Author’s response to reviews

Title: Low contrast visual acuity testing is associated with cognitive performance in multiple sclerosis: a cross-sectional pilot study

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Version: 3 Date: 26 September 2013

Author’s response to reviews: see over
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Version: 2 Date: 24 September 2013

Author’s response to reviews: see over
Dear Dr. Majithia,

Please find attached our revised manuscript entitled

"Low contrast visual acuity testing correlates with cognitive performance in multiple sclerosis: a cross-sectional pilot study"

which we would like you to consider for publication in *BMC Neurology*.

After carefully revising the manuscript based on the reviewers' comments, we now hope that you will find our manuscript suitable for publication in *BMC Neurology*.

Yours sincerely,

Friedemann Paul

Alexander U. Brandt

Deesha Majithia
- Executive Editor BMC Neurology -
Point-by-point commend to the reviewers’ comments:

Reviewer: Ralph Benedict

This is a well written manuscript that reveals significant correlation between low contrast visual acuity and neuropsychological testing in MS. A few other groups have reported on the same association, interpreting their findings as showing a confound between visual acuity and cognitive performance. This study is unique in that the design includes OCT. The sample size is also an asset for this study. The abstract highlights SDMT and PASAT and does not report that the entire BRNB was administered.

*We corrected the abstract and now mention the BRB-N.*

Throughout I find errors regarding the manner in which psychological constructs are defined. The BRNB does not include a test of sustained attention [eg continuous performance test] or focused attention for that matter. The use of the term ‘attention’ is not correct, and it matters not because in contrast to the manuscript there is little evidence that MS patients suffer from disordered attention. They do have impairment in processing speed and working memory.

*We corrected the manuscript accordingly.*

The authors acknowledge at the end of the Discussion that the data are cross-sectional and offer no inferences regarding causality. Yet the manuscript is littered with suggestions of causal effects. For example, in the Abstract, “our data show that cognitive impairment potentially diminishes performance.” To begin with, their data could just as easily be interpreted as showing that poor visual acuity impacts cognitive performance, rather than the other way around.

*We changed the abstract and other parts of the manuscript to imply less causality.*

Second paragraph of Introduction, first sentence, there is a missing word at the end of the sentence.

*We changed the end of the sentence.*

A methodological weakness is failure to exclude patients with other causes of cognitive impairment, including psychiatric illness.

*As also suggested by Dr. Gold, we included data on depression and fatigue into the cohort description. None of the patients showed major depression symptoms according to Beck’s Depression Inventory.*

On page 5, all of the cognitive tests should be referenced.

*We included references to the original works first describing the respective tests.*

From the outset the BRNB z score is not defined. Is this a composite z score?

*We clarified the included sentence at the end of the methods paragraph, reading now: “BRB-N z-scores were calculated as previously described against normative data for German MS patients using the original script kindly provided by Dr. Scherer.” with a reference to the respective work.*

In the analysis section only the PASAT and SDMT are discussed whereas all of the tests in the BRNB were analyzed.

*In the detailed analyses we focused on PASAT and SDMT since both test for information processing speed, but SDMT includes a visual component and PASAT does not. Our intention was to minimize a potential effect of the SDMT’s visual component (which of course could have been influenced by visual dysfunction). We state this now more clearly in the manuscript.*

In Table 2 and throughout the Results please present all of the standardized betas and the r values so that the reader can judge the effect sizes across all metrics.

*We included standardized Betas and r-values also for non-significant tests. To improve readability we moved now extensive GEE results from the text to a new table 3.*
The authors point out that this is preliminary work conduct with a sample that is not very impaired compared to other studies. It is premature to present cut scores that could easily be misapplied in clinical work with patients. I think this part of the paper should be deleted altogether. Furthermore I do not know what a ‘local regression analysis’ is.

We removed the discussion of cutoff values from the text. However, we left the figure so that the reader has a visual presentation of the data discussed in the result section. We further included a reference to the LOESS method:


The authors may be interested to know that LCVA and SDMT are proposed metrics for a revised MSFC as noted in recent task force meetings on this very topic [Cohen et al Lancet; Ontenada et al MSJ].

We included references to these two manuscripts in the introduction where we present this issue.

I am puzzled about one aspect of these findings. The authors argue that since RNFL was controlled for and there still is a relationship between various tests and LCVA, that means that cognitive ability is involved in the LCVA metric. They sometimes refer to these outcomes as complicated or complex visual tests. What is so complicated about them? Sure, the stimuli are harder to see than with a Snellen chart, but it is still a task of look at the board and tell us what you see. What is complicated about that? Moreover, how do you explain that memory tests are related to these outcomes – surely no memory performance is required?

We agree with Dr. Benedict that “complex” might be misleading and changed the wording to “challenging”. We do perform both cognitive and visual assessments on a daily routine in our clinic. Sloan and FACT testing are magnitudes more difficult to the examinee than regular Snellen charts. This might sound not intuitive at first, but the addition of “contrast” to the tests has severe impact on how the test feels to the participant. For example, in FACT the examinee is asked to make a “guess” for the last barely recognizable grate, which usually causes a strenuous reaction to achieve the best possible guess. Although we agree with Dr. Benedict, that low contrast visual tasks do not include specific cognitive tasks (other than recognizing letters or grating charts) the strain they put on the examinee is on par with several of the tasks used e.g. during the BRB-N.

I think there is an inferential error. The authors claim that overall disease burden is controlled by including RNFL in the model, but OCT-RNFL is NOT a proxy for overall disease burden. EDSS or MRI BPF would be closer to this idea.

This is a misunderstanding and we carefully revised sections of results and discussion where this might have happened. We fully agree with Dr. Benedict and do claim that RNFL is in fact not correcting for overall disease burden. Instead, we use RNFL as a measure for local damage to the anterior optic pathway only and discuss that we cannot rule out a correlation with overall disease burden that affects different systems equally.

In the Discussion these small effects, for example r = 0.34, are described a closely linked or strongly correlated, which of course is not true. EDSS correlates at this level with cognitive function. Do we then conclude that physical disability is closely linked with cognitive dysfunction?

We corrected the wording.

Reviewer: Stefan Gold

In this study, Wieder et al. investigate the association between visual acuity (as measured by low contrast testing) and cognitive function in a comparatively large sample of MS patients. They report significant (albeit small) correlations between measures of contrast sensitivity (CS) and widely used measures of processing speed (and to a lesser degree memory) as well as OCT-derived parameters of retinal pathology (RNFL thickness).

The paper is generally clearly written and the study design and analysis straight-forward and well-described. I have just a few comments:

Minor essential revisions:

While the authors point out in the discussion that this cross-sectional analysis does not imply causality, some wording in the abstract sounds like they are suggesting that cognitive impairment reduces visual acuity. In my mind, other explanations are at least as likely, i.e. lower visual acuity could cause poorer performance in cognitive tests or lower
acuity as well as poorer performance on the PASAT/SDMT could both be the result of degenerative components of MS pathology. Please rephrase.

*Also suggested by Dr. Benedict, we changed the wording in the abstract to indicate less causality.*

While the associations are significant, the partial correlations suggest to me that only approximately 10% of variance in CS is accounted for by cognitive function. This should be discussed.

*We included these data in the section where we discuss this.*

Moreover, the paper would in my view benefit from contrasting the reported association between CS and cognition with previous markers of brain atrophy and other MRI parameters previously shown to be associated with cognitive dysfunction in MS. What would the authors expect if one would add MRI markers to the equation? Are OCT, MRI, and CS measuring the same underlying mechanism of cognitive dysfunction? Or do they independently contribute? At least for CS and RNFL, this appears to be the case. What could that mean for our understanding of the causes of cognitive impairment in MS? The lack of MRI markers may also be briefly added to the limitations section.

*As suggested we discuss this now in more detail.*

Please state in the abstract that MS patients did not only undergo SDMT and PASAT testing but also completed tests of additional cognitive domains. It might be helpful to mention in the abstract that the BRB-N, a standardized and widely used neuropsych battery in MS research, was administered.

*We changed the abstract and now mention the BRB-N.*

Several reports have suggested that fatigue and/or depression can affect performance in neuropsychological tests. Have the authors obtained any measures of depressive symptoms or fatigue and if so, does entering them in the model change the results?

*As suggested by Dr. Gold and by Dr. Benedict, we included data on fatigue and depression in the cohort description. None of the included subjects showed major depression signs.*