Author's response to reviews

Title: Cognitive function and quality of life in multiple sclerosis patients: a cross-sectional study

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Author's response to reviews: see over
November 18, 2010
Melissa Norton, Editor-in-Chief
BMC Neurology editorial

Dear Melissa Norton, Angelina Ilievska, Jelena Drulovic, and Prof. Robert Zivadinov,


We thank you for accepting a new version of our manuscript. Please find enclosed a copy of our revised manuscript, in accordance with the comments of the three reviewers.

We highlighted all changes made in the manuscript (grey color).

In response to the comments of Reviewer 1 (Pablo Villoslada, point 1), we have proposed several changes. The reviewer proposed an alternate definition of cognitive impairment. In our response, we first discuss our initial choice. We performed supplementary analyses to illustrate our response. We propose two possibilities to satisfy the reviewer: 1. to keep our initial definition, or 2. to replace our definition with his definition. Our revised manuscript kept the initial definition, based on some arguments précised in the reviewer’s response. But these arguments can be discussed. If the editors and the reviewer prefer the second definition, we can change some areas, as proposed in our response (these changes were highlighted: yellow color).

The modified manuscript was edited by native English speaking editors at American Journal Experts (Key: F1CF-4A4F-1469-BD07-46A7) as suggested by one reviewer.

We hope that this new version will be acceptable.

Yours sincerely,

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Point-by-point response: reviewer's reports

Title: Cognitive function and quality of life in multiple sclerosis patients: a cross-sectional study

Reviewer 1: Pablo Villolslada

Major Compulsory Revisions

1. Authors use a very strict definition of cognitive impairment (they acknowledge such aspect in the discussion), which is less sensitive than others. I suggest to test another more sensitive definitions as used in ref 40-43 (e.g. 1.5 SD below the norm in 2 subtests) and assess is a more sensitive definition has an impact in the multivariate model.

Response:
We completely agree with this remark. We are aware that the choice of the definition of cognitive impairment affects the proportion of impaired subjects identified. Because no French norms were available (the version used by Dujardin et al. differs in terms of the content and the number of subtests), we arbitrarily decided to classify our sample using Camp’s norms. These criteria define impairment or deficit for one subtest as a score at least 2 standard deviation (SDs) below the mean normative values and cognitive impairment or deficit for the global battery as impairment in at least three of the eight subtests [Camp et al. Cognitive function in primary progressive and transitional progressive multiple sclerosis: a controlled study with MRI correlates. Brain 1999]. In this article, Camp et al. stated, “The chosen threshold determines the prevalence reported”. The authors justified their choice by emphasising that this definition is consistent with a previous publication [Comi et al. Brain magnetic resonance imaging correlates of cognitive impairment in multiple sclerosis. J Neurol Sci 1995].

However, the multivariate model we presented was not affected by these definitions. Indeed, we used continuous variables in the subtests rather than binary variables (impaired/not impaired). Our results (the multivariate model) were therefore independent of the definition of cognitive impairment. Our tables 1, 2, and 4 present results with the subtests used in a continuous format. On the other hand, the third table (table 3) proposed showing means comparisons of QoL scores between impaired and unimpaired subjects defined using Camp’s norms as two SDs in three subtests.

If the reviewer prefers to use his definition (cognitive impairment/deficit for one subtest if the score was at least 1.5 SD below the mean normative values and cognitive impairment/deficit for the global battery if the patient was cognitively impaired for at least two of the eight subtests), we are willing to change the relevant four areas of the manuscript as follows:

- In the abstract (page 3, lines 18-20):
  “Performance on BRB-N subtests varied widely (6% to 70% abnormal). The BRB-N classified 37% of the patients as cognitively impaired”
“Performance on BRB-N subtests varied widely (10% to 78% abnormal). The BRB-N classified 78% of the patients as cognitively impaired”.

- In the methods section (page 6, lines 7-11):
  “Cognitive impairment or deficit was defined using Camp’s normative values [24]. The subject was considered cognitively impaired or deficient for one subtest if the score was at least two SDs below the mean normative values, and he/she was considered cognitively impaired or deficient for the global battery if he/she was cognitively impaired for at least three of the eight subtests”
will be replaced by the following:
  “Cognitive impairment or deficit was defined using Camp’s normative values [24]. The subject was considered to have cognitively impaired or deficient for one subtest if the score was at least 1.5 SDs below the mean normative values, and he/she was considered cognitively impaired or deficient for the global battery if he/she was cognitively impaired for at least two of the eight subtests”.

- In the results section (page 7, lines 13-14):
  “Performance on BRB-N subtests varied widely (6% to 70% abnormal). The BRB-N classified 37% of patients as being cognitively impaired”
will be replaced as follows:
  “Performance on BRB-N subtests varied widely (10% to 78% abnormal). The BRB-N classified 78% of patients as cognitively impaired”.

- In table 3, section 7:

<table>
<thead>
<tr>
<th>Cognitive function</th>
<th>ADL</th>
<th>PWB</th>
<th>RFr</th>
<th>SPT</th>
<th>RFa</th>
<th>RHCS</th>
<th>SSL</th>
<th>COP</th>
<th>REJ</th>
<th>Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>No deficit</td>
<td>31.03</td>
<td>52.08</td>
<td>61.42</td>
<td>58.22</td>
<td>74.27</td>
<td>67.26</td>
<td>52.55</td>
<td>59.72</td>
<td>63.39</td>
<td>57.10</td>
</tr>
<tr>
<td>Deficit</td>
<td>(20.73)</td>
<td>(25.34)</td>
<td>(22.04)</td>
<td>(23.30)</td>
<td>(22.55)</td>
<td>(18.25)</td>
<td>(29.53)</td>
<td>(27.00)</td>
<td>(30.97)</td>
<td>(12.16)</td>
</tr>
<tr>
<td>p</td>
<td>0.34</td>
<td>0.86</td>
<td>1.00</td>
<td>0.25</td>
<td>0.42</td>
<td>0.36</td>
<td>0.31</td>
<td>0.15</td>
<td>0.11</td>
<td>0.68</td>
</tr>
</tbody>
</table>

will be replaced by this table:

<table>
<thead>
<tr>
<th>Cognitive function</th>
<th>ADL</th>
<th>PWB</th>
<th>RFr</th>
<th>SPT</th>
<th>RFa</th>
<th>RHCS</th>
<th>SSL</th>
<th>COP</th>
<th>REJ</th>
<th>Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>No deficit</td>
<td>35.92</td>
<td>58.13</td>
<td>64.47</td>
<td>62.19</td>
<td>77.71</td>
<td>68.42</td>
<td>70.00</td>
<td>69.38</td>
<td>65.00</td>
<td>62.31</td>
</tr>
<tr>
<td>p</td>
<td>0.08</td>
<td>0.25</td>
<td>0.40</td>
<td>0.18</td>
<td>0.36</td>
<td>0.79</td>
<td>0.007</td>
<td>0.03</td>
<td>0.72</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Whether the reviewer prefers the initial definition or his definition, we propose adding the following paragraph in the discussion section (page 12, line 3):

“Furthermore, a patient may be considered cognitively impaired for one test if the score is less than 2 SDs [46, 47], less than 1.5 SDs [48, 49], or less than the fifth percentile [50] of healthy controls. A patient can be considered cognitively impaired for a global battery in the case of at least three impaired tests [24, 47, 51], or two impaired tests [50], or even just one impaired test [46]. The proportion of cognitively impaired patients depended on these definitions. These disparities make comparisons difficult between studies”.

2. The dataset is biased to SP and more disabled patients, and they are more unemployed than younger populations. In this set of patients, QoL could be more dependent on other factors than cognitive impairment because they are not force to perform at same level than younger people with MS. Although this is acknowledge in the discussion, this should be assess by stratifying the dataset in RR and progressive patients.

Response:
We were attentive to these important remarks. As indicated in the statistical section, the variables relevant to the models were selected from the univariate MusiQoL index analysis based on a threshold p-value ≤0.20 (MFIS-To, BDI) or a threshold p-value ≤0.30 for the BRB-N subtests. A set of additional variables was included in the models owing to their clinical and sociodemographic interest (gender, age, marital status, EDSS, and disease duration).

The model accounted for the age of the patients (age was included in the model). We did not initially include the disease subtype in the model because: i) we did not find differences between dimension scores for the various subtypes in this sample, and ii) we did not find pertinent differences in the validation publication that studied a larger sample (n=1992) [Simeoni 2008]. However, to address the reviewer’s remarks, we propose to add this parameter to the multivariate models. We thus modified our text as follows:

- The statistical section (page 7, lines 1-2): “A set of additional variables was included in the models owing to their clinical and sociodemographic interest (gender, age, marital status, EDSS, and disease duration),” was replaced by, “A set of additional variables was included in the models owing to their clinical and sociodemographic interest (gender, age, marital status, EDSS, MS subtype, and disease duration)”.
- The result section (page 8, line 3): “The variables selected for the multivariate models were gender, marital status, age, EDSS, disease duration, MFIS-To, BDI, and the four subtests…” was replaced by, “The variables selected for the multivariate models included gender, marital status, age, EDSS, MS subtype, disease duration, MFIS-To, BDI, and the four subtests…”.
- The result section (page 8, line 5): “Marital status, age, EDSS, and depression were associated with the MusiQoL index. No links between the MusiQoL dimensions and
cognitive functions were identified, except in the case of the SPART-T with the RHCS and COP dimensions, or the WLG with the SSL dimension.” was replaced by, “Marital status, EDSS, and depression were associated with the MusiQoL index. No links between the MusiQoL dimensions and cognitive functions were identified, except in the case of SPART-T with RHCS”.

- Age was not linked to QoL (index) and was removed from the results and discussion sections.
- We added three lines, corresponding to the MS subtypes, to table 4.

3. Tables: indicate always what means values (e.g., “r” coefficient, or SD)
We completed and modified the table legends. We hope that they will now be more readable.
Reviewer 2: Christoph Heesen

Major Compulsory Revisions

1. However, the question arises how a quality of life scale with 2 items on cognitive symptoms might correlate to a set of 8 cognitive tests for which the relevance for daily living is not clear. An additional measure of perceived cognitive dysfunction in daily life as the MSNQ would have been helpful to obtain an idea if the lack of a correlation is:

Response:

a) due to lack of awareness on the patient side

We are not sure we clearly understand this comment. The model chosen as reference for the development of the MusiQoL does not refer to the cognitive dimension. The MusiQoL is a questionnaire of health-related quality of life; it is not a mixed questionnaire including symptoms and daily life activities. The MusiQoL assesses the consequences of the health status, including the cognitive disorders associated with multiple sclerosis, and addresses a coping dimension rather than a cognitive dimension. Consequently there is no strong correlation awaited and/or sought for cognitive dimensions. If our questionnaire had integrated a cognitive dimension as an additional measure of perceived cognitive dysfunction in daily life, the MSNQ would have been helpful to interpret the lack of a correlation.

b) Lack of sensitivity of the MusiQoL to cognitive dysfunction. Other QoL tools have shown to differentiate patients according to different levels of cognitive impairment and as well as studies have shown that cognitively disabled patients are able to give consistent answers to questionnaires (Gold 2001, Gold 2003).

The results of the initial publication [Simeoni 2008] found that the index of MusiQoL and the dimensions’ scores were well-correlated with the mini-mental status exam, with the exception of psychological well-being, relationships with family, and relationships with friends. We do not think that the lack of sensitivity of the MusiQoL can be used as a forceful argument. However, we entirely agree with the reviewer’s second sentence. If some studies have shown that cognitively disabled patients are able to give consistent answers to questionnaires, it seems necessary to demonstrate that patients suffering from multiple sclerosis who are cognitively disabled give consistent responses to MusiQoL; this result reinforces the validity and the acceptability of this questionnaire.

To clarify this point, we added the following sentence in the discussion (page 9, lines 17-21)

“Because the MusiQoL is based on the concept of a health-related quality of life measure, no strong correlations with cognitive status are expected or sought. This result reinforces the validity and the acceptability of this questionnaire and is consistent with studies reporting that cognitively disabled patients are able to give consistent answers to questionnaires (Gold 2001, Gold 2003).”
2. From the data presented further questions on the validity of the MusiQoL emerge. Why is the correlation of ADL with EDSS so low (0.4)?

Response:
The reported correlation is moderate (0.4) and differs from 0 (p-value = 0.001). We do not believe that this correlation challenges the validity of the MusiQoL. If the correlation between ADL and EDSS had been high, it would not have supported the validity of the MusiQoL. It would have indicated that the measurement of ADL by MusiQoL is redundant compared to the EDSS assessment, and consequently it would have decreased the validity of the tool. A middle correlation is awaited for this dimension as demonstrated in the initial validation of the MusiQoL, which involved more than 1900 patients [Simeoni 2008]. From our perspective, the purpose of this study was not to report new arguments regarding internal structure validity with a sample containing fewer patients than the original publication. This result is congruent with the previous report [Simeoni 2008]. We hope that our explanation will be sufficient. Therefore, no modification to the manuscript is proposed for this comment.

3. Why does coping and psychol. well-being not correlate with working status?

Response:
We did not find data in the current literature clearly demonstrating that coping and psychological well-being are clearly linked to working status in multiple sclerosis. From our point of view, it seems scientifically precarious to postulate that the validity of the instrument would be questionable due to the absence of links between these dimensions and the working status. Furthermore, our study was not intended to demonstrate this point. Based on the number of patients included in this study, we can suspect that this study lacks the power necessary to assess this goal. We hope that our response will be appropriate to the remark. Therefore, no modification to the manuscript is proposed for this comment.

4. However, the problem of having a real estimate for the impact on daily life from a cognitive test result as the Rao battery is an unsolved issue. Authors should discuss these problems.

Response:
We are not sure we understand this comment. Our study did not attempt to find a real estimate for the impact on daily life from a cognitive test result. In our opinion, it seems unrealistic to expect this study to solve the unsolved issue reported by the reviewer. Our goal was specifically to examine the relationship between cognitive dysfunction and QoL in a MS patient sample across disease subtypes while taking into account the key sociodemographic and clinical confounding factors to report that cognitively disabled patients with MS are able to give consistent answers to self-reported questionnaires.
To clarify this point we added the following sentence at the end of the introduction (page 4, lines 21-22):
“We examine the relationship between cognitive dysfunction and QoL in a sample of patients with MS, including any disease subtypes, while considering the key sociodemographic and clinical confounding factors to report that cognitively disabled patients with MS are able to give consistent answers to self-reported questionnaires.”

5. The Musiqol offers only a psychological wellbeing scale; 2 of the 4 items refer to cognition, the others to mood. Therefore, the subscale seems not a suitable comparator for cognitive performance.

Response:
We agree with the reviewer: the psychological well-being dimension of the MusiQoL is not a suitable comparator for cognitive performance. As reported above, the MusiQoL assesses the consequences of health status, including the cognitive disorders seen in multiple sclerosis, on quality of life. The psychological well-being dimension assesses the consequences of MS on psychological well-being but not symptoms such as cognitive impairment. The MusiQoL does not include a cognitive dimension. None of the four items of the psychological well-being scale (“felt anxious”, “felt depressed or gloomy”, “felt like crying”, “felt nervous or irritated by a few things or situations”) describes cognitive impairment.
We hope that our response to this comment will be adequate. Therefore, no modification to the manuscript is proposed.

6. The results section offers multiple tests without reporting a Bonferroni correction for significance levels. Many of the marginally significant correlations might thus be random effects. Furthermore, these large tables are difficult to read and should be condensed.

This point concerns only table 3 (table 1 detailed characteristics of the sample, table 2 provided correlations, and table 3 provided standardised beta coefficients). Table 3 showed the univariate analysis, which is considered the first step for performing linear regression. This step identifies the variables relevant to the multivariate model, in accordance with good practice summarised by standard references such as Vittinghoff [Vittinghoff E, Glidden DV, Shiboski SC, McCulloch CE. Regression methods in biostatistics: linear, logistic, survival, and repeated measures models. New York, USA, Springer (2004)]. This step does not require correction for multiple testing (Bonferroni’s method or other correction methods). The table provided information for selecting variables, not interpreting results. This is the reason that we did not perform correction methods.
To address the reviewer’s concern that table 3 is difficult to read, we have proposed a new presentation for table 3, which we hope will eliminate the difficulty.

7. Language needs substantial improving, some examples:
We apologise for the errors. The modified manuscript was edited by native English-speaking editors at American Journal Experts (Key: F29A-CBD6-8FAC-3402-FD81; key F1CF-4A4F-1469-BD07-46A7). We corrected the examples identified by the reviewer and we added other corrections in accordance with AJE’s suggestions. We hope that the language is more appropriate.

Page 3 abstract studies shown from ... (wrong verb)
The sentence was revised. ‘shown’ was replaced by ‘highlighted’

Page 7 “wrong qol” – what is this?
We replaced “wrong QoL” with “lower QoL scores”.

Page 11 iii) the passation requires? What is the meaning.
We replaced the term “the passation requires” with “the test performance requires” (page 11, line 19)

Conclusion: the relationship between cognitive function and qol is not contradictory, maybe studies are. The relation might be described as complex instead.
We agree with this remark, which concurs with the last sentence of our conclusion: “These preliminary results need to be confirmed with larger samples using more accurate tests of cognitive function”.

Minor Essential Revisions
1. Page 7 results: in which time-frame were patients enrolled?
We added this information in the results section (page 7, line 8):
“… were enrolled during a twelve-month period.”

2. From which settings (academic hospitals?) where patients enrolled?
We were not sufficiently clear in our initial version. In the methods section, we replaced “university” with “academic” (page 5, line 2)
“… of a French public, academic teaching hospital (Marseille, France).”
Reviewer 3: Julián Benito
I have just finished to revise the below paper. I have no special comments, except to applaud the authors because papers on the relationship between cognitive dysfunction in MS and health-related quality of life are of special interest. The paper is well written and the methods and results sections are adequate. The conclusions are in line with the results.

This third comment did not require changes or alterations.