Author's response to reviews

Title: Exploring impaired walking dynamics as a new clinical feature in multiple sclerosis

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Version: 2 Date: 7 November 2012

Author's response to reviews: see over
Response to reviewers:
firstly, we would like to thank all reviewers for their excellent and thorough comments on our manuscript. We made an effort to integrate all of them and are confident that the manuscript improved substantially. All changes which were undertaken are marked in the text. Additionally, we provide detailed comments to all issues on the next page. Should further changes seem warranted, we will be glad to consider them.

Sincerely,
Janina Burschka
Boxplots revealed that there were no outliers in the data. Correlation analysis was applied. The choice of Pearson correlations was an appropriate mean based on this analysis. Boxplots revealed that there were no outliers in the data. 

Data was checked for parametric test criteria before the analysis of three parameters of walking behavior i.e. trend analysis via orthogonal polynomials of the zeroth (mean walking speed), first (linear trend of walking speed) and second order (quadratic trend of walking speed). Nevertheless, it was not our intention to rate the fit of these models and draw differential conclusions. Based on our adjustment of the introduction and results section, we hope that this became clearer now.

The aim of our study was the exploratory analysis of three parameters of walking behavior i.e. trend analysis via orthogonal polynomials of the zeroth (mean walking speed), first (linear trend of walking speed) and second order (quadratic trend of walking speed). Nevertheless, it was not our intention to rate the fit of these models and draw differential conclusions. Based on our adjustment of the introduction and results section, we hope that this became clearer now.

We did test for linear and quadratic trends in the walking behavior on the basis of current literature. We did not test for L-shape as this has been described in literature as an attenuated u-shape (quadratic trend) and cannot be estimated via polynomial trend calculation. We did not test for L-shape as this has been described in literature as an attenuated u-shape (quadratic trend) and cannot be estimated via polynomial trend calculation.

We changed the division of the MS group according to the EDSS into persons with and without walking impairment (EDSS 0-3.5 and EDSS 4-5.5).

Our intention was to examine the walking behavior of participants within a standardized test setting, interfering as little as possible with the pacing strategy of the participant. In our clinic, the common practice with regards to the precise wheel as a measurement device is that therapists accompany patients with the wheel, in order to assess patients’ walking capacity. This may have been problematic for several reasons. First, some participants chose a very high walking speed, making it difficult for the examiner to keep up with the pace while simultaneously steering the wheel through the turning points. Second, a moving/accompanying examiner might have an influence on a patient's walking behavior. Based on these considerations, we chose the method as indicated in the manuscript. After the thorough comments of reviewer #1, we appreciate that an alternative strategy could have been to have patients walk with the wheel themselves. Nevertheless, based on the common practice in our clinic, we adopted this different approach.

With regards to the majority of studies reported on in the literature, this claim by reviewer #1 is correct. Nevertheless, it should be noted that our study placed an emphasis on what we refer to as “dynamic” walking characteristics (change in speed) throughout a test, and not the total performance. As our intention was to examine the change in walking speed over the tested time, we think it is necessary to keep the reference to walking speed instead of referring the total distance walked. This also allows for a consistent view on the data as the other two parameters (linear and quadratic trend components) also refer to walking speed. We made an effort to keep this nomenclature consistent throughout the test.

The aim of our study was the exploratory analysis of three parameters of walking behavior i.e. trend analysis via orthogonal polynomials of the zeroth (mean walking speed), first (linear trend of walking speed) and second order (quadratic trend of walking speed). Nevertheless, it was not our intention to rate the fit of these models and draw differential conclusions. Based on our adjustment of the introduction and results section, we hope that this became clearer now.

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We extended the introduction accordingly and report in more detail on articles on the 6MW and Multiple Sclerosis.

1. There are many published papers on the 6MW in persons with MS that are not reviewed in the Introduction. There is a paper on oxygen consumption and cadence during the 6MW in this journal, 6MW and fatigue in another journal through Pubmed, and still other papers on 6MW in MS. These should be reviewed for a comprehensive background on what is known about the 6MW in MS before stating what is to be done in this study.

2. The researchers divided the MS sample based on 6MW performance. This confounds the outcome with the intervening variable and is not acceptable. The groups should be formed based on a variable that is independent of the dependent variable. This should be the EDSS and there should be groups of mild, moderate, and severe based on previous research.

3. The method of measuring distance during the 6MW and 12MW is poor and there are published approaches for accurately measuring this using a precise wheel. Why was this not undertaken in this study and what are the potential consequences?

4. The researchers repeatedly state that one group walked slower or faster. This might be technically correct, but the 6MW is expressed in distance and not speed. Please change speed into distance throughout.

5. There is no indication on whether the linear model fit the data better or worse than the quadratic model per group. Please make this very clear and backed-up based on statistics.

6. Inspection of the figures suggests a linear change in severe, L-shape in moderate, and u-shape in controls. Did you test all of these models? If not, please do so.

We changed the division of the MS group according to the EDSS into persons with and without walking impairment (EDSS 0-3.5 and EDSS 4-5.5).

Minor Essential Revisions

1. There is no differential correlation between fatigue and 12MW between methods of describing performance. This should be made clear. Did you check the data for normality or outliers before correlations? Did you consider Spearman correlations as this would be preferred over Pearson?
We appreciate this suggestion and see how this nomenclature might be misleading. Originally, the terms static and dynamic were not meant to address the motion conducted, but referred to the quality/property of the test outcome. The linear and quadratic trend components can be used to describe the walking dynamics during the test, while the distance walked only captures the mean walking speed without taking dynamics in speed into account. We gave this issue considerable though, but eventually did not find an equivalent expression which is better suited to describe this differentiation. To meet the request by reviewer #2, we therefore excluded the nomenclature (static) and use paraphrases which hopefully rule out misunderstandings.  

We changed “severe” into “moderate” throughout.  

We included this information within an additional table (2).  

We now added essential information on this matter, as an elaboration on the applied statistical model and the detectable effect when this model is applied to a sample of the current size. In particular, the estimation occurred for an ANOVA model (repeated-measures, within factors). The power analysis revealed the necessity of N_{est} = 60, given the following characteristics (input parameters):  

\begin{align*}  
\text{Effect size: } f &= 0.21 \\
\alpha \text{ error probability} &= 0.05 \\
\text{power} &= 0.8 \\
\text{number of groups} &= 3 \\
\text{number of measurements} &= 2 \\
\text{correlation among measures} &= 0.5 \\
\end{align*}  

and yielding the following further output parameters:  

\begin{align*}  
\text{Noncentrality parameter } \lambda &= 10.58 \\
\text{Critical F} &= 3.16 \\
\text{Denominator df} &= 57 \\
\text{Total sample size} &= 60 \\
\text{Actual power} &= 0.82 \\
\end{align*}  

The 12MW did relate to subjective fatigue measures. Both, the mean walking speed and the linear trend component significantly correlated with subjective fatigue. In both tests, the correlation between the linear trend and subjective fatigue was higher than the correlation between mean walking speed and subjective fatigue. However, this difference reached statistical significance in the 6MW only, as indicated by the result of Steiger’s Z-test.  

We adapted the title accordingly.  

Thank you for this helpful suggestion. We now included the indicated articles.  

We changed the expressions accordingly.  

We included a more detailed description in the methods section.  

We included the proposed articles.  

1) Reviewer is uncertain about the classification as walking distance as static. I think this is inaccurate and somewhat confusing. A static measure would be isolated strength testing, perhaps. Reviewer feels that any walking measure is “dynamic”. Recommend authors give some thought to this and consider alternative descriptors.  

2) Group categorization of severe seems to strong, the group performance is on par with the “moderate group” in Goldman 2008 and the median EDSS is 4, there are no subjects with EDSS > 5.0 per provided range. Reviewer feels this group is more accurately described as a “moderate” group.  

3) Authors should provide total distance walked in each group to allow for comparisons to other manuscripts regarding study population.  

4) Author should provide information regarding sample size calculations  

5) It is unexpected the reviewer that the longer distance (12MW) did not relate to subjective fatigue measures, whilst the 6MW does. This seems counter to the hypothesis discussed. Authors should provide more thought/discussion regarding this. Perhaps this is a power issue? The discussion on page 10 regarding this feels inadequate to reviewer.  

6) Reviewer feels the title does not capture the manuscript. It is not clear this is a “new clinical feature in MS”. Ambulatory impairment is a well described feature and attenuation in MS subjects behavior has been described by other authors dating back at least to 1999 (Schwid). Reviewer recommends modification of title.  

7) Authors should review literature that relates to the concept of attenuation of MS patient performance during walking. Others have reported on this beyond Goldman, et. al. Authors should reference those works (for example: Schwid 1999, Belachew 2012).  

8) Background section, in some sections, reads as a criticizing others works rather than expanding/augmenting. For example, “…by applying appropriate data analysis” (as examples). Reviewer suggests consideration of alternate terms, such as “additional data analysis”.  

9) Authors should explain in further detail how the minute-minute distance measures were obtained.  

10) Author should be aware/cite Schwid, Neurology 1999 and Phan-ba PLoS 2012 – which also speaks to changes in MS subject speed/behavior during walking assessments.