Author's response to reviews

Title: Cognitive rehabilitation in Ugandan children after severe malaria: effects on cognition, academic skills and behaviour

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Author's response to reviews: see over
Dear Editor,

We are grateful for the useful comments from the reviewers. See our responses to each of their comments below.

Reviewer 1

1. The main problem I have with the manuscript is that the authors seem to think that their findings (or lack of findings) generalize to ALL computerized cognitive rehabilitation strategies. Their conclusion is that “computerised cognitive rehabilitation three months after severe malaria had a short-term effect on cognitive outcomes but did not appear to affect short-term academic achievement or behaviour”.

We corrected the conclusion in the abstract to read ‘our computerised cognitive training program three months after severe malaria had a short-term effect on cognitive outcomes but did not appear to affect short-term academic achievement or behaviour.’

In the discussion, we have stated; ‘We conclude that our computerised cognitive rehabilitation targeting different cognitive abilities may improve some cognitive abilities but not academic skills and behaviour three months after severe malaria.’

2. What adds to the problem is the fact that it is not even clear that the training strategy used here is specifically targeted to improve the main cognitive deficits experienced by these children (and what are the main impairments experienced by them in the first place).

We have stated in the Methods section under Intervention on page 6 what cognitive abilities are trained by our training package. The fourth line of the manuscript in the Background on page 3 mentions the main impairments suffered by children after severe malaria.

3. As introduced in the point above, I believe it is absolutely crucial that more information be provided on the actual training the children underwent. Without that information, it is impossible to reproduce these results or perhaps more importantly, attempt to understand what type of computer-based training does NOT work in these children. Some attempt to link the principles behind that training strategy with the deficits encountered by the children would also be necessary in my opinion. Again, think of it as a drug, there should be some rationale for using it this particular condition. Would it make sense to treat heart failure with an anti-epileptic? Or, conceptually more similar, to what extent would practicing arithmetic help for the remediation of dyslexia? Without a rigorous approach to cognitive training, it will be very difficult for this new field to gain any traction and credibility.

We have provided details of the training exercises in the Methods section under Intervention on page 6.

4. The outcome measures and their relevance should be more explicit. The main effects of the training strategy in this study were on “learning” and “working memory”. “Learning” can mean dozens of different things. A more thorough discussion of what exactly is being measured will also be very helpful to understand what could have worked/not worked with this particular training strategy.

The cognitive abilities measured by the different instruments have been explained in the Methods section on page 7.
5. On page 5 first line, the authors write that “cognitive deficits after MNI get more severe with time”. A reference would be needed for this. And if the authors really meant that the gap between the cognitive age vs actual age of the children is widening, I would suggest reformulating the sentence, as it would be misleading as it is. Are the cognitive performances really worsening (raw scores) or are these children more and more behind in their cognitive performance?

This sentence has been rephrased and references added to read ‘cognitive test performance is poorer in the long term than in the short term compared to controls.’

6. Both scenarios would have very different implications. Depending on the authors’ response, the sentence found shortly after in the text “This implies that interventions done long after the illness may have little benefit since the severity of cognitive deficits seems to worsen as the child matures” might have to be removed or changed.

This sentence has also been rephrased to read; ‘It is thus possible that interventions done long after the illness may have little benefit since the cognitive impact of the disease is more apparent in the long term. Early interventions may stall the development of these deficits.’

7. On page 6, the authors indicate that 15 children had withdrawn from the study or been lost to follow up. Is it known why they withdrew? Were they doing better? Is it conceivable that they formed a homogeneous group that would have been more likely to respond to therapy? I realize that the answer to this might not be known.

These children withdrew because the parents withdrew their consent. In most cases, mothers attend to children in the hospitals and they give consent. However when at home after discharge, the fathers may not agree and ask to be withdrawn. Other children could not traced because they gave poor home directions or had changed phone numbers or had shifted. We don’t believe that these children formed a homogeneous group that would respond to therapy. However, their inclusion would have increased the power of the study and affect the results. It is also not likely that they withdrew because they were doing better since the outcome measured by our tests (especially the cognitive outcomes) are subtle to be observed without testing.

We have also edited the numbers in this section on page 6 to tally with our flow chart (Figure 1).

8. Page 8, in the paragraph concerning the WRAT-3, the last sentence is redundant. It has been deleted

9. Based on the WRAT-3 results the authors conclude that the training strategy “did not appear to affect…academic achievement”. Could the authors indicate whether this test can really be used as a predictor of academic achievement? This test seem to correlate with past academic achievement and it is not clear to me that retaking the test 3 months later, considering a possible practice effect would allow to make such a conclusion.

We have decided to use ‘skills’ instead of ‘achievement in the manuscript.’ We have also revised the definition of the WRAT-3 in the methods section and added a reference to back this change.

Page 8, the authors explain that attention deficits are common in children recovering from severe malaria. It would be important to note/discuss somewhere that attentional difficulties will cloud all other cognitive measures and that a training strategy failing to address this difficulty would have a high risk of failure.

We have mentioned the potential effect of poor attention on other skills (see last paragraph page 8) and the need to train attention (first paragraph page 7).

It is also unclear to me how results on the KABC-II and WRAT-3 should be interpreted in the context of severe attentional benefits.
**It is likely that attention (and working memory) may have affected some of the other cognitive outcomes in this study. However investigation of this effect is beyond the scope of this paper since it is not looking at the cognitive outcomes after severe malaria but the effect of the intervention.**

Table 2 and 3, I believe that actual scores and not only differences between experimental and control groups would have been helpful. These would help decide whether cognitive performance really decreases with time in these children and could show important differences between the two groups.

**The suggested changes to the tables have been made.**

Reviewer 2

Note: These responses are from the comments the reviewer made onto the manuscript.

1. I suggest this is not a valid assumption- please see related remarks throughout the text.

**The section of the abstract where this comment was made has been revised.**

2. Line the Conclusion on page 11, the last paragraph of the abstract is appropriately cautious and factual

**The conclusions in the abstract and discussion have been changed.**

3. The suggestion of a "progressive problem as the child matures" is intriguing. I am uncertain if it implies a progressive disorder such as occurs with a 'slow virus', or an artifact: the domains of cognition one can test changes with age in the young from infancy to early childhood-is the apparent progressive problem related to what we test: similar to the plateau one see's in young children with even static mental impairment. I believe this requires some elaboration, perhaps latter in discussion. The sentence as it stands, may not convey the entire picture.

**This section on page 3, first paragraph has been revised to read: ‘...that cognitive impairment becomes more apparent in the long term as children are required to perform more complex cognitive tasks.’**

4. Put power calculations

**We have inserted power calculations on page 5 paragraph 2.**

5. Could the improvement have not been part of natural history- how can one attribute the improvement to the earlier intervention?

**This is unlikely since subjects were randomly assigned to the two study arms and benefit was observed in the intervention group, in line with prior research.**

6. A limitation. Therefore would the authors consider their study to be complementary to reference 29 (Bangirana et al 2009)?

*Yes, this study is complementary to our earlier study by comparing benefits for cognitive training initiated much earlier than was done in the 2009 study.*

7. Do these lines add any specific information to the message the authors want to convey? See earlier related remarks...
Yes they do. The sentence from the previous paragraph that mentions this same point has been deleted.

8. I found this highlighted paragraph confusing to read...in some ways these reflect limitations of the study design...can this not be stated more precisely and succinctly?

This section has been revised with one paragraph addressing the major limitation and a second paragraph outlining other study limitations.