidney injury, jaundice, pulmonary edema, significant bleeding, shock, and hyper-parasitaemia (World Health Organization, 2014). Many children are lost, but due to continued improvements in malaria treatment availability and effectiveness, more children are living longer and fewer are dying due to malaria. This is evidenced by a decline from 985,000 deaths in 2000 to 627,000 in 2010 (World Health Organization, 2010). Nonetheless, this improved outcome does not come without its unique challenges. Increasing amounts of children who do survive severe malaria are found to be left with lifelong effects, particularly in the area of neuropsychological functioning, including

cognitive and behavioral domains (Bangirana, Allebeck, Boivin, Page, Ehnvall & Musisi, 2011). Though children's lives have been saved from the malaria, they are now facing a new dilemma: how to achieve optimal quality of life with minimal therapeutic resources available for lasting cognitive consequences of their illness.

The increased survival rates combined with overall high incidence rates of malaria have resulted in malaria as a leading cause of impaired cognition for children in sub-Saharan Africa (Idro, Jenkins, & Newton, 2005; Idro, Marsh, John, & Newton, 2010). Children who are suffering from such impairments begin seeing the effects in their home and school environments. Memory, attention, problem solving skills and decision making abilities can all be significantly compromised in a child following severe malaria (Bangirana, Allebeck et al., 2011; M. Boivin et al., 2007; Holding, Stevenson, Peshu, & Marsh, 1999; Idro, Jenkins, & Newton, 2005). Deficits in these areas would likely make success in the classroom unattainable. The impact of a compromised educational experience leads to impaired social interaction. Ugandan communities place very high value on family and education, thus a lack of adequate educational performance results in children struggling to lead a fulfilling life with limited options for enhancement, while knowing the burden they bring to the family caring for them.

The high incidence of impairment from malaria, the social impact, as well as significantly diminished health outcomes for young children, call for a novel approach to care for this population. An economically viable intervention to counter these cognitive deficits could carry significant and lasting impact. Computerized cognitive rehabilitation therapy (CCRT) programs have been successful in improving cognitive impairments associated with medical and psychological illness (Bangirana, Giordani, John, Page, Opoka & Boivin, 2009). As pediatric malaria is a leading cause of cognitive impairments in sub-Saharan Africa, it is imperative that

the impact of CCRT be more clearly understood, characterized, and utilized in areas of high malaria incidence (Idro et al, 2010). Functional performance in everyday life must be studied to identify whether competencies related to CCRT translate into significant cognitive effects. The understanding of functional impact serves to inform health care and education policy change, along with wider implementation of CCRT. This post hoc analysis intends to explore the functional impact through the following aims.

Aim 1: Evaluate functional impact of CCRT in pediatric survivors of severe malaria.

Hypothesis 1: Children who have survived severe malaria will demonstrate greater improvement in academic performance following CCRT relative to healthy controls, with greatest improvement noted in children with active (titrated) CCRT.

Hypothesis 2: Risk factors (home environment, socio-economic status, biological) will moderate the relationship seen in hypothesis 1.

Aim 2: Investigate training success of CCRT and its impact on academic improvement.

Hypothesis 1: Within the active CCRT group, there will be a positive relationship between academic performance and extent of CCRT progress through successive training sessions.

Long-Term Investment & Impact Statement

The most recent estimate places the total population of Uganda at approximately 39.5 million people. About forty-eight percent of the population is under the age of 14 years (Central Intelligence Agency, 2017). Sustained, untreated pediatric cognitive impairments due to medical illness could significantly and negatively impact sub-Saharan Africa as these children struggle to move through the education system and attempt to enter the workforce. An easy to administer, portable, relatively available, computer-based intervention for cognitive impairment associated

with medical illness could markedly improve social, economic, and health outcomes as children would be better equipped to advance through the academic setting.

This research will not only provide a deeper understanding of the direct, every-day benefits of CCRT for children in Uganda, but it will also lay the ground work for a model of continued transdisciplinary efforts. These efforts will offer specific positive impact on children's cognitive competency, as well as their overall health outcomes.

Introduction & Literature Review

Malaria is a mosquito-borne parasite that attaches to red blood cells (RBCs) causing, among other things, inflammation and fever. If recognized early enough by parents or caregivers, many effective pharmaceuticals are available to prevent escalation and permanent brain damage caused by the disease. Unfortunately, many children do not access those treatments early enough in the course of the illness. Due to poor transportation, potentially low understanding of malaria by parents, and easier access to traditional herbs and medicines, significant amounts of children do not receive appropriate medical care until malaria has escalated in clinical severity.

In the course of this research, severe malaria (SM) is identified as having two forms: severe malaria anemia (SMA) and cerebral malaria (CM). These two types of severe malaria, SMA and CM, have been reported to lead to permanent decrements to cognitive performance (Bangirana et al, 2011). Severe malaria anemia occurs when the parasitic load becomes so great in the blood stream that RBCs are unable to effectively carry oxygen throughout the body (World Health Organization, 2014). Organs all over the body begin suffering the ill effects of poor perfusion. The brain is one organ of particular importance that undergoes damage due to poor supply of adequate oxygenation. In the case of CM, the parasite has crossed the blood brain barrier, settled in the ventricles and is directly damaging brain tissue (Idro et al, 2010). To be diagnosed with CM, a child must have a documented episode of coma (Idro et al, 2010). Quite clearly, SMA and CM have significant and detrimental effects to the young and still developing brains of children. The growing number of children suffering cognitive impairment and the unavoidable impact this will have on continued growth, development, and quality of life call for no small notice.

Pediatric cognitive impairments inhibit a child's ability to fully embrace optimal quality of life, because those impairments negatively impact multiple facets of their lives. Untreated impaired executive functioning can poorly influence an individual's ability to perform instrumental activities of daily living (IADLs) and maintain careers later in their life (Olness, 2003). Socially, children may often find themselves unable to interact with peers and feel isolated due to an inability to appropriately read the cues and norms within their culture. Academically, the ability to memorize, pay attention, and problem solve are often absent for children suffering from cognitive impairments (Olness, 2003). This not only prevents them from advancing in coursework at a pace steady with their peers, but limits options as they get older for life-satisfying and purpose-giving careers. Cognitive impairments are a significant hindrance to a child's access in attaining optimal quality of life. Though the type of impairment and cause may differ among pediatric populations globally, this is a health deficit requiring a marked increase of research and intervention in many professional disciplines.

Globally, children suffer from cognitive deficits that can result from complicated birth histories such as neonatal asphyxia or hypoxia, traumatic brain injury, and illnesses, like meningitis, encephalitis and lead poisoning (Olness, 2003). In low- and middle income countries (LMICs), cognitive impairments often arise from these situations compounded by other variables, such as malnutrition and infectious diseases (e.g. human immunodeficiency virus (HIV), helminthic infections, and malaria) (Olness, 2003). In the western world, early identification of impaired cognition is a priority for many healthcare providers, as well as caregivers, and is integrated into the school system through learning evaluation and accommodation programs. This type of vigilance provides enhanced access to treatments and rehabilitation. Access undoubtedly augments the opportunity to improve the child's health

outcomes throughout their lifespan. In addition to health providers and caregivers, many local governments are also intentional about providing appropriate resources for children in need through educational and healthcare settings (United States Department of Education, 2004). Children diagnosed with cognitive impairments struggle with successful learning in a classroom with non-cognitively impaired children. In many developed countries, cognitively appropriate curriculums are developed, so that children receive access to individualized educational experiences in cognitively conscious environments (United States Department of Education, 2004). These forms of care are not readily available in many LMICs, however. Even when there are systems and resources in place for children with severe cognitive deficits due to congenital illnesses or disability, such as autism or blindness, there are few to no opportunities for rehabilitation and learning accommodation for children who were previously healthy, but suffered from intense illness or injury that resulted in poor cognitive performance.

As of 2003, there were approximately 300-500 million people in sub-Saharan Africa diagnosed with malaria every year (Njama et al, 2003). Children are most severely affected by malaria and mortality rates can be as high as 1 million per year for children below 5 years of age (Njama et al, 2003). Mortality rates for children are significantly higher because they are more prone to the more severe cases of malaria, SMA and CM. Approximately 575,000 children in sub-Saharan Africa are yearly afflicted with CM (Idro et al, 2010). The past decade has greatly increased the availability of antimalarial medications in areas of high malaria incidence. The availability of treatment has reduced mortality rates of CM, but not necessarily the resulting morbidities. Anemia, as a result of malaria, and CM inflict significant damage to young and developing brains (Engle, Granthan-McGregor, Black, Walker & Wachs, 2007). The proven sequelae of cognitive deficits following recovery from CM have resulted in its becoming a

leading cause of cognitive impairments in sub-Saharan Africa (Idro et al, 2010). This entire population of children was born healthy and, barring other factors controlled for, would have developed in cognitive equivalence with their peers. However, being afflicted with this illness at such young ages has significantly damaged brain processing ability, leaving a potentially permanent impact, unless appropriate interventions are implemented.

Computerized cognitive rehabilitation therapy (CCRT) is an increasingly utilized resource in developed and high resource countries to stave off cognitive decline in many patient populations as well as retrain cognitive properties that have been lost or damaged due to illness. In the United States (US), CCRT has been studied among elderly individuals with Alzheimer's disease with positive results on neuropsychological outcomes (Pressler, Titler, Koelling, Riley, Jung, Hoyland-Domenic...& Giordani, 2015). In US pediatric populations, survivors of cancer have been treated with CCRT to retrain deficit areas post-illness, such as memory and attention (Hardy, Willard, & Bonner, 2011; Kesler, Lacayo, & Jo, 2011). In addition to American studies, children with Attention Deficit Hyperactivity Disorder (ADHD) in Spain who are trained with computerized cognitive programs have demonstrated potential to improve working memory and executive function (Bigorra, Garolera, Guijarro, & Hervás, 2016). The success of such studies motivated the endeavor to use this intervention in LMICs.

The increasing study of computerized interventions has been expanded to low resource settings. Research with CCRT among African children has been primarily focused on those who have survived malaria, as one in four children are found to experience cognitive deficits after recovery of the infection, but has also included children who are positive for the human immunodeficiency virus (HIV) (Bergemann et al., 2012; John, Bangirana, & Byarugaba, 2008). Computerized cognitive rehabilitation therapy was first studied on survivors of malaria in a

randomized trial for pediatric survivors of CM conducted by Bangirana and others in 2009. Sixty-five child survivors of malaria were randomized to receive either Captain's Log training for 8 weeks (n = 32) or no intervention in the non-treatment control group (n = 33). In this study, it was determined that administering CCRT a length of time following illness (45 months, in this case) enhanced cognitive performance, such as processing speed, working memory, learning, psychomotor speed, and internalizing problems (Bangirana et al, 2009).

A second study that used a computerized cognitive intervention for children was conducted in 2010 by Boivin and colleagues for children with HIV. The usual treatment for HIV, antiretroviral treatment, was found ineffective in improving cognitive impairments. Computerized cognitive rehabilitation therapy, based on success in improving cognition in other pediatric populations, was chosen for this study. This was a randomized controlled study comparing children receiving treatment as usual (TAU), n = 28, with children receiving Captain's Log CCRT in addition to the TAU, n = 32. The intervention group received 10 sessions of Captain's Log focused on attention and memory. It was concluded that CCRT administered to children with HIV could assist in the improvement of cognitive functions (Boivin et al, 2010).

A third study was published in 2011 which looked at the effect of CCRT administration closer to time of illness. Sixty-one children who had been previously diagnosed with severe malaria (SM) were randomized into intervention, n = 28, and control, n = 33, groups. In this study, children who received CCRT 3 months after illness experienced cognitive improvements in a few areas, such as learning, that were immediately measureable, where other areas, such as memory and academic and behavioral measures were not impacted by the training at all (Bangirana et al, 2011a).

Following this study, the same team of researchers conducted a follow up study with children who were survivors of severe malaria, in addition to recruiting healthy controls (Bangirana, Musisi, Boivin, Ehnvall, John, Bergemann & Allebeck, 2011b). This was a prospective case-control study, also carried out in Kampala, Uganda, with sixty-two children with a history of malaria and sixty-one community controls. The purpose of this specific study was to investigate the neurological involvement of malaria on cognitive ability, behavior and academic achievement. In both 2011 studies performed by Bangirana and others, academic achievement was studied through utilization of the Wide Range Achievement Test-Third Edition (WRAT-3). This measure assessed skills of reading, arithmetic and spelling, but no results were found to be significant in identifying change. Though this is a tool that has been used in prior research, no official validation has been performed to ensure that the codes they present are reflective of the academic setting in Uganda. In addition to those factors, the WRAT-3 was not translated into Luganda, potentially limiting its reliability, and based on the nature of the assessment to assess basic academic coding skills, it does not truly capture a child's cognitive competency in a functional setting.

One meta-analysis of computerized training and therapy among pediatric populations has been conducted (Karch, D., Albers, L., Renner, G., Lichtenauer, N. & von Kries R, 2013). The objective of that study was to determine the impact of computerized interventions on the improvement of cognition. Secondarily, they examined whether influence on behavior, school performance, and intelligence were noted in the included studies. They analyzed twenty-two publications that used either a computer training program or computer-aided intervention for children with cognitive impairments. The first two studies described above, Bangirana, 2009 and Boivin, 2010, were included in the meta-analysis. This meta-analysis found relatively low effects

for attention, memory, and executive function outcomes. There were positive, but non-specific effects for behavioral symptoms and slight effects for school performance and intelligence. Overall, they recognize the limitation of their meta-analysis being primarily that of including various patient populations, but found that many studies lacked scientific rigor to adequately state significant gains in cognitive outcomes (Karch et al, 2013).

The impact of computerized cognitive training on daily life and the amount of training needed for cognitive change must be further evaluated and understood. Improved knowledge surrounding CCRT impact on everyday activities can offer guidance in where and how this intervention can be implemented for greatest effect. In the few studies examining CCRT with children, there remains a lack of an objective measure that accurately captures the translational effect of cognitive training from the clinical to academic setting. Parental report via the Child Behavior Checklist is a subjective attempt, and the WRAT-3, as previously discussed has not been validated as a reliable measure for cognitive performance in the classroom among this population. A need exists for the impact of CCRT upon functional performance to be evaluated. Quantifying school records and analyzing change in performance is a promising opportunity to fill the gap for this intervention by demonstrating that cognitive gain through training may transfer to increased and lasting effects on educational attainment. The proposed research serves to fill this gap and act as a catalyst for implementing CCRT on a greater scale. Additionally, the data collected regarding performance success of CCRT will provide new insight into the mechanisms of CCRT and will begin the effort of determining potential appropriate amounts of training that might be required for children. The information offered by this data will shed greater light on understanding parameters of CCRT that may predict the effectiveness of CCRT in impacting school performance.

Identification of academic performance as an objective measure of success following CCRT exposure opens many opportunities for educational enhancement in Uganda. Medical, research, and educational professionals in Uganda have shared that CCRT could be a promising intervention, not only for children who have survived SMA and CM, but other children who may be struggling in the classroom (Finn, Lori, Lee, & Giordani, 2018). Computerized cognitive interventions that have proven effective in the research setting, with tangible benefits in the academic setting, could offer great benefit if implemented in the curriculum of the Ugandan educational system. Evidence of everyday, real-life positive effects builds the argument for large scale implementation and alignment with governmental initiatives for education. Ugandan professionals have spoken to the natural learning environment of schools to facilitate increased cognitive performance when exposed to CCRT (Finn et al, 2018). In order to meet the health care needs of children who have survived SMA and CM, intervention implementation must be creative and interdisciplinary.

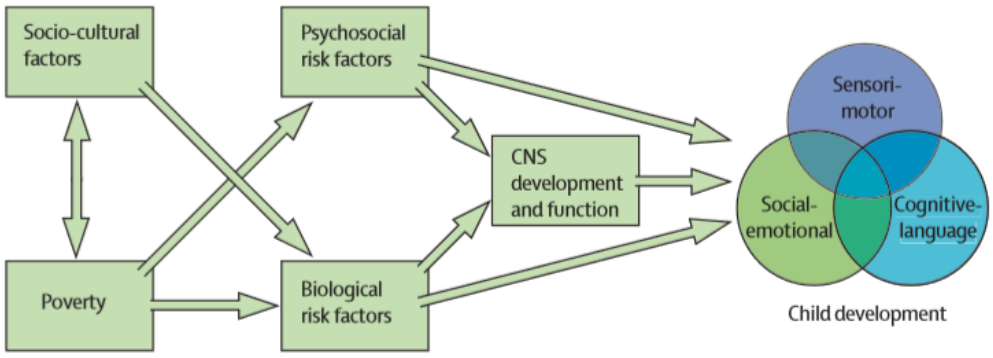
Cognitive improvement is a key aspect of overall health and quality of life. This research, hopefully, will not only help to better characterize the positive impact experienced by participants who enrolled in an RCT in Uganda, but also provide data to support health care and school policy change. Results of this research have potential to be disseminated to Ugandan health and educational systems in order to improve the quality of the many other lives of children in Uganda and potentially other countries, as well. The primary objective of this research is to evaluate the functional impact of CCRT among pediatric survivors of severe malaria. The hypothesis driving this objective is that CCRT-based cognitive improvements evident in school-age children, will also lead to improved performance in the academic setting. This objective will be addressed through three independent, yet related studies that examine the local perspective on

CCRT, academic performance differences among children, and finally, changes in cognitive performance that occur over time following CCRT.

Theoretical Foundation

This research is based upon a model adapted from Walker and others (2007) and Engle and others (2007) which was created to guide research on the development of the central nervous system of children in LMICs (Figure 1). The model, "Risk Pathway of Poor Child Development," was developed out of a desire to identify the leading causes of adverse outcomes and thus facilitate intervention development (Walker, Wachs, Gardner, Lozoff, Wasserman, Pollitt & Carter, 2007)

Figure 1. Risk Pathway of Poor Child Development

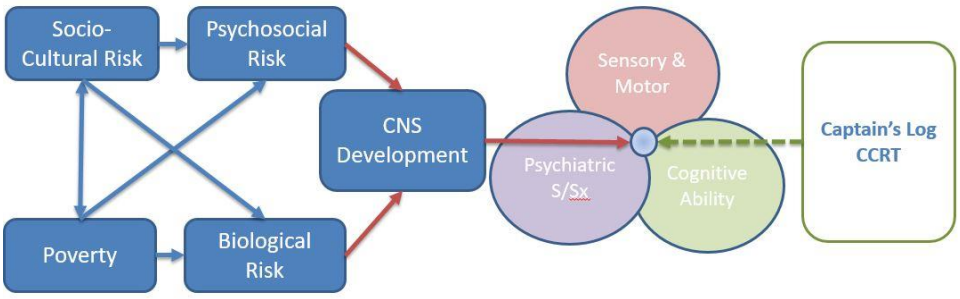


Walker et al (2007) have identified four primary risk factors of CNS development: socio-cultural risk, poverty, psychosocial risk, and biological risk. All risk factors interact with and are compounded by each other, contributing to an overall negative impact upon central nervous system (CNS) development. Poor CNS development manifests primarily under three domains: psychiatric symptoms, cognitive abilities, and sensory and motor control.

In the parent RCT of this research, it was hypothesized that the intervention, Captain's Log CCRT, would interact at the point of CNS development intersection to yield improvements

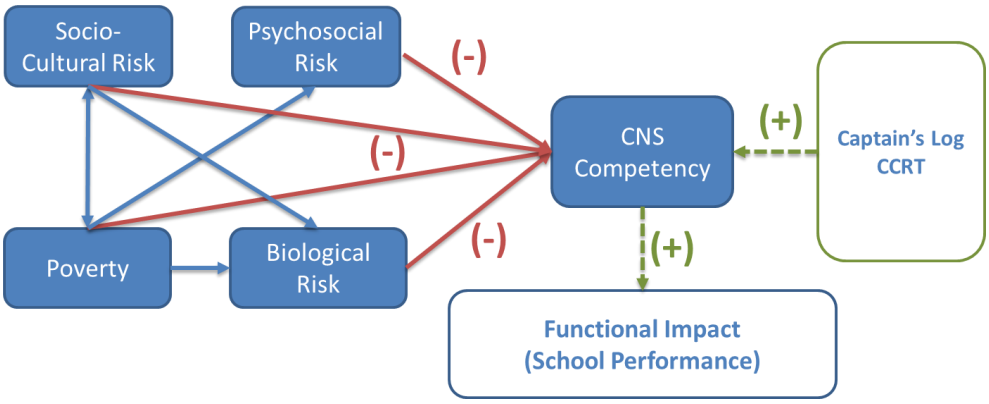
in the three effected domains, represented by uni-directional green dotted arrow in Figure 2. This hypothesis is founded on the theory of brain plasticity, in which the brain is viewed as malleable to external stimulation (Mahncke et al, 2006). Captain's Log training capitalizes on the brain's natural ability to learn by offering repetitive and increasingly difficult training modules (Boivin et al, 2010). This method contributes to enhanced cognitive performance through targeted training to result in positive outcomes in brain function (Mahncke, 2006). Additionally, it is a generally accepted principal that children are particularly susceptible to the training of cognitive tasks as their development is still ongoing. The guiding model of the parent RCT can be found in Figure 2.

Figure 2. Modified Risk Pathway for Poor Child Development



In this current research, Figure 3 depicts the four risk factors that are expected to directly act as negative moderators on the functional impact outcome: school performance. The hypothesis of this research is that upon improvement in the central nervous system functioning with CCRT, functional benefits will be observed and measureable in the form of school performance. Tangible outcomes of improved cognition from Captain's Log CCRT will be reflective of the translational effect of training from the clinical to academic setting.

Figure 3. Modified Risk Pathway for Poor Child Development and Cognitive Competency



As noted above, the measure of functional impact is school performance at one year following enrollment in the parent RCT. Socio-cultural risk is measured by opportunities for cognitive stimulation and parental involvement in the home. Poverty is measured by a child's socio-economic status. Psychosocial risk is measured by a test of a child's cognitive aptitude. Biological risk is measured by factors such as age, gender, and health status. Captain's Log will be measured by six internal measures of the training program. All factors will be described in further detail below.

Design & Data

This research utilizes a post hoc analysis approach to determine the functional impact (academic performance) of computerized cognitive rehabilitation therapy (CCRT) among child survivors of severe malaria (SM) and healthy community controls (CC). The original dataset from the parent RCT includes a significant amount of measurement data, however, for the purposes of this research, only variables related to academic achievement or directly to the Modified Risk Pathway of Poor Child Development and Cognitive Competency were chosen for analysis. The concept "Socio-Cultural Risk," is studied using Caldwell's Home Observation Measurement of the Environment (HOME) score. "Poverty" is represented by a socio-economic status score. "Biological Risk" includes the child's health screening and diagnosis. The internal data of Captain's Log will provide a picture of advancement through the training. And finally, the outcome of interest, CNS/Cognitive Competency (encompassing psychiatric signs and symptoms, sensory and motor skills, and cognitive ability), is the "Functional Impact" of 5 composite academic scores from school reports.

This dataset was provided from an RCT that was conducted between 2010 and 2016 in Kampala, Uganda. The primary site of research training and testing occurred at Mulago National Referral Hospital in collaboration with Global Health Uganda, Makerere University, the University of Michigan, and Michigan State University. Permission for use of these specific variables for analysis was been obtained from Dr. Michael Boivin, the Principal Investigator (PI) of this study and Dr. Bruno Giordani, a Co-Investigator and PI for University of Michigan site. A data use agreement was established with the primary investigators of the parent study and can be found in Appendix A. The University of Michigan Medical School Institutional Review Board

has reviewed and approved the aims and objectives of this research. The approval can be found in Appendix B.

Sample & Setting

The randomized parent trial (R01 HD064416-01A1) enrolled 300 children between the ages of 5 and 12 years over the course of 5 years in Kampala, Uganda. Children diagnosed with SMA or CM were recruited through an ongoing observational study (R01NS055349) at Mulago National Referral Hospital, led by Dr. John Chandy, which lacked a cognitive assessment component. In addition to the inclusion/exclusion criteria of the R01NS055349 protocol, children were also excluded if they presented with neurological deficits so severe their comprehension of basic instruction was impaired. Healthy children were recruited from the community through word of mouth of parents and families interested in the study.

The measurements and scores that represent theoretical constructs listed above are available for all 300 children. Baseline and one-year follow up school reports were collected on 161 children (Table 1) in the parent RCT through work by the PhD candidate over summer stays in Uganda during which she worked closely with the lead research assistant, Monica Lyagoba, who was under the direct supervision of Dr. Horacio Ruisenor, then a postdoctoral fellow working under Drs. Boivin and Giordani. In addition to children who were able to provide reports at both time points, 21 children were able to provide baseline reports and 55 children were able to provide school reports at the one year follow up.

Table 1. School Reports by Sample Arm

	Sample by Arm		
	Severe Malaria	**Community Controls**	**Total**
N	74	87	161
Intervention	27	37	64
Active Control	28	27	55
Passive Control	19	23	42

Reasons for missing reports stem from school report collection not being planned in the initial study implementation, thus parents were asked after the fact to recover reports from a specific time point. This delay in collection contributed to parents not being equipped or even able to provide such reports. The summary of missing reports and reasons are presented in Table 2. Training with CCRT was done either at Mulago National Referral Hospital, the child's school or the child's home, depending on their location and their parent's access to transportation. To the best of the PhD candidate's knowledge and the expertise of Ugandan collaborators, there appears to be no clear pattern to the missing data once collection took place. This suggests that missing data could be treated as random.

Table 2. Missing Data

Missing Reason	**Number @ Baseline**	**Number @ Follow Up**	***Total***
Damaged/destroyed	3	1	*3*
Lost	7	45	*75*
Not in School	21	16	*25*
Death	3	3	*3*
Inability to Contact Caregiver/Family Moved	20	22	*26*
Unpaid School Fees	6	6	*7*
Total	*127*	*93*	*139*

Measures

The objective of this research was to determine the functional impact of CCRT on academic performance. To fully understand that relationship, the moderating variables, discussed in the Risk Pathway of Poor Child Development and Cognitive Competency, were addressed through identified measures. These variables, socio-cultural risk, poverty, biological risk, and psychosocial risk, serve as moderators and will be analyzed as such when examining the impact training with CCRT has upon a child's academic performance in Uganda.

Socio-Cultural Risk – Caldwell Home Observation Measurement of the Environment (HOME)

The Caldwell HOME scale is an inventory of an individual's home environment for opportunities of learning and cognitive stimulation (Bradely, Caldwell, Brisby, Magee et al, 1992). This assessment serves to analyze homes, not based on income level, but available cognitive stimulation in the home (Bradely, Caldwell, Rock, Hamrick & Harris, 1988). Specifically within the study, the assessment for "Middle Childhood" was used. The 59 item scale was developed following psychometric testing for reliability and validity from the original 90 item scale (Bradely et al, 1988). The items are grouped into eight subscales: Emotional and Verbal Responsivity, Encouragement of Maturity, Emotional Climate, Growth-Fostering Materials and Experiences, Provision for Active Stimulation, Family Participation in Developmentally Stimulating Experiences, Paternal Involvement, and Aspects of the Physical Environment. Bangirana and others have previously found this to be an acceptable measure of home impact on cognitive development in Uganda (Bangirana, John, Idro et al, 2009). This tool can be found in Appendix D.

Poverty – Socio-Economic Status

A socio-economic status (SES) score was determined by a structured inventory taken of the material possessions present in the child's home and the type of living structured they inhabited. Quality of the living structure, living density, food accessibility, facilities for bathing and cooking, as well as access to electricity and clean water were also recorded. This inventory was conducted only during the child's enrollment period. It was carried out by Ugandan research team members and scores were recorded in the child's file and can be found in Appendix E.

Biological Risk – Physical Exam, Age, Gender, Health History

Upon recruitment for the parent study, children underwent a physical exam to determine their overall health status. This exam was to ensure there were no extraneous biological factors contributing to potential impaired cognitive performance—such as malnutrition or mental illness. In addition to health status, age and gender were recorded as factors influencing cognitive potential. This was done specifically due to the fact that younger children are at greater risk of impairment developmentally and girls are at more risk for impairment due to social factors. Diagnosis relates to method and timing of being diagnosed with SMA and CM. This was confirmed via blood smear results in the prior study from which children were recruited.

Psychosocial Risk—Non-Verbal Index

The Non-Verbal Index (NVI) variable from the Kaufman Assessment Battery for Children, Second Edition (KABC-II), was used to assess the children's basic cognitive processing/intellectual ability (Kaufman & Kaufman, 2004). The NVI score was chosen as a measure of psychosocial risk because of its ability to assess cognitive aptitude, even when English may not be the primary language of the child. This measure has been assessed and

validated for use among Ugandan children (Semrud-Clikeman, Regilda, Shapiro, Bangirana, & Chandy, 2016).

CNS Competency/Functional Impact - School Reports

In Uganda, the academic year is divided into three terms. For collection in our study, the end of term report that was most appropriate was selected. For example, reports from baseline were the most recently completed academic term prior to participation in the parent study. Reports collected for the one year follow up were from the term most recently completed prior to one year cognitive testing. Academic reports were collected through contacting caregivers of participating children and copies of the reports were made in the Ugandan research office, de-identified, and placed in the child's measurement results folder. Data from the school reports were entered into a FileMaker (FileMaker Pro 12.0v1, 2012) database created by the research team's local data manager. Each study participant had a form within the database where baseline and one year reports were viewable side by side. Additionally, there was a mandatory second copy required within each form to ensure that data from the reports were being recorded correctly and consistently.

Information in the form included study ID, presence of report, level of schooling, age, rank within the classroom, and teacher comments. Twenty eight categories of learning were included in the form, but the majority of cases provide scores for less than 10 categories. Children's reports were scored on a scale of 1 ("Need Help") to 5 ("Excellent") within each category. When reports provided qualitative marks from the teacher, e.g. under "Reading" the teacher writes "Excellent," a 5 would be recorded in the datasheet. When reports provided quantitative marks, e.g. under "Reading" the child's score was 80/100, a 5 would be recorded in the datasheet. According to the standards set forth by the Ministry of Education and Sports in

Uganda scores of 80-100 are valued as "A" marks or "Excellent," scores of 70-79 are valued as "B" marks or "Very Good," scores of 60-69 are valued as "C" marks or "Good," scores of 50-59 are valued as "D" marks or "Fair," and scores of 0-49 are valued as "E" marks or "Needs Help."

As the children are provided with different lessons as they advance through the primary school system, a method of appropriately comparing scores over time was developed with Ugandan support. Five variables of learning achievement were created based on the FileMaker database. They included: Reading Arts, Writing, English Language, Luganda Arts, and Arithmetic. For example, children in lower classes might have received a score under the subject heading "Numbers" at baseline and "Math" at one year follow up. Ugandan collaborators have endorsed the appropriateness of creating a broader variable for inclusion to analyze change over time. In a few cases, a child's report would include a "Numbers" score and a "Math" score. In such cases, most had the same value, but in the rare occasion they did not, the average of the two scores was recorded as their "Arithmetic" score.

Analysis

The specific aims described earlier are addressed through three individual manuscripts approaching various aspects of the broad research question, "Does CCRT have functional impact among Ugandan pediatric survivors of SM by improving their academic performance?" The first manuscript pursued a qualitative approach exploring the feasibility of CCRT implementation. It used thematic analysis to determine facilitators and barriers to implementation. The second manuscript employed ordinal regression to determine differences in academic performance between children with SM and CC. The third manuscript utilized linear modeling analysis to determine whether change in academic performance is influenced by CCRT exposure, diagnosis group, as well as other moderating factors.

To perform the necessary analyses for this research, the software program R 3.2.2 was used (R Core Team, 2015). R was chosen due to the software's adaptability and versatility of use, as well as it's compatibility with various datasets. The exact analyses used for this research will be addressed in greater depth in the supporting manuscripts, however, a brief description of aim-specific analysis is provided below.

Aim 1.

To achieve Aim 1 and evaluate the functional impact of CCRT in pediatric survivors of severe malaria, ordinal regression was used for the second manuscript (Chapter 2) and multiple linear regression was used for the third manuscript (Chapter 3). Regression analysis is a common method to determine the relationship that exists between a dependent variable (DV) and two or more independent variables (IV). In Chapter 2, the DV is an ordinal value, academic performance at baseline, and thus ordinal regression was used. The DV in Chapter 3 is the change in school performance from baseline and one year. This is a continuous variable and, as such, multiple linear regression was used. The IVs included training arm (Active/Titrated CCRT, Passive/Non-titrated CCRT, or TAU), and diagnosis group (SM or CC). Co-variables in the model included baseline SES and HOME scores, along with age and gender. This allowed for predictive analysis of differences in academic performance change by group and training exposure. Additionally, NVI was included in the linear regression to determine effect of baseline cognitive aptitude on change. Regression models were analyzed within each of the 5 academic domains—English Language, Luganda, Writing, Arithmetic, and Reading Arts.

Aim 2.

The analysis of Aim 2, investigating the training success of CCRT and its impact on academic improvement, used multiple linear regression and Kendall's Tau correlation test. .The

academic change score was the outcome variable of the regression and explanatory variables were diagnosis group, treatment arm, SES, gender, HOME, and the NVI. Kendall's Tau correlation was used to identify any existing relationship between CCRT success and degree of change experienced in academic scores. Success within CCRT was measured by six summary scores of training modules: memory, concentration, visual acuity, problem solving, auditory processing and self-efficacy.

Summary

In summary, this post hoc analysis of school repots will serve as a preliminary study to understand the functional impact of CCRT on child survivors of severe malaria in Uganda. The additive nature of this research to current measures of cognitive competency will continue to guide and inform future research that plans to explore computerized cognitive interventions in various pediatric populations.

Strengths & Limitations

Strengths and limitations are common in all research endeavors, and this dissertation research is not exempt from that norm. The first notable limitation was the degree of missing data on school performance. It was outside the scope of the PhD candidate or of the original research team to gather and record school performance reports on all 300 children recruited for the parent randomized trial. This limitation presents a challenge for analyzing the data and determining generalizable results. An additional limitation was the difficulty of maintaining open communication with the parent data source. The geographical distance between Ann Arbor, Michigan and Kampala, Uganda on top of the, at times, limited access to internet, compounds the difficulty in having questions answered in reasonable time.

One primary strength of this study is that the author played a leading role in beginning the collection process and coding of academic reports by trips to Uganda to work directly with the team. Though this is a post hoc data analysis, the author spent considerable time working with the team as a co-investigator to catalyze this academic data collection process. Through being a part of the preliminary stages in collection, the author has firsthand experience of the difficulty of contacting caregivers and maintaining adequate follow-up with the study participants. This serves as a strength as it provides unique insight into the process of data collection, as well as the data itself.

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CHAPTER I

Interdisciplinary Ugandan Perspectives on Computerized Intervention Implementation for Child Survivors of Severe Malaria: A Qualitative Analysis

Technology and technology-assisted interventions are quickly making waves in health sciences research. The ease and effectiveness of technology-based health interventions draw many researchers in with questions like "Will this phone-based application enhance my patient population's adherence to treatment?" or "Is an internet-based program able to reach a greater audience than a provider-based program?" And many patients are experiencing the improved health outcomes because of questions being asked and positive results being found.

A caution that many researchers must consider, however, is whether a technology program that works for one group of individuals may not be appropriate for another. This is particularly true when considering populations that are vastly different in terms of illness, socio-economic status, age, and resource availability. In addition to considering the challenges, researchers must engage with the community of interest to determine whether just such an intervention is desirable or feasible for what they hope to accomplish. Computerized Cognitive Rehabilitation Therapy (CCRT) is a promising intervention for individuals with cognitive impairment related to illness. Preliminary outcomes are positive for CCRT use among children

with cognitive impairments, but there has been no formal assessment to examine the community's opinion of such an intervention.

The first step of exploration in this research was to determine the opinion of Ugandan professionals involved with children who have survived severe malaria. Prior to the quantitative approaches of manuscripts two and three, the first takes a qualitative descriptive approach in order to give voice to the stakeholders most intimately involved with CCRT as a health care intervention. This manuscript and its results have been published in Applied Nursing Research[1].

[1] Finn, K.; Lori, J.; Lee, M.; Giordani, B. (2018). Interdisciplinary Ugandan Perspectives on Computerized Intervention Implementation for Child Survivors of Severe Malaria: A Qualitative Analysis. *Applied Nursing Research, 39*:154–159 https://doi.org/10.1016/j.apnr.2017.11.022

Abstract

Background: Severe malaria (SM) is the leading cause of pediatric cognitive impairment in sub-Saharan Africa. Computerized Cognitive Rehabilitation Therapy (CCRT), a promising intervention for children suffering from SM related cognitive delay, targets areas impacted by the disease (memory, attention, and executive function), but has yet to be implemented for daily use. This paper explores the perspectives of Ugandan professionals regarding CCRT implementation in the academic setting of Uganda.

Methods: A qualitative descriptive approach was taken to conduct interviews with Ugandan professionals directly or indirectly aware of an ongoing CCRT intervention trial. Eight individuals were consented and interviewed. Responses were analyzed thematically. Question topics included knowledge of malaria and CCRT, perspectives on implementation feasibility, and experience engaging in a global collaborative research endeavor.

Results: Facilitators included perceived value and environment. Potential barriers were geography and resource availability. Perceived value is seen, expected, and/or hoped for outcomes by adults involved in the child's development. Environment speaks to the internal environment of the CCRT program and external environment of the school setting. Geography presents as a barrier due to the difficulty of accessing CCRT in rural settings. Resource availability was a consistently identified barrier to implementation including aspects of technological, financial, and understanding deficits leading to difficulties in dissemination.

Conclusion: Results demonstrate optimism and hope of Ugandan professionals for CCRT in children who have survived SM. Professionals identify and prioritize needs for implementation uniquely, pointing to the value in interdisciplinary collaboration to ensure effective implementation of CCRT.

Introduction

Severe malaria anemia (SMA) and cerebral malaria (CM) are severe forms of malaria resulting in lasting neurocognitive deficits in children (Bangirana, Opoka, Boivin, Idro, Hodges, Romero… John, 2014; Bangirana, Opoka, Boivin, Idro, Hodges & John, 2016; Carter, Lees, Gona, Murira, Rimba, Neville, & Newton, 2006; Idro, Marsh, John & Newton, 2010). With over 50 percent of the Ugandan population under the age of 15 and an estimated 18 million cases of malaria in Uganda (World Health Organization, 2015), children are at significant risk of acquiring malaria and the negative neurocognitive sequelae. Malaria has become the leading cause of cognitive impairment in sub-Saharan Africa as young children's brains are still developing and highly vulnerable to injury from infection (Idro et al., 2010). The cognitive domains most acutely impacted by infection are memory, attention, visual spatial ability, speech and language, and executive function (Carter et al, 2006). Deficits in these critical areas at young ages negatively impact a child's ability to meet appropriate developmental milestones physically, academically, and socially. Until consistent means can be secured to prevent cognitive impairments resulting from malaria, rehabilitative interventions are being explored to meet this population's new neurocognitive needs.

Computerized cognitive rehabilitative therapy (CCRT) may be a promising intervention to improve cognitive outcomes in pediatric populations with lasting deficits from severe malaria (SM). In the United States, CCRT programs have been frequently used for children who have been diagnosed with traumatic brain injuries (TBI), Attention Deficit Disorder (ADD), or Attention Deficit/Hyperactive Disorder (ADHD) (Diamond & Lee, 2011; Holmes & Dunning, 2009; Homes, Gathercole, Place, Dunning, Hilton & Elliott, 2010; Kotwal, Burns, & Montgomery, 1996; Rabiner & Skinner, 2010; Steiner, Sheldrick, Gotthelf & Perrin, 2011).

Computerized cognitive rehabilitation therapy can vary in its presentation, but consistently is based on the theory of neuroplasticity – the idea that the brain is amenable to positive changes following repetitive and titrated training over a period of time (Mahncke, Bronstone, & Merzenich, 2006). The training program is frequently administered through various modules, or games, targeting a specific domain of cognitive functioning and advancing in difficulty as the individual progresses through the training regimen. In recent years, researchers have begun exploring CCRT use for children in multiple African countries, particularly in pediatric populations with heavy HIV and malaria burden (Bangirana, Giordani, John, Page, Opoka & Boivin, 2009; Boivin, Parikh, Page, Busman, Bangirana, Opoka & Giordani, 2010; Ruel, Boivin, Boal, Bangirana, Charlebois, Havlir… Wong, 2012). Preliminary research with CCRT in sub-Saharan African children has shown there can be significant improvement in short- and long-term cognitive abilities for populations who have suffered severe illness (Bangirana, Idro, John & Boivin, 2006; Bangirana et al., 2009).

Western and African researchers have adapted CCRT to the sub-Saharan context, validated neuropsychological measures, and identified populations who may benefit from CCRT. Neuropsychological batteries such as the Test of Variables of Attention (TOVA), Kaufman's Assessment Battery for Children-II (KABC-II), Cogstate, the Behavioral Rating Inventory of Executive Function (BREIF), and others have undergone testing and validation to ensure they are serving as accurate cognitive measures for children in Africa (Familiar, Ruisenor-Escudero, Giordani, Bangirana, Nakasujja, … Boivin, 2015; Nampijja, Apule, Lule, Akurut, Muhangi, Elliott, & Alcock, 2010; Semrud-Clikeman, Regilda, Shapiro, Bangirana, Chandy, 2016). While this work is critical to advancing pediatric cognitive health in sub-Saharan Africa, its potential to

impact sustainable health outcomes is limited by poor understanding of existing facilitators and barriers to CCRT implementation in this context.

"Facilitators" is a term used in research to describe aspects or things that serve to enable or equip another thing. Similarly used, "barriers" is a term used for things that prevent or present challenge to something else. Examination of facilitators and barriers to implementation of an intervention or practice change is common in nursing literature (Abrahamson, Fox, & Doebbeling, 2012; Jun, Kovner, Stimpfel, 2016). To date, no research has been done regarding the feasibility of implementing a computerized intervention for malaria. To develop a foundational understanding of structures in Uganda that may support or hinder intervention implementation, a qualitative descriptive study was conducted. This qualitative analysis examines themes from the perspectives of selected Ugandan professionals familiar with CCRT with the aim to identify potential facilitators for and barriers to CCRT implementation in the Ugandan academic setting.

Methods

Design

This study used a qualitative descriptive approach utilizing thematic analysis to identify facilitators and barriers. The study was guided by the recommendations presented in "Standards for Reporting Qualitative Research: A Synthesis of Recommendations" (O'Brien, Harris, Beckman, Reed & Cook, 2014). The Standards for Reporting Qualitative Research (SRQR) presents 21 criteria by which qualitative research can be planned, reviewed, critiqued, and analyzed in a consistent manner.

Qualitative descriptive methodology falls appropriately under the constructivist paradigm where learning occurs through interaction between the inquirer and the participant (Guba &

Lincoln, 2005). Data gathered through qualitative descriptive work emphasizes the value in presenting information as it appears in language that is readily understood. Qualitative descriptive methodology was chosen for the priority placed on learning between inquirer and participant. The inquirer in this study is a Western researcher and health practitioner while all participants were Ugandan, creating power dynamics that could skew the qualitative data. This approach enabled the researcher to approach the interviews as a learner while the participants felt empowered to share their experience and knowledge. It is imperative to accurately present Ugandan opinion, as these professionals are most likely to be the key stakeholders in CCRT implementation (Sandelowski, 2000).

Setting

Uganda is one of the forty-two countries in sub-Saharan Africa with a per captia gross national income less than $4,305 per year. By World Bank standards, Uganda is considered a low- to middle-income country (LMIC). Though there are some major cities, the majority of individuals (84%) live in rural communities with limited access to adequate healthcare and other necessities (Central Intelligence Agency, 2017). Kampala is the capital city of Uganda with a population greater than 1.9 million people (Central Intelligence Agency, 2017). At the time of this study, Kampala was home to one of the larger national referral hospitals in the country, Mulago. Individuals would travel to Mulago when in need of intensive care, but by the time they are accessing care there, the disease process has often advanced significantly. This creates a patient population of very sick individuals in need of innovative care and treatment.

Sample

Convenience sampling was used to gather participants during the first author's visit to Uganda in June 2016. Participant sampling was intentional and purposeful to incorporate the

opinions of individuals who have potential to engage and enact meaningful change through CCRT implementation. Participants were identified based on an earlier interaction between the first author and research collaborators in Uganda. The collaborators then assisted in recruiting the final sample of Ugandan professionals for this study. Participants were contacted by the local collaborator to introduce the first author regarding their interest in being interviewed for this study. The University of Michigan deemed the study exempt from Institutional Review Board oversight as minimal to no risk to participants was foreseen for this research. Ugandan research collaborators were contacted regarding the purpose of the study and it was determined unnecessary to seek further exemption from within Uganda.

Interviews

Eight participants were recruited for semi-structured, audio-recorded interviews with the first author, an American doctoral nursing student. Participants were read a consent form that included information regarding the purpose of the study, their ability to withdraw at any point, and the right to audio record interviews. They were allowed to ask questions and were enrolled in the study upon agreeing to participate with verbal and written consent. Participant preference determined interview context and environment, but the first author encouraged a private location be chosen where conversation could progress comfortably and at the participant's desired pace. The primary locations for interviews included Mulago National Referral Hospital and teacher offices at schools, all of which were in the city of Kampala, Uganda. The semi-structured interviews were composed of 10 open-ended statements that allowed the participant to share their knowledge on that topic. The interview statements can be found in Appendix C. The initial questions focused on malaria ("Tell me about current therapies for malaria and rehabilitation options following the illness"), cognition, and CCRT. Questions were then directed towards

perceived CCRT support by parents, teachers, schools, and the government ("Tell me about teacher and school support of CCRT use"). Upon hearing the participant's response to the leading prompt, the interviewer would then ask clarifying question. The interviews were conducted in English, the national language of Uganda. The teachers, however, did consent to allowing a Ugandan CCRT research team member to be present during their interviews to assist with communication, if necessary.

Participant recruitment and the interview sequelae constitutes the "discovery phase" of this study in the constructivist paradigm, the time in which information is gathered to answer the question "What is going on here?" (Guba & Lincoln, 2001). Interview data were audio recorded using the first author's private computer. In addition, the first author took notes during the interview to collect situational information that may not have been conveyed in the recordings. All digital study materials were stored on a password protected laptop and locked in a secure environment every night, along with all paper materials.

Interviews lasted from 23 minutes to just over 41 minutes with an average length of 32 minutes and standard deviation of 5 ½ minutes. Based on the recommendations by Fusch and Ness, data saturation was met when sufficient data was collected to replicate the study, when the ability to obtain new information was no longer present, and when new themes were not being presented (Fusch & Ness, 2015). The smaller sample size of this study allowed for data saturation to be reached quickly.

Analysis

The second stage in constructivist evaluation of qualitative descriptive work, assimilation, was then pursued to explore the data generation and integration from the interviews as novel data (Guba & Lincoln, 2001). The audio interviews were transcribed by a research

assistant at the University of Michigan and reviewed by the first author for accuracy. The research assistant was not present at the time the interviews were conducted, providing protection from researcher bias during transcription. Rigor was maintained through ensuring investigator responsiveness and strategies for verification throughout the project duration (Morse, Barrett, Mayan, Olson & Spiers, 2002).

In-depth transcription reading was conducted by research team to identify key points within the interviews. Collected data assimilation allowed for similarities across interviews to be identified and explored. An evidence table was constructed to identify themes in participant responses based on the questions asked. Within the evidence table, themes were coded as either positive (+) or negative (-) to provide initial insight to themes of facilitators and barriers. Categories of (+) and (-) themes were then analyzed for patterns, resulting in specifically identified facilitators and barriers.

Results

Sample participants included four CCRT research team members, two healthcare professionals, and two local teachers. Characteristics of the sample can be found in Table 3. Among the CCRT research team participants, two individuals had experience training children with CCRT, and two individuals had experience conducting neuropsychological testing with children trained with CCRT. The health care team members included one medical officer (doctor) and one nurse. The doctor and nurse were involved in the initial screening for children enrolled in a CCRT study as well as continued care throughout the child's participation in the study. The teachers who participated were from two different primary schools in Kampala. Though not directly involved in research with CCRT, these individuals were aware certain children in their classroom were participating in a computer-based research project. They had the

opportunity to view CCRT training take place in the academic setting. All the participants had varying levels of exposure to CCRT training, but all had expertise within their own field to comment on potential facilitators and barriers to implementing a computerized intervention in the academic setting.

Table 3. Demographic Results

Characteristics	**Results**
Age	
Range	28y – 44y
Mean (SD)	35.86y (7.289y)
Gender	
Male	50% (n = 4)
Experience	
Range	2m – 7.5y
Mean (SD)	2.93 years
Educational Experience	
< College	12% (n = 1)
>/= College	88% (n = 7)
Discipline	
Education	25% (n = 2)
Healthcare	25% (n = 2)
Neuropsychological Research	50% (n = 4)

Data of the semi-structured interviews with Ugandan participants were analyzed thematically to identify facilitators and barriers of CCRT implementation in Uganda. A description of the identified facilitators and barriers is found in Table 4.

Facilitators

Facilitators for CCRT implementation in the Ugandan academic setting were identified through thematic analysis of the eight interviews conducted with Ugandan participants.

Throughout the interviews, two positive themes arose as facilitators for CCRT implementation: "Perceived Value" and "Environment."

Perceived Value. Perceived Value, the first theme identified as being facilitative, was either ascribed to by the commenting participant or attributed to other individuals, such as parents, caregivers, teachers, or various community members. One participant noted,

> *"I think sending out CCRT to as much of our children would be a good idea. For those who have cognitive issues, yea it would be a good idea." ~002*

> *"They [teachers] were eager to find out what... would do [CCRT]" ~002*

Participants shared this was a positive indicator for CCRT implementation in the academic setting through what caregivers have seen, what they expect, and what they hope for. This theme of perceived value held by participants of the study and, almost more importantly, by those who may be the greatest advocates for implementation - parents – facilitates potential for CCRT implementation in Ugandan schools. In response to a question regarding parent support one participant stated,

> *"Yes, they are very supportive… Because they see that they [children] can [experience benefit]." ~003*

Environment. The second theme facilitating CCRT implementation in a Ugandan academic setting was labeled as "Environment." This theme encompasses the positive attributes of the internal and external environments that are present through training with CCRT. The

internal environment pertains to CCRT itself. The training programs are structured as games that are challenging, but encouraging. One participant noted,

> *"It's child friendly. The colors are really good. Even the program, the way it's programed, the praising bit of it in the games… It's not different from the normal life, like maybe the things they do, the things they see. And ya, it's child friendly. On rare occasions we get kids getting tired, feeling not that interested… they still want to play that game... Even kids that are struggling throughout they never show that they are tired… So being child friendly is good." ~001*

The children are excited to play and often do not see the program as training, but fun. Participants identified this aspect of CCRT as a reason implementation would be successful in Uganda. In response to a question asking if CCRT is good for children, one participant said,

> *"Yes. because that is what now they need to get. We only pray that if it was to continue it would be just now… in the whole school. Yes." ~007*

The external aspect of CCRT is related to the natural learning environment that is present in the academic setting. Participants felt learning should occur in academic settings, and as a learning intervention, the feasibility of implementing CCRT there would be convenient and appropriate. Two participants from different disciplines noted CCRT would be best received and administered in schools compared to research or clinical environments.

> *"I think it would be good to find them where they are. So I think school would be fine and better than a hospital" ~002*

> *"Of course definitely. The school be better- anything away from the hospital would be better. Yeah. So try to be better at school." ~006*

Table 4. Results of Facilitators and Barriers

Facilitators	***Barriers***
Perceived Value of stakeholders - *Optimism of CCRT implementation* - *Positive anticipation of improvement following CCRT training* - *Hope for the larger impact of CCRT* *Environment* - *Internal: CCRT environment as child-friendly* - *External: Academic setting as a natural environment for learning to occur, traditionally and through CCRT*	*Geography* - *Greatest burden of severe malaria is in the more rural areas* - *Greatest need is the most difficult to access and maintain* *Resource Availability* - *Many schools are already under-funded* - *Lack of reliable energy source* - *Concern for funds going to technology before immediate needs, such as food and first aid* - *Government not sharing in perceived value of parents, teachers and healthcare providers*

Barriers

Barriers serve as obstacles or difficulties to achieving a task. Two themes with potential to hinder implementation of CCRT in the academic setting identified through interviews with participants included "Geography" and "Resource availability."

Geography. Geography reflects the difficulty of offering all forms of rehabilitation, particularly computers, to children living in rural areas outside of Kampala. As one participant said,

> *"Well now, you seem be basing in Mulago mainly, and malaria looks to most severe in local communities than in the urban centers. [Should] extend the program in the local community [rather] than staying in the urban centers*

because this way even people who are still ignorant can come out to treatment." ~007

This theme of geography recognizes that children most in need of the CCRT intervention due to distance delaying appropriate treatment are likely to be the most challenging to reach with this intervention.

Resource Availability. The second theme identified as potential barrier to CCRT implementation is resource availability. Resource availability speaks to the limited amount of technology, finances, and government interest. Though one participant believes computers are becoming increasingly available in Kampala, "Yeah. Computers are everywhere yeah even in the villages you find them in people's home," (001) others identify limited access to computers as a major barrier for implementation. In order for the CCRT software to be downloaded, one must first have a laptop or desktop computer upon which to download CCRT. Computer availability combined with the lack of technology training and support is limited, serving as a significant challenge for this intervention. One participant described this lack of available computers,

"No. Probably a few [computers in school]. Private schools [might have computers] they really have to pay an extra fee for computer, though." ~004

It was well understood by all participants the first question that must be considered prior to CCRT implementation is who will be paying for program's dissemination. Several responses were given when participants were asked whether they felt the government would financially contribute to implementing CCRT.

"Expensive." ~000

> *"No I don't think so, because if they can't provide medicine to the hospitals I don't think they can provide laptops" ~004*

> *"This is private school… No [funds for computers]." ~005*

Many participants indicated that they do not count the government as a likely source of funding, at least early on in the early stages implementation. This is due to a general consensus that the government is unaware of this unique cognitive need of Ugandan children and thus unaware that rehabilitation programs are needed. One participant advocated for increased awareness at government levels,

> *"I think if the idea is well explained for them they can buy it because it is an interesting thing. I think they can embrace it depending on how you design it and show how it can work for the children; I think it can work and not just the sick kids." ~002*

Lack of understanding on the side of the government serves as a major constraint to resource availability and greatly contributes as a barrier to CCRT implementation in the Ugandan academic setting.

Discussion

The aim of this study was to identify Ugandan perspectives of facilitators and barriers to CCRT implementation in the academic setting. A qualitative descriptive study was conducted to identify themes from semi-structured, in-depth interviews. To the authors' knowledge, this is the first report to gather Ugandan perspectives on computerized intervention implementation for cognitively impaired children.

Analysis of interviews resulted in the development of four themes, two serving as facilitators for CCRT implementation in the school setting and two as barriers. The themes were developed from various disciplines in Uganda, including psychology, medicine, nursing, and education. The interviews demonstrated multi-disciplinary support for CCRT as an intervention, despite the potential barriers, due to the anticipated benefit it could offer children who suffer from cognitive impairments due to malaria. Slight differences in priority and means of implementation were observed between disciplines, indicating the value in addressing multiple perspectives when moving interventions from research into practice.

The facilitators identified for implementation in this study along with quantitative data finding CCRT's impact on cognitive benefit in other studies (Bangirana et al, 2006; Bangirana et al, 2009; Boivin et al, 2010), demonstrate CCRT's potential value through implementation in the academic setting. Though the government's limited awareness and suspected lack of financial investment is seen as a potential barrier, the interviewees agreed the next step for implementation would be approaching the Ugandan Ministry of Education and Sports (MOES) with CCRT research trial results. Unified support for implementation may significantly enhance MOES responsiveness and overcome the barriers identified in this study. If there is minimal support from the government, one participant recommended involvement from other sources such as non-government organizations or global grants. If impact can be made through legislation passed in Uganda to support rehabilitative care in the classroom, Uganda could serve as a model to other sub-Saharan African countries who also experience the high-burden of pediatric cognitive impairment due to malaria.

Limitations

As is common in all research, this study does have limitations to be considered. First, the first author conducting the interview is white and from a western country. It is likely that this influenced the power dynamics during interviews, despite best attempts at creating a partnering environment. Biased responses have potential to skew data, but the method of qualitative descriptive research was chosen to help prevent this, through empowering the interviewee as an equal participant in the interview dialogue. This must be considered when examining the responses of participants regarding facilitators and barriers to CCRT implementation. Secondly, only eight interviews were conducted, and they were conveniently sampled due to time and travel constraints by the primary researcher. The small participant sample limits the confidence in adequate result saturation. Additionally, the convenience sampling used increases potential for bias as the participants are key stakeholders in moving the intervention forward. There may be value, in future experiences, in extending the length of stay in country to allow for more participants to be recruited and interviewed.

Despite the restraints noted, the study also had several strengths. Multiple disciplines representing variety in gender, age, and expertise were sampled and interviewed which provided rich diversity in the sample and responses. Perspectives were sought not only from individuals actively involved in the intervention trial, but community members (teachers and healthcare providers). A second strength is the first author's experience working with Ugandans from previous travels. Though a cultural barrier will likely always exist, a prior understanding and respect of Ugandan culture facilitated ease of conversation during the interview process.

Conclusion

The perspectives of Ugandan researchers, doctors, nurses, and teachers portray CCRT as a promising intervention for children suffering cognitive impairments related to severe malaria. Many also noted the potential value for children with impaired cognition due to other causes. The most significant barrier, limited resource availability, is not an uncommon problem for intervention implementation in sub-Saharan Africa. However, this barrier must not be looked upon as unconquerable considering the growing support by local professionals and the expanding evidence base. The themes of perceived value and positive environments identified in this analysis can be used to strengthen arguments for CCRT implementation.

As suggested by one participant, CCRT implementation may have to begin in the private education sector through non-government funds before the government fully realizes its value. Success in the private schools may stimulate financial resource reallocation to fund the training in public schools. Computerized cognitive rehabilitation therapy implementation in Ugandan schools may improve the quality of life and future vocational and education prospects for Ugandan children while also serving as a treatment care model for cognitively impaired children throughout sub-Saharan Africa.

The perspectives presented here provide unique insight into potential challenges, such as resource gathering and financial support, as CCRT moves from research stages to real-world implementation. In-depth understanding assists in capitalizing on the positive outcomes and professional optimism regarding intervention implementation to enact change and improve quality of life. Locally-identified barriers and facilitators from various disciplines begin laying the groundwork for meaningful advancements to be made in pediatric care and cognitive rehabilitation following severe malaria.

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CHAPTER II

The Impact of Malaria in the Classroom

The first, and arguably the most important conversation that was addressed in the first chapter was whether Ugandan professionals see value in carrying forward a computerized intervention, and if it can improve quality of life and health outcomes of their children. With the understanding that the local perspective is in favor of dissemination, the next question to respond to is whether neuropsychological testing demonstrates that child survivors of SM perform more poorly than their healthy counter-parts. Within the clinical and research setting, this has been shown using research-based and traditional paper-and-pencil test measures. However, other than data suggesting that mothers may see benefit over the short term in home-based behaviors, little has been done in a non-clinic, "every day" setting to support moving forward with dissemination of CCRT-based techniques.

Based on the recommendations of Ugandan professionals, this intervention may demonstrate greatest effect in a natural learning environment—such as a school. The second manuscript of this dissertation explores the baseline differences that exist in the classroom based on health status. It is important to know in what areas of education children who survive SM and healthy controls may differ in their academic achievement. The functional impact of CCRT can only be understood when the phenomenon creating challenges is well understood. The following

paper compares the school performance of 182 Ugandan children who are survivors of SM and healthy CC. School performance was assessed in five academic domains to build a foundation upon which the full impact of SM on neurocognitive development could be better understood.

Abstract

Background: Sub-Saharan Africa carries heavy burden of malaria. In Uganda, over 8 million cases have been confirmed and more are suspected. Children are particularly vulnerable to malaria and the negative cognitive sequelae of severe cases. The cognitive impact of malaria among children has resulted in malaria becoming a leading cause of cognitive impairment in sub-Saharan Africa. However, the daily impact, if there is one, of this impaired cognition on everyday functioning and quality of life is unknown.

Methods: To assess the effects of malaria-induced cognitive impairment on a child's every day functioning, retrospective collection of school reports was performed for children enrolled in an ongoing randomized controlled trial. Children were enrolled in this trial if they were identified as survivors of severe malaria or matched as healthy community controls. Caregivers were contacted and asked to provide school reports for the term the child was enrolled in during the trial. Ordinal regression analyses were used to assess differences in academic performance between the two groups of children in five academic domains.

Results: School reports were collected for 182 of the 300 children in the trial. Significant results were found for effect of age upon performance in Arithmetic and English domains and SES was significant for performance in Arithmetic. Differences in academic performance between healthy children and survivors of severe malaria were non-significant in this analysis.

Conclusion: The results of this study cannot support the hypothesis that children with severe malaria experience poorer academic performance than healthy controls. Though the differences are not statistically significant in these analyses, the technical study limitations experienced serve to further inform future research in this area. An adequate sample size, controlled measurement,

and consistent environment could provide a deeper insight into the academic achievement potential for Ugandan children.

Background

Sub-Saharan Africa carries one of the heaviest burdens of malaria prevalence. There are estimated 300-500 million cases of malaria worldwide and ninety percent of those cases are in sub-Saharan Africa (Njama et al., 2003). In 2015, Uganda alone had an estimated report of nearly 8.5 million cases of malaria (World Health Organization, 2016). Increased availability of anti-malarial treatments has decreased yearly death rates to fewer than 700,000 (World Health Organization, 2010; World Health Organization, 2016). Despite the treatments available and widespread education efforts on prevention, cases of malaria continue to be reported. Severe cases, in particular, are increasingly diagnosed in the most vulnerable populations. Children are especially vulnerable to severe cases due to their lower circulating blood volume and the parasites ability to reach dangerous levels more quickly following infection (Cox, 2010; Newton & Krishna, 1998). In addition to high susceptibility of severe malaria, children are also dependent upon caregivers to recognize the illness and access appropriate care. The severe cases of malaria in children manifest as severe malaria anemia (SMA) and cerebral malaria (CM). In both forms of severe malaria (SM), lasting cognitive impairment has been reported to occur due to direct damage occurring to their young and developing brains (Idro et al., 2005).

The cognitive sequelae in children who survive SMA and CM manifest in deficits of memory, attention, visual and auditory processing, motor control and executive function (Bangirana et al., 2011; Bangirana, Musisi et al., 2011; Idro et al., 2005). Deficits in these areas detrimentally influence quality of life and overall health outcomes across the lifespan (P. Engle, Gantham-McGregor, Black, Walker, & Wachs, 2009; P. L. Engle et al., 2011; Grantham-

McGregor et al., 2007). Children with congenital cognitive impairments, such as autism, have some, but limited, access to modified learning environments and there is a glaring lack of cognitive rehabilitative care for children who experience deficits later in childhood due to illnesses like malaria. The lack of support in an educational environment can hinder a child's ability to develop in a manner appropriate to their societal norms (P. Engle et al., 2009; P. L. Engle et al., 2011; Grantham-McGregor et al., 2007). This can, in turn, create significant barriers to health promotion and social interaction as children enter adulthood and attempt to become positive contributors to their community.

The vulnerability of children to malaria infection and the vulnerability of their brains to functional damage has resulted in malaria becoming one of the leading causes of cognitive impairments in sub-Saharan Africa (Idro, Marsh, John, & Newton, 2010; Idro et al., 2005). Various neuropsychological tests have been used to examine the impact of malaria on cognitive performance (Bangirana et al., 2011; M. J. Boivin et al., 2010; Familiar et al., 2015). However, no test has been formally validated to examine the cognitive impact of malaria in a child's day to day life. The closest assessment that has been used in this population is the Wide Range of Achievement Test, Third Edition (WRAT-3) (Bangirana et al., 2011). Unfortunately, this measure was developed in America to assess learning achievement in an American academic setting. The Ugandan education system structure is strongly reflective of previous colonial influence. Not only is the use of WRAT-3 inappropriate because of educational structuring, but it has also not been validated for use in the Ugandan context, particularly in terms of the spelling and reading subtests.

Validating a psychological instrument can be a long and very complex, as well as costly, proposition. Another, more direct approach to assessing the impact of malaria may be to go

directly to the "source," the classroom—through teacher-provided school reports. An examination of performance in the academic classroom could offer important insights into the cognitive differences between children diagnosed with SM and healthy children. Thus, the aim of this study is to examine academic performance of children who are survivors of SM compared to their healthy community-matched controls (CC). The hypothesis is that children who have a history of SM will have lower performance scores on their school reports compared to CCs who have not been diagnosed with SM.

Methods

This quantitative study utilized ordinal regression analysis to determine the effect of health status on academic performance among school-aged children in Kampala, Uganda. An IRB amendment to retrospectively collect academic reports from participants in an ongoing randomized control trial (RCT) was submitted and approved by the University of Michigan Medical Sciences Institutional Review board.

Study Population and Recruitment

The RCT, "Neuropsychological Benefits of Computerized Cognitive Rehabilitation Training in Ugandan Children Surviving Severe Malaria: A Randomized Controlled Trial" (R01 HD064416-01A1), examined the impact of a cognitive intervention on the cognitive performance of child survivors of SM. The RCT recruited children five to twelve years of age who had been diagnosed with SM, as well as community-matched, healthy controls. This study collected demographic data as well as socioeconomic status and a measure of cognitive stimulation in the home.

Caregivers were retrospectively contacted regarding the possibility of providing their child's academic reports. The caregivers were reminded of the month during which their child

was enrolled in the RCT and were asked to find the report from the most recently completed academic term prior to enrollment in the study. If the caregiver was able to provide the report requested, the caregiver could choose to deliver the report to the research office and be reimbursed for travel fees or request report be collected by a research team member.

Setting

Children in the RCT were recruited from the city of Kampala, Uganda—the country's capital city. A 2017 estimate placed the population of Uganda to be approximately 39.5 million people and fifty-one percent female, with forty-eight percent of the population being under the age of 14 (Central Intelligence Agency, 2017; Uganda Bureau of Statistics, 2016). Children were recruited for the RCT following involvement in an observational study of children diagnosed with malaria at Mulago National Referral Hospital. This created a convenience sample of children, as they either lived close enough to the hospital to receive care or had access to adequate means of transportation. This facilitated the retrospective collection of school reports.

School Reports

The school reports represented a wide range of academic settings. The Ugandan education system follows British structure, from colonial influences. Children in the study, thus, were enrolled in one of three school levels: Nursery/Baby (equivalent to American kindergarten), Primary (equivalent to American elementary school), or Secondary (equivalent to American high school). In addition to reports coming from various school levels, there was also a variety in type of school, privately funded or government funded.

The retrospective nature of collecting the school reports precluded an opportunity to a priori control for the variability in educational level, specific school, and teacher grading preference. To standardize the school reports for comparison, ordinal scores of 1-5 for school

subjects were developed by recommendation of the Uganda Ministry of Education and Sports (MOES). The description of values attributed to create the ordinal scale can be found in Table 5.

In the original database of school reports, 27 different academic subjects were identified on the academic reports. Participants included all children from Nursey/Baby to Secondary school levels (children in the RCT were enrolled between the ages of 5 and 12 years). As may be expected, children in Nursery/Baby school levels were not studying subjects such as "Political Education" or "Agricultural," similarly, those in Secondary were not being graded on "Singing" and "Numbers." The majority of children would only receive scores on 3-5 academic subjects per report. In order to create a dataset that would allow for comparison of school performance based on health status, regardless of school level, notable time was spent with Ugandan collaborators to determine the most accurate and efficient way to understand a child's school performance. Five domains of academic training were identified during this process as critical to understanding a child's performance in the classroom. Those domains are: 1) Reading, 2) Writing, 3) Arithmetic, 4) English Language, and 5) Luganda Language. School reports were analyzed for school subjects that fell appropriately into these domains. Reliability of the specified domains was confirmed by Ugandan individuals familiar with the Ugandan academic training and reporting system.

Table 5. Grading Scale

Grading Scale					
Scale:	**1**	**2**	**3**	**4**	**5**
Numeric (out of 100)	0-49	50-59	60-69	70-79	80-100
Categorical	E	D	C	B	A
Descriptive	Needs Help	Fair	Good	Very Good	Excellent

Analysis

Ordinal regression was performed in the software R to determine if there was a notable effect on academic performance between children who have survived SM and health community controls. Ordinal regression was chosen due to the fact that the dependent variables (Reading, Writing, Arithmetic, English, and Luganda) were categorical and ordered. Variables such as socioeconomic status, home environment, age and gender were included in the model as moderating variables, due to the influence they may have on the strength of the relationship between health status and school performance. Socio-economic status (SES) was determined by a scaled inventory that was conducted by Ugandan research team members during the child's time of enrollment into the parent RCT. The measure of home environment was specifically targeted to aspects of cognitive stimulation and learning opportunities in the home. The Caldwell Home Observation Measurement of the Environment (HOME) was used based on previous use among similar populations (Bangirana et al., 2011; Bangirana et al., 2011; Bradley, Caldwell, Brisby, & Magee, 1992).

Results

Demographic

Of the 300 children in parent RCT, school reports could be collected on 182 (61%) of the children enrolled in the RCT. Initial enrollment for the RCT began in 2011 and collection of school reports was not initiated until 2015 which most likely contributed to many reports being unrecoverable. Reasons for missing reports included: damage (3%), loss (53%), child not being in school (19%), the child passing away (4%), inability to contact caregiver (19%), and inability of the caregiver to pay school fees (1%). Comparative demographic characteristics of the RCT and the study's sample can be found in Table 6.

Table 6. Demographic Characteristics

Demographic Characteristics						
	RCT			**Sample**		
	Severe Malaria	**Community Controls**	**P Test**	**Severe Malaria**	**Community Controls**	**P Test**
N	150	150		81	101	
Age years (Mean (SD))	6.97 (1.63)	7 (1.94)	0.898	7.12 (1.72)	7.04 (2.01)	0.766
Sex (% female)	59 (39.3)	83 (55.3)	0.008*	31 (38.3)	55 (54.5)	0.043*
Socioeconomic Status (Mean (SD))	9.75 (2.99)	10.04 (3.07)	0.413	9.98 (3.02)	10.33 (3.03)	0.437
Home Environment (Mean (SD))	37.2 (12.26)	41.03 (11.78)	0.006*	37.39 (11.45)	41.39 (12.08)	0.024*

**Indicates significant difference between SM and CC Groups at the 0.05 level.*

Academic Reports

Ordinal regression was performed for each academic domain individually to compare differences between children in the SM group and the CC group. The community control group served as a reference group for the regression. Variables of sex, age, socio-economic status (SES), and home environment (Home) were included in the models as fixed effects (Table 7). Across all academic domains – Reading, Writing, Arithmetic, English, Luganda – there were no significant effects on school performance between survivors of SM or healthy CCs. In the subjects of Arithmetic and English, Age had a significant effect. Additionally, SES was significant for its effect on performance in Arithmetic.

Table 7. Significance of Effects from Ordinal Regression

Ordinal Regression Effects					
	Reading (N = 143)	**Writing (N = 127)**	**Arithmetic (N = 177)**	**English (N = 139)**	**Luganda (N = 71)**
SM Group	0.839	0.375	0.63593	0.62691	0.834
Sex	0.708	0.867	0.58771	0.64725	0.389
Age	0.274	0.274	0.00041*	0.00407*	0.814
SES	0.432	0.116	0.02887*	0.25436	0.562
Home	0.892	0.983	0.96320	0.58130	0.585

Discussion

The aim of this study was to explore the academic performance of children who have survived SM and any differences that may exist between their performance and the school performance of children who have not been diagnosed with SM. Results from this study do not support the hypothesis that children who have survived SM would experience poorer academic performance than their healthy counter-parts. All five academic domains showed no significant effect of illness on academic performance using this ordinal scale.

Age was a significant effect on performance in the Arithmetic and English domains. This may be due to the fact that children are exposed to increased amounts of English and Arithmetic training, in classroom and other settings, as they get older. Alternatively, it may simply indicate that the older children were appropriately achieving the expected learning outcomes for their academic level, compared to younger children. Socio-economic status was also significant for its effect on performance in Arithmetic, indicating that a child's access to resources in society may directly influence their mathematical reasoning skills.

These results are consistent with previous research exploring the influence of malaria upon academic achievement in that there were no significant differences between survivors of SM and CCs (Bangirana et al., 2011; Bangirana et al., 2011). This, however, is not consistent with studies that identified cognitive differences between groups (M. Boivin et al., 2007; M. J. Boivin et al., 2010). There are many possible reasons academic achievement does not yield the same indicators of cognitive impairment following malaria the way other assessment measures do. One possible explanation is that academic concepts are not as challenging at younger ages and that greater differences in ability will be more noticeable in later stages of education. Another possibility is that academic performance is not being measured in a way that is as consistent or as focused as cognitive assessment batteries used in clinical settings. These, and other reasons, warrant further study to refine the understanding of cognitive competency among this population in the everyday setting, particularly the classroom.

Limitations

No study is without flaws and the influence of those flaws on this study's results must be acknowledged. Retrospective collection of academic reports led to various limitations for this study that must be recognized. The first limitation is missing data. Though a total 182 academic reports were recovered for the time point of a child's enrollment in the RCT, 49% of the RCT participants were unable to provide school reports, despite considerable effort of the Ugandan research assistants. Additionally, each child's report did not include all 5 academic domains described above. Missing data resulted from the inability to collect reports for every child and from the variability of subjects taught during different points of the academic year. A related second limitation is the lack of consistency between schools where the children were studying. It was not within the scope of this study to examine differences in school funding (whether public

or private) nor the educational requirements of teachers at those schools. The inability to control for variation between school setting and teacher training is a notable limitation to this study.

Despite the limitations encountered in this study, it is important to continue examining the functional impact of SM on a child's everyday living. The Ugandan school setting is a unique environment where children are assessed cognitively, through their academic studies, and also behaviorally, through their interactions with classmates. Poor cognitive performance in the clinical setting is likely to also manifest in the academic setting, however, the differences in clinical data have yet to predict similar differences in the classroom. Pediatric survivors of SM deserve holistic assessment of their cognitive competency, in the clinical and everyday setting, in order to meet their cognitive needs and equip them to pursue optimal quality of life.

Conclusion

In conclusion, though SM is known to influence cognitive impairment (Bangirana et al., 2011; Bangirana et al., 2011; M. Boivin et al., 2007; M. J. Boivin et al., 2010), no direct effects of the infection are distinguishable on five academic domains of reading, writing, arithmetic, English, and Luganda, at least with the currently available academic assessment options. The creation of an ordinal scale of performance was a novel approach to standardizing school reports. The scale does, however, simplify a child's academic presentation and may create space for finer notes of variance between children's performance to be missed. The lack of consistency between schools, teachers, and school subjects makes comparison and rigorous analysis challenging for clinical researchers. Though a standard is set forth by Uganda's Ministry of Education and Sports, it may prove beneficial to perform further study in performance and grading mechanisms between schools and teachers. To move this research forward, it would be beneficial to develop a standardized assessment process that is consistent across school environments and ages. This

could be done through increasing utilization of the current MOES standards or those standards could be enhanced to provide a stronger guideline of teaching and learning goals.

The academic setting is a critical environment in which to truly understand the impact of malaria on school-aged children's cognitive development. School is the space where children perform their daily activities, learn and integrate social norms, and advance through curriculum designed to enhance their future productivity. Though this study was inconclusive in identifying specific areas of performance difference among survivors of SM and healthy children, it does inform future research by taking the preliminary steps necessary to exam the overall quality of life among child survivors of severe malaria.

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CHAPTER III

Functional Impact of Computerized Training on Cognitive Competency in Pediatric Survivors of Severe Malaria

Unexpectedly, the hypothesis that children with a history of SM would perform more poorly in the classroom than CCs was not supported in the prior study. The baseline descriptive study could not provide evidence that Ugandan children enrolled in an RCT had statistically significant differences in academic performance at baseline compared to CCs. In the RCT, children with SM had decreased performance on neuropsychological batteries, compared to CC children, which lends to the idea that the ordinal scale used in the baseline descriptive study was not able to fully capture the cognitive competency of the these children.

Though difference in academic performance could not be determined at baseline (prior to CCRT exposure), it remains important to answer the aims of this research in determining the functional impact of CCRT among Ugandan children who are survivors of SM. It has been hypothesized that children exposed to CCRT will experience gains in cognitive competency. This competency has been assessed in the clinical setting, but not evaluated in the everyday setting of children's lives. It is hypothesized that cognitive gains experienced through CCRT in the clinical setting will transfer to other settings where skills requiring sufficient cognitive competency are present.

To determine the functional impact of CCRT, or the school performance change, academic reports were assessed one year following a child's exposure to CCRT. A change score was created from the difference in performance from baseline enrollment in the CCRT and at one-year following intervention administration. The change score was then used as the outcome variable in a linear regression model to determine the effects of CCRT, diagnosis status, and other moderating variables. Severe malaria may not have been found to result in decreased academic performance compared to healthy controls in the earlier study. However, this does not foretell the ability of CCRT to improve academic performance in five educational domains among Ugandan children over time.

Abstract

Background: Over the past decade, increased availability to anti-malarial treatments has significantly lowered global mortality rates due to malaria. Mortality may be dropping, however prevalence continues to increase—especially among vulnerable populations. Children in low- and middle-income countries are often at a disadvantage to fully utilize preventive strategies placing them at higher risk of infection. In addition to limited access to preventative means, children also have lower circulating blood volume that increases their risk to severe forms of malaria if treatment is not quickly sought. Severe malaria has been named a leading cause of cognitive impairment among children in sub-Saharan Africa due to its lasting negative neuropsychological effects. The cognitive impairment among this population has generated the hypothesis that children with severe malaria are likely to perform more poorly in the classroom than their healthy counterparts and thus have poorer health-related outcomes as they age. Computerized Cognitive Rehabilitation Therapy (CCRT) is an intervention that targets cognitive domains impaired by malaria with the intention to retrain lost skills.

Methods: To determine whether CCRT is effectively training children to perform better in school, school reports were collected for 216 children in Kampala, Uganda who were enrolled in a randomized trial for CCRT. These reports were from baseline, when the children were enrolled, and one-year post-intervention, when the children returned for follow-up assessment. Five academic domains were chosen to analyze: writing, reading arts, English, arithmetic, and

Luganda arts. A change score was created from the two time points and linear regression modeling was used to determine the effect of CCRT on change over time, adjusting for moderating factors (i.e., socio-economic status, home environment, gender, cognitive processing ability).

Results: 216 total reports were collected, however, only 161 children were able to provide reports for both baseline and one-year time points. There was no statistically significant effect of CCRT training on academic outcomes; however, factors such as gender, socioeconomic status and a non-verbal indicator of cognitive competency did have some effect.

Conclusion: The results from this study did not support the hypothesis that children exposed to CCRT would experience greater gains in academic performance over time, but they did serve to inform the potential hypotheses and methodology of future research. It would be beneficial, for future research in this area, to partner with teachers to better assess specific skills and have the children graded on these subjects at the same age, in similar environments, and with a standardized metric, all of which would most likely require government influence.

Background

The detrimental effects of cerebral malaria (CM) and severe malaria anemia (SMA) have resulted in malaria becoming a leading cause of cognitive impairments among children in sub-Saharan Africa (Idro et al., 2010; Idro et al., 2005). Children in sub-Saharan Africa have unique vulnerabilities creating increased susceptibility to severe malaria (SM) cases. These vulnerabilities are primarily developmentally related, but manifest in a variety of ways. Physiologically, children have lower circulating blood volume than adults, allowing the parasite to reach dangerous levels more quickly than in adults (Cox, 2010; Newton & Krishna, 1998). Environmentally, a child's access to preventive measures (e.g., mosquito nets) is limited by their caregiver's ability to acquire such things. Unfortunately, preventative methods such as mosquito nets and vaccine development are poorly utilized and understood. This creates increased need for appropriate treatment and rehabilitative modalities for individuals who live in malaria endemic areas. Access to anti-malarial treatment has increased due to the funding priorities locally and internationally (World Health Organization, 2010; World Health Organization, 2015). However, although access has increased and death rates are dropping, prevalence rates are not dropping in similar fashion.

Options for rehabilitation following malaria historically have been limited to physical therapy. Increased understanding of cognitive impact in recent years, however, has stimulated explorative efforts into cognitive rehabilitation are being performed. In Uganda, Computerized Cognitive Rehabilitation Therapy (CCRT) is an intervention most recently under study among pediatric survivors of SM (Bangirana et al., 2011; M. J. Boivin et al., 2010). Computerized Cognitive Rehabilitation Therapy is guided by the principle of brain plasticity—the understanding that the brain is malleable to change and neuronal development with appropriate

training (Mahncke, Bronstone, & Merzenich, 2006). The CCRT training model used in Uganda includes eight weeks of exposure to a training program that targets areas of memory, attention, visual and auditory processing, and executive function (M. J. Boivin et al., 2010). The program is repetitive, but titrated, meaning training modules build upon one another in difficulty as the child demonstrates proficiency on a certain task. The continued exposure to exercises that are repetitive and increasingly difficult is hypothesized to create a training effect, ideally leading to new neuronal pathways and improved cognitive performance.

The research examining CCRT for pediatric survivors of SM is innovative and yielding positive outcomes for children (Bangirana et al., 2011; M. J. Boivin et al., 2010). Assessment measures such as the Test of Variables of Attention (TOVA), Kauffman's Assessment Battery for Children, Second Edition (KABC-II), Behavioral Rating Index of Executive Function (BRIEF) and Cogstate have been used to determine the immediate and long-term effects of CCRT on cognitive performance. The most recent studies have found significant improvement in mental and sequential processing as well as psychomotor function for survivors of SM (Boivin et al., In Process). Though measures of daily impact—such as a caregiver's report through the Child Behavior Checklist (CBCL)—were used, an accurate measure of cognitive competency in daily life was not incorporated into the earlier studies. Primary environments for children are often home and school, CBCL provides insight into behavioral change and cognitive control in the home setting, but school performance may prove to be an unbiased measure outside the home of cognitive change following intervention exposure.

The hypothesis guiding this research is that CCRT is an effective intervention to improve cognitive competency in children who have survived SM. The first objective of this study is to determine if CCRT improves academic performance and thus has functional impact on Ugandan

children's quality of life after adjusting for moderating variables (i.e. age, gender, home environment, socio-economic status). The next objective is to determine if children trained with the titrated version of CCRT will experience a greater degree of academic change than children who were trained with a non-titrated version of CCRT. The third objective of this study is to explore the relationship between the level of success in training (defined by number of successfully completed modules) in CCRT and the degree of academic change.

An IRB amendment to retrospectively collect academic reports from participants in a randomized control trial (RCT) was submitted and approved by the University of Michigan Medical Sciences Institutional Review board (HUM00071923). This amendment and approval can be found in Appendix B.

Methods

Participants

Children enrolled in the RCT were between the ages of 5 and 12 years. They were recruited from an ongoing longitudinal study observing the neurodevelopmental effects of malaria. The RCT recruited children who were survivors of SM as well as healthy, community-matched controls (CC). Children in the CC group were community-matched through asking caregivers of the SM children if there were other siblings, cousins, or neighbors from their home who may be eligible for recruitment. All caregivers signed informed consent and children over the age of 7 years gave assent to participate in the RCT.

Caregivers of children in the RCT were contacted regarding their ability to provide academic reports for research purposes. Caregivers were asked to provide academic reports for the most recently completed academic terms prior to enrollment in the RCT and prior to the one year follow-up assessment.

Setting

All children were recruited from the greater Kampala, Uganda area for the RCT. Uganda is considered a low-/middle-income country (LMIC) by World Bank Standards (World Bank, 2017). Kampala's population is 1.9 million of the 39.5 million in the country and forty-eight percent of the Ugandan population is under the age of 14 years (Central Intelligence Agency, 2017). Though many of the children remained in the area throughout the duration of the RCT, some families had shifted following the completion of their training period, creating challenges for the collection of academic reports at both time points.

Computerized Cognitive Rehabilitation Therapy

The CCRT program used in the RCT, Captain's Log, was developed by the BrainTrain Corporation in the mid-80's (Sandford, 2007) and has gone through a number of expansions since that time. This program has been utilized in various patient populations and has been adapted for use in twenty-three countries (Sandford, 2007). Different modules target areas of memory, attention, visual processing, and executive function. Two forms of the training program were used. The first is the standard, or titrated, version. In this form, the training of the CCRT program is intentionally repetitive and increases in difficulty as the child successfully completes training modules for memory, concentration, etc. Each trained cognitive domain has thirty-two levels of difficulty. The second form, or non-titrated version, presents a fixed set of easy and harder training modules in no structured order and randomly presented over the course of training. Providing both options allowed for an active control arm to monitor for change occurring simply from exposure to challenging computer games and not change related to targeted training through titration.

A measure of success for CCRT was determined by the total number of modules completed successfully at the end of eight weeks of training within each cognitive domain represented by the CCRT modules. Children were trained with CCRT in the clinical setting, their school, or their home—based on caregiver preference. The training period consisted of approximately forty-five to sixty minute laptop sessions where the child received individual attention from a specialized Ugandan trainer. These sessions were conducted, on average, three days a week over a period of eight weeks. This was based on previous research by the parent study team that cognitive gains were notable after eight weeks of training (Boivin et al., 2010).

School Reports

The academic year in Uganda is composed of three terms. The variability of time points during which children were recruited and enrolled in the RCT required intentional planning during the collection period. In order to have the school term report that most accurately reflected the child's current performance in the classroom, caregivers were reminded of the month and year during which their child was recruited for the RCT and asked to provide the most recently completed school report prior to that date. School reports represented Nursery, Primary, and Secondary levels of education. Often times, the child would be in a lower level at the baseline time point, but have advanced to the next educational level at the one year follow-up time point. In this British system of education, Nursery is equivalent to American kindergarten, Primary to elementary school, and Secondary to high school. The variety of subjects taught and method of assessment was significantly varied based on age, school, and teacher, necessitating a standard scale by which all reports could be compared.

The Ugandan Ministry of Education and Sports (MOES) set forth a standard of performance that recommended five categories of performance. Schools could use numeric

scores based out of fifty or one hundred (i.e., 45/50 or 75/100), categorical scores using letters (i.e., A, B, C), descriptive scores (i.e., Needs help, Excellent), or a combination of all three scales. With the help of Ugandan research team members who were familiar with the school system, a standardized ordinal scale was created based upon the MOES recommendations. The scale can be found in Table 8. Whether the school reports included numeric, categorical, or descriptive scores, this scale allowed the grades to be consistently delineated on a 5-point ordinal scale. It was on the ordinal values 1-5, that analyses for this study were run.

Table 8. Grading Scale

Grading Scale					
Scale:	**1**	**2**	**3**	**4**	**5**
Numeric (out of 100)	0-49	50-59	60-69	70-79	80-100
Categorical	E	D	C	B	A
Descriptive	Needs Help	Fair	Good	Very Good	Excellent

Home Environment

The Caldwell Home Observation Measurement of the Environment (HOME) scale is a structured inventory that rates an individual's home environment based on opportunities for learning and cognitive stimulation (Bradely, Caldwell, Brisby, Magee et al, 1992). This assessment serves to analyze homes, not based on income level, but based on available cognitive stimulation in the home (Bradely, Caldwell, Rock, Hamrick & Harris, 1988). The items on this measure are grouped into eight subscales: Emotional and Verbal Responsivity, Encouragement of Maturity, Emotional Climate, Growth-Fostering Materials and Experiences, Provision for Active Stimulation, Family Participation in Developmentally Stimulating Experiences, Paternal Involvement, and Aspects of the Physical Environment. Bangirana and others have previously

adapted (including standardized translation/back translation and item evaluation and adaptation based on focus groups) and then validated it, demonstrating it to be an acceptable measure of home impact on cognitive development in Uganda (Bangirana, John, Idro et al, 2009).

Socio-Economic Status (SES)

Socio-economic status (SES) was a score determined by a structured inventory taken of the material possessions present in the child's home and the type of living structured they inhabited at baseline (Boivin et al., 2010). Quality of the living structure, living density, food accessibility, facilities for bathing and cooking, as well as access to electricity and clean water were also recorded.

Non-Verbal Index (NVI)

The Non-Verbal Index (NVI) variable from the Kaufman Assessment Battery for Children, Second Edition (KABC-II), was used to assess the children's basic cognitive processing/intellectual ability (Kaufman & Kaufman, 2004). The NVI score was chosen as a summary score from this battery because of its ability to assess cognitive aptitude, even when English may not be the primary language of the child. This measure has been assessed and validated for use among Ugandan children (Semrud-Clikeman, Regilda, Shapiro, Bangirana, & Chandy, 2016). The NVI was included in this study's analysis to allow for examination of change in academic performance adjusting for baseline intellectual functioning.

Analysis

The software program R was used to conduct analyses of the study objectives. For the first and second objectives, multiple linear regression analysis was performed on the school reports collected. This method was chosen for the ability to assess the effect of two or more variables (diagnosis, treatment arm, socio-economic status, etc.) on the outcome variable

(academic achievement score change). The regression outcome variable was the change score within each academic domain. For example, to create a change score for writing, the ordinal value from baseline writing was subtracted from the ordinal value of writing at one year (Time 2 minus Time 1), creating a continuous response variable. Within the dataset, a variable was created for the interaction between diagnosis group and treatment arm to explore the effect of the interaction between SM/CC and the Intervention Arm, Active Control Arm, and Passive Control Arm. The academic change score was the response variable in the linear model with diagnosis group, treatment arm, diagnosis/treatment interaction, SES, gender, home environment, and NVI at baseline as explanatory variables.

For the third objective, Kendall's Tau correlation tests were done in order to determine if a correlation existed between the number of successfully completed modules of CCRT and the amount of change in academic performance from baseline to one year. A set of summary success scores from each of the six training domain outcomes of the CCRT program were used as measures to compare with academic performance. The six measures were memory, concentration, visual acuity, problem solving, auditory processing, and self-efficacy.

Results

The first objective of this study was to determine if CCRT improves academic performance and has functional impact on Ugandan children's quality of life after adjusting for moderating variables (i.e. age, gender, home environment, socio-economic status, and intellectual ability). Of the 300 enrolled in the parent RCT, school reports were collected at baseline and one year for 161 children. School reports for both time points (baseline and one year) were collected for seventy-four pediatric survivors of SM and eighty-seven children in the CC group. The reasons for missing reports can be found in Table 9. The most common reason

was that the reports had been lost by the caregiver and the caregiver was unable to obtain a copy from the child's school.

Table 9. Summary of Missing School Reports

Missing School Reports			
Missing Reason	**@ Baseline**	**@ Follow Up**	**Total**
Damaged/destroyed	3	1	*3*
Lost	7	45	*75*
Not in School	21	16	*25*
Death	3	3	*3*
Inability to Contact Caregiver/Family Moved	20	22	*26*
Unpaid School Fees	6	6	*7*
Total	*127*	*93*	*139*

The number of reports collected by intervention training arm can be found in Table 10. Descriptive statistics provided demographic results on the study sample as well as the sample used in the RCT (Table 11). Of note, in this study sample, the HOME score was significantly lower among the SM group than the CC group, and the SM group was nearing significance for a lower percentage of girls compared to boys.

Table 10. Summary of School Reports by Intervention Arm

Sample by Arm		
	Severe Malaria	**Community Controls**
N	74	87
Active Intervention	27	37
Active Control	28	27
Passive Control	19	23

Each academic domain was a unique regression model, and the results of these analyses can be found in Table 12. Contrary to expectation, there was no statistically significant main effects or interactions for diagnosis group and treatment arm on academic change in this population. For these models, results are discussed in terms of positive or negative "effects." These effects refer to the amount and direction of change that would occur in the dependent variable (ex. Writing Change) if there was a one unit change in the independent variable (ex. SES) and all other variables were held constant. Writing and Arithmetic were the only two domains with effects nearing significance in demographic effects, (P<0.071) for Home environment and (p<0.075) for sex, respectively. The negative effect of the interaction term between diagnosis and treatment arm (P<0.066) in the English domain was also nearing significance.

Table 11. Demographic Characteristics

Demographic Characteristics						
	RCT			**Sample**		
	Severe Malaria	**Community Controls**	***p* <**	**Severe Malaria**	**Community Controls**	***p* <**
N	150	150		74	87	
Age years (Mean (SD))	6.97 (1.63)	7 (1.94)	0.898	7.15 (1.76)	7.10 (2.04)	0.882
Sex (% female)	59 (39.3)	83 (55.3)	***0.008***	29 (39.2)	48 (55.2)	*0.062*
Socioeconomic Status (Mean (SD))	9.75 (2.99)	10.04 (3.07)	0.413	10 (3.07)	10.3 (3.08)	0.539
Home Environment (Mean (SD))	37.2 (12.26)	41.03 (11.78)	***0.006***	37.71 (11.53)	41.99 (12.25)	***0.025***
Non-Verbal Index (Mean (SD))	24.08 (7.00)	25.07 (8.34)	0.265	24.09 (7.45)	26.14 (8.76)	0.117

The lack of statistically significant results prompted further exploration into the data. Descriptive statistics were done on the change scores to examine average change within domain and can be found in Table 13. A change in NVI score from baseline to one year was also included to see if changes in a neuropsychological summary score were similar to the academic change scores. The average change was positive, with the exceptions of Arithmetic and NVI, but mean change scores were very small compared to their standard deviations, suggesting marked differences in the scores, as reflected in their ranges presented in the Table 13

A third objective to this study was to explore the relationship between the level of success in CCRT, determined by module completion, and the degree of performance change within academic domains. Scatter plots were used to visualize the relationship and Kendall's Tau correlation tests were used to assess each training measure with each academic domain for correlating effects. The scatter plots indicate that there was no linear relationship between CCRT success measures and change in academic performance. The Kendall's correlation analysis confirmed that there was no significant relationship. To provide a sample of the relationship, scatter plots of the relationship between CCRT and change in Arithmetic can be found in Figure 4. The scatter plots of the other academic domains were similarly distributed. These results are consistent with the linear regression above in noting no statistically significant change in academic performance. The majority of academic performance scores cluster around zero, regardless of level of CCRT success, and thus no positive or linear relationship could be associated between academic performance and CCRT success. Additionally, across academic domains, success in the auditory training module was notably less than all other categories.

Discussion

The effects of diagnosis group and treatment arm were not significant across academic domains. The hypothesis that children who have suffered cognitive damage from SM and are trained with the titrated version of CCRT would experience a greater degree of academic change than healthy CCs could not be statistically supported through the data and methods used. Sex nears statistical significance for having a negative effect on Arithmetic scores. For this sample, being female was significantly associated with poorer performance in Arithmetic at the one year follow-up compared to baseline. Home environment was approaching statistical significance for having a positive effect on writing change over time. For this sample of Ugandan children, a higher score from the HOME measurement (i.e., more cognitive stimulation in the home), may contribute to improved performance in Writing from baseline to one year follow-up, regardless of CCRT training arm.

Though previous studies have identified differences in cognitive performance between survivors of SM and CCs, school performance as a measure of cognitive competency was not able to identify similar differences between groups. The parent RCT discovered that non-titrated CCRT carried greater benefits than titrated CCRT for certain outcomes with survivors of SM, such as mental and sequential processing and psychomotor function. The outcomes of the regression analysis, however, found no statistically significant change in academic performance, positive or negative, for children based on their diagnosis status or training arm.

Building an ordinal scale, even though it was based on Ugandan standards, may have limited the ability for statistically relevant data to be explored. This study was not able to establish an effect of CCRT training on performance in the Ugandan classroom, nor was a relationship found between a child's success in progressing through the training and their

performance in the classroom. What was found, though, was consistent with the knowledge that girls are at a greater disadvantage to excel in Arithmetic than their male counterparts. Also that the cognitive stimulation and parental involvement at home plays a substantial role in a child's potential for optimal cognitive development. It must also be noted, that the level of success on modules requiring auditory processing was notably behind those focusing on other domains. This could be due to language barriers between the child and program or an environment that challenged the child's ability hear the program and thus be successful. These results may further inform the practice and utilization of interventions, such as CCRT, among pediatric populations in LMICs, as the influence of home and culture on cognition, and thus academic performance, are taken into account.

Electronic devices have increased in access and availability, as has availability to broad band networks, but determining the everyday impact of health-related interventions is critical prior to advocating for widespread dissemination of such interventions. Researchers must actively seek to ensure their work and interventions are meeting a legitimate need of certain populations. Interventions must be need-driven, for unless there is a need that can be quantifiably met, health-promoting interventions may not actually be serving the community's need to their best potential. The need for some approach to cognitive rehabilitation has been identified in that one in four pediatric survivors are found to have decreased cognitive performance. And now, the impact of parental involvement in the home and equity of achievement between boys and girls in the classroom is seen to play a role in the functional impact of CCRT among this population. This understanding can facilitate future development and implementation of computerized interventions targeting cognitive skills for academic performance in the classroom.

Limitations

There were limitations to this study that may provide explanation to the lack of statistical significance for these analyses. The post-hoc collection of data for analysis prevented a comprehensive collection of all school reports for all children in the RCT. Secondly, collection of teacher/caregiver-provided school reports prevented the ability to ensure accuracy across reports. Due to the variety of school settings, teachers grading techniques, and subjects taught, there were limitations as to how well the children's school reports could be standardized and appropriately compared with one another.

Conclusion

In conclusion, this study has provided preliminary insight into the challenges of assessing the functional impact of CCRT in non-research and non-clinical settings for pediatric populations. Health-related interventions, especially among vulnerable populations, need to be fully understood for their potential and ability to be generalized beyond the research environment. It would be beneficial for future examinations of the functional impact of CCRT to develop a validated English and Luganda-based academic assessment that can be implemented in private and public schools. This assessment could either be refined by government standards or developed by the investigators and distributed to teachers who are trained to use it. This may allow for the development of a standardized tool with which Ugandan classroom performance could be used as a measure of cognitive competency and functional impact of cognitive interventions. This approach would control for a significant amount of variation that was found between academic reports and increase the confidence in the degree of functional impact that CCRT can have on pediatric survivors of SM in Uganda.

Nurses are in a pivotal role to participate in and move this type of research forward. The scope of nursing prioritizes the patient above all else. This mindset can assist the process of identifying appropriate measurement, assessment, and implementation approaches for computerized interventions, such as CCRT. The lens of nursing serves to partner well with other disciplines in tackling the challenges of computerized intervention implementation in LMICs. This interdisciplinary approach will strengthen the endeavors of health scientists as they seek to improve the quality of life for this vulnerable population.

Table 12. Significance of Effects from Linear Regression

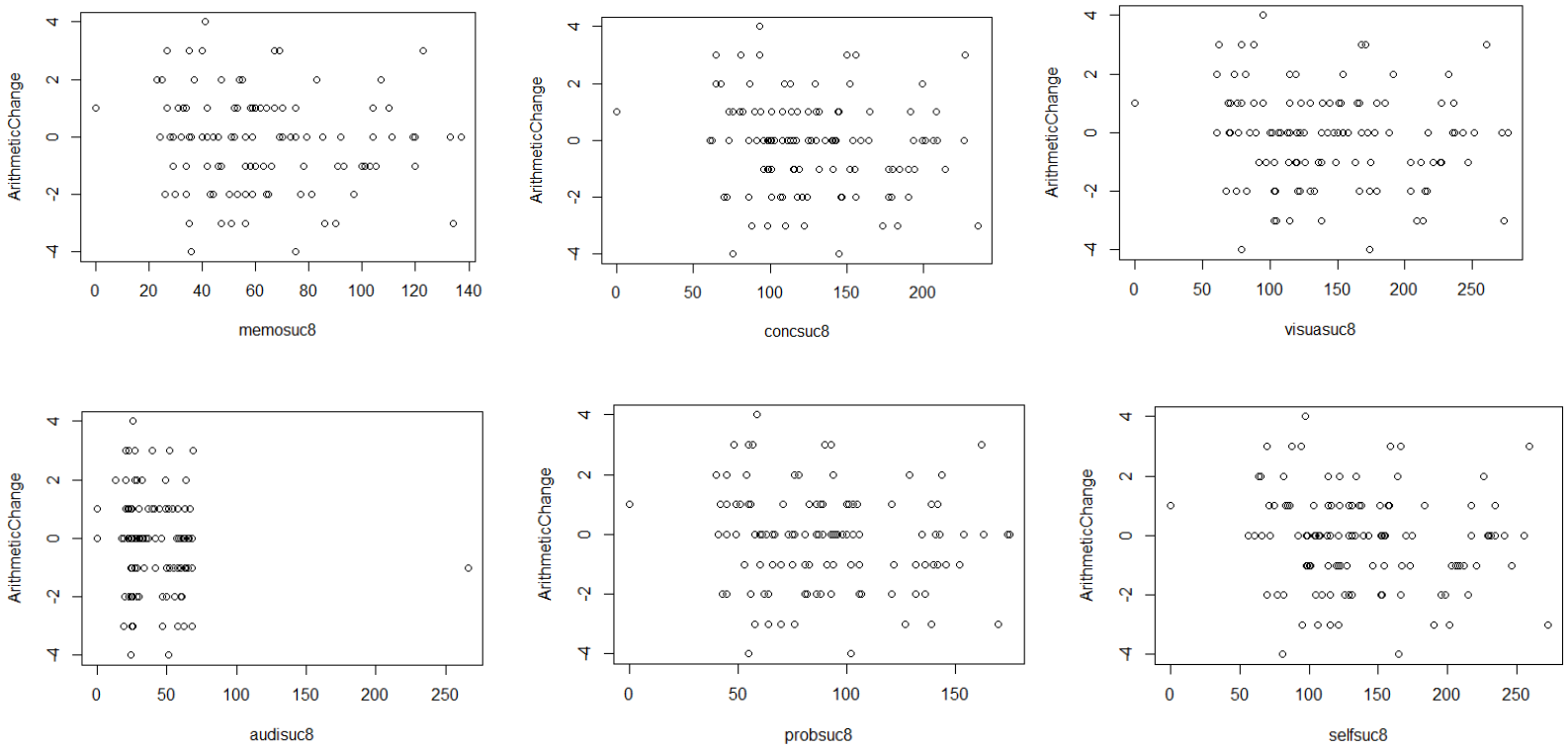
Linear Regression Effects										
	Writing Change		**Reading Change**		**English Change**		**Arithmetic Change**		**Luganda Change**	
	N = 63		**N = 93**		**N = 111**		**N = 153**		**N = 38**	
	Estimate	P-Value	Estimate	P-Value	Estimate	P-Value	Estimate	P-Value	Estimate	P-Value
SM Group	-0.679	0.332	-0.171	0.763	0.761	0.153	-0.233	0.608	-0.787	0.505
Active/Titrated CCRT	0.448	0.431	0.187	0.687	0.654	0.133	-0.025	0.945	-0.715	0.444
Passive/Non-Titrated CCRT	0.758	0.360	0.165	0.553	0.709	0.208	-0.387	0.406	-0.407	0.715
Dx/Tx Interaction	0.159	0.759	-0.026	0.953	-0.733	***0.066***	0.000	0.999	0.560	0.513
SES	-0.041	0.555	0.012	0.850	-0.051	0.355	-0.011	0.796	-0.009	0.933
Sex	-0.124	0.766	0.044	0.901	-0.130	0.690	-0.470	***0.075***	-0.464	0.509
HOME	0.029	***0.071***	0.015	0.304	-0.007	0.591	-0.006	0.5838	-0.026	0.371
NVI	-0.017	0.525	0.003	0.896	-0.023	0.245	-0.023	0.172	0.002	0.965

Table 13. Average Academic Change from Baseline to One Year

Average Academic Chance					
	N	**Mean**	**Standard Deviation**	**Minimum**	**Maximum**
Writing Change	63	0.06	1.49	-3	4
Reading Change	93	0.22	1.55	-4	4
English Change	111	0.02	1.58	-4	4
Arithmetic Change	153	-0.12	1.58	-4	4
Luganda Change	38	0.03	1.79	-3	4
NVI Change	161	-0.23	7.5	-20	25

Figure 4. Arithmetic Change Score by CCRT Success Measures

Arithmetic Change Score by CCRT Success Measures



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CONCLUSION

In sum, severe malaria (SM) is a global problem and significant burden is carried by low- and middle-income countries (LMICs). Though forty percent of the world lives in malaria endemic areas, over ninety percent of reported cases of malaria occur in the countries of Africa. Despite optimistic efforts of prevention, education, and eradication, malaria continues to afflict populations with increasing levels of prevalence. Thankfully, the availability of anti-malarial therapies is continuing to increase, meaning that even though prevalence remains higher than desired, mortality rates due to malaria are dropping.

As noted earlier, children are particularly vulnerable to malaria. The increasing prevalence rate, partnered with the increased access to life-saving treatments, has led to more and more children living through severe episodes of malaria. The impact of the illness, however, leaves its mark through detrimentally effecting the child's cognitive competency. This manifests through impaired cognition, behavioral functioning, and motor control deficits. Physical therapy is has been utilized for children suffering severe physical effects from SM, but limited work has been done to address the cognitive impairments following illness. Computerized cognitive rehabilitation therapy (CCRT) could be a promising intervention for its ability to target areas of cognitive function—memory, attention, executive function—and facilitate neuronal development through various training modules.

School performance among children who were survivors of SM and exposed to CCRT was the primary object of interest during this research. A child's achievement within the classroom was studied for its potential to serve as a measure of cognitive competency following a child's training with CCRT. Cognitive competency refers to the overall ability of a child to perform at a developmentally appropriate level in skills of motor, behavioral, and cognitive domains. School performance was chosen as a measure of cognitive competency due to its potential ability to provide a picture of CCRT's functional impact upon a child's daily life.

To assess the functional impact of CCRT on cognitive competency, qualitative and quantitative efforts were pursued to provide a broad understanding of this problem and a proposed solution. In the qualitative analysis, it was found that Ugandan professionals were hopeful for the implementation of CCRT in the school systems. They also identified likely barriers that could be encountered in the dissemination process—such as resource availability and geographical challenges. The next study explored differences in academic performance among children who were survivors of SM and those who were CCs. An ordinal scale was created based on MOES recommendations and ordinal regression was utilized to identify any differences. From this initial analysis, a statistically significant effect on performance ability between SM survivors and CC children could not be determined. Though differences in academic performance were not found among this population at baseline, the impact of CCRT was still uncertain. Thus, a final study was conducted to examine the influence of CCRT on academic performance over time. Similar to the second study, statistically significant effects of CCRT and diagnosis group were not found on the academic performance measures of change.

The results of this research did not support the guiding hypotheses that children who are survivors of SM would experience greater benefit from titrated CCRT than CC children or a non-

titrated version of CCRT. The results did, however, provide greater insight into multiple aspects of CCRT research. First and foremost, this research demonstrates the importance of including a measure of functional impact with interventions such as CCRT. Researchers must be able to identify tangible improved health outcomes or activities of daily living (ADLs) in their patient population. This study was a first attempt to measure functional impact within the existing educational structure. The hope was to provide insight into CCRT's tangible effects on children's academic performance and thus, their ADLs. This research also demonstrates the importance of data collection in the moment of interest. Though a post hoc analysis was all that was feasible for this trial, the retrospective nature of data collection may have contributed to limited control over the data. Despite the challenges of post hoc analysis, the number of school reports that were recovered for analysis is truly remarkable. The ability of the caregivers to provide school reports from months and years past speaks to the value these families place on providing their child with an education. Many mothers, fathers and grandmothers were proud to present the folder that held each report they had received from their child's school. This pride is often driven by a hope that their children will continue to learn, grow, and advance in their educational pursuits.

It is for this purpose, to partner with the deep desire of caregivers to promote optimal learning, development and quality of life for children, that a full understanding of the functional impact of CCRT is necessary. This research was limited in its ability to determine specific effects of CCRT on academic achievement, but the need is still present. Ongoing, interdisciplinary research is necessary to move this intervention forward as a quality of life-improving instrument. As evidenced by the comments of doctors, nurses, teachers, and neuropsychological experts in the qualitative study, each discipline approaches the cognitive needs of children differently, but their individual training provides unique awareness into the

potential and capability of CCRT among Ugandan children. The scope of nursing must be an active and participating voice in the ongoing research and care of these children. Nurses are uniquely equipped to step into interdisciplinary areas of research and improve the various methodological and measurement approaches due to their patient- and family-centered lens. Not only are nurses a vital asset to a team of health scientists, but they also serve to inform the various disciplines involved. As nursing is foundational to healthcare—especially in LMICs—they act as natural mediators between other health care disciplines, such as medicine, psychology, social work and pharmacy. A team such as this is capable of overcoming the challenges that were faced in this research and determining the true functional impact of CCRT among healthy and sick children.

There are many steps to be taken to continue exploring the functional impact of CCRT and improving the quality of life for Ugandan children who are survivors of SM. The first step is establishing a team of stakeholders who are dedicated to the health promotion of this population. A team of health and education experts, as well as government officials and caregivers in the community would have the potential to encounter and overcome barriers of further implementation and dissemination. This type of team, possibly pursuing community-based participatory research methods, has potential to engage the community at all levels to promote effective and sustainable cognitive health promotion interventions for children.

Next steps in reforming and refining CCRT for this population could focus on ensuring an appropriate setting for administration. Specifically, areas related to classroom versus tutoring, module focus, and titration effects of training. Do children enjoy the training because of the one-on-one attention that is provided or would CCRT be effective in a large group setting? Does the limited success in auditory processing demonstrate a language barrier or environmental

challenges? In what ways do titrated verse non-titrated CCRT training influence cognitive competency and how will the relationship influence theoretical underpinnings of brain plasticity? These questions are only the beginning of those that need to be further explored.

APPENDICES

Appendix A.

Mulago CCRT R01 Data Request Form

Send to Alex Mutebe (mutebe2@gmail.com), with copy to Dr. Michael Boivin (Michael.Boivin@hc.msu.edu), Dr. Bruno Giordani (giordani@med.umich.edu), and Dr. Horacio Ruisenor (horaciore@gmail.com) so that they may approve the request.

Name of requester: Katherine Finn

Date of request: March 15, 2017

Requested format: STATA _____ SPSS _____ **Excell**

Please answer briefly the following questions:

1. What are your overall goals, specific aims and hypotheses?
    a. Aim 1: Evaluate functional impact of CCRT in pediatric survivors of severe malaria.
        i. Hypothesis 1: Children who have survived severe malaria will demonstrate relatively greater improvement in academic performance following CCRT than healthy controls.
        ii. Hypothesis 2: The greatest improvements in academic performance will occur in children who have been diagnosed with cerebral malaria

compared to children diagnosed with severe malaria anemia or healthy controls.

   b. Aim 2: Investigate training success of CCRT and its impact on academic improvement.
      i. Hypothesis 1: A positive relationship is expected between CCRT success and academic performance.

2. Who are your collaborators and who on the team are you including and who is the person responsible for the data? If a student, who is your mentor who is taking responsibility for the project?

   a. I, Katherine Finn, will be responsible for the data. My PhD mentor is Dr. Giordani. Committee members who will be assisting in this research endeavor include Dr. Barry Fishman, Dr. Jody Lori, and Dr. Chris Liu.

3. Do you have IRB approval for a post-hoc analysis?

   a. Yes.

   b. HUM00071923 - Computerized Cognitive Rehabilitation in Children after Sever e Malaria

4. Do you have papers planned and tentative author lists?

   a. With this data, I plan to write my dissertation which will be composed of 3 papers.

      i. Paper #1: Children CCRT Literature review with emphasis on underserved and underdeveloped populations.
      ii. Paper #2: Academic performance at baseline across diagnostic groups considering demographic and illness factors – descriptive
      iii. Paper #3: Relationship between change in training success and academic performance - outcomes

   b. The tentative list of authors will be my committee members: Dr. Barry Fishman, Dr. Jody Lori, Dr. Chris Liu, and Dr. Bruno Giordani.

Please indicate what time points and variables are required to conduct analyses

Data Needed (check all that apply)

	Malaria	**Controls**
Baseline	√	√
Post-intervention		
12 Months	√	√

CCRT R01

- Physical Exam
- Labs
- TOVA
- KABC
- BOT
- BRIEF
- CBCL
- Ten Questions Questionnaire
- MC-HOME √
- SES √
- Captain's Log √
- Cogstate

Appendix B.

Institutional Review Board Approval

3/30/2017

Print: HUM00071923 - Computerized Cognitive Rehabilitation in Children after Severe Malaria

https://errm.umich.edu/ERRM/ResourceAdministration/Project/PrintSmartForms?Project=com.webridge.entity.Entity%5BOID%5BA016ED63BD8C284… 1/13

Date: Thursday, March 30, 2017 3:07:35 PM Print Close 01. General Study Information

All questions marked with a red asterisk (*) require a response. Questions without a red asterisk may or may not require a response, depending on those questions' applicability to this study.

1.1* Study Title: Computerized Cognitive Rehabilitation in Children after Severe Malaria

1.1.1 Full Study Title: Computerized Cognitive Rehabilitation in Children after Severe Malaria

1.1.2 If there are other U-M studies related to this project, enter the eResearch ID number (HUM#) or IRBMED Legacy study number. Examples of related projects include, but are not limited to: Projects funded under the same grant

IRBMED Legacy study being migrated into eResearch

Previously approved Umbrella applications (such as Center Grants or approvals for release of funding) Previously approved projects for which this is a follow up study

1.2* Principal Investigator:

Bruno Giordani Note: If the user is not in the system, you may Create A New User Account...

1.3 Study Team Members: Study Team Member Study Team Role Appointment Dept Appointment Selection Complete? Student Friend Account COI Review Required Edit Rights Accepted Role? PEERRS Human Subjects?

Bruno Giordani

PI Psychiatry Department

Yes no No no yes N/A yes

Michael Boivin

CoInvestigator

Psychiatry Department

Yes no No no yes Yes yes

Katherine Finn

CoInvestigator

No yes No no yes Yes yes

1.8* Project Summary:

150 children with severe malaria (both cerebral malaria and severe malarial anemia) and 150 community control children will be recruited and randomly assigned to one of the following thre e

study arms: a cognitive rehabilitation arm, an active control arm that receives a none-therapeutic computer training, or a passive control arm that receives no treatment. Pre-intervention cognitive and psychiatric assessments will be done prior to the intervention. Post-intervention assessments will be done a week after completion of the intervention training and at a one year follow-up visi t.

Repeated measures analysis of variance and structural equation modeling will be used analyze ai ms 1 and 2 respectively.

Projedt PI is Dr. Michael Boivin at Michigan State University. Dr. Giordani's role is to assist wit h project set up and then to assist with data analysis and report preparation. No HIPPA-related information will be reviewed or kept at UM. Dr. Giordani will only review de-identified data sets stored on MSU server.

1.9* Select the appropriate IRB: IRBMED

1.10* Estimated Study Start Date (Not required for IRBMED): (mm/dd/yyyy) 2/28/2012

1.11* Estimated Duration of Study: 1/31/2016

01-1. Application Type

1-1.1* Select the appropriate application type. Standard, non-exempt, research project

3/30/2017

Print: HUM00071923 - Computerized Cognitive Rehabilitation in Children after Severe Malaria

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webridge.entity.Entity%5BOID%5BA016ED63BD8C284… 2/13

Date: Thursday, March 30, 2017 3:07:35 PM Print Close 01-2. Standard Study Information

1-2.1* Who initiated this study? Other

If other, please specify: Overall Project PI Dr. Michael Boivin initiated this study.

1-2.2* Are you or any students working on this project being paid from a federally funded training grant? Yes No

1-2.3 This study is currently associated with the following department. To associate this research with a different department, click Select. If the department has defaulted to "student", click select to specify the department through which this application is being submitted. Psychiatry Department

1-2.4 Will the study utilize resources from the following centers? Select all that apply:

There are no items to display

1-2.5* Does this study require review by the UM Health System Comprehensive Cancer Center Protocol Review Committee (PRC)? Yes No

1-2.6* Has the scientific merit of this study already been peer reviewed (i.e., reviewed by one or more recognized authorities on the subject)? Yes No

1-2.6.1* List the peer-review organization(s). Peer Review Organization

External sponsor review process (e.g. study selection)

1-2.7* Is this a clinical trial? Yes No

1-2.8* Would the integrity of this research study be compromised if the subject were able to view results of their research tests or medications in the Patient Portal of MyUofMHealth.org? Research results displayed to the subject in MyUofMHealth.org will include: lab results, radiology examinations and outpatient medication lists. Contracts and protocols should be assessed by the Principal Investigator for specific language regarding blinding of subjects and their research results.

(NOTE: Additional actions are required in order to limit the subject's view into their electronic medical record. Contact the IRB for additional information or see additional guidance for blinded studies at https://research.medicine.umich.edu/officeresearch/institutional-review-boards-irbmed/guidance/blinded-studies) Yes No

3/30/2017

Print: HUM00071923 - Computerized Cognitive Rehabilitation in Children after Severe Malaria https://errm.umich.edu/ERRM/ResourceAdministration/Project/PrintSmartForms?Project=com.webridge.entity.Entity%5BOID%5BA016ED63BD8C284… 3/13

Date: Thursday, March 30, 2017 3:07:35 PM Print Close Study Team Detail

1.4 Team Member: Bruno Giordani Preferred email: giordani@umich.edu Business phone 734-764-3169 Business address:Neuropsychology Clinic2101 Commonwealth Ste C48105-5716

1.5 Function with respect to project: PI

1.6 Allow this person to EDIT the application, including any supporting documents/stipulations requested during the review process: Yes

Credentials: Required for PI, Co-Is and Faculty Advisors

Upload or update your CV, resume, or biographical sketch. Name Version

Dr. Bruno Giordani CV | History 0.01

Conflict of Interest Detail: Required for all roles except Administrative Staff

Current Disclosure Status in M-Inform: This study team member has disclosed outside interest(s) or relationship(s) in M-Inform.

D1 Do you have an outside interest or relationship with a non-UM entity that relates to this research in one of the following ways: The entity is sponsoring this research

The entity's products are used in this research

The entity has licensed your invention (e.g. device, compound, drug, software, survey, evaluation or other instrument) being used in this research

Part of the work on this project will be subcontracted to the outside entity

Other relationship not listed above

No

D2 If "Yes" to the question above, name the entity or entities and provide a brief description of the relationship(s).

1.4 Team Member: Michael Boivin Preferred email: michael.boivin@ht.msu.edu

Business phone 517-432-4204 Business address:Psychiatry

909 Fee Rd - 321 West Fee Hall48824

1.5 Function with respect to project: Co-Investigator

1.6 Allow this person to EDIT the application, including any supporting documents/stipulations requested during the review process: Yes

1.7 Include this person on all correspondences regarding this application: (Note: This will include all committee correspondence, decision outcomes, renewal notices, and adverse event submissions.) Yes

Credentials: Required for PI, Co-Is and Faculty Advisors

Upload or update your CV, resume, or biographical sketch. Name Version

BoivinBiosketchHIV14April11 | History 0.01

Conflict of Interest Detail: Required for all roles except Administrative Staff

Current Disclosure Status in M-Inform: This study team member has not yet disclosed in MInfo rm.

D1 Do you have an outside interest or relationship with a non-UM entity that relates to this research in one of the following ways: The entity is sponsoring this research

The entity's products are used in this research

The entity has licensed your invention (e.g. device, compound, drug, software, survey, evaluation or other instrument) being used in this research

Part of the work on this project will be subcontracted to the outside entity

Other relationship not listed above

D2 If "Yes" to the question above, name the entity or entities and provide a brief description of the relationship(s).

3/30/2017

Print: HUM00071923 - Computerized Cognitive Rehabilitation in Children after Severe Malaria

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Date: Thursday, March 30, 2017 3:07:35 PM Print Close Study Team Detail

1.4 Team Member: Katherine Finn Preferred email: kgfinn@umich.edu Business phone Business address:UMH Nursing Administration300 N. Ingalls48109-5436

1.5 Function with respect to project: Co-Investigator

1.6 Allow this person to EDIT the application, including any supporting documents/stipulations requested during the review process: Yes

1.7 Include this person on all correspondences regarding this application: (Note: This will include all committee correspondence, decision outcomes, renewal notices, and adverse event submissions.) Yes

Credentials: Required for PI, Co-Is and Faculty Advisors

Upload or update your CV, resume, or biographical sketch. Name Version Finn.CV | History 0.03

Conflict of Interest Detail: Required for all roles except Administrative Staff

Current Disclosure Status in M-Inform: This study team member has indicated in M-inform that they do not have any outside interests to disclose.

D1 Do you have an outside interest or relationship with a non-UM entity that relates to this research in one of the following ways: The entity is sponsoring this research

The entity's products are used in this research

The entity has licensed your invention (e.g. device, compound, drug, software, survey, evaluation or other instrument) being used in this research

Part of the work on this project will be subcontracted to the outside entity

Other relationship not listed above

No

D2 If "Yes" to the question above, name the entity or entities and provide a brief description of the relationship(s).

3/30/2017

Print: HUM00071923 - Computerized Cognitive Rehabilitation in Children after Severe Malaria

https://errm.umich.edu/ERRM/ResourceAdministration/Project/PrintSmartForms?Project=com.webridge.entity.Entity%5BOID%5BA016ED63BD8C284… 6/13

02. Sponsor/Support Information

The following sections request details about the current or pending sponsorship/support of this st udy. Consider all of the choices below and complete the appropriate sections.

* Note: At least one of the following sections must be answered. Multiple sponsors or sources of support must be added one at a time.

2.1 External Sponsor(s)/Support: Type Name Other Direct Sponsor/Support

Support Type

Has PAF?

View Government - Federal without Stimulus Plan (American Recovery and Reinvestment Act) funding

Health and Human Services (HHS), Department of-National Institutes of Health

Financial yes

2.5 Internal UM Sponsor(s)/Support: [Including department or PI discretionary funding] Type

Department Sponsor Support Type There are no items to display

2.8 Check here if the proposed study does not require external or internal sponsorship or support:

External Sponsor Detail

2.2* Direct Sponsor/Support:

Health and Human Services (HHS), Department of-National Institutes of Health

If the Direct Sponsor/Support does not appear in the Select list, enter the name of the Direct Sponsor/Support below:

2.2.1* Sponsor Type:

Government - Federal without Stimulus Plan (American Recovery and Reinvestment Act) fundin g

If other, please specify:

2.2.2* Support Type: Financial

2.2.3* Is the support confirmed? Yes No

2.2.4* Is there an existing Proposal Approval Form (PAF) for this IRB Application Yes No

2.2.5* Please select the PAF(s) associated with this study. Clicking the Add button will allow for the selection of a PAF based on selected criteria. After the PAF(s) has been associated with the human subjects research application, clicking on the PAF link will

access the Proposal Management system and will display the current PAF information.

Access to the PAF is based on account information in the Proposal Management system.

Proposal ID 10-PAF05773 09-PAF02252 08-3079

2.3* Is this a subcontract to UM? Yes No

2.3.1* Indicate the Prime Sponsor/Support (the original source of funding):

Health and Human Services (HHS), Department of-National Institutes of Health

If the Prime Sponsor/Support does not appear in the Select list, enter the name of the

Prime Sponsor below:

2.3.2* Prime Sponsor Type:

Government - Federal without Stimulus Plan (American Recovery and Reinvestment Act) fundin

g

2.3.3* Prime Support Type: Financial

2.3.4* Is the Prime Support confirmed? Yes No

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03. UM Study Functions

3.1* Indicate all functions that will be performed at University of Michigan locations.

Select all that apply: Other

If other, please specify. "No" - Data storage and analyses to be completed at MSU. UM is a consultation site and for review for de-identified data and results.

03-1. Performance Sites

3-1.1* Performance Sites: Location Country "Engaged" in the research?

Performance Site Type

Site Function

Makerere School of Medicine

Uganda yes Qualitative research,Intervention,Storage,Interaction,Analysis,Observation,Recruitment

Michigan State University

USA yes Analysis,Coordinating Center

University of Michigan

USA no Other

Performance Site Detail

3-1.2* Location or Institution: Makerere School of Medicine

3-1.3 Address: City kampala State Country*Uganda

3-1.4* Function of this location with respect to this study: Select all that apply:

Recruitment (including screening)

Interaction (e.g., information gathering, survey, interview, focus groups, etc.)

Intervention (e.g., use of drug or device, medical procedures, educational intervention, group intervention, social/psychological intervention etc.) Observation of behavior (direct or indirect)

Qualitative research (e.g., 'member checking', open-ended questions, etc.)

Primary or secondary analysis (data/specimen)

Storage (data and/or specimen): Responsible for the management, security and transfer of study data and/or specimens.

If other, please specify:

3-1.5* Will this site be "engaged" in the conduct of the research? Yes No

3-1.6 If known, provide the Federalwide Assurance (FWA) number for this location. 0000 1293

3-1.7 If applicable, indicate what organization, agency or government office has reviewed this research and provided its approval (e.g., IRB, ethics committee, school district office, prison official, nursing home administrator).

Ugandan National Council for Science

3-1.8 Upload any location site approval documentation here: Name Version

20120529CCRT_UNCST renewal.pdf | History 0.01

approvalLetterapprovalLetterCCRT_RO1_SOMREC_amendmanet 2012.pdf | History 0.01

3/30/2017

Print: HUM00071923 - Computerized Cognitive Rehabilitation in Children after Severe Malaria

https://errm.umich.edu/ERRM/ResourceAdministration/Project/PrintSmartForms?Project=com.

webridge.entity.Entity%5BOID%5BA016ED63BD8C284… 8/13

Performance Site Detail

3-1.2* Location or Institution: Michigan State University

3-1.3 Address: City east laning State MI Country*USA

3-1.4* Function of this location with respect to this study: Select all that apply:

Primary or secondary analysis (data/specimen)

Coordinating Center (of multiple engaged sites, e.g. statistical, data coordination, lead, or operations center)

If other, please specify:

3-1.5* Will this site be "engaged" in the conduct of the research? Yes No

3-1.6 If known, provide the Federalwide Assurance (FWA) number for this location. 0000 4556

3-1.7 If applicable, indicate what organization, agency or government office has reviewed this research and provided its approval (e.g., IRB, ethics committee, school district office, prison official, nursing home administrator). IRB

3-1.8 Upload any location site approval documentation here: Name Version 19Nov12BIRB r040893_Renewal letter.pdf | History 0.01

Performance Site Detail

3-1.2* Location or Institution: University of Michigan

3-1.3 Address: City State Country*USA

3-1.4* Function of this location with respect to this study: Select all that apply: Other

If other, please specify:

"No" - Data storage and analyses to be completed at MSU. UM is a consultation site and for revi ew for de-identified data and results.

3-1.5* Will this site be "engaged" in the conduct of the research? Yes No

3-1.6 If known, provide the Federalwide Assurance (FWA) number for this location.

FWA00004969

3-1.7 If applicable, indicate what organization, agency or government office has reviewed this research and provided its approval (e.g., IRB, ethics committee, school district office, prison official, nursing home administrator).

3-1.8 Upload any location site approval documentation here: Name Version

There are no items to display

3/30/2017

Print: HUM00071923 - Computerized Cognitive Rehabilitation in Children after Severe Malaria

https://errm.umich.edu/ERRM/ResourceAdministration/Project/PrintSmartForms?Project=com.webridge.entity.Entity%5BOID%5BA016ED63BD8C284… 9/13

05. Research Design

5.1* Is there a stand-alone scientific protocol document and/or research plan associated with this application? Yes No

5.1.1* Click ADD to attach the document(s) electronically.

Name Version Protocol Ver3 Final 08March17.docx | History 0.03

Tracked-Changes Version | History 0.01

5.1.2* Indicate the section where each of the following are covered in the attached protocol:

Objective page 7 Specific Aim/Hypothesis page 7 on Background Information page 9 on Methodology page 15 on Statistical Design page 19 on

5.1.3* Study team Experience: Briefly outline the experience and competence of the study team to pursue the proposed study.

Study team has been collaborating in over 25 years of research in subSaharan Africa in research primarily related to HIV and cerebral malaria.

5.2* Will the involvement of ANY subjects in this study be limited to analysis of their existing data or specimens? Yes No

5.3* Will the study involve recruitment and/or participation of subjects in order to produce new data (e.g., surveys, interaction, intervention)? [Require sections 8-1 and 11-3] Ye s No

5.4* List the inclusion and exclusion criteria for this study population and/or data set. (If covered in attached protocol, indicate section) page 16

5.5 Identify any racial, ethnic, or gender group(s) that will be specifically excluded from participation in this research study and provide a compelling justification for such exclusion: none

5.6* Indicate the age range (in years) of the subject population in this study. Minimum Age: 5 Maximum Age: 12If no upper limit, enter "999"

06. Benefits and Risks

6.1 * Describe the potential benefits of this research to society.

Important to understand if the long-term cognitive effects of cerebral malaria can be improved wi th readily available cognitive rehabilitation programs.

6.2 * Will results of the research be communicated back to the subjects? Yes No

6.2.1 * Explain the plan and process.

Chilren and their families will most likely see improvement in children's performance as computerized tasks progress. At the end of the study, it is routine to bring families together at the study sites to thank them and review results.

6.3 * Describe any direct risks to the public or community, which could result from this research? none

6.4 * Does this project involve study arms that have differing levels of benefit or risks to subjects? Yes No

6.5 * Benefits and Risks:

Click "Add" to begin entering the benefit and risk level detail information associated with this st udy.

Name Risk Level Direct Benefit View HUM00071923 No more than minimal risk yes

3/30/2017

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https://errm.umich.edu/ERRM/ResourceAdministration/Project/PrintSmartForms?Project=com.

webridge.entity.Entity%5BOID%5BA016ED63BD8C28… 11/13

Benefits and Risk Level Detail

If a study involves multiple arms or phases that pose different levels of risk or direct benefits to s ubjects, then create an entry for each

arm or phase using the "OK and Add Another" option at the bottom of this page. Only one entry is necessary if the risk level and the

direct benefit to subjects is the same for the entire project, even if the study involves multiple ar ms or phases. 6.5.1 * Name of Arm (experimental group, study wave, etc.) HUM00071923

6.5.2 * Description of Arm (experimental group, study wave, etc.)

6.6 * Are there potential direct benefits of this research to the subjects? Yes No

6.6.1 * Describe the potential direct benefits.

children may benefit from either of the arms of the study, since there is involvement of study personnel and possible benefit from cognitive training programs.

6.7 * Provide a description of the foreseeable risks to subjects. For studies involving multiple arms or phases, enter the risks for this arm or phase only.

Provide a description of the foreseeable risks to the subjects.

For EACH identified risk, include: Likelihood of the risk, Seriousness to the subject; and What measures will be taken to minimize the risk (for example, study design includes the substitution of procedures already being performed on the subject for diagnostic or treatment purposes, or in a study of Post-Traumatic Stress Disorder, the investigator takes steps to identify, manage, or refer as appropriate, subjects for whom the study may evoke very difficult emotions)

If possible, please use the following categories to assess the likelihood:

"Common" (i.e., approximate incidence > 25%)

"Likely" (i.e., approximate incidence of 10-25%)

"Infrequent" (i.e., approximate incidence of 1-10%) "Rare" (i.e., approximate incidence < 1%):

Children completing the computerized cognitive rehabilitation arms could become somewhat fatigued, but since these are inherently fun computer games, this is not expected and the likeliho od of risk is rare.

6.8 * What is the level of risk of harm to the subjects, resulting from this arm of the research? For studies involving multiple arms or phases, enter the level of risk for this arm or phase only. No more than minimal risk

6.9 * Discuss why the risks to the subjects are reasonable in relation to the anticipated benefits. Anticipated benefits may help children learn in school and this should outweigh risk of fatigue.

3/30/2017

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https://errm.umich.edu/ERRM/ResourceAdministration/Project/PrintSmartForms?Project=com.webridge.entity.Entity%5BOID%5BA016ED63BD8C28… 12/13

44. Additional Supporting Documents

44.1 Please upload any additional supporting documents related to your study that have not already been uploaded. Examples include, but are not limited to, data collection sheets, newsletters, subject brochures, and instructional brochures. Name Version

There are no items to display

44.2 Enter any information that should show in a “Supporting Documents” list on the current submission’s approval notice, such as document names and version numbers or version dates. Text entered here will AUTOMATICALLY appear word-for-word on the approval letter.

Appendix C.

Interview Guide

Demographics

Age:
Education:
Current Position and number of years in that position:
Have you worked directly with Computerized Cognitive Rehabilitation Therapy? (yes/no)

1) Tell me about your understanding of the impact of malaria on cognition.
2) Tell me about current therapies for malaria and rehabilitation options following the illness.
3) Tell me about your experience with the intervention CCRT.
    a. How many years have you been exposed to the project?
    b. What is your role in regards to CCRT?
    c. What is your understanding of the mechanisms of CCRT?
    d. Have you found CCRT to appropriate for the culture within which it is being used?
4) Tell me about the educational experience for children in nursery and primary school in Uganda.
    a. Are programs in place to accommodate individualized learning experiences?
    b. Are children required to meet certain criteria before advancing in classes?
    c. Are teachers aware of cognitive deficits that can occur following malaria?
    d. Are teachers equipped to identify when children are not meeting appropriate developmental milestones?
5) Tell me about the setting in which children are receiving CCRT.
    a. Do more children receive training at the hospital or at school or in another environment?
    b. Do you think training received at school is as effective as other settings?

6) Tell me about parent support of CCRT use.
    a. Do they accommodate schedules for the child to receive training?
    b. Are they optimistic about cognitive outcomes for the children?
7) Tell me about teacher and school support of CCRT use.
    a. Do they accommodate time for children to receive training?
    b. How is the communication between schools and the research team?
    c. Do the schools demonstrate optimism towards use of CCRT in this population?
8) Tell me about your opinion on long-term use of CCRT for this population.
    a. Is this intervention able to be scaled up?
    b. Is there support from the local government for adapting the program for general use?
    c. Are laptops and necessary technology available to populations who could benefit from CCRT?
9) Tell me about your experience collaborating with international researchers.
    a. Is it difficult to maintain contact with the primary investigators?
    b. Do you feel adequately supported by team members who are not in Uganda?
    c. In your experience, have international collaborators been responsive to suggestions or concerns that you have presented?
10) Is there anything else you have thought about over the course of this conversation that you would like to share with me?

Appendix D.

Caldwell Home Observation Measurement of the Environment

Date I__I__I/I__I__I/I__I__I__I__I Visitor_____ Parent present_____
Day Month Year
If other than parent, relationship to child_____
Language spoken_____
Is mother employed?_____ Type of work when employed_____
Is father employed?_____ Type of work when employed_____
Current child care arrangements_____
Other persons present during visit_____

SUMMARY

Subscale	Score
I. RESPONSIVITY	
II. ENCOURAGEMENT OF MATURITY	
III. EMOTIONAL CLIMATE	
IV. LEARNING MATERIALS AND OPPORTUNITIES	
V. ENRICHMENT	
VI. FAMILY COMPANIONSHIP	
VII. FAMILY INTEGRATION	
VIII. PHYSICAL ENVIRONMENT	
TOTAL SCORE	

Place a plus (+) or minus (-) in the box along side each item if the behaviour is observed during the visit or if the parent reports that the conditions or events are characteristic of the home environment. Enter the sub totals and the total on the summary sheet.

I. RESPONSIVITY			
1. Family has fairly regular and predictable daily schedule for child (meals, day care, bedtime, TV, homework, etc).		21. Parent has not cried or been visibly upset in child's presence more than once during past week.	
2. Parent sometimes yield to child's fears or rituals (allows night light, accompanies child to new experiences).		22. Child has a special place in which to keep his/her possessions.	
3. Child has been praised at least twice during past week for doing something.		23. Parent talks to child during visit (beyond correction and introduction).	
4. Child is encouraged to read on his own.		24. Parent uses some term of endearment or some diminutive for child's name when talking about child at least twice during visit.	
5. Parent encourages child to contribute to the conversation during visit.		25. Parents does not express overt annoyance with or hostility toward child (complains, describes child as "bad," says child won't mind, etc.).	
6. Parent shows some emotional response to praise of child by visitor.		**IV. LEARNING MATERIALS AND OPPORTUNITIES**	
7. Parent responds to child's questions during visit.		26. Parent buys and reads a newspaper daily.	
8. Parent uses complete sentence structure and some long words in conversing.		27. Family has a dictionary and encourages child to use it.	
9. When speaking of or to child, parent's voice conveys positive feelings.		28. Child has visited a friend by him/herself in the past week.	
10. Parent initiates verbal interchanges with visitor, asks questions, makes spontaneous comments.		29. Child has free access to TV or radio (can freely switch on radio or TV)	
II. ENCOURAGEMENT OF MATURITY		30. Child has free access to musical instrument (piano, drum, ukulele or guitar, etc.).	
11. Family requires child to carry out certain self care routines, e.g., make bed, clean room, clean up after spills, bathe self.		31. Child has free access to at least ten appropriate books.	
12. Family requires child to keep living and play area reasonably clean and straight.		32. Child has free access to desk or other suitable place for reading or studying.	
13. Child puts own outdoor clothing, dirty clothes, night clothes in special place.		33. House has at least two pictures or other type of art work on the walls.	
14. Parents set limits for child and generally enforce them (curfew, homework before TV, or other regulations that fit family pattern).		**V. ENRICHMENT**	
15. Parent is consistent in establishing or applying family rules.		34. Family has a TV and it is used judiciously, not left on continuously.	
16. Parent introduces visitor to child.		35. Family encourages child to develop and sustain hobbies.	
17. Parent does not violate rules of common courtesy during visit (welcomes, greets, offers visitor a sit)		36. Child is regularly included in family's recreational hobby.	
III. EMOTIONAL CLIMATE		37. Family provides lessons or organizational membership to support child's talents (Kids' sports league, swimming lessons, tennis lessons etc.).	
18. Parent has not lost temper with child more than once during previous week.		38. Child has ready access to at least two pieces of playground equipment and toys in the immediate vicinity.	

19. Parent reports no more than one instance of physical punishment occurred during past month.		39. Child has access to a library card, and family arranges for child to go to library once a month.	
20. Child can express negative feelings toward parents without harsh reprisals.		40. Family member has taken child on (or arranged for child to take) a plane or bus trip within the past year.	

VI. FAMILY COMPANIONSHIP		50. Child has remained with this primary family group for all his life aside from 2 – 3 week vacations, illnesses of mother, visits of grandmother, etc.	
41. Family visits or receives visits from relatives or friends at least twice a month.		**VIII. PHYSICAL ENVIRONMENT**	
42. Child has accompanied parent on a family business venture 3 – 4 times within the past year (to garage, clothing shop, appliance repair shop, etc.).		51. Child's room has picture or wall decoration appealing to children.	
43. Family member has taken child to (or arranged for child to attend) some type of live musical or theatre performance.		52. The interior of the apartment is not dark or perceptually monotonous.	
44. Family member has taken child on (or arranged for child to take) a trip of more than 50 miles from his home (50 miles radial distance, not total distance).		53. In terms of available floor space, the rooms are not overcrowded with furniture.	
45. Parents discuss TV programs with child.		54. All visible rooms of the house are reasonably clean and minimally cluttered.	
46. Parent helps child to achieve motor skills – ride a two wheel bicycle, play football, etc.		55. There is at least 100 square feet of living space per person in the house.	
VII. FAMILY INTEGRATION		56. House is not overly noisy – TV, shouts of children, radio, etc.	
47. Father (or father substitute) regularly engages in outdoor recreation with child.		57. Building has no potentially dangerous structural or health defects (e.g., plaster coming down from ceiling and walls, leaking roof, rodents, etc.).	
48. Child sees and spends some time with father or father figure 4 days a week.		58. Child's outside play environment appears safe and free of hazards.	
49.Child eats at least one meal per day, on most days with mother and father (or mother and father figures)			
TOTALS **I_____ II_____ III_____ IV_____ V_____ VI_____ VII _____ VIII _____ TOTAL_____**			

Appendix E.

Socio-Economic Status Scale

Circle the numbers or letters of all correct answers.

EDUCATION

1. Is the child currently in school? 1. Y 2. N
2. If child is in school, what level? 0 1 2 3 4 5 6 7 (0=kindergarten)
3. If N, was child ever in school? 1. Y 2. N
4. If Y, what was the highest level of education the child reached? 0 1 2 3 4 5 6 7
5. Is child's primary care giver able to read and write? 1. Y 2. N
6. What was the highest level of education for the child's primary care giver?
   0 1 2 3 4 5 6 7 8 (Secondary) 9 (Tertiary)
7. Is child's father able to read and write? 1 Y 2N
8. What was the highest level of education for the child's father?
   0 1 2 3 4 5 6 7 8 (Secondary) 9 (Tertiary)

SE STATUS

1. How many brothers and sisters does this child have?
   0 1 2 3 4 5 6 7 8 9 10 11 12 >12
2. How many people live under the same roof as this child?
   0 1 2 3 4 5 6 7 8 9 10 11 12 >12
3. What type of roof do you have?
   1. Thatch 2. Iron sheets 3. Tile 4. Other
4. What kind of water supply do you have?
   1. Carried in jerry can to home 2. Water source near home 3. Running water
5. What kind of cooking fuel do you use?
   1. Firewood 2. Charcoal 3. Paraffin 4. Gas/Electricity
6. Does the family eat meat at least once a week? 1 Y 2 N
7. Does the family have food all year round? 1 Y 2 N
8. Which of the following items are owned by you or found in your home?

Circle the number if the family has the item; put an X through if not.

Add circled values for total.

Item	Score	Item	Score
Electricity	3	Bicycle	1
Shoes for subject	1	Motorcycle	2
Radio	1	Motor vehicle	3
Television	2	Cows (>2)	2
		TOTAL	

MIGRATION

	Village/Town	**District**
In which village/town was the subject born?		
In which village/town has the child lived for most of his/her life?		
In which village/town did the subject usually live for the past 12 months		

SES done by_____ Date |__|__|/|__|__|/|__|__|__|__|
Day Month Year