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# Cognitive Impairment After Cerebral Malaria in Children: A Prospective Study

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## Abstract

**OBJECTIVE—**This study was conducted to assess prospectively the frequency of cognitive deficits in children with cerebral malaria.

**METHODS—**Cognitive testing in the areas of working memory, attention, and learning was performed for Ugandan children 5 to 12 years of age with cerebral malaria ($n$ = 44), children with uncomplicated malaria ($n$ = 54), and healthy community children ($n$ = 89) at admission and 3 and 6 months later.

**RESULTS—**Six months after discharge, 21.4% of children with cerebral malaria had cognitive deficits, compared with 5.8% of community children. Deficits were seen in the areas of working memory (11.9% vs 2.3%) and attention (16.7% vs 2.3%). Children with cerebral malaria had a 3.7-fold increased risk of a cognitive deficit, compared with community children, after adjustment for age, gender, nutritional status, school level, and home environment. Among children with cerebral malaria, those with a cognitive deficit had more seizures before admission (mean: 4.1 vs 2.2) and a longer duration of coma (43.6 vs 30.5 hours), compared with those without a deficit. Children with uncomplicated malaria did not have an increased frequency of cognitive deficits.

**CONCLUSIONS—**Cerebral malaria may be a major cause of cognitive impairment in children in sub-Saharan Africa. Cognitive deficits in children with cerebral malaria are more likely for those who have multiple seizures before effective treatment for cerebral malaria.

### Keywords

cerebral malaria; cognitive; deficit; impairment; sequelae



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It has been estimated that each year 575 000 children suffer from cerebral malaria (CM) in sub-Saharan Africa. [1] CM is among the deadliest complications of malaria, with an estimated mortality rate in sub-Saharan Africa of 18.6% among hospitalized children.[2] Neurologic deficits are seen frequently at the time of hospital discharge for children with CM, but most resolve within 6 months after discharge.[3] However, several retrospective studies suggested that cognitive deficits in children with CM are more frequent (occurring in 11%–28% of children with CM) and persist for a far longer time (3–9 years after the CM episode) than neurologic deficits.[4–8] The data from those studies were strong and generally consistent, but one study found no evidence of increased cognitive deficits.[9] Furthermore, the original clinical and social assessments of those children were performed as part of studies investigating other aspects of CM and not as part of a study designed specifically to address the question of cognitive deficits in children with CM. Initial cognitive testing was performed for case and control subjects several years after the episode of CM. History, physical examination, and laboratory data were limited to those collected from medical charts, and data on potential confounding risk factors for cognitive deficits, such as home environment and level of schooling at the time of enrollment, either were not collected or were collected through questionnaires and therefore were subject to significant recall bias. In addition, the case subjects studied were those who could be found at the time of follow-up assessment. Loss to follow-up monitoring might have occurred for a number of reasons, many of which might be related to the risk of cognitive deficits. Finally, in those studies, healthy children were compared with children with CM, but there was no assessment of whether the risk of cognitive deficits was specific to CM or occurred even with uncomplicated malaria (UM). To address these issues and to obtain a robust estimate of the frequency of cognitive deficits in children with CM, we conducted a prospective study of cognitive function in the key cognitive areas of working memory, attention, and learning in Ugandan children (5–12 years of age) with CM, children with UM, and healthy community children (CC).

## METHODS

### Study Population and Recruitment

The study was conducted at Mulago Hospital (Kampala, Uganda) from November 2003 to February 2005. Children 4 to 12 years of age were recruited as part of 2 studies assessing the complications of CM. Longitudinal assessment of cognitive test performance was performed only for children 5 to 12 years of age, because the ability of children 4 years of age to perform the different tests was highly variable. A total of 187 children 5 to 12 years of age were enrolled, including 44 children with CM, 54 children with UM, and 89 CC without evidence of acute or chronic illness.

Children with CM were enrolled if they were admitted to Mulago Hospital and met the World Health Organization criteria for CM, namely, coma (Blantyre Coma Scale score of ≤2 or Glasgow Coma Scale score of ≤8), *Plasmodium falciparum* on blood smears, and no other cause of coma. Lumbar punctures were performed to rule out meningitis and encephalitis. Ugandan Ministry of Health national guidelines for drug treatment of CM (quinine for 7 days, with a loading dose of 20 mg/kg administered intravenously and then 10 mg/kg every 8 hours) were followed. Additional treatment guidelines included an infusion of 25% dextrose (2 mL/kg) for children with blood glucose levels of <2.2 mmol/L (<40 mg/dL), treatment of acute seizures with intravenously or rectally administered diazepam (with the addition of phenobarbital for refractory seizures), and blood transfusions for children with hemoglobin levels of <5 g/dL. Children with UM were enrolled from the acute care clinic or from an outpatient malaria clinic at the hospital that was sponsored by the University of California, San Francisco. Children were considered to have UM if they had symptoms of malaria (fever, chills, vomiting, or headache), *P falciparum* on blood smears, and no evidence of malaria

complications or other acute illnesses. Children with UM were treated according to the Ugandan Ministry of Health guidelines (chloroquine plus sulfadoxine/ pyrimethamine) in the acute care clinic or with combination therapy (either amodiaquine plus sulfadoxine/ pyrimethamine or amodiaquine plus artesunate) at the University of California, San Francisco, outpatient clinic. Medication doses were as follows: chloroquine, 10 mg/kg on days 0 and 1 and 5 mg/kg on day 2; sulfadoxine/pyrimethamine, 25 mg/kg and 1.25 mg/kg, respectively, in a single dose; amodiaquine, 10 mg/kg on days 0 and 1 and 5 mg/kg on day 2; artesunate, 4 mg/kg daily for 3 days. CC were recruited from the neighborhoods of the children with CM or UM. CC and children with UM were recruited to be in the same age range (4–12 years) as children with CM. Parents of children with CM or UM were asked if there were children in their extended family or neighborhood in the study age range, and parents of eligible children were contacted and informed about the study. If they agreed to participate, they were given an appointment for study evaluation. A history and physical examination were performed to confirm that the CC were healthy at the time of enrollment. Exclusion criteria for enrollment in all 3 groups included (1) a history of meningitis, encephalitis, or any brain disorder, including CM; (2) a history of developmental delay; (3) previous admission because of malnutrition; and (4) a history of chronic illness. In addition, children recruited for the CC cohort were excluded if they had evidence of acute illness on physical examination, had been treated for an acute illness in the past 1 month, or had been admitted for treatment of malaria in the past 6 months. All CC were tested for asymptomatic *P falciparum* infection through microscopic evaluation of peripheral blood smears; 19 children were infected and were treated with chloroquine and sulfadoxine/pyrimethamine. These children were not excluded from the study.

Written informed consent was obtained from the parents or guardians of study participants. Ethical approval for the study was granted by the institutional review boards for human studies at Makerere University Faculty of Medicine, University Hospitals of Cleveland, Case Western Reserve University, and Indiana Wesleyan University.

## Clinical and Demographic Assessments

All study participants underwent complete physical examinations. Detailed physical findings, including specific neurologic findings, were recorded for children with CM. Nutrition was assessed by comparing weight for age with published normative values and obtaining a standardized *z* score (Epi Info 6; Centers for Disease Control and Prevention, Atlanta, GA). Socioeconomic status was assessed by using a scoring instrument incorporating a checklist of material possessions, quality of home environment and home structure, living density, food resources, cooking and bathroom facilities, and access to electricity and clean water. Home environment was assessed by using a version of the Home Observation for Measurement of the Environment inventory[10] adapted for Uganda. The Home Observation for Measurement of the Environment inventory, as modified, is a 58-question assessment of the stimulation and learning opportunities offered by the child's home environment. Levels of education of the child, mother, and father were scored as follows: none = 0; nursery = 1; primary school grades 1 to 7 = 2 to 8, respectively; secondary education = 9; and postsecondary school = 10.

## Cognitive Testing

Neurocognitive assessments tested previously among children from other sub-Saharan African countries were used in the present study. Instructions and verbal items for all tests were translated into and back-translated from Luganda (the most commonly spoken local language) and were pilot tested with 30 healthy schoolchildren (5–12 years of age). Neurocognitive assessments focused on cognitive ability and memory (the Kaufman assessment battery for children [K-ABC]), attention (the visual form of the computerized tests of variables of attention [TOVA]), and tactile- kinesthetic learning (the tactual performance test [TPT]).

The K-ABC, a comprehensive assessment of cognitive ability, was performed as tested in several other African countries.[4,8,11–14] K-ABC tests were performed in the areas of sequential processing (hand movements, number recall, and word order) and simultaneous processing (face recognition, spatial memory, triangles, matrix analogies, gestalt recognition, and photograph series). The visual form of the TOVA, a computer-based, continuous performance test that assesses basic constructs of attention, [15] was performed as tested in several other cross-cultural settings.[4,16] TOVA scores assessed included omission error rates, commission error rates, correct signal response time variability, and the *d′* signal detection measure (signal detection sensitivity). The TPT, part of the Reitan-Indiana neuropsychological assessment battery for children,[17] was performed as tested previously among rural African children.[18] The TPT is a good overall measure of brain/behavior development, and performance depends on a variety of abilities. Measures assessed included total time per block, percentage improvement in time per block performance, memory score, and location score. Primary outcome measures used to define cognitive deficits were summary variables that assessed working memory (sequential processing of the K-ABC), executive attention (*d′* test of the TOVA), and learning (total time per block of the TPT). Tests were performed at the time of hospital discharge (children with CM) or initial enrollment (children with UM and CC) and 3 and 6 months later.

### Statistical Analyses

To account for the influence of age on the neurocognitive assessments, each raw outcome was converted into an age-specific standardized score (*z* score), on the basis of the scores of CC for each year of age. Eleven- and 12-year-old children were grouped together because of the small numbers of children of those ages. When appropriate, data were logarithmically transformed to approximate normality before *z* scores were calculated.

A cognitive deficit was defined as a *z* score of less than −2 for working memory and attention and a *z* score of ≥2 for learning. The primary outcome variable, namely, the presence of a cognitive deficit in ≥1 of the summary variables 6 months after the initial assessment, was decided before data analysis. The proportions of cognitive deficits among children with CM and UM were compared with those among CC by using generalized estimating equations with a binomial distribution and a logit link and were reported as odds ratios (ORs).[19] The SAS 9.1 (SAS Institute, Cary, NC) Genmod procedure was used for OR analyses. This method allows for the possible correlation between children with malaria and CC from the same family. Estimates were adjusted for age (with the use of the age-specific *z* score), child's school level, gender, nutrition (weight for age), and home environment score. Adjustment for parental education and socioeconomic status did not result in significant changes to the model. A sample size of 45 children with CM and 90 CC was calculated to have 80% power detect a 20% frequency of cognitive deficits in children with CM at 6 months, compared with a 3% frequency in CC ($\alpha = .05$).

## RESULTS

### Baseline Characteristics of Children With CM, Children With UM, and CC

Children with CM were more frequently male than CC (66% vs 50%; $P = .07$), but children with CM, children with UM, and CC did not differ significantly with respect to age, weight, nutritional status, education level, maternal or paternal education level, socioeconomic status, or home environment score (Table 1). Follow-up rates were excellent for all groups (95.4%, 98.1%, and 97.8% at 3 months and 95.4%, 96.3%, and 97.8% at 6 months for children with CM, children with UM, and CC, respectively).

### Cognitive and Neurologic Deficits in Children With CM

Six months after discharge, children with CM had a significantly higher frequency of deficits in ≥1 area of cognition than did CC (21.4% vs 5.8%; $P = .01$) (Table 2). Children with CM had more-frequent deficits in the areas of working memory (11.9% vs 2.3%; $P = .04$) and attention (16.7% vs 2.3%; $P = .005$) than did CC (Table 2), and only children with CM had deficits in ≥2 cognitive areas (7.7%, compared with 0% of CC; $P = .03$). Six months after discharge, children with CM had a 3.7-fold (95% confidence interval [CI]: 1.3–10.7-fold; $P = .02$) higher risk of a cognitive deficit in ≥1 area, compared with CC, after adjustment for age, gender, nutritional status, school level, and home environment score. Children with CM also had increased frequency of deficits in ≥1 area of cognition at the time of discharge (36.4% vs 11.2%; $P = .0006$) and 3 months later (19.1% vs 6.9%; $P = .07$) (Table 3). As expected, children with CM also had more-frequent deficits in several secondary cognitive outcomes at the time of discharge, compared with CC, including TOVA omission (11.4% vs 0%; $P = .003$) and commission (9.1% vs 0%; $P = .01$) error rates and signal response time variability (14.6% vs 0%; $P < .0001$) and TPT memory scores (23.3% vs 4.5%; $P = .002$). No significant differences in secondary outcomes between children with CM and CC were present at 3 months, and only TPT memory scores differed at 6 months (17.1% vs 4.6%; $P = .04$). Neurologic deficits were seen frequently in children with CM at discharge (28.2%), but rates decreased to 9.5% at 3 months and 0% at 6 months.

### Cognitive Deficits in Children With UM

Children with UM had similar frequencies of cognitive deficits, compared with CC, at the 6-month follow-up assessment (Table 4) and at baseline and 3-month follow- up assessments (Table 5). At the 6-month follow-up assessment, there was no difference in the adjusted OR of a cognitive deficit in ≥1 area in children with UM, compared with CC (OR: 1.79; 95% CI: 0.44–7.21; not significant). There were no significant differences in the frequencies of secondary cognitive outcomes between children with UM and CC at any time point, except for the percentage of improvement in time per block performance at 3 months (11.3% vs 1.2%; $P = .01$).

### Association of Clinical Factors With Cognitive Deficits in Children With CM

A number of clinical factors were compared with cognitive outcomes, including antimalarial drug use before admission, number of seizures before admission, type of seizure, seizure history, temperature, blood pressure, presence of malnutrition, oxygen saturation, deep respirations, decorticate or decerebrate posturing, dehydration, papillary dilation and reactivity, total duration of coma, duration of coma after quinine treatment, presence and number of seizures after admission, focal neurologic findings, and neurologic deficits at the time of discharge. In addition, laboratory tests compared with cognitive outcome included admission peripheral blood parasite density; total leukocyte, platelet, granulocyte, lymphocyte, and monocyte counts; levels of hemoglobin, glucose, sodium, bilirubin, and creatinine; and presence of stool helminth infection. The only factors that differed significantly between children with and without a cognitive deficit at 6 months were number of seizures before admission (mean ± SD: 4.1 ± 2.7 vs 2.2 ± 2.3; $P = .03$) and total duration of coma (mean ± SD: 43.6 ± 18.6 vs 30.5 ± 21.4 hours; $P = .05$), both of which were risk factors for neurologic sequelae in a previous study.[3] The other risk factor for neurologic sequelae in that study, depth of coma, was not a risk factor for cognitive sequelae in the present study. Hypoglycemia was very uncommon in the children in this study (only 1 of the 44 children with CM had a glucose level of <2.2 mmol/L [<40 mg/dL] during the study); therefore, the relationship of hypoglycemia to cognitive deficits could not be assessed. Neurologic deficits at the time of discharge were neither sensitive (38%) nor specific (76%) for prediction of cognitive deficits

at 6 months. Recurrent seizures after discharge were uncommon, occurring for one child at 3 months and for another between 3 and 6 months.

## DISCUSSION

The present study is the first prospective study to assess cognitive sequelae in children with CM. Six months after an episode of CM, 21.4% of children had deficits in ≥1 area of cognition, and children with CM had a 3.7-fold increased risk of cognitive deficits, compared with healthy CC (95% CI: 1.3–10.7-fold), after adjustment for potential confounding factors. If children with CM in other areas of sub-Saharan Africa have similar frequencies of cognitive deficits, then CM-attributable cognitive impairment may occur in >36 000 children 5 to 9 years of age each year (determined by using the baseline CM incidence estimates reported by Murphy and Breman[1]). If cognitive deficits are seen at similar frequencies in children with CM who are <5 years of age, then the numbers of children with cognitive impairment attributable to CM could be even larger. Our study findings suggest that CM may be a major cause of cognitive impairment in children in sub-Saharan Africa.

Our findings are consistent with those of several previous retrospective studies on CM and cognitive sequelae. [4–8] However, the enrollment of a control cohort from the same neighborhoods as children with CM or UM permitted assessment of changes over time for this comparison group and helped to ensure that comparison children were not significantly different from children with CM in several important areas that might affect cognitive function. Age, gender, nutrition, home environment, and school level were also adjusted for in our statistical analyses. With these methodologic and statistical controls, we are confident that the cognitive deficits seen in children with CM in this study were likely related to CM. Prospective assessment also allowed us to demonstrate that differences in cognitive deficits in the areas of working memory and attention were greater at 6 months than at 3 months in children with CM, compared with CC, which suggests that cognitive impairment in CM may be attributable to impairment in learning new cognitive skills in addition to the loss of specific skills at the time of disease. As in previous studies, most gross neurologic deficits resolved by 6 months[3] but cognitive impairment persisted, which indicates that different mechanisms may be involved in gross neurologic deficits, compared with more-subtle cognitive deficits. The lack of association between neurologic and cognitive deficits supports this idea.

We were also able to measure accurately multiple clinical factors of potential importance and to relate them to cognitive outcomes. We demonstrated that children with cognitive deficits had a higher frequency of seizures before admission and a longer duration of coma. We did not document association with several other clinical factors noted in previous retrospective studies, including hypoglycemia, neurologic deficits at discharge, and previous seizure history. [8,20] This might be related to a smaller sample size in our study, the older age of children in our study (eg, hypoglycemia, which occurs more frequently in children <5 years of age, was uncommon in our study), or potential selection bias in the retrospective studies for children with medical problems (eg, previous seizure history or neurologic deficits at discharge), because such children may be more likely to seek continued medical care. Our study findings do complement the findings of retrospective studies that documented a relationship between persisting epilepsy after discharge in children surviving CM and developmental disabilities over a period of years in the areas of attention, word-finding memory, phonology, and language use.[5,6,20] Taken together, the findings from the present study and previous studies suggest that early treatment of CM and aggressive seizure prevention and treatment may provide a way to reduce cognitive sequelae in children with CM. However, seizure management and particularly prevention in CM are complicated; a study in Kenya documented increased mortality rates for children with CM who were given phenobarbital as seizure prophylaxis, in addition to diazepam as needed for seizure control.[21] Efforts at seizure treatment and prevention must

balance the potential for prevention of long-term injury with the risk of short-term respiratory depression, and alternatives to phenobarbital for seizure treatment and prevention in CM may be necessary.

Memory[22] and working memory and language[5,8,20,23,24] have been proposed as the mediators of long-term language deficits observed in children with CM. The developmental lag in attention and working memory performance we observed in our children with CM between the 3-month and 6-month follow-up assessments may help to explain the long-term deficits in higher-order language development identified in these retrospective studies up to 9 years after the CM episode. Functional neuroimaging studies in children have revealed an overlap in brain processes that are recruited in directed visual attention and in visuospatial working memory. These processes are related to activity in the dorsolateral prefrontal, orbital frontal, and anterior cingulate gyrus areas of the brain.[25] Future prospective longitudinal studies using functional neuroimaging could substantiate the involvement of these areas of the brain in CM. Such studies could also help to differentiate between localized neuropathogenesis for CM (eg, hypoxic ischemic effects on temporal lobe/hippocampal tissue) and a more-diffuse global process (eg, hypoxic/ischemic effects on subcortical white matter, with subsequent global disruption of cortical neural network development).

We did not document significant differences in cognition between children with UM and CC, which suggests that cognitive differences are specific for severe malaria. However, without a comparison group of non-cerebral severe malaria, we cannot exclude the possibility that other forms of severe malaria may also be associated with cognitive impairment. Other limitations of our study included a relatively small sample size, the lack of testing for children <5 years of age, and the lack of follow-up monitoring beyond 6 months. We are currently conducting 2-year follow-up studies to address the latter limitation, and we hope, with the advent of new cognitive testing methods, to conduct similar studies with younger children in the future.

## CONCLUSIONS

Our study demonstrates that ~21% of children >5 years of age with CM have cognitive deficits 6 months after discharge and that increased seizure frequency and prolonged coma duration are associated with persistent cognitive deficits. CM may be a major cause of cognitive impairment in children in sub-Saharan Africa. Additional studies on the pathogenesis of cognitive deficits in CM and on treatment to prevent these deficits are urgently required.

## Abbreviations

CM, cerebral malaria; UM, uncomplicated malaria; CC, community children; K-ABC, Kaufman assessment battery for children; TOVA, tests of variables of attention; TPT, tactual performance test; OR, odds ratio; CI, confidence interval.

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**TABLE 1**

Characteristics of Children With CM, Children With UM, and Healthy CC Enrolled at Mulago Hospital (Kampala, Uganda)

| | CM (*n* = 44) | UM (*n* = 54) | CC (*n* = 89) | *P* |
|---|---|---|---|---|
| Age, y | 7.5 ± 2.1 | 8.3 ± 2.2 | 7.9 ± 2.0 | .17 |
| Height, cm | 119.8 ± 12.5 | 125.3 ± 13.7 | 120.8 ± 12.2 | .07 |
| Weight, kg | 22.1 ± 7.1 | 23.4 ± 6.1 | 22.5 ± 6.2 | .61 |
| Weight-for-age *z* score | −1.2 ± 1.6 | −1.2 ± 1.0 | −1.1 ± 1.1 | .81 |
| School level | 2.6 ± 2.0 | 3.5 ± 2.3 | 3.0 ± 1.8 | .12 |
| Highest maternal education | 6.0 ± 2.7 | 6.1 ± 2.6 | 6.2 ± 2.2 | .90 |
| Highest paternal education | 6.9 ± 2.5 | 7.6 ± 1.7 | 7.1 ± 2.0 | .33 |
| Socioeconomic status | 11.3 ± 2.8 | 12.0 ± 3.6 | 11.0 ± 2.7 | .23 |
| Home environment score | 32.2 ± 6.3 | 33.4 ± 7.9 | 30.7 ± 7.4 | .11 |

Values are shown as mean ± SD. See “Methods” for scoring of school level, parental education, socioeconomic status, and home environment.

**TABLE 2**

Frequency of Cognitive Deficits in Children With CM, Compared With CC, 6 Months After Initial Testing

| Cognitive Deficit | Frequency, % | | *P*[a] |
|---|---|---|---|
| | CM (*n* = 42) | CC (*n* = 87) | |
| ≥1 impairment | 21.4 | 5.7 | .01 |
| Working memory | 11.9 | 2.3 | .04 |
| Attention | 16.7 | 2.3 | .005 |
| Learning | 4.8 | 1.1 | .25 |

[a] $\chi^2$ test.

**TABLE 3**

Frequency of Cognitive Deficits in Children With CM, Compared With CC, at Initial Testing and 3 Months Later

| Cognitive Deficit | Frequency, % | | | | | |
|---|---|---|---|---|---|---|
| | Baseline Assessment | | | 3-mo Assessment | | |
| | CM (*n* = 44) | CC (*n* = 89) | *P*[a] | CM (*n* = 44) | CC (*n* = 89) | *P*[a] |
| ≥1 impairment | 36.4 | 11.2 | .0006 | 19.0 | 6.9 | .07 |
| Working memory | 25.0 | 2.2 | <.0001 | 7.1 | 2.3 | .33 |
| Attention | 15.9 | 2.2 | .006 | 9.5 | 3.4 | .21 |
| Learning | 23.8 | 6.7 | .005 | 7.1 | 1.1 | .10 |

[a] $\chi^2$ test.

**TABLE 4**

Frequency of Cognitive Deficits in Children With UM, Compared With CC, 6 Months After Initial Testing

| Cognitive Deficit | Frequency, % | | *P*[a] |
|---|---|---|---|
| | UM (*n* = 52) | CC (*n* = 87) | |
| ≥1 impairment | 13.5 | 5.7 | .13 |
| Working memory | 3.8 | 2.3 | .63 |
| Attention | 3.8 | 2.3 | .63 |
| Learning | 5.8 | 1.1 | .15 |

[a] $\chi^2$ test.

**TABLE 5**

Frequency of Cognitive Deficits in Children With UM, Compared With CC, at Initial Testing and 3 Months Later

| Cognitive Deficit | Frequency, % | | | | | |
|---|---|---|---|---|---|---|
| | Baseline Assessment | | | 3-mo Assessment | | |
| | UM (*n* = 54) | CC (*n* = 89) | *P* Value[a] | UM (*n* = 54) | CC (*n* = 89) | *P*[a] |
| ≥1 impairment | 13.0 | 11.2 | .76 | 5.7 | 6.9 | 1.00 |
| Working memory | 3.7 | 2.2 | .63 | 1.9 | 2.3 | 1.00 |
| Attention | 1.9 | 2.2 | 1.00 | 0 | 3.4 | .29 |
| Learning | 7.4 | 6.7 | 1.00 | 5.7 | 1.1 | .15 |

[a] $\chi^2$ test.