THE NEUROPSYCHOLOGY OF CEREBRAL MALARIA

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We accept this dissertation as conforming to the required standard

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photocopying or other means, without the permission of the author.
The purpose of this study was to investigate the effects of cerebral malaria on the neuropsychological functioning of non-immune Ghanaian children. Twenty hospital-referred children between ages 7 and 16 years who met the World Health Organization (WHO, 1986) research criteria for the diagnosis of cerebral malaria, and who had no known history of other neurological disease were recruited for this study. Twenty matched control healthy children without a history of malaria or other neurological disease were also assessed. Each subject was administered a battery of neuropsychological tests judged to be highly sensitive to brain injury and relatively impervious to linguistic or other cultural factors.

These results (from comparisons using the general linear model) are the first to provide evidence of subacute neurobehavioural sequelae of cerebral malaria in children. Subjects demonstrated deficits in such functional domains as accuracy of visual scanning, immediate and delayed visual memory, bimanual tactile discrimination, perceptual abstraction and rule learning skills, right ear auditory information processing, and dominant hand motor speed. A strong negative association between coma duration and bimanual tactile discrimination performance was also found. Contrary to expectations, no evidence for emotional dysfunction resulting directly from cerebral malaria emerged from this study. Nonverbal reasoning, visuospatial
processing, auditory attention and sequencing, verbal fluency, and fine motor dexterity were found to be intact.

The pattern of neuropsychological test performance in this study was judged to be consistent with a small-vessel cerebrovasculitis secondary to infection with *plasmodium falciparum*. Implications and limitations of this investigation, as well as directions for future research were discussed in the context of malaria endemicity.

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I am most grateful to my supervisory committee members for the time spent reading drafts of this dissertation, and for their input and constructive criticisms. Special thanks in this regard are owing to my supervisor, Dr. Frank Spellacy, whom I am honoured to call my mentor.
DEDICATION

To the memory of my late father, and to Albert.
INTRODUCTION

Malaria is a disease acquired from the “bite” of an infected female anopheles mosquito. The mechanism of transmission is simple. Whilst probing for food, the mosquito injects microscopic parasites (hematozoa) which were previously acquired from a malaria patient into a healthy individual. These parasites then invade the liver, where they develop and multiply over approximately a fortnight. After this incubation period the parasites migrate into the red blood cells. Following further multiplication and a variable period of time ranging from days to weeks, the red blood cells are destroyed, resulting in anemia.

Most of the antimalarial medications currently available are ineffective in preventing primary infection. Their effects lie instead at the post-hepatic phase of the disease process in the blood stream, where they typically repress parasite maturity and in so doing prevent the onset of clinical symptoms.

Historical perspectives

Malaria, a term that literally means “bad air,” was until only a century ago believed in Europe to be caused by the inhalation of poisonous marsh vapours. Although Ross is said to be the first to draw a link between mosquitoes and malaria, as early as 1854 the British explorer Sir Richard Burton recorded but dismissed the widespread belief in Somalia that mosquitoes cause malaria (cited in
Heppner et. al., 1993). It is historically important to note that malaria used to be a common disease in the non-tropics. It is therefore not surprising that at the end of World War I the Viennese psychiatrist von Wagner-Jauregg began inducing malaria as a treatment for general paresis of the insane (see Wagner-Jauregg, 1994), an effort that later earned him the Nobel Prize (White, 1993).

There are four species of human malaria parasites in the genus Plasmodium (P), although a wide phenotypic variety can be found within each group (Garnham, 1966). These are P. Falciparum, P. Vivax, P. Ovale, and P. Malariae. Of the four, P. Falciparum causes the most morbidity, mortality, and multiple drug resistance. Cerebral malaria (CM), a disease first described by Kraeplin in 1881 as “febris pernicosa comatosa”, is one of the most serious complications of P. Falciparum infection (Nagatake et. al., 1992; Oo et. al., 1987). Indeed, according to MacPherson and his colleagues (1985) between 20 to 50% of all deaths from falciparum malaria are due to the direct involvement of the central nervous system (CNS). Bell et al (1976) suggest that CM is probably “the commonest (and most important) cause of acute encephalopathy in the tropics”. The only plasmodial strain that produces CM in humans is P. Falciparum (Toro & Roman, 1978). Untreated CM is invariably fatal (Gelfand, 1973). The term cerebral malaria is probably a misnomer, because it is a multisystem disease that typically shows its effects on many other organs of the body including the liver, spleen, and kidneys.
Oliguria, uremia, and renal failure are some frequent complications of falciparum malaria (see Most, 1969). While the more appropriate term “malaria with cerebral dysfunction” is advised in terms of its technical accuracy, the traditional designation of “cerebral malaria” will be retained throughout this monograph for convenience reasons.

Some epidemiological considerations

Cerebral malaria occurs at all ages in non-immune individuals, but shows a predilection for children under five years in holoendemic areas (Schmutzhard & Gerstenbrand, 1984). Only few adults in hyperendemic regions develop the severe clinical manifestations of falciparum malaria (Phillips & Solomon, 1990), including pregnant mothers who experience a decrease of immunity against malaria, and non-immune adults who interrupt prophylactic treatment (Toro & Roman, 1978). Despite the acquisition of protective immunity among indigenous people in endemic areas, the prevalence rates of asymptomatic malaria parasitemia remain high (Molyneux & Fox, 1993). Jackson (1985) has reported an overall parasite rate of 68% in a survey of 500 Liberian children, with the dominant species (i.e., 71.7%) being P. Falciparum. In Ghana where 8% of all annual deaths are attributed to malaria, the crude parasite rate in a recent community survey
(Agyepong, 1992) of 112 asymptomatic female teenagers was 49%, with over 90% being P. Falciparum.

Congenitally acquired malaria is said to be rare; its prevalence estimated at 0.3% of all malaria cases in endemic areas (Hindi & Azimi, 1980). The underlying processes involved in congenital infection are not well understood; however, placental damage (Logie & McGregor, 1970) and any other opportunity for maternal and fetal blood exchange at birth may be significant factors. Jackson’s (1985) data, which found microscopic confirmation of malaria in 22% of newborns and infants tested in Liberia, shows that congenitally acquired malaria may not be as uncommon as some researchers think.

The epidemiological pattern of malaria in much of tropical Africa is changing quickly, with increasing numbers of indigenous adults succumbing to CM (Brewster et. al., 1990). This instability of malaria endemicity is probably because the acquisition of immunity with increasing age is proceeding at a slower rate than in the past (McGregor, 1987). There is evidence (Kirkham et. al., 1991) that CM shows different clinical manifestations in South East Asian adults and in African children: in Thai adults, the coma of CM is typically more prolonged than in African children (Phillips & Solomon, 1990). It has been observed (Edington, 1954; 1967) that CM rarely occurs with kwashiorkor or marasmus in children.
There are as yet unconfirmed reports in parts of Central Africa that the Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) predispose to severe malaria (White & Looareesuwan, 1987). All these complicating factors make it impossible to reach an accurate understanding of the epidemiology of malaria.

**Diagnostic criteria for cerebral malaria**

Warrell and his colleagues (1982) have cogently observed that the malariology literature is characterized by many different definitions of CM. This may explain the wide disparities in observed clinical features, incidence of neurological sequelae, mortality, and efficacy of treatments. Commey (1984) has argued for the adoption of a set of diagnostic criteria of CM that will enable treatment and outcome from different research centers to be effectively compared. In attempting to satisfy this need, the World Health Organization (WHO) Malaria Action Program (WHO, 1986) has proposed what appears to be the most comprehensive definition criteria for CM yet. These are listed below:

1. “Unarousable” coma (defined as either absent or non-localizing motor response to noxious stimuli) lasting over six hours after a generalized convulsion.
2. Exclusion of other encephalopathies. The coma, for example, must not be due to hypoglycemia, meningio-encephalitis, head injury, metabolic disorders, or cerebrovascular accidents.

3. Infection of the asexual form of P. Falciparum (which must be demonstrated ante mortem in peripheral blood or bone marrow smear, or post mortem in a brain smear).

There have been many criticisms of these definitional criteria. Leaver et. al. (1990) have pointed out that the term “unarousable coma” is imprecise, and advocate its replacement with a scale score (11 or less) on the Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974). This suggestion has itself been criticized by Newton and his colleagues (1990) who point out that the GCS was designed to monitor coma rather than provide a complete neurologic description of the patient, the latter being the main objective of the W.H.O criteria. The GCS, because of its heavy reliance on verbal responses, is not well suited for use with infants who form the majority of CM cases. Another potential shortcoming is the specification of methods used in demonstrating falciparum infection. Intradermal skin prick, for instance, has been found (MacPherson et. al., 1985) to be a more sensitive method of diagnosing P. Falciparum malaria than bone marrow aspiration. Sophisticated
experimental methods such as DNA probes and acridine orange fluorescence (Lanan et. al., 1989) are quickly rendering the current methods obsolete.

**The neuropathogenesis of cerebral malaria**

Little is known about the underlying causes of CM (Looareesuwan et. al., 1983; Phillips & Solomon, 1990), although many pathogenic possibilities have been raised. The essential pathologic feature of severe falciparum malaria is sequestration of parasitised erythrocytes (i.e., red blood cells) in cerebral venules and capillaries where they are known to adhere to endothelial cells (Gordeuk et. al., 1992; MacPherson et. al., 1985; Nagatake et. al., 1992; Udeinya et. al., 1981; W.H.O., 1986). A distinct pathologic feature of CM is the presence of small petechial (ring) hemorrhages typically concentrated in the white matter of the cerebral hemispheres (MacPherson et. al., 1985; White & Looareesuwan, 1987).

Although some of the older theories of the pathogenesis of CM are currently discounted, they will be included in this discussion because of their historical impact on malariology.

According to Migasena and Maegraith’s (1967) theory, toxins in P. Falciparum parasites cause CM by increasing capillary permeability and a breakdown in the blood-brain and blood-cerebrospinal fluid barriers. It was believed that the extravasation of serum proteins from the cerebral capillaries cause
vascular stasis and cerebral edema, culminating in a clinically evident coma. Unfortunately this theory is not supported by clinical and experimental evidence: blood-cerebrospinal fluid barrier is known to be relatively intact throughout the clinical course of CM (Warrell et. al., 1986), papilloedema is rare, and cerebrospinal fluid (CSF) opening pressure is also normal in CM patients. Besides, dexamethasone, a glucocorticoid known to reduce cerebral vasogenic edema, is actually contraindicated in comatose CM patients (Warrell, et. al., 1982). It is currently believed that any cerebral edema in CM patients is usually an agonal phenomenon, implying a terminal infection.

Another theory, which like the permeability theory is based on research with animals (Ehrich et. al., 1984; Rest, 1982), has attempted to link immune responses with the pathogenesis of CM. Toro and Roman (1978), and Posner and Roman (1991) contend that the pathology of CM is consistent with an “acute disseminated vasculomyelinopathy” (i.e., microscopic lesions), an immune reaction of the CNS to P. Falciparum infection. This is said to result in an immune complex vasculitis of the cerebral vessels, and demyelination. The immune theory has however not received serious attention probably because histological evidence is lacking in fatal cases of falciparum malaria (W.H.O., 1986).
A third hypothesis that is widely accepted as the most plausible explanation for CM today is the "mechanical" theory (Goodall & Brobby, 1982; Miller et. al., 1972; Nagatake et. al., 1992; Warrell et. al., 1988). According to this view, adhesion of parasitized erythrocytes to the endothelial cells results in an obstruction of the cerebral microvasculature. When this obstruction occurs, normal erythrocytes must either undergo considerable deformation in order to traverse the capillary beds or they are unable to traverse them altogether. This kind of capillary obstruction is also known to occur when erythrocytes are unusually rigid, reminiscent of sickle cell disease. The consequences of this mechanical obstruction include a reduction in cerebral blood flow and oxygen delivery, which result in cerebral hypoxia and subsequent anaerobic glycolysis. Nagatake and his colleagues (1992) found a significant difference between the cerebral cortex and white matter in the percentage of cerebral microvessels showing parasitized red blood cell sequestration (an average of 31.3% and 40% respectively). This finding indicates a predilection for white matter microvascular obstruction in CM. A neuropathologic examination of 19 cases of CM at postmortem reported by Toro and Roman (1978) also revealed congestion and petechial hemorrhages preferentially involving cerebral white matter in 79% of their patients, with macroscopic slate-gray discoloration of the cortex and basal ganglia occurring in only 21% of the cases. Warrell et al.'s (1988) finding that mature parasites have an extremely active
metabolism, converting up to 90% of ingested glucose into lactic acid, is supported by other research data (Sherman, 1979; Jensen et. al., 1983) which point to the fact that parasitized red cells consume between 20 to 30 times more glucose than non-parasitized red cells. These investigations therefore support the hypothesis of a stagnant anoxaemia resulting from a critical reduction in blood flow. It is entirely possible that watershed infarctions in the areas of the brain with limited vascular reserve will suffer most from cerebral arterial occlusion due to CM (see Brewster et. al., 1990). Indeed, Goodall and Brobby (1982) have speculated that the minor cerebral ischemic lesions that result from the choking activity of parasitized sickled cells may modify cerebral dominance in young children, and account for the rather high prevalence of stuttering among many West Africans.

The newest theory of the pathogenesis of CM (Clark, Rockett, & Cowden, 1991) suggests a link between cytokines, nitric oxide, and CM. According to this theory nitric oxide (a molecule that is generated from cells in response to cytokines, and which shows very high levels in CM patients) crosses the blood-brain barrier and impairs neurologic function through increased vasodilation and raised intracranial pressure. Despite the novelty of this hypothesis, however, it has already received mixed empirical reviews (see Cot et. al., 1994; and Nussler et. al., 1994).
Regardless of which theory one favours, there is no gainsaying the fact that (some form of generalized) anoxia is a significant pathophysiological mechanism that contributes to the clinical manifestations of CM; this has been recognized for at least fifty years (see Rigdon & Fletcher, 1945).

**The clinical picture of malaria**

Some common symptoms of clinical malaria are fever, myalgia, fatigue, photophobia, anorexia, and vomiting. Altered consciousness has been described as the single most characteristic feature of the clinical manifestation of CM (Molyneux et. al., 1989). Phillips and Solomon (1990) have also indicated that convulsions may herald the onset of CM in about 82% of children.

**The psychopathology of cerebral malaria**

Although many psychiatric disorders have been attributed to malaria, there is a gross lack of empirically sound basis for many of the conclusions regarding the psychiatric complications of this disease. Its psychological symptoms are generally believed to be nonspecific (Anderson, 1927), and can present with a wide array of clinical symptoms.

From a historical perspective, even as early as 400 B.C., the ancient Greeks made the association between malaria fever, personality changes, and melancholy
(see Jones, 1909). In the late 17th century Sydenham observed mania to be a complication of malaria. Pasamanik (1897) also noted psychosis, depression, acute dementia, and agitated melancholy to be the most common sequelae of malaria. In what may well be the first documented medico-legal consideration of malaria and psychopathology, Anderson (1927) noted that malaria can induce organic mental changes that may render an individual unaccountable for illegal and/or socially inappropriate actions.

Carothers (1953) suggested that malaria accounted for between three and four percent of all first-time admissions to mental hospitals in Kenya. Blocker et al (1968) reported that 1.6% of U.S. soldiers in Vietnam showed psychiatric symptoms in association with malaria; Daroff and his colleagues (1967) reported somewhat similar figures (from 1.2 to 2.3%) for U.S. hospitals during the second World War. Arieti (1946) provided an early four-group classification of the psychiatric manifestations of CM. First, there is an acute delirium, which according to Toro and Roman (1978) may resemble alcohol intoxication. Second, there are paranoid syndromes where the delusional state is dominant. Thirdly, one may observe psychoses secondary to the organic illness. Finally, there is the presence of organic (neurologic) signs directly attributable to the specific CNS lesions from CM. Daroff et al (1967) noted acute personality changes, and point out that the cerebral effects of chronic malarial infection may be indistinguishable from the
symptoms of antisocial personality disorder, chronic anxiety states, or conversion hysteria. Prakash and Stein (1990) reported the case of an adult woman who presented with a hysterical stupor occurring in the context of an atypical depression. These findings suggest that malaria (not just cerebral malaria) may be directly or indirectly associated with psychiatric disorders, although their specific clinical manifestations and chronicity have not been systematically studied. Sowunmi (1993) has gone further in arguing for long-term prospective investigations of the clinical spectrum of psychopathology in pediatric CM, following his report of brief psychotic disorders in two children following medical recovery from CM induced coma.

A counter-intuitive phenomenon is that there may be certain conditions where the effects of malaria result not in psychiatric disorders, but rather in their resolution (see Lipper and Werman, 1977). With discussions of psychiatric disorders invariably arise issues regarding the efficacy of psychotherapy; this has not yet been empirically pursued in malaria. Funkenstein (1949) was far ahead of his time in suggesting the need for psychotherapy efficacy studies in anxiety caused by “chronic” malaria.

Medications used in treating CM have been known to produce various mental disorders. Chloroquine therapy is known to cause a toxic confusional state
with psychosis (Brookes, 1966; Good & Shader, 1977; Rockwell, 1968), as well as a manic episode (Lovestone, 1991).

**The neurologic effects of cerebral malaria**

Nervous system examinations of CM patients reveal a long list of neurological signs and symptoms. Although seizures occur in at least half of all CM patients (White et al., 1985), it is not known whether seizures predispose to epilepsy in later life (White & Looareesuwan, 1987). Molyneux et al (1989) have noted that 34% of children with CM exhibit decerebrate and decorticate signs (including extensor rigidity, sustained limb posturing, opisthotonus, and generalized flaccidity) at hospital admission. Corneal reflexes are notably absent in about 56% of those with poor prognosis (Molyneux et al., 1989), while survivors of CM tend to have intact corneal, pupillary, and occulovestibular reflexes. Retinal hemorrhages are common, and occur between 14 to 28% of cases (White & Looareesuwan, 1987). Any eye movement abnormality (such as ocular bobbing, dysconjugate eye movements, nystagmus, and sixth cranial nerve palsies) tends to be transient among CM survivors. Lewallen and her colleagues (1993) have used ophthalmologic examinations of the ocular fundi in children to report that papilledema and extramacular retinal edema can help differentiate between good versus poor prognosis in CM. Other common neurological signs include bruxism,
ankle clonus, and a snout reflex. Although an acute extrapyramidal syndrome is
typically rare, there has nevertheless been a reported case of just such an
occurrence (Jayaweera et. al., 1977). Medications such as chloroquine may cause
involuntary movements of the extrapyramidal type (Umez-Eronini & Eronini,
1977). Children with CM have been said to regain consciousness from coma more
quickly than adults, with a mean coma duration in African children being 12 hours
(White & Looareesuwan, 1987).

Despite the lack of well designed long term outcome studies, many authors
(e.g., Harinasuta & Bunnang, 1988; Molyneux et. al., 1989; Toro & Roman, 1978;
W.H.O., 1986; White et. al., 1985; White & Looareesuwan, 1987) have argued
that complete neurological recovery is the rule among CM survivors. Studies of
the neurological sequelae of CM are limited in many respects. The typical duration
of follow-up investigations that many researchers seem happy with is six months
after hospital discharge (see for example, Brewster et. al., 1990; Greenwood et.
al., 1987; Schmutzhard & Gerstenbrand, 1984). Also, some researchers (e.g.,
Brewster et. al., 1990) have relied solely on secondary reports of patients' family
members in arriving at conclusions of neurological sequelae. To all intents and
purposes, it seems that in contrast to the medical emergencies that many CM
patients present with, any recovery is deemed substantial, and therefore complete.
Remarkably, however, the longest follow-up study to date (i.e., 12 to 16 months
following hospital discharge) in Nigeria by Bondi (1992) revealed neurological deficits in 17.7% of all those who did not die from CM. He indicated the most prominent neurological manifestations to be cortical blindness, monoparesis, and "speech" deficits.

The percentages of persisting neurological sequelae following survival of CM have ranged from 2.3% in Uganda (Musoke, 1966), 4.7% in Papua New Guinea (Stace et al., 1982), 6% in Thailand (Warrell et al., 1982), 11% in Malawi (Molyneux et al., 1989), to 16.7% in Tanzania (Greenwood et al., 1987). Despite these figures, however, it is still believed that the true rate of neurological disability from CM is much higher (Schmutzhard & Gerstenbrand, 1984).

Brewster and his colleagues (1990) found hemiplegia to be the most common residual neurological abnormality in their series, followed by cortical blindness (despite normal funduscopia, intact pupillary reflexes, and normal eye movements). In their research on persistent hemiplegia following CM, Omanga and his coworkers (1983) used carotid angiography to show anterior cerebral artery occlusion in half of their sample; however, Collomb et al's (1967) carotid angiography results were normal in 75% of their sample with hemiplegia. The presence of neurological sequelae appears to be related to coma duration, profound hypoglycemia, duration of hospital stay, and recurrent and prolonged
convulsion (Brewster et. al., 1990). Marsden and Fowler (1989) speculate that repeated CM may be a risk factor in vascular dementia, a view that has not yet been subjected to empirical validation.

Unfortunately, neuroradiological investigations to date have failed to yield localizing physical signs in CM. Looareesuwan et al.'s (1983) study of CM patients did not show any consistent and diagnostic abnormality on CT scanning. Electroencephalographic (EEG) studies have shown some temporal theta-wave activity, associated with drowsiness and symmetrical slow wave activity (Prakash & Stein, 1990). More recently Newton and his colleagues (1994) used CT scans with 14 comatose Kenyan children to conclude that loss of CSF spaces (indicative of brain swelling) was the most remarkable pathological finding in CM. Probably one of the most definitive localizing neuroradiological findings to date has been Millan et al.'s (1993) Magnetic Resonance Imaging (MRI) studies, which showed a small hemorrhage adjacent to an area of infarction in the parieto-occipital lobe in a man with acute malaria.

**Psychological testing in cerebral malaria**

Some researchers (e.g., White & Looareesuwan, 1987) have concluded that CM patients regain their premorbid personality and intellect, without citing any supporting empirical evidence. Kastl and his colleagues (1968) are probably
the pioneers in relying on psychometric tests to study the psychological effects of CM. This study will therefore be evaluated in more detail.

The investigation by Kastl and his coworkers was aimed at measuring the effects of CM on intellectual functioning, while documenting any other subtle residual signs of an organic mental disturbance following medical recovery from malaria. Their subjects were 18 U.S. soldiers (i.e., nine patients diagnosed with CM and nine matched controls with malaria alone) who were hospitalized in South Vietnam. Matching variables included age, military rank, years of schooling, number of days afebrile when first examined, and number of days to re-test. Each subject was tested on the Wechsler Adult Intelligence Scale (WAIS), Wechsler Memory Scale (WMS), Bender Motor Gestalt Test, and Rorschach Inkblot Test during the acute/subacute phase of the disease process. Psychometric testing was repeated during convalescence about seven days later. At various times during hospitalization, each subject responded to the Minnesota Multiphasic Personality Inventory (MMPI). Although initial test results were consistent with mild to moderate organic dysfunctioning, subsequent testing indicated a disappearance of the organic pattern. Initial test results during the acute phase showed common deficits in intellectual functioning of both groups as manifested in such areas as recent memory, psychomotor speed, visual motor integration, and visual organization. Poor performance by the CM group on the Rorschach (i.e., smaller
number of Whole responses) and Bender Gestalt Test when they were acutely ill, but which dissipated upon re-test led the researchers to make the following conclusion: “On every test and measure but two, the performance of the cerebral malaria patients when recovered is either indistinguishable from, or superior to, a group of matched malaria patients without cerebral involvement” (Kastl et. al., 1968, p. 561). There are major conceptual and methodological flaws in this study. First, the diagnosis of CM was loosely made; no clear differentiation between the comparison groups was provided. The mere demonstration of P. Falciparum parasites is not enough justification for CM (see W.H.O., 1986), nor is the similarity of body temperature patterns a defensible basis for matching subjects as was done in this study. It can therefore be argued that the classification system used by Kastl and his colleagues lack discriminative validity in separating these two comparison groups adequately (see Morris & Fletcher, 1988, for a discussion of classification in clinical neuropsychological research methods). Secondly, the small number of subjects limits the confidence that can be placed in these results. Third, the rather short re-test interval of seven days enables the interplay of practice effects on subsequent test performance. Fourth, since this study was limited to non-immune American adults, one cannot extrapolate its results to adults born and raised in malaria endemic areas.
According to Richardson, Varney, & Roberts (1989), it is an oversimplification to assume that CM leaves no neuropsychiatric effects on its victims. From their follow-up studies with 30 U.S. Vietnam veterans with a history of CM, Richardson and her colleagues (1989) present evidence to support the view that within 10 to 15 years of surviving (and being "cured" of) the acute stages of the disease, a plethora of neurologic and psychiatric disorders were still evident. Their findings revealed such psychiatric problems as intractable depression, and a high frequency of irritable and abusive behaviour directed mainly toward family members. The neuropsychological status of these individuals (as demonstrated by their relatively poor performance on a dichotic listening task) was interpreted to indicate inefficiencies in processing auditorily presented information. Digit span testing showed some problems with attention and concentration, and there were indications of a poor retention capacity for short prose passages. These authors are of the view that there may be a "post-malarial behavior syndrome" with a subacute progressive course, since most of their subjects developed more neuropsychiatric problems over a decade following malaria than was evident in the first couple of years post-malaria. This view would explain why Kastl et al's (1968) study found no psychological deficits in the period immediately following acute infection with malaria. Richardson and her colleagues attempt to explain the progressive nature of the post-malarial behavior syndrome by noting that their
subjects' complaints resembled complex partial seizure-like phenomena, which responded well to carbamazepine (an anti-convulsant) medication. They conclude by arguing that the neuropathological changes associated with CM may predispose survivors to develop subtle electrophysiological abnormalities akin to those found in patients with complex partial seizures. Clearly, the relationship between CM and the development of subsequent seizure-like phenomena still warrants further study. The value of Richardson and her colleagues' study lies in its provision of preliminary data supporting the view that (at least in non-immune patients) there are certain distinct long-term neuropsychological effects of CM.
AIM OF STUDY

Cerebral malaria is still a poorly understood disease. Whether infection with P. Falciparum with or without CM is associated with any neuropsychological problems has not been adequately studied. If there are indeed any neuropsychological problems, the question of whether medical recovery from the acute stages of CM leads to total or partial neurobehavioural recovery is also still far from answered. There has been a long debate over the validity of full neurological recovery from CM (see Brewster et. al., 1990). Progress in understanding and accepting the neurologic sequelae of CM has been hampered largely because its essential CNS deficits have never been considered to have a sound syndromic basis in mainstream neurology. These same problems would likewise bedevil an acceptance of the neuropsychological effects of CM; a most regrettable possibility because behaviour is the most important measure of integrity of the nervous system. Extensive neuropsychological evaluations of higher cortical functions have historically been invaluable in elucidating the nature, course, and severity of many neurologic disorders. Cerebral malaria must not be an exception.

The goal of the present study, therefore, was to systematically explore the neuropsychological functioning of children who had recovered from the acute stages of CM. The rationale behind studying children in a malaria endemic region such as Ghana is to enhance generalizability of findings across areas known to
have a high incidence and prevalence of falciparum malaria. This is of particular relevance, although the clinical features (Kirkham et. al., 1991) and coma duration (Phillips & Solomon, 1990) of CM in African children are different from those seen in many other malaria endemic regions.

Kastl et al’s (1968) research with non-immune adult American soldiers, although lacking methodological elegance, indicates negligible short-term psychometrically-based sequelae of CM. In order for a more lucid picture of the short-term neuropsychological effects of CM in children to be made, we need not extrapolate findings with non-immune adult populations to children, but rather to study the disease process as they occur in children themselves separately.

The question arises regarding psychopathology and emotional distress in children with a history of CM. Another aim of this study was to grossly explore the views of research participants and their family members concerning any noticeable changes in mood states following recovery from CM.
SPECIFIC RESEARCH QUESTIONS

**Question 1: Does cerebral malaria affect an individual’s efficiency and speed of information processing?**

It has been pointed out that a consistent pathologic feature in CM is the presence of small, petechial hemorrhages typically concentrated in the white matter of the cerebral hemispheres (MacPherson et. al., 1985; White & Looareesuwan, 1987). Toro and Roman’s (1978) view of CM as an acute disseminated vasculomyelinopathy implicates demyelination as a possible effect of the disease (the presence of myelin, a fatty sheath that wraps around most mature axons serves to conserve energy, and to maintain faster rates of nerve impulse transmission).

Flechsig (1901) described how myelin development in the cerebral cortex co-occurs with chronological age. Flechsig’s “terminal fields”, which are the last to myelinate (i.e., between 4 months postnatally and 14 years), include the classical cerebral association areas known to subserve higher cortical functions. Since Flechsig’s original position on myelinogenetics still remains a valid approach to the study of structural neural development today, it can be assumed that CM would disrupt the normal progressive myelination process in children.

If the cerebral white matter is most affected by CM, and widespread demyelination of neurons occurs in this disease, then one can expect obvious
deficits on behavioural measures that depend on processing speed for optimal performance.

**Question 2: Do children with a history of cerebral malaria show tactile interhemispheric transfer inefficiencies?**

A question related to information processing abilities in CM has to do with the integrity of the corpus callosum. The corpus callosum is the single largest white matter structure in the brain which allows effective communication between the cerebral hemispheres. It is conceivable that if CM shows a predilection for the brain white matter, one may expect to find some interhemispheric transfer inefficiencies on neuropsychological testing.

**Question 3: Are any residual attentional difficulties associated with cerebral malaria?**

Coma is one of the common clinical signs of CM, and usually lasts an average of 12 hours in African children (White & Looareesuwan, 1987). Heilman, Schwartz, and Watson (1978) have reported hypoarousal in patients with the neglect syndrome, and suggest a defective arousal system arising from lesions in the corticolimbic reticular loop. Circumscribed pontine lesions seen on MRI studies have been associated with CM (Kampf et al., 1993), indicating brainstem involvement. Weinstein and Friedland (1977) have suggested an association
between anosognosia and unilateral neglect. Taken together, these studies invite the question that subtle attention and concentration problems (of which patients may not spontaneously complain) would occur as a result of the CM episode.

**Question 4: Does cerebral malaria leave any residual dysphasic disturbances?**

Bilateral diffuse hemisphere lesions appear to be more likely than focal abnormalities in CM (Brewster et. al., 1990), although the converse has been demonstrated (Kampfl et. al., 1993). Whatever the hypothesized pathogenesis of CM might be, infarctions to the watershed areas of the brain (which have limited vascular reserve) appear to be a likely candidate in CM. The isolation syndromes (Geschwind, Quadfasel, & Segarra, 1968) have been known to occur from wide lesions to hemispheric cortical watershed areas. Echolalia, which is typically seen in mixed transcortical aphasia, often indicates a border zone location of pathology (Heilman & Valenstein, 1985). Other speech difficulties such as stuttering have been noted to be prevalent in malaria endemic areas. In Ghana for instance, McCallien (1956) found the prevalence of stuttering to be 3.5% of all school children in the capital city where this present research was conducted. Goodall and Brobbey (1982) have implicated CM as providing an organic basis for stuttering. It is therefore expected that expressive dysphasias and stuttering will persist following recovery from acute CM.
**Question 5: Is memory dysfunction associated with cerebral malaria in children?**

The hippocampal region of the brain is known to be especially sensitive to ischemia (Kolb & Whishaw, 1990). It would therefore not be surprising to see evidence of medial temporal lobe degeneration following CM. Memory difficulties are known to occur after even small and temporary reductions in vascular supply to certain brain regions. It is postulated that recent memory in particular, and temporal lobe integrity in general, will be affected by CM.

**Question 6: Does cerebral malaria leave any lateralized motor disturbances?**

Extrapyramidal movement disorders are rare in CM, and antimalarial medications such as chloroquine have been known to cause isolated movement disorders (Umez-Eronini & Eronini, 1977). Studies of persistent hemiplegia following recovery from acute CM using carotid angiography have produced somewhat contradictory results (see Collomb et. al., 1967; and Omanga et. al., 1983), although hemiparesis is still commonly seen during the acute stages of the disease process. Looareesuwan and his colleagues’ (1983) CT scan study, which failed to yield localising physical signs, provides converging evidence to support the view that consistent lateralized motor dysfunctions are rare in CM. Clinical reports (Senanayake, 1987) and pathological confirmation (Sein et. al., 1993) support the
view that cerebellar involvements (especially cerebellar ataxia) are also very common in CM. It would therefore be particularly important to know the extent to which CM affects motor speed and dexterity.

**Question 7: Is cerebral malaria associated with any sensory-perceptual deficits?**

Cortical blindness is often noted in acute CM. It would be important to determine whether there are any visual field defects associated with CM. Gross auditory discrimination testing, as well as testing for graphesthesia will likewise be made.

**Question 8: Are there any emotional and personality changes associated with cerebral malaria?**

Richardson and her colleagues (1989) found long term emotional problems, presumed to be associated with CM, in U.S. Vietnam war veterans. Affective symptoms (including depression, anxiety states, and anger outbursts) are known to occur in complex partial seizure-like symptoms (Roberts et. al., 1992), and seizures/convulsions occur in 50 to 82% (Phillips & Solomon, 1990; White et. al., 1985) of children with CM. An investigation of the study participants, as well as collateral information from family members, will be useful in disclosing any subtle changes in mood states following CM recovery.
METHOD

**Ethical considerations**

Ethical guidelines provided by the W.H.O. and Council for International Organizations of Medical Sciences (CIOMS) (1982), as well as the American Psychological Association (A.P.A., 1992) were followed. Approval for the conduct of this research was obtained from both the University of Victoria Ethics Committee, and the University of Ghana Medical School Ethics Committee.

Informed consent (see Appendix A) from parents and guardians of all minors was sought and obtained. Consent was also separately obtained from parents themselves before they were asked to provide additional information regarding their wards' behaviours and mood states.

**Subjects**

The study participants, who were local residents of the city of Accra, Ghana, were selected from both hospital and school sources. Referrals from hospital sources were invited from physicians at the Korle-Bu Teaching Hospital, Ghana Military Hospital, and Achimota School Hospital. Matched control group subjects were recruited from the Achimota School (Primary/Junior Secondary School Department).
Criteria for inclusion in this study as clinical subjects were a history of clearly diagnosed cerebral malaria according to the W.H.O. (1986) standards. See page 5 for a description of these criteria. Potential subjects were excluded if they were known to have a previous history of perinatal birth complications, head injury, sickle cell trait or disease, diabetes, and if their mother was known to have had malaria during pregnancy.

The matched control group subjects were also expected to meet all the criteria set for the clinical group, but with one exception: no prior medically documented history of malaria infection.

Forty participants who met the research criteria were studied, with twenty subjects having a clearly documented history of cerebral malaria. Another group of twenty healthy individuals without a history of malaria was matched to each of the "clinical group". Matching criteria included age, gender, educational level, and handedness. Table 1 shows the demographic and biomedical characteristics of the entire sample. Of the entire sample, 14 (i.e., 35%) were males, and 26 (65%) were females. All the subjects except 4 were right handed, implying that two left-handed subjects had a prior history of CM and the other two were matched controls, since handedness was a controlling factor in this study.
Materials

Test materials commonly used to assess certain neurobehavioural functions were selected from a broader neuropsychological test battery. Standardized materials for use with each of these tests were employed without major modification. At least 17 tests were used, and they were selected for their established sensitivity and specificity in measuring the domains of interest to this research. Another determining factor that went into the choice of these tests was the relative ease with which they could be meaningfully used in a culture that is different from the (North American) setting in which they were originally devised. The tests used are listed below.


3. Rey-Osterrieth Complex Figure Test (Osterrieth, 1944).

4. The Halstead Reitan Neuropsychological Test Battery (Finger Tapping Test, Sensory-Perceptual Examination, and Trail Making Test) (Reitan & Wolfson, 1985).

5. Visual and Auditory Reaction Times (University of Victoria Plate).


8. Dichotic Listening (Words) Test


13. Roughness Discrimination Test (materials included two 2x2 inch strips of three different grades of sandpaper, each pasted on a smooth photographic paper).

   Local Ghanaian manufactured sandpaper grades 220, P120, and P60 were used.


**Procedure**

Potential research subjects and their parents were first interviewed in order to identify and eliminate those with any of the exclusion criteria noted above. A brief description of the aims and objectives of this project (see Appendix B) was provided to all the subjects and their parents, after which informed consent was
obtained for participation in the study. Appointments were then set up for testing, and medical records were reviewed. Each participant was in the interim referred to his or her local hospital for laboratory examination of current malaria infection at cost to the researcher.

Each subject was tested individually, and the same order of test administration was followed for every participant. Order of administration was Corsi Block Span, Block Design, Digit Span, Rey Complex Figure (copy), Finger Tapping, Visual and Auditory Reaction Times, Word Fluency, Rey Complex Figure (delay), Booklet Category, Coding, Sensory -Perceptual Examination, Dichotic Listening, Trails A & B, Test d2, Roughness Discrimination, 2-Point Discrimination, Purdue Pegboard, and Raven’s Progressive Matrices respectively. The duration of testing time for each subject was between 2 and 3 hours. Following completion of this stage of the evaluation, each subject was interviewed to determine any notable behavioural change post-CM. Parents were also interviewed for collateral information, and then provided with the investigator’s contact address for purposes of feedback regarding the research findings.

**Statistical analysis**

The Statistical Package for the Social Sciences (SPSS) for Windows version 6.0 (Norusis, 1993) statistical software on IBM PC was used to analyze
the neuropsychological test data of individuals with a history of CM and their matched controls (hereby designated as the non-CM group). A single factor-design (using the CM and non-CM groups) was employed, where the "independent" variable was defined as the presence/absence of a prior history of clinically diagnosed CM, and the dependent variable was defined in terms of performance on a battery of neuropsychological tests. A multivariate analysis of variance (MANOVA) was computed to help answer some of the research questions. The use of a multivariate procedure on some factors was based on the rather limited sample size, and therefore expected to offer some protection from the experiment-wise Type I error rate. To further ensure against Type I error, given the large number (31) of analyses, all analyses were run with alpha set at the .01 level. Pearson product moment correlation analyses were performed using the 2-tailed significance level for decision making. Univariate F tests, and where appropriate, independent- or paired- samples t-tests were used in making pair-wise comparisons. Appropriate effect size measures (e.g., eta squared and confidence limit intervals) were used to estimate the proportion of variance in the dependent variables accounted for by differences among the research groups.
RESULTS

The raw neuropsychological test data for all the subjects in this study are presented in Appendix C. Bivariate correlation coefficients for the major test scores by age and by gender are also presented in Appendix E.

Table 1 below shows the major biographic variables for the entire sample, which are classified according to the factorial design in this study. As each individual comprising one group was carefully matched to cohorts in the other group, it is not surprising that the inter-group means and standard deviations of the variables listed in the table display identical values.

Table 2 shows the salient biomedical characteristics of the CM group that were determined at the time of admission to hospital for CM. All the CM subjects were brought to hospital in an "altered state of consciousness", hence the exact onset of coma was determined in most cases from parents and other caretakers of the individuals in question. Laboratory confirmation of P. falciparum parasitemia was made from thick peripheral blood smears using geimsa staining.

A consideration that preceded all analyses was whether the subject groups would differ in intelligence, thereby introducing a systematic bias in results. This potential confounding factor was addressed by the administration of Raven's Progressive Matrices Test to all subjects. There was little foundation for this
Table 1 Demographic variables for CM (n=20) and non-CM (n=20) Groups and Statistical Tests of Subject Group Differences.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measure</th>
<th>Statistic</th>
<th>CM</th>
<th>non-CM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>years</td>
<td>M (SD)</td>
<td>11.10(3.34)</td>
<td>11.10(3.34)</td>
</tr>
<tr>
<td>Gender</td>
<td>male</td>
<td>n</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>female</td>
<td>n</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Education</td>
<td>years</td>
<td>M (SD)</td>
<td>6.10(3.34)</td>
<td>6.10(3.34)</td>
</tr>
<tr>
<td>Handedness</td>
<td>Right</td>
<td>n</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>n</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 2. Disease-Specific Biomedical Information for the CM group (n=20).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Statistic</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration (hours) of CM</td>
<td>M (SD)</td>
<td>9 (2.27)</td>
</tr>
<tr>
<td>Age (years) of diagnosis</td>
<td>M (SD)</td>
<td>7.3 (2.18)</td>
</tr>
<tr>
<td>Crude Parasite Rate (%)</td>
<td>M (SD)</td>
<td>62 (1.68)</td>
</tr>
</tbody>
</table>
concern, as the CM (M=25.15, SD=11.76) and non-CM (M=28.95, SD=11.78) groups showed no significant difference in performance on the Progressive Matrices Test, \( t(38) = -1.02, p = .31 \) (the 99% confidence interval for this difference ranges from -13.89 to 6.29). On the basis of these findings, therefore, it was judged that introducing intelligence/reasoning test scores (or for that matter, scores obtained from the Progressive Matrices Test) as a covariate in subsequent analyses are unwarranted.

**Question 1: Does cerebral malaria affect an individual's efficiency and speed of information processing?**

The Visual and Auditory Reaction Time Tests, and Trail Making Tests (A & B) were employed to answer this question. Mean latency to task completion (expressed in seconds for the Trail Making Tests, and milliseconds[ms] for the Reaction Time Tests) was computed for each group as shown in table 3 below.

Contrary to prediction, the CM group did not differ significantly from the non-CM group in mean time taken to complete the Trails A \( t(38) = 1.18, p = .25 \). The Pearson product moment correlation analysis yielded a small, negative association \( \rho (40)= -.19, p= .25 \) on the Trails A test between the research groups.
Table 3. Mean (& SD) scores on the Trail Making and Visual Reaction Time Tests By Research Grouping.

<table>
<thead>
<tr>
<th>Measure</th>
<th>CM [n=20]</th>
<th>non-CM [n=20]</th>
<th>Total Sample [N=40]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trails A</td>
<td>41.40 (14.31)</td>
<td>37.00 (8.62)</td>
<td>39.20 (11.87)</td>
</tr>
<tr>
<td>Trails B</td>
<td>108.00 (55.07)</td>
<td>73.05 (19.07)</td>
<td>90.53 (44.36)</td>
</tr>
<tr>
<td>Visual Reaction</td>
<td>303.91 (87.61)</td>
<td>310.19 (48.85)</td>
<td>307.05 (70.09)</td>
</tr>
<tr>
<td>Time (Left Hand)</td>
<td>311.49 (60.77)</td>
<td>295.10 (59.02)</td>
<td>303.30 (59.71)</td>
</tr>
<tr>
<td>Visual Reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time (Right Hand)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The CM group, however, took significantly longer to complete the Trails B task than the non-CM group \(t(38) = 2.68, p = .01\). In comparing each individual’s score to the total sample (N=40) mean score, three subjects, all from the CM group, had scores 1 standard deviation below the group mean. No member of the non-CM group performed that poorly. Interestingly, however, when individual performance 1 standard deviation above the group mean was looked at, two subjects from the CM group and only one from the non-CM group performed that well. This finding is supported when one looks at the larger standard deviation values (see Table 3) for the CM group as opposed to the matched control group.

Only a small, positive association (\(r = .23\)) between the duration of coma among the CM subjects and their Trails B scores emerged. Assuming that coma duration is indicative of severity of the disease process, one would have expected to find a stronger association. Results from performance on both Trails A and B provide some insights. There was no statistically significant difference between the CM and non-CM groups on Trails A, a measure highly dependent on rapid visual search and visuospatial sequencing of overlearned digits. Upon introducing an element of executive control where the task demands of an alternating sequence (in fluidly shifting from numbers to letters) contributes to successful completion, a significant difference between the two groups emerged.
On visual reaction time testing, separate data were obtained for left and right hand response latencies (see Table 3). The CM and matched control groups did not differ significantly on either left hand \( t(38) = -0.28, p = 0.78 \), or on right hand \( t(38) = 0.86, p = 0.39 \) reaction times.

In utilizing visual reaction time responses to determine lateralized differences among the CM group, a paired \( t \) test comparing right- to left- hand response conditions was undertaken. Results showed that it did not take the CM group any longer to respond to a visual stimulus with either hand \( t(19) = -0.48, p = 0.64 \). A modest positive correlation in response latencies \( \tau (20) = 0.59, p = 0.01 \) between the left and right hand for the CM group was found.

To compare the CM and non-CM groups on auditory reaction time performance, the MANOVA test was conducted. Given the non-significant results of the omnibus MANOVA (Wilk's lambda = 0.715, exact \( F = 2.19 \), \( p = 0.07 \)), no univariate analyses could be performed. The mean auditory response latencies across various ear (and hand) modalities are however presented in Figure 1 below. It is apparent from this graphical representation that the CM group show consistently longer mean auditory response latencies than their matched controls. Upon closer scrutiny one finds the biggest difference between the research groups in mean latency of right hand responding to sounds presented to the right ear.
the other hand, the smallest difference between these groups is on left hand responding to sounds presented to the left ear. These results, taken together, appear to indicate a tendency toward a right ear advantage for the non-CM group as opposed to the CM group’s better performance on left ear responses.

**Question 2: Do children with a history of cerebral malaria show tactile interhemispheric transfer inefficiencies?**

A test of tactile roughness discrimination given to each individual (where each blindfolded subject was presented with two small square strips of same or different sandpaper to feel and tell whether they were of identical roughness), and correct judgements out of 15 paired presentations were scored.

The mean responses for each group revealed a significant difference \( t(38) = -3.45, p = .01 \) in tactile roughness discrimination as predicted. While only 6 (i.e., 15%) individuals from the CM group were able to make the correct discriminations for all the items presented, 14 (35%) subjects from the matched control group made no error. The coma duration data and the roughness discrimination test scores for the CM group showed a high negative association (\( Y = -0.72 \)), indicating that higher coma duration is associated with lower performance on tactile roughness discrimination.
Figure 1. Mean Auditory Reaction Time Scores [ms] by Group

Note: L = Left, R = Right, B = Both.
Table 4. Mean (& SD) scores on the Roughness Discrimination Test by Research Grouping.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CM Group</th>
<th>non-CM Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (correct)</td>
<td>13.20</td>
<td>14.55</td>
</tr>
<tr>
<td>Standard Deviation</td>
<td>1.54</td>
<td>0.83</td>
</tr>
</tbody>
</table>
Question 3: Are any residual attentional difficulties associated with cerebral malaria?

It was predicted that the CM subjects would show impaired performance on tasks of attention. Given the number and variety of measures used in assessing attention, the MANOVA was employed and the presence of significant multivariate differences judged to be adequate justification for further examination of performance on a test by test basis. Data pertaining to measures of attentional abilities of the subjects can be seen in Table 5. The omnibus MANOVA (with the three tests listed in Table 5 as dependent variables) showed the main effect of research grouping to be significant (Wilk's lambda = .54, exact F = 7.62, p<.001). The univariate F tests revealed that the differences were significant only on the Test D2 error variable (see Table 5). The results show that in the auditory-verbal medium (digit span test scores), there was no significant difference in attention between the two groups under study. A moderate negative association (r = -.48) was found between coma duration and digit span performance among the CM group. When concentration endurance/visual scanning speed were analyzed using the Test d2 total score and the WISC-III Coding subtest, there were no significant differences between the CM and non-CM groups. A moderate negative association between coma duration and scores on the Coding test (r = -.66) was found.
Table 5. Attention Measures comparing CM and non-CM groups: Means (SDs), F values, and Effect Sizes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CM Group</th>
<th>Non-CM</th>
<th>Univariate</th>
<th>p</th>
<th>Effect size (η²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group</td>
<td></td>
<td>F(1, 38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span</td>
<td>13.65(2.87)</td>
<td>15.00(2.99)</td>
<td>2.12</td>
<td>.15</td>
<td>.053</td>
</tr>
<tr>
<td>Coding</td>
<td>38.75(11.70)</td>
<td>43.65(10.21)</td>
<td>1.99</td>
<td>.17</td>
<td>.05</td>
</tr>
<tr>
<td>Test D2 Total</td>
<td>184.80(47.93)</td>
<td>198.85(52.27)</td>
<td>.785</td>
<td>.38</td>
<td>.02</td>
</tr>
<tr>
<td>Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test D2 Error</td>
<td>22.40(9.18)</td>
<td>9.55(5.00)</td>
<td>30.20</td>
<td>.00</td>
<td>.44</td>
</tr>
</tbody>
</table>
The prediction that subjects with a history of CM would be most impaired on tests of attention was supported only when accuracy of visual scanning was assessed through the number of commission/omission errors made on Test d2. Again, as the Table 5 effect size category shows, the non-CM group scored almost half a standard deviation better than the CM group in number of errors made (with an observed power at .01 α level of .996). When subjected to the Pearson product moment correlation analysis, a rather small association was found between duration of coma and number of errors on the test d2 \( \chi(20) = .10, p = .66 \).

**Question 4: Does cerebral malaria leave any residual dysphasic disturbances?**

The semantic Word Fluency Test and Dichotic (Words) Listening Test were used to assess language functioning. The significant omnibus MANOVA results (Wilk’s lambda = .64, \( F = 6.63, p = .001 \)) permitted further analyses using the t-test and univariate F tests, all restricted to .01 alpha level.

Contrary to expectations, the CM group (\( M = 28.25, SD = 9.06 \)) performed no worse than their matched controls (\( M = 33.35, SD = 6.88 \)) on the Word Fluency test, \( t(38) = -2.01, p = .05 \) (confidence interval for this difference at 99% probability ranged from -11.99 to 1.79). A correlation analysis revealed a rather small negative association \( \chi(20) = -.15, p = .53 \) between coma duration and performance on the Word Fluency test among the CM group. Together, these
findings show that spontaneous generation of words from semantic knowledge under time restricting search conditions does not differ significantly according to the disease condition of CM, nor does the duration of coma of up to 14 hours correlate with poor oral word production. Furthermore, clinical observations (as well as collateral information from parents) failed to provide evidence of stuttering difficulties among the CM subjects.

Table 6 shows the subjects' test performance on the dichotic listening test. No significant difference between the CM and non-CM groups was found in left ear scores. There was a significantly higher performance among the control group in the right ear modality (with an effect size of .23) which indicates a relatively stronger right ear advantage than the CM group.

Dichotic listening test performance, while used to assess integrity of the temporal lobes, also provided an indirect measure of laterality in CM. In order to test the difference between the CM group's left and right ear scores on the dichotic listening test, a paired-samples \( t \)-test was employed. Results for the CM group were not significant \( t(19) = -2.00, p = .06 \) (99% confidence interval for the difference ranged from -9.59 to 1.69). As expected (in light of the right ear advantage described above), the paired-samples \( t \)-test yielded a significant difference between
Table 6. Dichotic Listening Test Scores: Mean (SD), F Test, and Effect Size comparing CM and non-CM groups.

<table>
<thead>
<tr>
<th>Modality</th>
<th>CM Group</th>
<th>non-CM</th>
<th>F(1, 38)</th>
<th>p</th>
<th>Effect Size (η²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ear</td>
<td>12.05(5.20)</td>
<td>14.65(3.36)</td>
<td>3.53</td>
<td>.068</td>
<td>.09</td>
</tr>
<tr>
<td>Right ear</td>
<td>16.00(5.75)</td>
<td>21.90(5.44)</td>
<td>11.12</td>
<td>.002</td>
<td>.23</td>
</tr>
</tbody>
</table>
the left and right ear scores for the matched control group \( [t(19) = -5.90, p = .00] \).

Together, these results provide evidence that CM may play a role in compromising
the expected right ear advantage typically seen in most healthy individuals, which
was demonstrated by the control group in this study.

**Question 5: Is memory dysfunction associated with cerebral malaria in
children?**

The measures used in assessing memory functions were restricted to the
Corsi Block Span, Digit Span, and Rey-Osterrieth Complex Figure tests.

On the Corsi Block-Tapping Test, the CM (M=8.25, SD=1.55) group
performed significantly poorer than the non-CM (M=10.05, SD=1.39) group
\([t(38) = -3.86, p = .000]\), a finding with effect size of \( \eta^2 = .28 \) which indicates that
immediate visual spatial memory is impaired in individuals with a history of CM.
Coma duration however shows a rather small association (\( \gamma = .28 \)) with Corsi Block
Span performance.

The mean scores on the Rey-Osterrieth Complex Figure Test are presented
in Figure 2. There was no significant difference between the research groups in
their copy of the design \([t(38)= -2.36, p = .02]\), a finding that indicates roughly
equivalent planning and organizational skills and visual-constructive ability. The
non-CM group, however, performed significantly better than the CM group on the
30 minute delayed recall version of the Rey-Osterrieth Complex Figure Test, 
$t(38)=-3.63, p = .001$. The effect size, although small ($\eta^2=.26$) at statistical power 
of .81, is of similar magnitude to that found with the Corsi Block-Tapping test 
results, and indicates a relatively poor delayed visual recall ability for the CM 
group. Both the copy and delayed recall versions of the Rey-Osterrieth Complex 
Figure Tests were found to be moderately associated (i.e., $\gamma=-.47$, and -.35 
respectively) with coma duration in the CM group. The proportion recalled, 
expressed as percent savings scores, was derived and is presented in Figure 2. 
Although the mean (% savings) score for the CM group (SD=16.89) is larger than 
the non-CM group (SD=10.03), this difference is however not statistically 
significant [$t(38)= 2.38, p=.02$].
Figure 2. Mean Scores on the Rey-Osterrieth Complex Figure Test By Group
**Question 6: Does cerebral malaria leave any lateralized motor disturbances?**

The measures for motor speed and manual dexterity included the Finger Tapping and Purdue Pegboard Tests. It was predicted that subjects with a history of CM would be most impaired on these motor tasks in comparison to their matched controls. An ancillary (exploratory) hypothesis was to determine whether the test performance suggest any lateralized motor deficits. The significant MANOVA results (Wilk's lambda = .59, exact F = 4.63, α = .002) permitted univariate analyses.

Results from multiple pairwise comparison tests provide only partial support for this prediction. For example, Purdue pegboard test results comparing the CM and non-CM groups showed no significant difference on the left hand \[t(38) = -1.11, p = .28\], the right hand \[t(38) = -1.52, p = .14\], or on both hands \[t(38) = -2.50, p = .02\]. While there was no significant difference between the research groups on left hand Finger Tapping speed \[t(38) = -2.12, p = .04\], the non-CM group performed significantly better with their right hand \[t(38) = -4.31, p = .00; \eta^2 = .33\]. Figures 3 and 4 display the mean results for each group on the Purdue Pegboard and the Finger Tapping tests respectively. Taken together, these results show that while CM does not impair finger dexterity, it may
Figure 3. Means Scores on Purdue Pegboard Test by Group

Note: Scores refer to number of pins (and for both hands, pairs of pins) correctly inserted.
Figure 4. Mean Scores on Finger Tapping Test

Scores (# of taps)

Left hand  Right hand

CM Group  Non-CM Group
be associated with dominant right hand pure motor slowing.

**Question 7: Is cerebral malaria associated with any sensory-perceptual deficits?**

In order to determine the pattern of deficits that follow CM (while ruling out more basic sensory deficits as likely causes for any neurocognitive deficits), sensory-perceptual examination of visual fields, auditory acuity, graphesthesia, and 2-point discrimination testing were conducted.

Each participant’s visual fields were full to confrontation testing. Gross examination of dynamic eye movements showed intact voluntary saccade initiation, as well as normal horizontal and vertical smooth pursuit. Basic auditory acuity was found to be grossly intact, and no dysgraphesthesia was evident from fingertip number writing examination.

On the 2-Point Discrimination test, there was no significant difference between the CM group (M = .78, SD = .25) and the non-CM group (M = .68, SD = .13) on the left hand, \( t(38) = 1.53, p = .06 \). Results on right hand testing of 2-Point Discrimination ability also showed no significant difference \( t(38) = 1.73, p = .09 \) between the CM group (M = .79, SD = .18) and the non-CM group (M = .68, SD =
57

.22). These findings, therefore, indicate that the CM and non-CM groups do not differ in somatosensory discrimination thresholds.

**Question 8: Are there any emotional and personality changes associated with cerebral malaria?**

A semi-structured interview was conducted separately with each participant and his/her available parent. The essence of these interviews was to gain an insight into any core or recurring emotional and personality problems that may be associated with CM. With the striking exception of the parents of a set of fraternal twin daughters (one of whom had suffered from CM, and the other without such a history), no other respondent observed any emotional changes following recovery from CM. The parents of these twin subjects reported a relative decline in the energy level and gregariousness in their twin who suffered from CM. While conceding that these twins have continued to perform at par in school, their parents were of the opinion that the one with a history of CM seemed more apathetic than before she contracted CM. The researcher’s clinical impressions from behavioural observations found no differences in activity levels or apathy between these twins.
Results from testing with the Category (Booklet) Test and WISC-III Block Designs Test.

The Booklet Category Test was selectively administered to all subjects 14 years and older in age. Sixteen subjects (comprising 8 CM and 8 non-CM individuals) were therefore given this test. The non-CM group tended to make fewer errors ($M= 48.25$, $SD= 16.10$) than the CM ($M= 88.38$, $SD= 19.32$) group, and this difference was found to be statistically significant ($t(14) = 4.51$, $p = .001$). While these results may provide useful preliminary suggestions regarding visual perceptual abstraction and concept formation skills in CM, the rather small number of subjects call for caution in interpreting these data.

The Block Designs test was administered as a constructional praxis measure to determine the extent to which CM subjects differ from their cohorts in ability to visually guide motor action in forming appropriate three-dimensional structures. No characteristic pattern of qualitative errors emerged to differentiate between the groups, and scoring was based on the WISC-III criteria. The CM ($M= 24.55$, $SD= 13.12$) and non-CM ($M= 31.95$, $SD= 9.92$) groups showed no significant difference in scores on this task, $t(38) = -2.01$, $p = .05$, with confidence interval at 99% probability ranging from -17.37 to 2.57. Findings from this test,
together with evidence from the copy version of the Rey-Osterrieth Complex Figure Test, show that constructional apraxia is not associated with CM.

The Discriminant Function Analysis procedure was used strictly as an exploratory measure to determine the extent to which the neuropsychological tests in this study have any utility in discriminating between individuals from the CM and non-CM groups. In view of the rather small sample size, only the tests that showed significant differences between the research groups were used. The Category test was excluded from this analysis simply because it was not administered to every subject. Measures included in this analysis were scores on the Corsi Block Span, Test D2 errors, Dichotic Listening (Right ear only), Finger Tapping (Right hand), Roughness Discrimination, Trails B, and Rey-Osterrieth Complex Figure (Delay) tests.

With the prior probabilities for both groups equal (i.e., at .50) and the "independents" entered together, the canonical correlation was .795, and Wilk's lambda was .368 ($\chi^2[7] = 34.46, p<.001$). An impressive 92.5% of the subjects were correctly classified into their respective groups using these seven core tests. Table 7 below shows the classification results, which, regardless of true-positive/true-negative rates, must be viewed with appropriate caution given the absence of any cross-validation studies.
Table 7. Discriminant Function Analysis Classification Results of Selected* Measures.

<table>
<thead>
<tr>
<th>Actual Group</th>
<th>Number of Cases</th>
<th>Predicted Group Membership</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CM group</td>
</tr>
<tr>
<td>CM</td>
<td>20</td>
<td>17 (85%)</td>
</tr>
<tr>
<td>non-CM</td>
<td>20</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

* The selected tests were: Corsi Block Span, Test D2 errors, Dichotic Listening Words (Right ear), Finger Tapping Test, Roughness Discrimination Test, Trails B, and Rey-Osterrieth Complex Figure Test (Delay).
DISCUSSION OF RESULTS

The focus of this study was to investigate the effects of CM on the cognitive abilities of children from a malaria endemic region. These findings are the first to demonstrate sub-acute neurocognitive effects following medical recovery from CM. Clearly, the results are a poignant initial demonstration of the neuropsychological consequences of CM, regardless of effect size produced. In fact, the strength of these demonstrations derives not from the proportion of variance in allocations that group membership can account for, but instead from the fact that such small sample sizes can account for any variance at all.

Contrary to expectations, the current results failed to demonstrate a significant impairment in efficiency and speed of information processing following CM. How can this be explained? It is very likely that the simple reaction time paradigm used here is not sensitive enough to reveal patterns of poor performance in this sample. Choice reaction time tasks are generally acknowledged to be more sensitive to the subtle effects of brain damage than are simple reaction time tests (Benton, 1986; Gronwall & Sampson, 1974). It is also important from a theoretical viewpoint to remember that reaction time slowing may itself reflect several different underlying factors ranging from generalized slowing of information processing (Nebes & Madden, 1988), the differential involvement of
sensorimotor versus so-called "central" stages of processing (Pirozollo et. al., 1981), to a breakdown in the response preparation and execution stages of responding (Vrtunski, et. al., 1983). In spite of these rather multifarious, non-specific attributes of reaction time performance, it still remains an important measure of active information processing capacity. Additional evidence in support of grossly intact information processing speed in CM come from the subjects’ performance on other measures (e.g., Coding, Trails A, & Total Score on Test D2) which are known to load heavily on this factor. The mean coma duration of nine hours in this study was relatively shorter than what tends to be reported for African children in general; this may indicate a less severe disease process in the current sample, hence accounting for the current findings. This study was conducted in an urban setting where hospital and other emergency medical facilities are relatively more easily accessible than in rural Ghana. In areas where medical facilities are not readily available, one can expect the duration of coma to be longer, and with that an increased likelihood of more severe neurobehavioural deficits.

The hypothesis that attentional deficits persist following neurologic recovery from acute CM was not fully supported by the present data. No evidence was found that significant auditory attention and sequencing problems result from
a history of CM. The findings of Richardson et al (1989), who assessed non-immune war veterans ten years post-CM, however, did document attention and concentration problems among their sample. There are a number of plausible explanations for this discrepancy. First, neuropathologic and emission tomographic data indicate that there is great variability in the regional distribution of structural abnormality in CM (Looareesuwan et. al., 1983; MacPherson et. al., 1985; Posner & Roman, 1991). It is therefore possible that these differences in neurocognitive test findings are associated with disparate anatomic or physiologic cerebral involvement across samples. Chlopan and colleagues (1990) have demonstrated that both laterality and caudality of lesions are important factors to consider in the interpretation of results from digit span testing, a measure that was used in both these studies. Second, it is likely that expression of the behavioural syndrome of CM is manifested differently in children than in adults. We know (from White & Looareesuwan's 1987 finding) for instance, that children with CM tend to regain consciousness from coma more quickly than adults. Besides, CM in adults unlike children, is invariably a multisystem disease. Furthermore, there appears to be geographical variations in the clinical symptom picture of CM. With the passage of time, drug-resistant strains of malaria parasitemia have appeared in different malaria endemic regions and point to an ever changing disease process which may show variations in neuropsychological dysfunction. Another explanation originally
proposed by Richardson et al (1989) is a progressively occurring “post-malarial behavioral syndrome”, which if valid, would hardly account for the lack of observed deficits in auditory attention and concentration in the current study. The present data, however, show that the CM patients were very poor in their accuracy of time-constrained visual scanning, indicating impaired sustained attention in the visual modality. This pattern of performance clearly differentiated the CM group from their controls. One may ask whether this is due to the behavioural manifestations of a neglect syndrome. Pure sensory loss does not account for this performance, nor does extinction to double simultaneous stimulation (in visual, auditory, or tactile modalities) given the subjects’ accurate responses on sensory-perceptual examination. As regards the possibility of hemispatial neglect, an examination of each CM subject’s pattern of omission errors on the test d2 letter cancellation task revealed no clear evidence of unilateral inattention. Patients with hemispatial neglect frequently demonstrate associated visuospatial defects and constructional apraxia (Heilman, Watson, & Valenstein, 1985). Millan et al’s (1993) MRI study localized a small hemorrhage adjacent to an area of infarction in the nondominant parieto-occipital lobe (an area of the brain frequently implicated in neglect and visuospatial deficits) in a man with acute malaria. The patients in the present study, however, showed no visuospatial defects or evidence for constructional apraxia which typically accompany parietal lesions. On the whole,
the pattern of errors demonstrated by the CM group does not support the presence of a classic neglect syndrome. Apparently, children with a history of CM may show intact attentional encoding abilities despite having severely compromised concentration endurance abilities. One can propose brain stem involvement as the likely neuroanatomic substrate of these deficits since the latter purportedly subserves our ability to sustain attention over time (Mirsky et. al., 1991). Supportive evidence for an isolated brain stem lesion in CM comes from the case study of Kampfl and his colleagues (1993) who localized a pontine lesion from serial MRI studies.

Support for a deficit in the CM group’s ability to make accurate bimanual tactile comparisons was observed on the roughness discrimination task. One is tempted to speculate that this is the result of callosal dysfunction in view of the nonsignificant findings on primary somatosensory (i.e., 2-point discrimination) testing. A callosal lesion may be due to vascular etiologies such as those known to occur in CM. Besides, commissural dysfunction may reflect the operation of diachisis. Coma duration in CM is known to be strongly associated with cerebral edema and raised intracranial pressure (Brewster et. al., 1990; Newton et. al., 1994; Warrell et. al., 1982). This study found a strong negative correlation between performance on the roughness discrimination task and coma duration. It is
therefore quite possible that delayed effects of mechanical compression on the cerebral commissures following raised intracranial pressure is in some way related to the observed tactile interhemispheric transfer inefficiencies. Should this compression explanation be well-founded, one would expect to find callosal dysfunction in other modalities. This was not so. For instance, no double hemianopia was revealed on confrontation testing of the visual fields, nor was the almost complete right ear advantage typically seen after cerebral commissurotomy in dichotic listening tasks evident in this sample. Perhaps a more plausible explanation for this finding has to do with the fact that young children are generally not competent on cross-matching/cross-localization tasks (Galin et. al., 1977, 1979) because their commissures are not yet fully functioning (Yakovlev & Lecours, 1967). This, of course, still does not explain why the age-matched controls in this study performed better. Lassonde et. al. (1986) show that (even among children ranging from ages 6 and 16 years) transections of callosal pathways relatively early or late in childhood life can lead to differences in interhemispheric transfer of tactile information. It may be the case that CM interferes with the normal functional development of commissural structures. Unlike the visual, auditory, speech, and motor systems, the somatosensory system does not have the ability to send projections through other commissures. When the body of the corpus callosum is therefore even mildly compromised, clinically
evident tactile interhemispheric transfer difficulties may be the only prominent finding, as this study shows. No claim is however is being made of definite callosal lesions in this sample, as this would of course require a more sophisticated methodology (see Banich & Shenker, 1994; for a review) than was used in this study, as well as repeated examinations over time.

In assessing language and retrieval skills, this study failed to provide support for the hypothesis that CM has a deleterious impact on verbal fluency. The category fluency task administered here is a generative naming test that depends on the integrity of semantic knowledge (Butters et. al., 1987; Martin & Fedio, 1983). The successful performance of the CM subjects on this task in comparison to matched controls indicates their ability to quickly initiate systematic search and retrieval of appropriate exemplars from a semantic knowledge base. A number of authors (e.g., Nelson & McEvoy, 1979; Ober et. al., 1986) have argued that letter fluency naming (a task dependent on phonemic and/or lexical cues in guiding oral production) is intrinsically more difficult than category fluency naming. Unfortunately the letter fluency task was not administered in this study. Impaired verbal fluency has been demonstrated particularly with dominant frontal lobe damage (Milner, 1974; Ramier & Hecaen, 1970), and the CM subjects' intact performance implies a low probability of left frontal lobe dysfunction. However,
verbal fluency tasks are complex and involve several cognitive processes. While not memory tasks per se, they also have a critical memory component because competent performance requires an intact working memory ability that helps an individual keep track of the items already produced. The lack of perseverative responses in the CM group's performance may attest to a functionally intact working memory store.

Results from utilization of the dichotic listening task (to assess extent of language lateralization and receptive linguistic abilities) lends some support for Richardson and her colleagues' suggestion of auditory information processing inefficiencies in CM. In the present study, the CM group failed to demonstrate the expected significantly superior right ear performance (Connolly, 1985; Kimura, 1967) as did their matched controls. The left ear performance between the non-CM and CM groups were however equivalent, pointing to intact performance in the latter. Although certainly not the case in this study, severely compromised left ear scores on dichotic listening tests are frequently seen in diffuse periventricular white matter diseases including multiple sclerosis (Rao et. al., 1989; Rubens, et. al., 1985) and normal pressure hydrocephalus (Junque et. al., 1987), which usually indicate lesions in the auditory callosal pathway. Collectively, the current findings demonstrate a mildly compromised right ear advantage in the CM group when
compared with their matched controls. Ipsilateral auditory pathways are thought to be inhibited by the contralateral ones under dichotic conditions. Should one need to propose the most likely lesion areas following compromised right ear advantage, any part of the route proceeding from the right ear along the pontine (trapezoid body) decussation in the brainstem to the geniculotemporal pathway will be the most vulnerable subcortical areas.

The results appear to support the hypothesis of impaired immediate visual memory in CM. Frontal lobe mediated organizational strategies do not seem to play a role in this observed visual memory disorder, as both the CM and non-CM groups organized their copy of the Rey-Osterrieth Complex Figure design in a similar manner. Furthermore, evidence from Block Designs test performance attest to intact visual-spatial skills in CM. On this basis, one can appreciate that the deficient recall is not due to a disorganization at the encoding stage of processing, but may lie at the retention and/or recall stages of memory. Incorporating a visual recognition task would help clarify between a retention and recall problem here; unfortunately recognition was not assessed although information about retention capacities was obtained from mean savings scores (i.e., percent retained over the delayed period) on the Rey-Osterrieth Complex Figure test. Given their grossly equivalent rates of forgetting, the lack of a statistically significant difference
between the CM and non-CM groups on mean savings scores casts doubt on retention as the primary culprit in visual memory dysfunction. Since traditional recall measures primarily assess the end result of a complex series of events (including orientation, attention, encoding, information processing time, storage, and retrieval) and provide little information regarding the actual learning and recall process itself, more research is needed to clarify the expression and effect of CM on visual learning and memory.

With respect to motor skills testing, the current results showed no CM-related deficits in fine motor dexterity, although finger tapping test performance did reveal significant dominant hand motor slowing. These findings are quite intriguing in that Brewster and his colleagues (1990) found hemiplegia to be the most common residual neurological abnormality in CM. Exactly how long these “residual” deficits last is as yet unknown. What is known, and which further complicates matters, is that anti-malarial medications such as chloroquine have been implicated in motor dysfunction (Umez-Eronini & Eronini, 1977). It is tempting to invoke an anti-malarial medication effect to explain the dominant hand motor slowing found among the CM group. A number of studies (e.g., Jayaweera et. al., 1977; Kastl et. al., 1968; Molyneux et. al., 1989) have found psychomotor slowing, and other movement disorders to occur only during the acute phase,
pointing to a likely interaction between the CM disease state itself and medication side-effects. Chloroquine, by far the most commonly prescribed anti-malarial medication, is notorious for its long plasma half-life especially in the presence of renal or hepatic insufficiency. None of the subjects in the study were on any anti-malarial medications at the time of assessment, although the cumulative effects of this medication cannot be ruled out. In any case, whether the isolated dominant hand slowing found in this study is due entirely to CM or partly to lingering medication effects cannot be conclusively answered at this time.

Interview reports from both the CM subjects and their parents did not indicate the presence of active, CM-related psychopathology. These findings contradict the opinions of many malariologists (see Weiss, 1985 for a comprehensive review of the relationship between malaria and mental disorders). In the absence of long-term prospective studies of psychiatric disorders in pediatric CM (Sowunmi, 1993), most of the currently available research must be viewed with caution. In fact, apart from Richardson and her colleagues’ (1989) study, many accounts of psychopathology in CM have been limited to the acute stages of the disease where patients were often delirious, sometimes in reaction to antimalarial medications. The observation of parents of the twins in this study goes
to show that only few gross changes in psychiatric functioning, if any, may be seen in the subacute post-CM stage.

Evidence from the Category Test, a rule learning task that is dependent on perceptual abstraction abilities (Perrine, 1993) lends more support to the view that CM is a disease associated with clinically evident neurobehavioural dysfunction. The usefulness of the category test in this study lies in its sensitivity in demonstrating the presence of cerebral lesions regardless of their location. The demonstration that a smaller core of seven neuropsychological tests can correctly classify 92.5% of all subjects into their respective groups does have widespread clinical and research implications. Should a quick screening estimate of cognitive dysfunction in CM be needed, there is much to recommend the use of these tests.

In considering which underlying pathophysiological brain mechanisms may explain this overall pattern of cognitive performance, neither compromised immune function, electrophysiological dysfunction, structural changes in subcortical and cortical regions, or possible neurotransmitter depletion can be ruled out completely. Perhaps the behavioural data obtained in this study should be examined without the restraint of inferred cerebral lesions at such a rudimentary stage of knowledge regarding the neuropathogenesis of CM. This notwithstanding, CM appears to affect cognitive functioning in a way that lends itself to
identification of likely areas of brain dysfunction. More specifically, it appears that
the pattern of deficits shown in this study point to some cortical involvement, a
phenomenon that has been downplayed in neuropathologic studies of the disease.
By the same token, the white matter involvement (at least in this sample) is
certainly not so severe or widespread as to result in a clinically evident
bradyphrenia. Of course, there is no denying the fact that overall cortical
functioning depends on subcortical integrity (Geschwind, 1965; Luria, 1973). No
consistent picture of lateralized hemispheric involvement emerges from the pattern
of neuropsychological deficits. A parsimonious neuropathologic explanation for
these results is a small-vessel vasculitis secondary to an infectious agent, in this
case P. Falciparum. To propose a secondary vascular inflammation invariably
implies an end organ ischemia (Moore & Calabrese, 1994). Cerebral malaria,
according to this model, is consequently both a vasculature and parenchymal
disease.
DIRECTIONS FOR FUTURE RESEARCH

In order to establish a direct, unequivocal relationship between CM and the neuropsychological sequelae that were documented in this study, it is necessary to ask whether the pattern of performance may be equally attributable to other conditions such as malnutrition or hyperpyrexia, rather than the CM disease process itself. While the effects of nutritional deficiencies may introduce unwanted variability in test performance (see for example, Davies & Parkin, 1972; McKay et al., 1978), the presence of a carefully matched control group should reduce these effects to a minimum. Along these lines, a caveat against comparing these results with those of North American age and/or gender cohorts must be advised. The question of hyperpyrexic effects is more difficult to address since raised body temperature is a common symptom feature of CM, and idiopathic hyperpyrexia is itself a risk factor for poor neurocognitive function (Varney et al., 1994). Algid cerebral malaria, although highly uncommon in frequency, can be studied in comparison to the febrile variety in a bid to partial out the effects of raised body temperature in CM.

This study was based on only 40 subjects from a malaria endemic region. More research with larger numbers is obviously needed, although finding appropriate research subjects will continue to be an uphill task for a number of
reasons. First, it is not very common to find well nourished children who fully satisfy the W.H.O. diagnostic criteria for CM and who do not have a past history of other tropical diseases or neurologic illness. Second, recruiting healthy individuals from malaria endemic regions (who have never been exposed to malaria parasitemia) to serve as control subjects is generally difficult. Thirdly, it may be necessary to control for the number of times a research participant had clinical malaria prior to evaluation, since the number of illness episodes per se may be an important risk factor for increased neuropsychological morbidity.

There is a need for longitudinal studies to help document the long-term effects of CM across the life span. Such investigations may enable us to understand the role of protective factors in the acquisition and maintenance of immunity against severe malaria. Furthermore, since seizures are a hallmark of the clinical presentation of CM, the proclivity for epilepsy in later life needs to be studied (Commission on Tropical Diseases of the International League Against Epilepsy, 1994). Whether or not there are any cognitive effects of asymptomatic malaria in immune adults will also become better understood through a developmental approach to the study of CM. Longitudinal research will be useful in determining whether a history of only one CM illness is both necessary and sufficient in causing a progressively occurring "post-malarial behavior syndrome" (Richardson et. al.,
1989). As the risk of suffering frequent attacks of severe malaria in endemic areas is incredibly high, better knowledge of the cumulative and/or synergistic neurobehavioural effects of multiple malaria attacks is essential insofar as one conceives of CM as a possible risk factor for vascular dementia. Age of onset of CM is also an important factor that needs to be addressed in future studies.

From a methodological standpoint, newer and more sophisticated techniques for detecting malaria parasites with higher accuracy (than the customary microscope-based examination of stained blood films) have been developed (Arai et. al., 1994; Long et. al., 1994). Future studies using these more sensitive detection methods will go a long way to improve the overall quality of malariology research.

With the emergence of various drug resistant strains of malaria parasites and geographically-based differences in clinical symptoms of malaria, multisite research collaboration is required to determine variations in the neuropsychological expression of this disease worldwide.

It is not known how malaria in expectant mothers affects the well-being of the fetus; the neuropsychological effects of congenital malaria transmission is hence in need of study. When pregnant mothers are infected with P. Falciparum
malaria or suffer from CM, the disease is likely to have a disruptive influence on the normal neurologic development of the child even if frank neurologic signs do not show at parturition. One can only surmise on the possible role of congenital malaria in the high incidence of stuttering, sinistrality, neural tube defects, twinning rates and learning disabilities in West Africa, as observed by Geschwind and Galaburda (1985).

The effects of anti-malarial medications on neurocognitive function are not well understood, although they can lead to a broad array of consequences ranging from retinopathy, fetal damage (i.e., congenital hearing loss or abortion), toxic psychosis, to death if taken in overdose. Prospective investigations will need to determine the independent effects of the various antimalarial medications on neuropsychological well-being. Preliminary findings from Zaire by Boivin and his coworkers (1993) suggest no change in cognitive status (using the Kaufman Assessment Battery for Children [K-ABC] Mental Processing Component) in children treated with chloroquine for sub-clinical malaria.

This current research did not undertake a comprehensive study of many aspects of memory function (i.e., recognition memory, remote verbal memory), language (e.g., naming, oral and written comprehension), and praxic skills. Future research incorporating comprehensive assessment of these domains is therefore
required if a complete knowledge of the neuropsychological competence of CM patients is to be achieved.
CONCLUSIONS

This study, the first of its kind, sought to examine the extent to which a history of postacute cerebral malaria in Ghanaian children affects their neuropsychological well-being. It was motivated in part by the lack of empirical investigations into the neurobehavioural sequelae of malaria in general, and cerebral malaria in particular. A battery of neuropsychological tests judged to have minimal cross-cultural bias was chosen to help answer some specific research questions. The use of a single factor-design with two carefully matched groups allowed for interpretations relatively free of ethnocultural bias to be made.

Perhaps the most striking finding to emerge from this research is that CM is associated with neuropsychological dysfunction. Regrettably, the reality is that soon after surviving the high mortality risk associated with CM, an overwhelming majority of patients are left with undiagnosed neurocognitive deficits and erroneously assumed to have achieved full recovery.

A prolonged duration of coma in CM tends to be associated with residual neurological abnormalities (Brewster et. al., 1990) and eventual death. This study however found small to moderate correlations between coma duration and most cognitive areas assessed. Perhaps, coma severity rather than its duration is more
strongly associated with neuropsychological morbidity in CM. If this is indeed the case, an expansion in diagnostic criteria of CM to include coma severity ratings may be warranted. The current inclusion criterion of “unarousable” coma (see page 5) is rather vague and uninformative from a neuropsychological perspective. Oriot (1994) suggests that coma rating scales may be more useful in assessing children’s consciousness when they include such brain stem criteria as mimic, photomotor, cornea, and cough reflexes, vestibular responses, and pupil reactions. When applied to CM, these criteria can provide relatively precise information about the integrity of the different levels of the brain stem.

Results from this study revealed intact performance in such areas as cognitive information processing efficiency, auditory attention and sequencing, verbal fluency, tactile, and auditory sensory discrimination, graphesthesia, psychomotor speed, motor dexterity, visual-spatial construction, and non-verbal reasoning. No clinically significant psychopathology or other acute emotional distress secondary to CM was found. In contrast, deficits were demonstrated in accuracy of visual search and attention, recent and remote visual memory, perceptual abstraction, and tactile roughness discrimination. Also, dominant hand motor slowing, and inefficiencies in right ear processing of dichotically presented verbal information were observed. Of course, the small sample size and limited test
battery, coupled with the rather stringent rules for statistical decision making
hamper any definitive conclusions.

While still preliminary, some implications of these findings can be deduced.

This study has implications for learning efficiency in school children. Insofar as
visual attention and memory, and perceptual abstraction/rule learning are
compromised following CM, optimal performance in traditional classroom learning
situations may suffer. Also, there is strong evidence that impaired visual scanning
accuracy (as was demonstrated in this study) is associated with accident-prone
behaviour (Diller & Weinberg, 1977). Another implication from this study pertains
to a possible arrest or delay in cognitive maturation after the impact of CM
relatively early in life. It is important that a history of CM (and to a lesser extent,
severe falciparum malaria) in any individual at any age be considered a risk factor
in neuropsychological dysfunction as would be any other well studied neurologic
disease.

A model of brain dysfunction proposed in this study is that of a non-
specific small-vessel vasculitis secondary to *falciparum* malaria. This model is in
many respects a combination of two theories of CM neuropathogenesis (see page
8): First, Toro and Roman's (1978) hypothesis of an "acute disseminated
vasculomyelinopathy", (except that no suggestion is being made here of an
immune complex-mediated process); and second, the mechanical theory (Miller et. al., 1972) which posits hypoxia and ischemia as consequences of cerebral microvascular obstruction by parasitised erythrocytes.

The epidemiological pattern of malaria in tropical Africa is changing quickly. More indigenous African adults are succumbing to CM (Brewster et. al., 1990), which is strong evidence for attrition in the protectiveness of acquired immunity. Also, children are now acquiring immunity at relatively later ages than in the past. Treating sub-clinical malaria appears to be relatively ineffective in leading to improved cognitive function (Boivin et. al., 1993), a fact that calls for stronger malaria prevention efforts. Exposure to malaria parasites is still pervasive in most tropical regions of the world; in certain Tanzanian villages it is estimated that everyone receives more than 300 *Plasmodium falciparum*-infected mosquito bites per year (Smith et. al., 1993). All these factors, in addition to the high mortality rates from malaria, are compelling reasons for a stronger commitment toward eradicating the disease altogether. The seminal efforts by Patarroyo and his coworkers (1987; 1988) which culminated in the development of SPf66, a synthetic polypeptide vaccine against *P. falciparum* with at least 31% protective efficacy, have provided a ray of hope against this devastating disease. It is quite difficult to remain hopeful that malaria, a disease which continues to produce between 300 and 500 million
clinical cases (and 1.5 to 2.7 million deaths) a year, will be eradicated in the foreseeable future.
REFERENCES


Africa. Transactions of the Royal Society of Tropical Medicine and Hygiene, 81, 478-486.


GLOSSARY OF SELECTED TERMS

Acridine orange fluorescence: A modern, experimental technique used in the detection of malaria parasites. Acridine is a dibenzopyridine compound used in the synthesis of dyes and drugs.

Afebrile: Without symptoms of fever.

Agonal: Pertaining to terminal infection.

Anaerobic glycolysis: The utilization of sugar within the living organism without the benefit of air/oxygen.

Anosognosia: Loss of ability to recognize/acknowledge a bodily defect.

Asymptomatic parasitemia: Demonstrable infection with parasites, but without any overt clinical symptoms.

Bruxism: The compulsive, unconscious grinding of the teeth, especially during sleep.

Endothelial: Pertaining to the layer of cells that form the lining of the vascular system and other closed cavities of the body. It consists of thin, flat, connective-tissue cells.

Erythrocyte: Red blood cell.

Extravasation: A discharge or escape (as of blood) from a vessel into the tissues.

Holoendemic: The prefix “holo” is a combining form meaning entire, or pertaining to the whole. As used in the text, it implies endemicity in the larger community with little seasonal variation.

Hypoxia: An inadequate or reduced tension of cellular oxygen, characterized by cyanosis, tachycardia, hypertension, dizziness, and mental confusion.

Ischemia: Deficiency of blood, partly due to functional constriction, or actual obstruction of a blood vessel.
**Isolation syndromes**: May be the result of extensive crescent-shaped infarcts within border zones (sometimes called watershed zones) between major cerebral vessels. Some causes include anoxia, occlusion/stenosis of the carotid artery. The syndromes are marked by isolation of the speech areas from other higher cortical areas. Typically, repetition of speech is preserved.

**Kwashiorkor**: The clinical presentation of a predominantly protein-deficient diet in young children.

**Marasmus**: Progressive wasting and emaciation, especially in young children due to a predominantly calorie-reduced diet.

**Myalgia**: Diffuse muscle pain, usually accompanied by malaise, and occurring in many infectious diseases.

**Oedema (Edema)**: A combining form meaning swelling resulting from an extensive accumulation of serous fluids in the tissues of the body in "specific" locations.

**Opisthotonuos**: A form of tetanic spasm in which the head and heels are bent backward and the body bowed forward.

**Papilloedema**: Swelling of the optic papilla due to raised intracranial pressure, malignant hypertension, cerebral edema, or raised cerebrospinal fluid. It may indicate the presence of brain tumors or increased pressure in the brain. Visual acuity is only affected much later.

**Pathophysiology**: The study of the biologic and physical manifestations of disease as they correlate with the underlying abnormalities and physiologic disturbances. Treatment of diseases are not directly dealt with; rather, the processes within the body that result in signs and symptoms of a disease are the major focus of study.

**Petechial**: Pertaining to a small, circular spot formed by the effusion of blood.

**Plasmodial**: Pertaining to a genus of the Sporozoa containing malaria organisms.

**Sequestration**: From sequester, meaning to detach, separate, or isolate.
Sickling: Tendency of red blood cells to acquire a sickle-like, or crescent shape.

Stagnant anoxemia: The anoxic (lack of oxygen) effects due to a chronic retardation of the flow of blood.

Watershed infarction: The border, terminal regions which are supplied by major arteries are called border zones or watershed zones. An infarction occurring in such a region is called a watershed zone infarct. See also isolation syndromes.
APPENDICES
APPENDIX A

Sample Consent Form for research participants

I hereby fully consent to Mr. Anthony T. Dugbarthey performing a psychological assessment on ______________________ in my capacity as the latter’s legal guardian. I also consent to Mr. Dugbarthey obtaining copies of any previous medical and/or academic school reports that may be relevant to the current assessment. I have been fully informed about the purposes of this evaluation, and it is my understanding that due care has been taken to ensure that no foreseeable harm from this assessment befalls the participant. I agree that on condition of anonymity, the information obtained from this assessment shall be used for educational and research purposes. Upon request, I shall have access to the assessment findings as well as a synopsis of the overall research findings.

Signed: ___________________________  ___________________________
Client/Parent/Guardian  Date

Witnessed: ___________________________  ___________________________
Date
Thank you kindly for agreeing to take part in this study. As part of requirements for the Ph.D. degree in Psychology, I am conducting a research into some of the effects that cerebral malaria has on the behaviour of children.

Two groups are involved in this study, those who have a history of being medically diagnosed with cerebral malaria at any time in their lives, and a comparison group who have never before suffered from malaria. At least forty participants are expected to be involved in this study.

Each participant will be involved in a variety of interesting tasks that are aimed at finding out whether the malaria has affected your ability to remember things, how quickly you can do certain things with your hands, and so on. It is best to set aside at least two half days for testing, although the entire assessment may not last that long.

Before taking part in this study, each individual will be interviewed in order to find out whether he or she actually meets other criteria, such as the absence of other medical conditions that are not the focus of this study. It is also expected that all those who satisfy the criteria for taking part in this study will not be currently suffering from malaria. If you have not been tested in the last few days, please let me know as we will pay your transport and hospital fees for you to get tested at any hospital of your choice. If your blood test results show that you have malaria parasites, we may pay for your medicines as long as you bring receipts and a copy of your doctor's prescription form for those medicines purchased.

It is my hope that through this exercise, we will gain a better understanding of how malaria affects people’s behaviours. Any observation that you have made about yourself, your child or even friends with malaria will be most welcome too.

For further information, please contact me at the following addresses:

P.O. Box ..., Achimota, Ghana (tel ), or

Department of Psychology, University of Victoria, Box 3050, Victoria, Canada (tel: 604-721-7525).
APPENDIX C

RAW NEUROPSYCHOLOGICAL TEST DATA
Variable List  id, age, gender, edulevel, durcoma, fas, dicholft, dichort, digspan, corsiblk, blckdsgn, coding, trailsa, trailsb, category, ravenpm, d2total, d2errors, reycopy, reydelay, purdleft, purdrght, purdboth, ftapleft, ftaprght, twoptlft, twoptrlft, vrlft, vrtrght, sanpaper, grouping, rcftsavi, aurerh, aurelh, aulerh, auberh, aubelh


Variable Labels (and column position):

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<td></td>
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D2errors,    Test D2 Error scores(18)
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reydelay,    Rey-Osterrieth Design, Delayed recall score(20)
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purdrght,    Purdue Pegboard, Right hand score(22)
purdboth,    Purdue Pegboard, Both hands score(23)
ftapleft,    Finger Tapping, Left hand score(24)
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twoptlft,    Two Point Discrimination, Left hand score(26)
twoptrht,    Two Point Discrimination, Right hand score(27)
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vrtright,    Visual Reaction Time, Right hand score(29)
sanpaper     Roughness Discrimination Test score(30)
grouping,    Research subject grouping(31)
rcftsavi, Rey-Osterrieth Design percent savings score(32)
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aurelh, Auditory Reaction Time. Right ear, left hand score(34)
aulerh, Auditory Reaction Time. Left ear, right hand score(35)
aulelh, Auditory Reaction Time. Left ear, left hand score(36)
auberh, Auditory Reaction Time. Both ears, right hand score(37)
aubelh, Auditory Reaction Time. Both ears, left hand score(38)

Value Labels

gender (1) Male, (2) Female

grouping (1) Cerebral malaria group (2) healthy [non-CM] group
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| 02 | 20 | 16 | 15 | 11 | 39 | 37 | .79 | .79 | 373.8 | 366.6 | 15 | 1 | 39.39 |
| 03 | 2 | 15 | 11 | 9 | 34.6 | 41 | .64 | .64 | 256.4 | 335.2 | 15 | 1 | 69.23 |
| 04 | 16 | 15 | 18 | 10 | 34.8 | 41.6 | 1.11 | 1.11 | 216.4 | 256.2 | 12 | 1 | 36 |
| 05 | 13.5 | 13 | 13 | 11 | 36.6 | 29.2 | .79 | .79 | 221.6 | 253. | 12 | 1 | 28.95 |
| 06 | 28.5 | 14 | 15 | 12 | 49.6 | 59.2 | 1.59 | 1.59 | 205.8 | 232. | 14 | 1 | 10.94 |
| 07 | 14.5 | 14 | 15 | 11 | 54.4 | 58.6 | .79 | .79 | 195. | 223.4 | 15 | 1 | 57.97 |
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| 09 | 9.5 | 10 | 11 | 8 | 29.2 | 34.4 | .48 | .48 | 421. | 392.6 | 13 | 1 | 40.63 |
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| 11 | 3.5 | 9 | 12 | 7 | 30.6 | 36.6 | .64 | .64 | 273.6 | 325.8 | 10 | 1 | 22.22 |
| 12 | 10 | 14 | 12 | 11 | 34.6 | 39.8 | .64 | .64 | 394.2 | 413. | 15 | 1 | 66.10 |
| 13 | 18 | 12 | 14 | 11 | 23.2 | 28 | .95 | .95 | 351.4 | 343.4 | 15 | 1 | 43.75 |
| 14 | 9 | 10 | 11 | 7 | 32.4 | 36.6 | .64 | .64 | 363. | 327.8 | 13 | 1 | 35.71 |
| 15 | 19.5 | 11 | 15 | 6 | 31.2 | 37 | .64 | .64 | 217.4 | 300.8 | 11 | 1 | 30.36 |
| 16 | 8 | 18 | 21 | 13 | 31.9 | 34 | .64 | .64 | 209.4 | 342. | 11 | 1 | 70.37 |
| 17 | 16.5 | 11 | 13 | 7 | 46.1 | 42.9 | .95 | .95 | 200.4 | 296.3 | 14 | 1 | 48.44 |
| 18 | 14 | 10 | 15 | 8 | 20.7 | 21.8 | .64 | .64 | 349.7 | 256.8 | 13 | 1 | 26.32 |
| 19 | 4.5 | 10 | 11 | 7 | 19.4 | 38.2 | .64 | .64 | 415.7 | 382.4 | 12 | 1 | 59.09 |
| 20 | 11 | 14 | 16 | 11 | 22.4 | 30.4 | .64 | .64 | 409.3 | 221.7 | 15 | 1 | 63.33 |
| 21 | 19 | 14 | 16 | 11 | 42.8 | 67.8 | .79 | .79 | 318.4 | 259.6 | 15 | 2 | 29.63 |
| 22 | 18.5 | 15 | 12 | 10 | 40.9 | 33.7 | .64 | .64 | 244. | 329.4 | 15 | 2 | 38.33 |
| 23 | 14 | 13 | 16 | 10 | 39.7 | 46.6 | .64 | .64 | 407.4 | 392. | 15 | 2 | 44 |
| 24 | 18 | 12 | 12 | 11 | 41.3 | 52.7 | .79 | .79 | 380.7 | 324.5 | 14 | 2 | 34.55 |
| 25 | 16.5 | 14 | 17 | 10 | 32.3 | 48 | .64 | .64 | 301.6 | 207.9 | 14 | 2 | 31.25 |
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| 27 | 19.5 | 15 | 18 | 13 | 38 | 44.9 | .95 | .95 | 261.4 | 200.9 | 15 | 2 | 39.06 |
| 28 | 21 | 14 | 17 | 12 | 40.1 | 51.6 | .64 | .64 | 301.9 | 294.7 | 15 | 2 | 38.24 |
| 29 | 12.5 | 9 | 14 | 8 | 38.7 | 48.6 | .32 | .32 | 327.6 | 393.8 | 15 | 2 | 60.94 |
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| 38 | 21 | 12 | 16 | 9 | 43.8 | 57.4 | .79 | .79 | 290.8 | 262.4 | 13 | 2 | 36.36 |
| 39 | 16.5 | 13 | 15 | 12 | 32.9 | 48.1 | .79 | .79 | 268.7 | 304.5 | 15 | 2 | 28.26 |
| 40 | 22 | 16 | 17 | 11 | 49.8 | 60.8 | .48 | .48 | 289.4 | 274.6 | 15 | 2 | 35.29 |
APPENDIX D

MANOVA TABLES
### Table D1

Total Sample (N=40): Groups by Auditory Reaction Time Scores.

**Multivariate Test**

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**Univariate F-Tests (1, 38 d.f)**

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Table D2

Total Sample (N= 40): Groups by Digit Span, Coding, Test D2 Error/Total Score

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Univariate F-Tests (1, 38 df)

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Total Sample (N = 40): Groups by Language Measures (FAS, Dichotic Listening)

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Univariate F-Tests (1, 38 df)

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Table D4

Total Sample (N=40): Groups by Motor Tests (Purdue, Finger Tapping)

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Univariate F-Tests (1, 38 df)

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Pooled Within-groups correlation matrix by gender

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ROUGH 1.00000?
### Pooled within-groups correlation matrix by age

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