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Computerized rehabilitation for cognitive deficits after central nervous system malaria in Ugandan children

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To Clare, Pearl and Carl

ABSTRACT

Background: Malaria infecting the central nervous system (CNS) affects over 575,000 children annually in sub-Saharan Africa leading to cognitive deficits. The effect of this form of malaria on everyday behaviour and academic achievement has not been investigated in Uganda. In addition, no interventions have been carried out for children whose cognitive functioning has been affected by CNS malaria.

Main objective: To investigate the effectiveness of a rehabilitation program for cognitive deficits in Ugandan children after CNS malaria.

Methods: Five studies were carried out (I-V). Study I investigated the long-term cognitive outcomes of CNS malaria. Children were given cognitive assessments 24 months after the malaria episode. In Study II, this same cohort of children were followed up and randomly assigned to receive either computerised cognitive rehabilitation training or treatment as usual, approximately four years after the CNS malaria episode. Pre- and post-intervention cognitive and behavioural assessments were done. The construct validity of a new cognitive test battery, the Kaufman Assessment Battery for Children second edition (KABC-II), was validated in Study III. The effect of CNS malaria on cognition, behaviour and academic achievement was investigated in Study IV. Study V investigated the effect of immediate computerised cognitive rehabilitation training on cognition, behaviour and academic achievement after an episode of CNS malaria. Chi-square and multiple linear regression analyses were used in Study I, analysis of covariance in studies II, IV, V and factor analysis in Study III.

Results: There was a 26.3% prevalence of cognitive impairment two years after CNS malaria with attention most affected. CNS malaria was associated with a 3.67 increased risk for impairment (Study I). At three months assessment, children with malaria had lower attention scores (estimated mean difference = 0.32, 95% confidence interval (CI) = 0.01 to 0.63) and more internalising behavioural problems (0.31, CI, = 0.05 to 0.56) than the community controls (Study IV). Cognitive rehabilitation initiated four years after the illness resulted in improvement in spatial working memory, learning, psychomotor speed and internalising behaviour (Study II) while cognitive rehabilitation initiated three months after the malaria episode improved Learning only (mean difference in adjusted scores between intervention and control groups (standard error), 12.46 (6.05) (Study V). Factor analysis of the KABC-II resulted in five factors measuring Working Memory, Visuospatial skills, Learning and Planning. The fifth factor was composed of items that did not measure a specific cognitive ability (Study III).

Conclusion: Both delayed and immediate computerised cognitive rehabilitation result in improved cognition and behaviour after CNS malaria in Ugandan children.

Keywords: CNS malaria, cognition, cognitive rehabilitation, child health.

LIST OF PUBLICATIONS

I. John CC, **Bangirana P**, Byarugaba J, Opoka RO, Idro R, Jurek AM, Wu B, Boivin MJ: Cerebral malaria in children is associated with long-term cognitive impairment. Pediatrics 2008, 122(1):e92-99.

II. **Bangirana P**, Giordani B, John CC, Page C, Opoka RO, Boivin MJ: Immediate Neuropsychological and Behavioral Benefits of Computerized Cognitive Rehabilitation in Ugandan Pediatric Cerebral Malaria Survivors. Journal of Developmental & Behavioral Pediatrics 2009, 30(4):310-318.

III. **Bangirana P**, Musisi S, Allebeck P, Giordani B, John CC, Opoka OR, Byarugaba J, Ehnvall A, Boivin MJ: A preliminary examination of the construct validity of the KABC-II in Ugandan children with a history of cerebral malaria. African Health Sciences 2009, 9(3):186-192.

IV. **Bangirana P**, Musisi S, Boivin MJ, Ehnvall A, John CC, Allebeck P: Malaria with neurological involvement in Ugandan children: effect on cognitive ability, academic achievement and behaviour. (Manuscript).

V. **Bangirana P**, Allebeck P, Boivin MJ, John CC, Page C, Ehnvall A, Musisi S: Cognitive rehabilitation in Ugandan children after severe malaria: effects on cognition, academic achievement and behaviour. (Manuscript).

The papers will be referred to by their Roman numbers I-V

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention deficit hyperactivity disorder
CBCL	Child Behavior Checklist
CCRT	Computerised cognitive rehabilitation training
HIV	Human Immunodeficiency Virus
KABC	Kaufman Assessment Battery for Children
KABC-II	Kaufman Assessment Battery for Children, second edition
TNF-α	Tumour necrosis factor alpha
WHO	World Health Organisation

OPERATIONAL DEFINITIONS

Academic achievement: Problem solving ability learned at school and related to reading, spelling and arithmetic.

Behaviour: Actions and mannerisms of the child observed by the caregiver or teacher.

Central nervous system (CNS) malaria: Severe malaria with manifestations of CNS involvement including; cerebral malaria, malaria with seizures and malaria with impaired consciousness.

Cerebral malaria: A neurological complication of malaria characterised by unarousable coma.

Cognition: The different ways humans process information to understand and solve problems in everyday life.

Cognitive rehabilitation training: Treatment of cognitive deficits resulting from brain injury. It involves either re-training the impaired skill over time to make it better or helping the patient to adapt to his/her environment after a particular cognitive skill has been permanently impaired.

Cognitive skills: The different functions involved in information processing and learning e.g. memory, attention and visuospatial skills.

Computerised cognitive rehabilitation training: Treatment of cognitive deficits resulting from brain injury using computer exercises.

1 INTRODUCTION

1.1 Malaria burden

It is estimated that over two billion of the world's population are exposed to malaria infection with over 500 million clinical cases reported annually (Snow et al., 2005). The majority of these cases (75%) are in sub-Saharan Africa and 25% in Asia with children under five years being the most affected age group. This makes malaria one of the most important parasitic infections.

Malaria is a febrile illness caused by the *Plasmodium* parasite and commonly presents as fever, with general weakness and vomiting. The spectrum of malaria infection includes asymptomatic malaria (parasites in the blood but no symptoms), uncomplicated symptomatic malaria (parasites in the blood with symptoms but no other complications) and complicated malaria (parasites in the blood with symptoms and dysfunction of body systems like the nervous, renal and respiratory systems).

Estimates put the number of deaths attributed to malaria at 1 million annually (1 death every 30 seconds), with over 75% of these being African children (Breman, 2001, Greenwood and Mutabingwa, 2002). In malaria endemic areas, about 25% of all the deaths in children aged 0 to 4 years are caused by malaria (Snow et al., 1999). In Uganda, malaria is responsible for 30% of the paediatric admissions and 18% of the paediatric deaths (Opoka et al., 2008).

The high morbidity and mortality of malaria also has socioeconomic implications that go beyond the economic costs of medical care, work lost to sickness and public expenditure on malaria treatment (Deressa et al., 2007, Chima et al., 2003, Sachs and Malaney, 2002). Fecundity in endemic populations may increase to cater for the lives lost to malaria resulting in pressure on school fees, reduction in female productivity, school absenteeism, avoidance of malaria endemic countries by investors and poor cognition in children (Sachs and Malaney, 2002). The latter, the effect of malaria on cognition, is the main scope of this thesis and is reviewed further below.

1.2 Central nervous system malaria

Malaria is the commonest parasitic infection of the brain and a leading cause of neuro-disability in tropical countries (Newton and Warrell, 1998, Idro et al., 2010b). Cerebral malaria, the most severe form of malaria, has traditionally been given most attention when dealing with malaria affecting the central nervous system (CNS). This

leaves out other important forms in the malaria spectrum that can potentially damage the brain (Idro et al., 2007). A new phrase, 'malaria with neurological involvement' has been proposed to include all forms of malaria affecting the CNS and this includes; malaria with agitation, prostration, complex seizures, impaired consciousness, or coma i.e. cerebral malaria (Newton and Warrell, 1998, Idro et al., 2007). In this thesis, 'CNS malaria' will be used throughout to refer to all forms of malaria with neurological involvement. However, the specific forms of CNS malaria will be mentioned when discussing aspects that are specific to them.

Cerebral malaria is the most severe form of malaria. The patient often presents with unarousable coma that cannot be attributed to any other disease or disorder and there are asexual forms of *Plasmodium Falciparum* in the blood film (WHO, 2000). It has an incidence of 1.12/1000 per year (Snow et al., 2003) and affects 575,000 children annually with a case fatality rate of 19% (Murphy and Breman, 2001). In Uganda cerebral malaria contributes 8% of all malaria admissions but has the highest case fatality rate at 17% compared to other malaria complications (Opoka et al., 2008). Malaria with complex seizures has a higher incidence than cerebral malaria of 5.8/1000 per year (Waruiru et al., 1996) occurring in 38% of infected East African children (Idro et al., 2007). Malaria with impaired consciousness has been defined as a coma score below the normal level of consciousness and occurs in 13% of East African children admitted with malaria (Idro et al., 2007). Prostration refers to the inability to sit up in a child who would normally do so, or inability to drink if child is not old enough to sit up and occurs in 20.6% of East African children admitted with malaria (Idro et al., 2007). Agitation (high level of activity and irritability) is the least common form of CNS malaria occurring in 2.8% of East African children (Idro et al., 2007).

1.3 Causes of brain injury in central nervous system malaria

The mechanisms of brain injury in CNS malaria are not clearly understood but insights into these processes can be derived from the pathogenesis of cerebral malaria. Some theories have been advanced to try and explain why some children get cerebral malaria and others don't.

Presence of infected and non-infected red blood cells in cerebral capillaries is a common finding in cerebral malaria (Idro et al., 2005, Mishra and Newton, 2009). Infected red blood cells are able to adhere to the epithelial cells in blood capillaries (cytoadherence) using proteins expressed on the red blood cell surfaces (Mishra and Newton, 2009, Idro et al., 2005). This sequestration can be increased when infected red

blood cells bind with other infected red blood cells (autoagglutination), or with non-infected red blood cells (rosetting) (Idro et al., 2005). Presence of these infected and non-infected red blood cells in the capillaries reduces blood flow and hinders supply of oxygen and glucose to some parts of the brain. This is because infected red blood cells become rigid and therefore can't deform as they pass through the capillaries thus reducing transportation of nutrients in the brain (Mishra and Newton, 2009, Idro et al., 2005). The resulting hypoxia may aggravate (or even cause) coma, a hallmark of cerebral malaria (Idro et al., 2010b). With reduced oxygen and glucose supply, injury to the brain is more likely especially when seizures (which are common in febrile illnesses) occur. This neural injury is more likely if the patient is hypoglycaemic, a condition common in childhood malaria (Idro et al., 2010b).

Infection with *P. Falciparum* increases the production of both pro- and anti-inflammatory cytokines whose role in malaria pathogenesis is not clearly understood (Mishra and Newton, 2009, Idro et al., 2005). Increased levels of tumour necrosis factor (TNF-α), interleukin 1, interleukin 6, interleukin 8, interleukin 10 and interferon gamma have been reported in cerebral malaria (John et al., 2006, John et al., 2008b, Idro et al., 2005, Mishra and Newton, 2009). However, it is TNF-α that's more likely to be involved in the pathogenesis of cerebral malaria since it is linked to the up regulation of adhesion molecules that aid the binding of infected red blood cells to the capillary epithelium in the brain (Miller et al., 2002). TNF- α also up regulates inducible nitric oxide synthase which in turn produces nitric oxide that disrupts the blood brain barrier, neuronal function and reduces levels of consciousness (Mishra and Newton, 2009, Idro et al., 2005, Idro et al., 2010b). The observation that TNF-α is associated with neurological and cognitive deficits in cerebral malaria is further evidence linking TNF-α to cerebral malaria pathogenesis (John et al., 2008b). Other processes occurring during cerebral malaria infection that may cause neural injury include apoptosis, production of endothelial microparticles, intracranial hypertension and blood brain barrier dysfunction (Idro et al., 2010b).

The cause of seizures in CNS malaria is not clearly understood but is thought to be a consequence of ischemia and hypoxia (due to sequestration) and the effect of immune mechanisms (Idro et al., 2005). The ruling out of genetic polymorphisms and deletions as causes further complicates the aetiology of seizures in children with malaria (Idro et al., 2008). Seizures may not directly contribute to neural injury but may however do so if they are prolonged (Idro et al., 2010b).

1.4 Cognitive functioning after central nervous system malaria

Cognitive deficits after CNS malaria were first described in a retrospective Ghanaian study in 1995 where children with a history of CNS malaria had deficits in learning, visual and auditory information processing, psychomotor skills and memory (Dugbartey et al., 1998). Further retrospective studies in Kenya and Senegal found similar deficits with some children displaying cognitive deficits up to eight years after CNS malaria (Holding et al., 1999, Carter et al., 2005b, Boivin, 2002, Kihara et al., 2009). A systematic review of studies looking at the cognitive outcomes of CNS malaria in children shows that five main cognitive functions are affected. These are memory, attention, visuospatial skills, language and executive functions (Kihara et al., 2006).

The retrospective nature of the above studies presents some problems that may affect the accuracy of the results. Boivin and colleagues argue that in retrospective studies there is a possibility of recall bias by the parents about the child's clinical history, medical records may not have captured some vital information relevant to studying the cognitive outcomes of malaria, potential confounders like the home environment may not be assessed at the time and loss to follow-up that occurred may have been related to the risk of cognitive deficits (Boivin et al., 2007). They carried out a prospective study among Ugandan children that addressed these limitations. Children admitted with CNS malaria were assessed at discharge and at three and six months later. Test scores were compared to age matched community controls. The quality of the home environment was assessed and controlled for in the analyses. The CNS malaria group had more children cognitively impaired than the control group at three months (19% vs 6.9%, $p = 0.07$) and six months (21.4% vs 5.4%, $p = 0.01$). Children who had CNS malaria had a 3.7 increased risk of cognitive impairment compared to the controls. Unlike neurological deficits which resolve a few months after discharge, the subtle cognitive deficits appear to persist at six months (Opoka et al., 2009, Boivin et al., 2007).

Recently, retinal examination has been shown to improve the accuracy of cerebral malaria diagnosis and is highly recommended (Lewallen et al., 2008, Birbeck et al., 2010a). This is because many of the deaths in children having cerebral malaria are caused by other factors which the current diagnostic criteria cannot pick (Taylor et al., 2004). Birbeck, Boivin and colleagues have gone ahead and looked at the cognitive outcomes of retinopathy confirmed cerebral malaria in Malawian children. Compared to a control group, the cerebral malaria group had a higher frequency of

neurodisabilities (23.1 % vs 0.8%, p=0.0001), were more at risk for clinical diagnosis of attention deficit hyperactivity disorder (ADHD) and had language delay (Birbeck et al., 2010b, Boivin et al., In press).

It is estimated that 250,000 children develop cognitive deficits annually after CNS malaria with risk factors like occurrence of seizures, coma depth and duration, neurological abnormalities on admission, neurological deficits at discharge, malnutrition and intracranial hypertension being associated with these deficits (Holding et al., 1999, Idro et al., 2006, Boivin, 2002, Boivin et al., 2007, Carter et al., 2005b, Boivin et al., In press). Different cognitive deficits are associated with different risk factors suggesting different mechanisms of neuronal damage leading to these deficits (Idro et al., 2006).

The consistent finding of working memory and attention deficits after CNS malaria raises the possibility of low academic performance in school after CNS malaria infection, since working memory and attention are requisite skills in reading and arithmetic proficiency (Andersson and Lyxell, 2007, Bull et al., 2008, Passolunghi and Cornoldi, 2008, Silva-Pereyra et al., 2010, Swanson et al., 2009).

Furthermore, there is growing evidence that child survivors of CNS malaria may develop behavioural problems though this has not been evaluated in well designed prospective studies (Idro et al., 2010a, Bangirana et al., 2009b). These studies have identified a mix of overt behavioural problems like aggressiveness, hyperactive behaviour and covert behavioural problems like anxiety and depression. In line with these behavioural features, recent studies examining the structure of psychopathology have identified internalising and externalising symptoms as the two broad factors underlying psychopathology (Clark and Watson, 2006, Slade and Watson, 2006). The externalising factor is comprised of substance dependence, attention-deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder/antisocial personality disorder. The internalising factor has ‘distress/misery’ comprising generalised anxiety disorder, overanxious disorder and depressive disorders and ‘fear’, which includes simple and social phobias, separation anxiety disorder and panic disorder (Clark and Watson, 2006). These two broad categories of internalising and externalising behaviour were the outcomes for behaviour in this thesis.

1.5 Neuropsychological assessment in sub-Saharan Africa

Children in sub-Saharan Africa, like in other low income countries, are faced with difficult circumstances that compromise their cognitive development. These

include physical illness especially chronic infectious diseases suffered by the children (or their caregivers resulting in poor care for the child), malnutrition, political conflict, unstimulating environments and poverty (Walker et al., 2007, Olness, 2003). It is estimated that over 200 million children under five years in low income countries are not achieving their full cognitive potential (Grantham-McGregor et al., 2007).The actual impact of these factors on cognition is not known and the above estimates of the number of children with impaired cognition have been based on other indicators like poverty and stunting and not actual neuropsychological assessment scores (Grantham-McGregor et al., 2007). Psychological assessment in at risk children (who are exposed to the above risk factors) can help identify which particular cognitive skills are affected and appropriate interventions can then be planned.

Most studies looking at the neuropsychological outcomes of brain injury in African children have used test batteries developed in the Western world. Though having sound psychometric properties in the Western world, these tests may not accurately assess the cognitive abilities they are designed to measure in African children because they may not measure the same outcome in different cultures (Greenfield, 1997). In addition people from different cultures may use different approaches to arrive at the same result meaning the test could measure different cognitive abilities (Sternberg, 2004). Furthermore, children from different cultures may not answer questions the same way when posed by adults (Holding et al., 2004).

The Kaufman Assessment Battery for Children (KABC) measuring memory and visuospatial skills in children aged 2.5 to 12 years is one of the mostly widely used tests in sub-Saharan Africa. It has stable construct validity, is sensitive to the effects of HIV, CNS malaria, quality of the home environment, nutritional status, education level, helminth treatment and iron supplements on the brain (Boivin et al., 1995, Boivin et al., 2007, Bangirana et al., 2009a, Boivin and Giordani, 1993, Boivin et al., 1993, Boivin, 2002, Giordani et al., 1996). It does not require much verbal input from the examiner making it a useful instrument to use in sub-Saharan Africa (Kaufman and Kaufman, 1983). Holding and colleagues adapted the KABC to children in Kenya by modifying and substituting few items with those culturally relevant to the Kenyan context (Holding et al., 2004). The resulting test battery was shown to have stable construct validity and was sensitive to malarial infection and school attendance prompting the authors to conclude that tests developed in the West can be adapted to suit different cultures including those in Africa (Holding et al., 2004).

The above studies attest to the KABC's utility as a suitable measure of cognition in African children exposed to various risks. The KABC however has some limitations as it only measures three cognitive abilities (memory, visuospatial skills and achievement) and has a limited age range of 2.5 to 12.5 years. A newer version of the KABC, the Kaufman Assessment Battery for Children, second edition (KABC-II) has been developed measuring memory, visuospatial skills, planning, learning and knowledge in children aged 3 to 18 years (Kaufman and Kaufman, 2004). The KABC-II maintains the features that made the KABC a useful measure of cognition in African children. With the inclusion of more abilities to assess and a wider age range, the KABC-II is superior to its predecessor as an instrument of choice for cognitive assessment in sub-Saharan African children. Unlike its predecessor however, the KABC-II has not been widely used in sub-Saharan Africa hence little is known about its cross-cultural applicability.

1.6 Cognitive rehabilitation for CNS malaria

The application of cognitive rehabilitation training can be traced back to environmental enrichment studies in mice. Mice reared in bigger cages with play toys and stimulation showed more hippocampal neurogenesis, increased length and density of dendrites, number of glial cells and synaptic density than those reared without these amenities (Kempermann et al., 1997, Brown et al., 2003, Kolb and Whishaw, 2009). The conclusion that can be drawn from these environmental enrichment studies is that environmental enrichment and stimulation induces plasticity in the brain through physiological changes in the brain that may translate into improved cognitive ability.

Computerised cognitive rehabilitation training (CCRT) has been shown to be effective in improving cognitive functioning in children and adults suffering from stroke, ADHD, schizophrenia and HIV infected children in Uganda (Westerberg et al., 2007, Klingberg et al., 2005, Shalev et al., 2007, Boivin et al., 2010, Bellucci et al., 2003, Poletti et al., 2010, Sjo et al., 2010, van 't Hooft et al., 2007). The cognitive deficits resulting from the above conditions are also observed in CNS malaria. It is therefore likely that CCRT may be of benefit to children who have suffered from CNS malaria.

Computerised cognitive rehabilitation training involves presenting exercises on a computer that requires the player/patient to use a specific or several cognitive abilities to solve a task. Its effect is based on the premise that repeated exercising of a cognitive skill results in its improvement by strengthening the neural connections undergirding

the skill. Increased brain activity, dopamine availability and changes in white matter structure in children and adults after CCRT have been observed suggesting that cognitive training induces physiological changes in the brain that lead to improved cognition (McNab et al., 2009, Hoekzema et al., 2010, Olesen et al., 2004, Takeuchi et al., 2010). Despite the evidence in support for CCRT, there is still need for more trials to test the effectiveness of CCRT on not only the trained cognitive tasks (e.g. attention and working memory) but also the non trained functional areas (e.g. everyday behaviour, academic achievement and other activities of daily living).

In sub-Saharan Africa, CNS malaria whose cognitive outcomes have been widely studied provides an excellent opportunity to present further evidence as to whether CCRT has any benefit on the cognitive functions after brain injury. As noted above, there is a dearth of evidence that CNS malaria affects behaviour and academic skills. Including these as outcomes can also provide some answers whether CCRT has any benefit on these non-trained functional areas.

2 THEORETICAL FRAMEWORK

Cognitive functioning after CNS malaria is predicted by factors occurring before, during and after the infection. Pre-infection factors include pre-morbid cognitive function, maternal education and gravidity, developmental delay, prior history of head injury, malnutrition, education level and the quality of the home environment (Bangirana et al., 2009a, Kolb and Whishaw, 2009, Abubakar et al., 2010). Factors predicting outcome during infection include peri-infection factors such as coma depth, coma duration, seizures, hypoglycaemia, TNF-α levels, anaemia, malnutrition, neurological signs while post-infection factors will include seizures, further cerebral insult, poor feeding and the quality of the home environment (Bangirana et al., 2009a, Opoka et al., 2009, Idro et al., 2006, John et al., 2008b, Boivin, 2002, Boivin et al., 2007, Holding et al., 1999). In the assessment of cognition after CNS malaria, these variables need to be controlled for by either excluding children with these risk factors or controlling for them in the analyses.

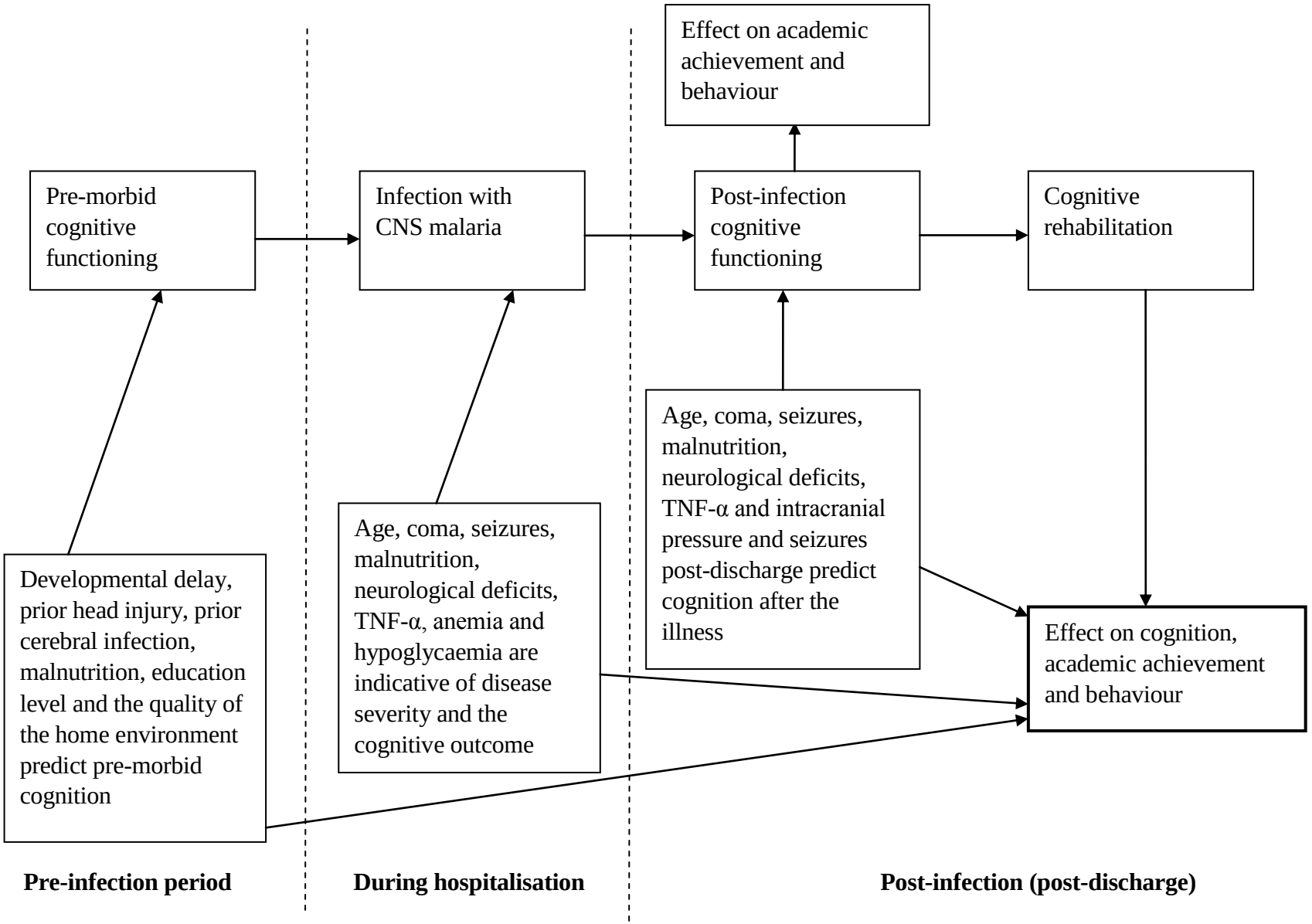
A wide range of cognitive functions are affected after CNS malaria but not all children will have the same cognitive abilities impaired. A robust intervention targeting a wide range of cognitive abilities is thus needed for effective rehabilitation of the resulting deficits. Many CCRT programs meet this requirement in being able to target a specific skill or train a variety of cognitive skills. As earlier noted, there is a likelihood that other important functional areas like academic achievement and behaviour may be affected by CNS malaria. Including them as outcomes in the rehabilitation process will shade more light on the debate whether CCRT improves not only the trained skills but the untrained skills as well (Dickinson et al., 2010, Owen et al., 2010). The above pre-, peri- and post-infections factors can also affect outcomes of the intervention.

3 RATIONALE FOR THE STUDIES

Central nervous system malaria is one of the main causes of cognitive deficits in children in sub-Saharan Africa (Carter et al., 2003b, Idro et al., 2010b). Studies from Africa show several cognitive skills impaired as a result of malaria infection as reviewed above. However well designed prospective studies have not been carried out to describe the long-term cognitive deficits of CNS malaria. In assessing children at risk of cognitive deficits after malaria or other CNS infections, several challenges arise as to whether culturally appropriate psychological tests are being used. Even still, most studies have focused on the subtle cognitive functions and not assessed overt functional activities like behaviour and academic achievement. It has been noted than much as CNS malaria leads to cognitive deficits, interventions are still lacking in the region leaving children to suffer the cognitive burden of the disease (Idro et al., 2010b, Bangirana et al., 2006).

The present study attempts to address the above concerns by describing the cognitive, academic and behavioural outcomes of CNS malaria and examining the effectiveness of CCRT in improving these outcomes.

Figure 1. Conceptual framework depicting development of cognitive deficits after CNS malaria and the possible benefit from CCRT



4 STUDY OBJECTIVES

4.1 General objective

The general objective of this study was to investigate the effect of CCRT on cognition, academic achievement and behaviour after central nervous system malaria in Ugandan children.

4.2 Specific objectives

i) To describe the long-term cognitive outcomes of central nervous system malaria.

ii) To investigate the effect of computerised cognitive rehabilitation training on cognition and behaviour four years after central nervous system malaria.

iii) To examine the construct validity of the Kaufman Assessment Battery for Children second edition.

iv) To examine the effect of central nervous system malaria on cognition, academic achievement and behaviour.

v) To investigate the effect of computerised cognitive rehabilitation training on cognition, academic achievement and behaviour three months after central nervous system malaria.

5 METHODS

5.1 Study area

This study was conducted in Uganda, a land locked country of 241,551 sq. km and a population of 32 million with children 6 to 12 years accounting for 6.3 million (19.7%) of the population (Population Secretariat, 2010). The male to female sex ratio is 95:100, infant mortality rate stands at 78 per 1000 live births, under five mortality rate at 134 per 1000 live births and maternal mortality rate is 550 per 100,000 live births (WHO, 2008). The life expectancy for males and females is 49 and 51 years respectively (WHO, 2008). The Baganda are the largest tribe with 17.3% followed by the Banyankore with 7.8% of the population (UBOS, 2002).

Patient recruitment was done from Kampala, the capital city of Uganda. It has a population of 1.5 million spread out in five divisions (UBOS, 2002). Mulago, Mengo, Nsambya and Rubaga hospitals, the four largest hospitals in Kampala served as recruitment sites. Mulago hospital is Uganda's national referral hospital receiving about 6300 paediatric malaria cases annually (Opoka et al., 2008). It is a 1500 bed facility providing specialist services and acts as a district hospital for Kampala city and teaching hospital for Makerere University School of Medicine. Being the national referral hospital, it receives patients from surrounding districts and from the whole country. It was convenient for the study since there are already existing facilities for research on cerebral malaria that were used in this thesis. Mengo, Nsambya and Rubaga hospitals were included as other sites to increase the catchment area as the number of children with CNS malaria above five years in Mulago was low. These four hospitals are strategically located in three of the five divisions of Kampala district ensuring that most of the malaria cases in Kampala presenting to these hospitals and meeting the inclusion criteria below were recruited as well as some from surrounding districts.

5.2 Study population

Two cohorts were recruited for this thesis. The first cohort of children aged 5 to 12 years was recruited between November 2003 and February 2005. In this cohort, three groups of children were recruited; children with cerebral malaria, uncomplicated malaria and community controls. Children with cerebral malaria were recruited if they presented to Mulago Hospital with the WHO criteria for cerebral malaria (i.e. positive blood smear for *P. Falciparum,* unarousable coma and no other cause for coma). The

uncomplicated malaria group were recruited if they had a positive blood smear for *P. Falciparum* and no neurological or other complications of malaria. Community controls were recruited from the homes or neighbourhoods of the cerebral malaria and uncomplicated malaria children and had no malaria. Studies I, II and III used this first cohort of children.

For Studies IV and V, another cohort of children was recruited from Mulago Hospital, the National Referral Hospital of Uganda, and from Nsambya, Rubaga and Mengo Hospitals all located in Kampala, Uganda's Capital City. The latter three are large private mission hospitals. Participants were children aged 5 to 16 years presenting with malaria (*P. falciparum* on blood smears) and either one or more of the following; 1) convulsive seizures lasting over 15 minutes or repeated seizures observed by the parent, 2) impaired consciousness (Glasgow coma scale score of 14 and below), 3) coma i.e. (unarousable coma with normal cerebrospinal fluid). A medical history and physical examination were done on admission by a medical officer.

At discharge, home directions and telephone contacts were obtained from the parents/caregivers and an appointment given for the baseline assessment three months later. In the interim period, a home visit was made to assess the quality of the home environment and to recruit a control child. Preference was given to a child within 2 years of the child who was sick, but within the 5 to 16 years age bracket. The control child was required to come to Mulago Hospital with the identified case for the baseline assessments at three months.

The exclusion criteria for both cohorts were; history of or present meningitis, encephalitis, prior CNS infections, sickle cell disease, epilepsy, multiple seizures, developmental delay and history of hospitalization for malnutrition.

All studies were approved by the Makerere University School of Medicine Research and Ethics Committee and the Uganda National Council for Science and Technology.

5.3 Study assessments

5.3.1 Kaufman Assessment Battery for Children (KABC)

The KABC is one of the most widely used paper-pencil test of cognition for children in sub-Saharan Africa. It consists of three main scales measuring working memory, visuospatial skills and achievement in children 2.5 to 12.5 years (Kaufman and Kaufman, 1983). The test was designed to be administered with little emphasis on language making it particularly appropriate for cross-cultural studies especially in non-

English speaking settings. Studies in Africa and Asia have found it to be sensitive to disease effects on the brain, socioeconomic status, the child and parent's education, nutritional status and the quality of the home environment (Bangirana et al., 2009a, Boivin, 2002, Boivin et al., 1996, Boivin and Giordani, 1993). It was used in Study I to measure working memory.

5.3.2 Kaufman Assessment Battery for Children, Second Edition (KABC-II)

The KABC-II is an improvement of its predecessor; it includes scales measuring working memory, visuospatial skills like the original KABC and three new scales measuring learning, planning and knowledge for ages 3 to 18 years (Kaufman and Kaufman, 2004). It still does not rely heavily on language during test administration like the original KABC making it useful in cross-cultural research. It was used in Studies III, IV and V to assess memory, visuospatial skills, learning and planning.

5.3.3 Tactual Performance Test

The Tactual Performance Test is a task performed by hand measuring spatial learning. While blindfolded, children are required to place six shapes into corresponding holes in a board placed upright. The task is first performed with the dominant hand, then non-dominant hand and finally both hands. The average time to complete the task in all three trials was the outcome measure for learning in Study I. Tactual Performance Test scores have been found to be related to nutritional status of the children in Uganda and Laos (Bangirana et al., 2009a, Boivin et al., 1996).

5.3.4 Test of Variables of Attention

This continuous performance test measures different variables of attention using a computer. Children are required to press a switch immediately the target stimulus appears on the screen and refrain from pressing the switch when the non-target stimulus appears. Attention variables measured include inattention (failing to react when target appears), impulsivity (reacting to a non-target), reaction time (time taken to react) and D' prime (measure of overall attention capacity) (Dupuy and Greenberg, 2005). D' prime was the outcome measure for attention in Studies I, IV and V. This measure of attention has consistently proven sensitive to cerebral insult from malaria in Senegalese and Ugandan children (Boivin, 2002, Boivin et al., 2007).

5.3.5 CogState

The CogState is a brief computer administered neuropsychological test battery (Pietrzak et al., 2008). It uses playing cards and mazes in game-like fashion which makes the tasks enjoyable and reduces chances of boredom. In the card tasks, respondents have to press a particular key on the mouse or keyboard if the presented card is red (identification), is face up (detection), is similar to the previous card (memory) or has been presented before in the task (learning). In the maze task, the respondent uses the mouse to follow a target across the maze (maze chasing) or undercover a path beneath the maze through trial and error (maze learning) (Pietrzak et al., 2008).

5.3.6 Child Behavior Checklist (CBCL)

The CBCL is one of the most widely used measures of child and adolescent behaviour. It contains 120 items measuring different behavioural profiles like anxiety, depression, attention problems, somatic complaints, aggressive behaviour and social problems (Achenbach and Rescorla, 2001). These test items can be collapsed into externalising, internalising or total behavioural problems. The CBCL has been validated in many societies around the world and has fair reliability when used in Ugandan children (Bangirana et al., 2009b, Ivanova et al., 2007).

5.3.7 Wide Range Achievement Test, Third Edition

The Wide Range Achievement Test is a measure of academic achievement in arithmetic, reading and spelling (Wilkinson, 1993). It is a simple to administer test of brief duration lasting 10 to 30 minutes. It has been used to measure achievement in Ugandan children with HIV (Bagenda et al., 2006).

5.3.8 Middle Childhood Home Observation for the Measurement of the Environment

This instrument measures the amount of stimulation and learning opportunities a household offers the child (Caldwell and Bradley, 2001). It has been used in assessing the quality of the home environment in Ugandan children (Bangirana et al., 2009a, Boivin et al., 2007). It contains 59 items though one item was removed because it was deemed not appropriate for Ugandan families. Its score is predictive of cognition in

Ugandan children and was used as a covariate in the statistical analyses (Bangirana et al., 2009a).

5.4 Cognitive intervention

Captain's Log is the cognitive intervention program used in the studies consisting of 35 brain training exercises for a variety of cognitive skills (Sandford, 2007). Fifteen exercises were chosen based on their minimal use of language and few movements with the mouse since children in Uganda are not very familiar with computers. Of these 15 exercises, four trained attention, four trained memory and conceptual skills, three were for visuomotor skills and four for logic. The training program used in the studies consisted of 16 brain training sessions lasting 45 minutes each. Two sessions were performed each week for eight weeks. The first session of training started at the simplest level and increased in difficulty as the training progressed based on the child's performance.

5.5 Study designs

5.5.1 Study I: Long-term cognitive outcomes of CNS malaria

In this prospective cohort study, 38 children admitted with cerebral malaria and 48 children with uncomplicated malaria at Mulago Hospital, Kampala, were followed up and given psychological testing at 24 months post discharge. Test scores were compared to 79 age matched community controls. Assessments done at discharge, three and six months have been described elsewhere (Boivin et al., 2007). Areas assessed in these children included working memory, attention and learning. The amount of stimulation, caregiver-child interaction and learning opportunities in the household was measured and used a covariate in the analyses as this affects cognition in Ugandan children. A checklist was also administered to measure the child's socioeconomic status and compare it across the three groups.

Age adjusted z scores were derived from the scores of the control group. A z score equal or lesser than 2 indicated impaired working memory and attention while a z score equal or greater than 2 indicated impairment in learning. A child was defined as being cognitively impaired if he/she was impaired in any one of the three areas tested. Frequency of impairment was analysed using chi square or Fisher's exact test where appropriate while the performance in the cognitive testing was compared between the groups using multiple linear regression. The child's school level, gender, nutritional

status and quality of the home environment were controlled for in the regression analyses.

5.5.2 Study II: Effect of delayed CCRT on cognition and behaviour

This randomised controlled trial was done approximately 18 months after the 24 months testing in Study I above. Thirty seven of the 38 children with a history of cerebral malaria were followed up and given baseline neuropsychological testing for learning, working memory, visuospatial skills, planning, psychomotor speed and attention and behavioural assessment for internalising, externalising and total behavioural problems. An additional 28 children admitted with cerebral malaria at the same time as the above 37 (November 2003 to February 2005) were also enrolled into this study and given the same baseline assessments. These 65 children were later randomised to either a CCRT arm or to a treatment as usual arm. The CCRT intervention consisted of 16 cognitive training sessions done bi-weekly for eight weeks. Post-intervention assessment was done two months after the baseline testing.

Post-intervention test scores between the two groups were compared using analysis of covariance while controlling for age, grade, weight for age z scores (nutritional status), quality of the home environment, sex, and baseline pre-intervention score of the same outcome.

5.5.3 Study III: Construct validity of the KABC-II

The KABC-II was administered to the same children in Study II above for this cross sectional study. Approximately 18 months after the 24 months testing in Study I above, 37 of the 38 children with a history of cerebral malaria were followed up and assessed with the KABC-II. An additional 28 children admitted with cerebral malaria at the same time as the 37 above were also enrolled into this study and assessed with the KABC-II. Thirteen subscales of the KABC-II were administered to these children. These included; Atlantis, Rebus, Atlantis Delayed, Rebus Delayed measuring Learning. Hand Movements, Word Order, Number Recall measuring Working Memory. Block Counting, Rover, Triangles, Gestalt Closure measuring Visuospatial Skills. Pattern Reasoning and Story Completion measuring Planning. All items in these subscales were administered except seven items from Gestalt Closure which were omitted because they were not culturally appropriate. This was after a consensus with the research team.

Prior to testing, all instructions for the KABC-II were translated into Luganda, the commonly spoken language in Kampala by a research assistant and then back translated to English by another research assistant before testing. Factor analysis using principal components analysis was applied to these 13 subscales to identify those measuring the same outcome.

5.5.4 Study IV: Cognition, academic achievement and behaviour after CNS malaria

A new cohort was recruited for this study. In this prospective cohort study, sixty two children admitted with CNS malaria at Mulago, Rubaga, Mengo and Nsambya Hospitals in Kampala were recruited and followed up at three months and given tests for cognition (working memory, visuospatial skills, planning, learning and attention), academic achievement (arithmetic, reading and spelling) and behaviour (internalising and externalising behavioural problems). Home visits were also done to measure the care-giving environment, socioeconomic status and to recruit age matched community controls. Test scores were compared to 61 age matched controls.

Analysis of covariance was used to compare cognitive ability, academic achievement and behaviour between the malaria group and the control group. The child's age, level of education, home environment score, weight for age z score and sex were entered as covariates in the model. A linear regression model was used to identify whether cognitive ability is predictive of academic achievement.

5.5.5 Study V: Effect of immediate CCRT on cognition, academic achievement and behaviour

After the baseline assessment in Study IV above, children were randomised to either a CCRT or a treatment as usual group for this randomised controlled trial. The randomisation procedure was stratified for the three different groups of CNS malaria; cerebral malaria, malaria with seizures and malaria with impaired consciousness. The cognitive training was similar to what was provided in Study II above. To assess the effect of the intervention while controlling for other covariates, analysis of covariance was run on the post-intervention score with covariates age, weight for age z score, quality of the home environment, sex, time between admission and post-intervention assessment and baseline pre-intervention score on the same outcome variable.

5.6 Overview of methods

Table 1. Summary of study designs

Study	Design	Setting	Methods	Period
Study I	Prospective cohort study	Mulago Hospital	Cognitive test scores of 38 children with a history of CNS malaria and 48 children with uncomplicated malaria were compared to scores of 79 community controls.	2005 to 2006
Study II	Randomised controlled trial	Mulago Hospital	65 children with a history of CNS malaria were randomly assigned to either CCRT or treatment as usual. Pre-and post-intervention cognitive and behavioural testing done.	2007 to 2008
Study III	Cross sectional study	Mulago Hospital	65 children with a history of CNS malaria were assessed for cognitive functioning using the KABC-II.	2007 to 2008
Study IV	Prospective cohort study	Mulago, Mengo, Nsambya and Rubaga Hospitals	Cognitive, behavioural and academic test scores of 62 children with a history of CNS malaria were compared to scores of 61 community controls.	2008 to 2010
Study V	Randomised controlled trial	Mulago, Mengo, Nsambya and Rubaga Hospitals	65 children with a history of CNS malaria were randomly assigned to either CCRT or treatment as usual. Pre-and post-intervention cognitive, academic and behavioural testing done.	2008 to 2010

6 RESULTS

6.1 Study I: Long-term cognitive outcomes of CNS malaria

This study aimed to investigate the long-term cognitive outcomes of CNS malaria. Children with CNS malaria had a higher frequency of impairment in at least one of the three areas tested than the community controls (26.3% vs 7.6%, p = 0.006). Attention was mainly affected where the CNS malaria group had a significantly higher frequency of cognitive impairment than the controls (18.4% vs 2.5%, p = 0.005) and a greater severity of impairment as indicated by the estimated mean difference of -0.71 (95% confidence interval [CI]: -1.10 to -0.32). Children with CNS malaria had a 3.67 fold increased risk for cognitive impairment at 24 months compared to the community controls (95% CI: 1.11 to 12.07). Hyporeflexia at admission and having any neurological deficit at three months were associated with impaired cognition at 24 months.

6.2 Study II: Effect delayed CCRT on cognition and behaviour

The aim of this study was to investigate the effect of CCRT on cognition and behaviour four years after a CNS malaria episode. The intervention group and the treatment as usual group had similar demographic characteristics though the intervention group had a longer period in days between pre- and post-intervention assessment (61.6 vs 80.9, p = 0.0001). The intervention group showed an improved performance in all outcomes assessed but this was significant for maze learning [group effect (standard error) 0.08 (0.02); p < 0.001], maze chasing [0.14 (0.03); p < 0.001], detection [0.14 (0.07); p < 0.04] and for internalizing problems [-3.80 (1.56); p < 0.02]. Time between pre- and post-intervention assessments did not affect the neuropsychological outcomes.

6.3 Study III: Construct validity of the KABC-II

This study was carried out to evaluate the construct validity of the KABC-II in Ugandan children. Majority of the respondents were male (62%) with an average age of 9.9 years (SD = 2.5). The 13 items of the KABC-II loaded on five factors. The first factor was composed of three of the four Learning tests; Rebus, Rebus Delayed and Atlantis. The second factor was mainly composed of three of the four Visuospatial tests; Gestalt Closure, Triangles and Block Counting. All three Working Memory tests (Hand Movements, Word Order and Number Recall) loaded on the third factor. The

fourth factor was composed of all Planning tests (Story Completion and Pattern Reasoning). The fifth factor did not have tests measuring specific abilities loading on it with Number Recall (Working memory) and Atlantis Delayed (Learning). The four factor structure is in line with the test's original development thus proving a valid test in Uganda.

6.4 Study IV: Cognition, academic achievement and behaviour after CNS malaria

The aim of this study was to describe the effect of CNS malaria on cognition, academic achievement and behaviour. Children in the malaria group had low attention scores (estimated mean difference = 0.32, 95% confidence interval (CI) = 0.01 to 0.63) and more internalising behavioural problems than the community controls (0.31, CI, = 0.05 to 0.56). No significant differences were observed in any other outcome scores between the two groups. In the malaria group, Working Memory predicted Reading (Coefficient = 0.34, CI = 0.06 to 0.62) and Spelling (0.43, CI = 0.09 to 0.77) and Visuospatial ability predicted Arithmetic (0.17, CI = 0.05 to 0.28).

6.5 Study V: Effect of immediate CCRT on cognition, academic achievement and behaviour

Study V was designed to investigate the effect of CCRT initiated three months after CNS malaria on cognition, academic achievement and behaviour. Both the intervention and control group had similar demographic characteristics. At baseline assessment, cognitive, behavioural and academic achievement scores were similar across the groups. After adjusting for education level, sex, weight for age z score, quality of the home environment, time between admission and post-intervention testing and the pre-intervention score, intervention effects were observed in Learning, (group effect (standard error) -12.46 (6.05); p = 0.04). However, the intervention group had lower working memory scores at post-intervention (2.08 (0.01); p = 0.04). No effect was observed for other cognitive outcomes or in any of the academic or behavioural measures.

7 DISCUSSION

This thesis attempted to answer three questions regarding cerebral insult in children in sub-Saharan Africa;

1) What areas of functioning (i.e. cognitive, academic achievement and behaviour) are affected by CNS malaria?

2) Can psychological tests developed in the West measure these cognitive deficits in Ugandan children as they were intended to measure?

3) Can cognitive rehabilitation ameliorate these observed deficits?

The results of the studies designed to answer these questions are discussed below focusing on the new information generated, comparison with other studies, implications for practise, the limitations and suggestions for improved studies.

7.1 Effect of malaria on cognition, academic achievement and behaviour

The two outcome studies in this thesis showed that attention is mostly affected by malaria infection which is consistent with findings from other studies in Senegal, Kenya, Uganda and now recently in Malawi. Boivin (2002) in his retrospective study with Senegalese children observed lower attention scores in children who had had cerebral malaria compared to healthy controls. These attention scores were also correlated with indicators of diseases severity like coma duration (Boivin, 2002). Holding et al., (1999) had earlier observed attention problems in children with a history of malaria with impaired consciousness. A subsequent study from Uganda also showed attention problems after malaria (Boivin et al., 2007).

A recent study comparing event related potentials among Kenyan children with CNS malaria and controls seems to suggest that attention may be an underlying deficit. Kihara and colleagues observed that children with a history of CNS malaria had abnormal event related potential signals to novel auditory and visual stimuli compared to controls (Kihara et al., 2010a). They went on to state that their results are suggestive of atypical processing in the brain regions responsible for orienting one's attention to novelty.

Birbeck and colleagues noted that several of their cohort of children discharged after cerebral malaria met clinical diagnosis of ADHD (Birbeck et al., 2010b). Idro and colleagues also observed externalizing behavioural problems especially ADHD-like symptoms in Ugandan children attending a specialist neurology clinic (Idro et al., 2010a). However, behavioural outcomes in this thesis are not consistent with the

Malawi or Idro's findings. There were no ADHD-like behaviour observed in this thesis, children instead displayed more internalizing behavioural problems unlike the externalizing behaviour seen in Birbeck's or Idro's studies.

These inconsistent findings call for more long-term follow-up studies to describe the development of behavioural problems after CNS malaria more accurately. It is worth noting that the Malawi study used children with only cerebral malaria with retinal findings indicative of cerebral insult. These children therefore had a more severe form of malaria compared to the children in study IV which may partly explain the different behavioural outcomes in these studies.

In addition to describing the cognitive outcomes of cerebral malaria, study I identified some risk factors for long term cognitive deficits. Neurological signs like hyporeflexia on admission and presence of any neurological deficit at 6 months were associated with cognitive impairment at 24 months. Earlier, a follow-up study on these same children at six months identified seizures and coma duration as being associated with cognitive impairment (Boivin et al., 2007). For clinical practice, measures to manage seizures, resolve coma and other factors associated with neurological outcome may prove beneficial in reducing the frequency of cognitive impairment in Africa.

Whereas these studies looked at clinical features associated with cognitive outcome, other factors that may be involved in brain injury during malaria infection like elevated cytokine release, nitric oxide and endothelial micro particles were not collectively analysed. Analysis of these likely causes of brain injury together may help identify which factors contribute more to the cognitive outcomes of cerebral malaria. This may also shed light on the poorly understood pathogenesis of cerebral malaria and possibly other encephalopathies. Adjunct therapies for cognitive deficits after CNS malaria could then be developed based on these associated factors.

One drawback to understanding the cognitive outcomes of cerebral malaria and their pathogenesis is lack of a consensus among the different research groups on what to test and which test batteries to use. This is mainly due to the limited culturally sensitive tests for use in this setting. As a result, some sites show different outcomes of CNS malaria compared to others due to different tests used. For example, Boivin and colleagues in Uganda have shown consistently that attention is affected (Boivin et al., 2007, John et al., 2008a) while Carter and colleagues in Kenya show speech and language being commonly affected (Carter et al., 2006, Carter et al., 2005a, Carter et al., 2003a, Carter et al., 2005b). The studies in Uganda did not assess speech and

language in these children making comparison of cognitive outcomes between different sites difficult.

A further limitation of Studies I and IV is the limited follow-up time. Whereas Study I looked at outcomes after 24 months, evidence from earlier studies in Kenya show deficits persisting at 8 years and more after CNS malaria (Carter et al., 2005b). A longer follow-up would give a better picture on the course of these cognitive deficits. Finally, these studies were carried out in children five years and older yet malaria is more prevalent in those five years and below. This was mainly due to lack of appropriate tests for these young children.

7.2 Neuropsychological assessment

Study III looked at the construct validity of the KABC-II which was found to measure the same cognitive abilities as it was designed to measure. Thirteen of the KABC-II's subtests loaded on four factors corresponding to four abilities; Working Memory, Visuospatial skills, Learning and Planning. However this study did not look at other psychometric properties like reliability, sensitivity and specificity. Future studies may need to go further and assess these other properties using other already validated tests as a gold standard or seeing how well the KABC-II scores are associated with other variables.

Malda and colleagues have also found the KABC-II to be valid as well as reliable when used with Indian children (Malda et al., 2010). This was after carrying out adaptation of the KABC-II through item modification and changes to item administration (Malda et al., 2008). Other attempts at developing culturally appropriate tests for Africa by modifying items from Western tests to suit the African setting have been done (Abubakar et al., 2007, Holding et al., 2004, Nampijja et al., 2010).

Children in sub-Saharan Africa are at risk for cognitive deficits as a result of physical illness, inadequate nutrition, poverty and war violence (Walker et al., 2007). With few culturally appropriate tests to assess the cognitive outcomes of the above risk factors, adaptation of existing Western tests is a possible option. However cultural biases must first be ruled out. For younger age groups, paper-pencil tests like the KABC-II above can be difficult to administer and interpret. Even for the older children, there is a possibility of test instructions not being administered uniformly or children from one culture solving the same problem differently thus having different skills being tested (Sternberg, 2004). It is crucial therefore to identify more suitable tests that are not heavily dependent on language and are tailored to each culture.

Kihara and colleagues have piloted the use of event related potentials in Kenyan children (Kihara et al., 2010b). Event related potentials are electrical signals produced in the brain in response to a stimulus (Kolb and Whishaw, 2009). In Kihara's study, familiar and unfamiliar stimuli were used to test the children's visual and auditory processing basing on the timing of the signals produced. It was observed that brain wave responses in these children are age dependant indicating maturation processes affect cognitive functions (Kihara et al., 2010b). This method is devoid of the cultural biases that most Western paper-pencil tests have. Its downside is the cost of the equipment which may limit its widespread use in this region.

In their cross-cultural studies in Africa, Stenberg et al have identified two types of testing; dynamic testing where feedback is given to the child to measure the processes involved in learning and change and static testing where the emphasis is measuring the products of pre-existing skills and no feedback is given (Sternberg et al., 2002). They go on to argue that for children brought up in environments that may compromise their cognitive development, dynamic testing is a better way to assess the child's developing abilities (Sternberg et al., 2002). This may serve as an indicator of a child's actual abilities. Static assessment will measure the child's developed abilities, which may be low due to the environmental pressures. Taken together, dynamic assessments are therefore sensitive to long term environmental impoverishment while static assessments appear more sensitive to actual brain insult. This may explain why attention (a static assessment) is consistently observed as a deficient skill in children affected by cerebral malaria (Boivin, 2002, Boivin et al., 2007, John et al., 2008a) and not abilities derived from dynamic testing like learning ability.

The implication here for neuropsychological practice in sub-Saharan African is to first identify the risk groups being assessed before carrying out the testing. Short of this, children cognitively compromised by say cerebral malaria, may score within the normal if given dynamic testing. In the studies in this thesis, learning ability, a dynamic assessment, was not affected by cerebral malaria but attention was.

In clinical practice, there may be some difficulties given that Uganda like most sub-Saharan African countries lack enough mental health specialists to administer these lengthy tests (Ndyanabangi et al., 2004, Ovuga et al., 2007). Short of either developing shorter versions of the neuropsychological tests or beefing up the human resource, neuropsychological assessment and rehabilitation are a long way from becoming routine clinical practise in this region.

7.3 Computerised cognitive rehabilitation training

The two cognitive intervention studies showed some benefit although the effect was not as hypothesized. Basing on Study I where the severity and frequency of cognitive deficits was higher at 24 months than what was seen at three and six months, it was hypothesized that immediate interventions would have better outcomes than delayed interventions by halting the worsening of the cognitive deficits. Study II carried out four years after the malaria episode showed improvement in all the outcomes with significant improvement observed in three of the outcomes. Study V was an immediate intervention carried out three months after the malaria episode. Contrary to the hypothesized effect of an immediate intervention, mixed results were observed in this study with only one of the ten outcomes showing improvement after the intervention. Surprisingly, in one outcome (working memory), the intervention group had poorer scores than the treatment as usual group.

These results put the above hypothesis to question and seem to imply that benefit is greatest for those who are more cognitively compromised. It is therefore likely that individuals who are more cognitively compromised (patients in Study I) have more gains to make in cognitive function after CCRT compared to those less compromised (Study V patients). This may explain why the delayed intervention was more effective than the immediate intervention. In other words, the more cognitively compromised children have their functioning much lower below their normal function compared to those less compromised. The former therefore make more gains in cognitive functioning from the intervention than the latter who are nearer their normal functioning.

These results however necessitate further work in cognitive rehabilitation for malaria infection. If delayed interventions are better, how delayed should the intervention be; 6 months, 1 year or 4 years as we did in Study I? Secondly, the mixed results from study V may require re-thinking the number of training sessions and the content of the cognitive training. Other successful cognitive intervention studies have used more training sessions than the 16 which were used in both studies II and V (Holmes et al., 2009, Klingberg et al., 2005, Sjo et al., 2010, van 't Hooft et al., 2007). Thirdly, training of specific cognitive abilities may be more effective than training several cognitive abilities as was done in the two studies. Training of working memory only has proven effective in improving cognitive functioning (both trained and untrained skills) in children (Holmes et al., 2009, Klingberg et al., 2005). Fourthly, are these cognitive benefits sustained? We did not do any long-term follow up to provide

any answers to this important question. Finally, there is a likelihood that the improved test scores in the intervention groups were due to the computer exposure as well as the prolonged interaction with the trainers who also happened to administer the tests and not the direct effect of the intervention (Iverson et al., 2009).

The majority of the children who suffer from malaria and therefore bear the brunt of the resulting cognitive effects are under five years. This vulnerable group cannot perform the cognitive exercises we used or other computer based cognitive interventions. They clearly need appropriate interventions to help them achieve their full cognitive potential.

7.4 Conclusions and policy implications

This study has three main messages with policy implications:

1) CNS malaria leads to long-term cognitive deficits in Ugandan children.
2) These deficits can be detected using neuropsychological tests developed in the West after a few modifications.
3) Computerised cognitive rehabilitation can resolve some of these deficits.

The policy implications from these messages are:

1) Given that the risk factors for impaired cognition in children are common in the Ugandan environment, there is need for routine neuropsychological testing for children admitted with illnesses having cerebral involvement like cerebral malaria and meningitis, possibly also other conditions like malnutrition.
2) Interventions should be planned for children with apparent cognitive deficits or those at risk of developing them.
3) The attainment of the two above goals relies on adequate staffing of national and regional referral centres with specialists to carry out these tasks. This calls for training and capacity building.

7.5 Future studies

There are several studies that can be carried out that may provide some answers to the unresolved issues raised in the discussion above. Future studies of CNS malaria could assess cerebrospinal fluid and serum cytokines as well as endothelial microparticles and other clinical and laboratory variables that have been associated with cognitive deficits in cerebral malaria. Analyses of all these risk factors could shed some light on the pathogenesis of cerebral malaria and the resulting cognitive

outcomes. Such studies could in the long run develop adjunct therapies for these cognitive deficits once the risk factors are identified.

Much as the two intervention studies in this thesis showed improved cognitive outcomes, it is still not clear whether these improvements are due to examiner bias since no blinding was done or due to the increased interaction with the testers and computers. Future interventions should include another type of control group that will play computer exercises that do not train cognitive skills while the treatment group will play the cognitive exercises. This will create a similar computer and experimenter exposure for the children in the two groups which was not possible with the two studies in this thesis. Blinding too should be introduced in these future studies.

All the interventions here have been done with children five years and older yet children below five years are the ones mainly affected by malaria. Interventions for these children are definitely needed.

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