Author's response to reviews

Title: Neglect-like characteristics of developmental disregard in children with cerebral palsy revealed by event related potentials

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Author's response to reviews: see over
Dear Dr Shipley,

Please find enclosed the revised version of the manuscript “Neglect-like characteristics of developmental disregard in children with cerebral palsy revealed by event related potentials”.

We would like to thank the Editor and reviewers for their time and their valuable comments. We highly appreciated the constructive criticisms! When revising the manuscript we closely followed the reviewers’ comments. We are confident that the manuscript has been greatly improved. Below, we provide an itemized response to all comments.

We hope that the manuscript is now acceptable for publication in BMC Neurology. We look forward to your decision.

Sincerely,

Ingar Zielinski, Bert Steenbergen, Marjolein Baas, Pauline Aarts, and Marijtje Jongsma
Reviewer 1: Dr Dido Green

Abstract - discretionary revision
1. This is clear and concise although the conclusion is not as clear from the evidence presented that the NI is associated with diminished visuo-spatial attention in children with DD. Furthermore, the hypothesis stated that they expected the N2 and P3 ERP components to be enhanced and not necessarily the N1. This make become more apparent with the recommendations (see below).

# 1: We do agree with you that the conclusions regarding the different ERP components were not clear in the abstract. We changed this accordingly. (page 3)

Introduction - compulsory revisions
2. This was clear and well formulated however, there is limited information on the visual spatial aspects underpinning unilateral neglect in Stroke and or hypothesized in DD. Discretionary but an early paper by Rizzolatti and Cmarda (1967) makes interesting reading (Neural Circuits for Spatial Attention and Unilateral Neglect, Advances in Psychol. 45, 289-313).

# 2: Thank you for calling our attention to the paper by Rizzolatti and Cmarda. In the revised manuscript we used the premotor theory of Rizzolatti and Carmada to elaborate on the visual spatial aspect underpinning unilateral motor neglect. (introduction: Page 5, first paragraph; discussion: page 19, second paragraph)

3. While the authors have discussed the complexity of the developmental issue in UCP, paragraph 4 beginning ‘Apart from’ doesn’t consider the considerable changes in Executive Function development and attention-response inhibition processes that occur in middle childhood. Bearing in mind the ages of the children in this study, it would be helpful to elaborate on these points.

# 3: We do agree with the reviewer that changes in Executive Function (EF) development are of special interest in our current study, especially those that are related to goal-directed motor behavior. In our first draft we used the term cognitive control instead of EF. This has been adapted in our revised manuscript and changed to EF.

Our main aim was to study if DD can (partly) be explained by a developmental delay in EF. The aspects of EF we focused on were those that are of primary interest in motor behavior: attention, response switching and inhibitory control. This has been elaborated in the introduction of the revised manuscript. (page 6)

4. Para 8 beginning ‘ERP components’ doesn’t make mention of the N1 and its role in visual spatial attention – therefore it is difficult to link the results and discussion to the literature.

# 4: The reviewer is right and we agree that not mentioning the N1 component makes it very difficult to link the results to the theoretical background. We therefore added some information about this component to our introduction (page 7, second paragraph).
However, the primary research question of the current study concerned cognitive control (or EF) processes involved in motor behavior. Our research was therefore initially focused on the N2 and P3 component that are commonly associated with cognitive control in a go/nogo-task. We therefore decided not to add a very elaborate theoretical background of the N1 to the introduction, but did further elaborate on this component in our discussion (page 19, first paragraph).

Methods - compulsory revision
5. Please define MACS and VOAA-DDD-R before using abbreviation and provide more information for readers not familiar with these scales and assessments.

# 5: The definitions have been added to the revised version of the manuscript. Furthermore, some information explaining both assessments has been added. (page 8, first paragraph under ‘Participants’)

6. Please also outline whether any information on cognitive ability was available and vision or visual perceptual functions (e.g. did any children have homonymous hemianopia?). Please also confirm if any of the children were colour blind bearing in mind the colour selection for the stimuli.

# 6: This information has been added accordingly. (page 8 and 9, second paragraph under ‘Participants’)

7. Please define what was the motor response required eg. to touch the screen or a switch and at what distance of reach.

# 7: This information has been added accordingly. (Page 9, first paragraph and page 10, third paragraph)

8. Please explain how t-tests were adjusted for repeat testing (eg. Bonferroni adjustment) and why other post-hoc analyses were not chosen.

# 8: We thank the reviewer for pointing this out. In our revised manuscript we did account for multiple testing, by using the Bonferroni correction. Due to this correction the results of the nogo-N1 component were no longer significant. This was adjusted accordingly. We now consistently show that there are no group differences with respect to the nogo-stimuli.

Results
9. It would appear from Table 1 that, while the means and SDs of age are not significantly different between groups, the ages of the children do suggest more older children (9 years plus) in the non DD group. While there is a younger child in this group (4.8 years) the mean is higher (8.8) while the DD group has an older child but with a lower mean. In view of the significance of age on attention control and EF, an on-line supplement of individual characteristics would be helpful to understand whether the younger children were less impaired (MACS level) etc. As
such, it would be helpful to re-run all analyses to control for age and severity (and interaction) as covariates.

# 9: We do agree with the reviewer that the developmental trajectory during middle childhood may influence results related to attention control and EF. Furthermore, we agree that level of impairment (MACS) is an important factor to control for in such a study. For this reason, we did control for differences concerning these two factors as well as for differences between genders. Because no significant differences were found between groups in our initial analyses, these factors were not included in the main analyses. Including all these factors (age, gender and MACS) would significantly reduce the power of these analyses.

We do however understand the reviewers concern, as especially age is known to significantly interact with executive functioning. Therefore, exploratory analyses with age as covariate have been conducted. The results show that controlling for age doesn’t change the significant group differences. The output of these analyses is shown below.

a) behavioral data --> number of mistakes

• initial group effect: F(1,22) = 7.10; p = .014
• group effect with age as covariate: F(1,21) = 5.69; p = .027
• no significant interaction effects with age have been observed

b) Go_P3

• initial group effect: F(1,22) = 9.00; p = .007
• group effect with age as covariate: F(1,20) = 8.11; p = .010
• no significant interaction effects with age have been observed

c) Cue N1

• initial group effect: F(1,22) = 7.01; p = .015
• group effect with age as covariate: F(1,20) = 6.26; p = .021
• no significant interaction effects with age have been observed

d) Go N1

• initial group effect: F(1,22) = 5.36 ; p = .030
• group effect with age as covariate: F(1,20) = 4.82; p = .039
• no significant interaction effects with age have been observed

Furthermore, also based on comment # 3b of reviewer 3, we added multivariate linear regression analyses with age as independent variable. This was done whenever group differences were observed, to explore possible developmental changes within the groups that might explain the group differences.
10. Para 3 of Results final sentence states ‘these electrodes’ and refers readers to figure 4 which includes 3 electrodes. The analyses have only reported on two. Also – for both Figure 4 and 5, please provide the electrode label for each bar to aid interpretation.

# 10: Electrode labels have been added to figures 4 and 5. Furthermore, brackets have been added to each figure to clarify for which electrodes significant results have been found.

11. Para 6 – it would be helpful to clarify across which electrodes or all of which differences were found and for both hands or one in particular as it is not clear from Figure 5.

# 11: See # 10.

Discussion and Conclusion - Essential revisions

12. More discussion on the NI links to visual spatial attention are required to support interpretation as well as greater consideration to the limitations of the study with respect to availability of cognitive and perceptual information on the children.

# 12: We thank the reviewer for pointing out the deficit of the manuscript concerning the limited information on the visual spatial aspects underpinning unilateral neglect (also # 2) as well as the link between the N1 component and visual spatial attention. We added this information (also by using the recommended literature by Rizzolatti & Carmada) (introduction page 5, first paragraph; discussion: page 19, second paragraph) and are convinced that these changes have significantly improved the manuscript.

Furthermore, the limitations of the study have been elaborated accordingly (page 20, third paragraph).

Minor

13. Methods para 2 final sentence should be ‘to’ and not ‘till’

# 13: This has been adjusted in the revised manuscript.


# 14: This has been adjusted in the revised manuscript.

15. Methods para 6 please define GLM before using

# 15: This has been adjusted in the revised manuscript.
Reviewer 2: Dr Catherine Elliot

Abstract
1. The methods are unclear in the abstract. The participants should be in the first line of the methods. The study design then needs to be stated upfront – prospective cross-sectional study. The primary outcome EEG and variables (ERP, N1...) then need comment on (there is no mention of EEG in the abstract). It is hard to follow as the design is not specified or EEG mentioned.

# 1: We agree with the reviewer that the methods written in the abstract needed clarification. We have changed the order according to the reviewers’ comment and added the name of the study design. (page 2)

However, we do not fully agree with the reviewers’ suggestion concerning the study design. As we did not follow the children over time, we do not agree to label this design a prospective design. We do however agree that this was a cross-sectional design and changed this accordingly (page 2 in Abstract and page 9 under ‘Methods’).

Furthermore, we also added some information about the different ERP components to the abstract as well as mentioned that these components were extracted from the ongoing EEG. (page 2)

2. It is also unclear in the abstract what the clinical implications are of the study. Why is it important to understand the general delay in cognitive control of motor behavior and how will this lead to a change in assessment and treatment of children with cerebral palsy?

# 2: The clinical implications have been added to the conclusion section of the abstract. (page 3)

Methods
3. The VOAA-DDD-R is not a common assessment. Could you please include a couple of lines about its psychometric properties (Refer to Houwink 2014). This is very important that the reader is confident in how DD has been assessed and children are grouped.

# 3: We agree with the reviewer that further information about the VOAA-DDD-R is needed. This information has been added in the reviewed version of the manuscript. (page 8, under ‘Participants’; also see reviewer 1, comment #5).

4. More information about the population would be useful. What was the sensation like for children in both groups? What was their cognition like? It would be very interesting to know how function relates to the both groups. Do the children with DD perform as well on functional measures like the Assisting Hand Assessment? These are really important factors in this study.
# 4: More information about the children concerning their visual capacity and their cognitive functioning has been added in the revised manuscript (Page 8 (last paragraph) & 9 (first paragraph); also see reviewer 1, comment #6). As indicator for cognitive functioning of these children we used the information on whether they were attending a regular or special school.

However, we do not have scores of the Assisting Hand Assessment for every child, as we did not mean to include this data to our study. To indicate manual ability we used scores of the Manual Ability Classification System.

**Design**

5. Can you please review the study design? I would consider it a prospective cross sectional study.

# 5: The study design has been added. Please see point # 1 for further elaboration.

6. For readers who have not familiar with EEG it would be useful to have a brief line about the different variables (ERP, N1…) this is covered in methods but difficult to flick back and forwards.

# 6: We think that the reviewer is commenting on the Result section.

We added some information of all components to the Result section (Page 13, second paragraph).

**Conclusion**

7. The link to clinical implications here is important and well explained. What therapies aimed at motor neglect might the authors recommend? Have these therapies been trailed in children with cerebral palsy?

# 7: We could not agree more with the reviewers’ opinion that the clinical implications of these motor neglect findings are very important, especially as there does not even seem to be a valid diagnostic tool for diagnosing motor neglect in children. More studies are therefore warranted to elaborate on the phenomenon of motor neglect in unilateral CP as well as to study the efficacy of therapies when treating children with unilateral CP and DD. In our revised version of the manuscript, we added a line to the conclusion that “To our knowledge, there are no therapies for children with unilateral cerebral palsy directly aiming at reducing motor neglect” (page 21, under ‘Conclusion’).
**Reviewer3: Prof Rodney C. Scott**

1. The main issue for this reviewer relates to the biological underpinnings of the ERP data. The authors seem to be arguing that DD is related to cognitive control of movement during the task and that the ERP provides insight into that process. As I understand it the authors are suggesting that in the absence of DD neural circuits are formed and that those circuits lead to changes in ERP parameters. However, there is something about the initial injury that leads to the DD in the first place and therefore it seems possible that the ERP is simply a reflection of that underlying brain injury and is entirely unrelated to subsequent brain development. It is not possible to establish whether this is true as there are no data on the nature, site, severity etc of the injury that is leading to the hemiplegia. Without this information it is extremely difficult to establish what the ERP data are saying about the biology of DD.

   # 1: We do agree with the reviewer that the missing information about the underlying brain injury might pose difficulties in interpreting the results. In the revised manuscript we have emphasized this in our study limitations (page 20, last paragraph).

However, to answer our main aim about the underlying factors of DD, we did use a control group of children with similar brain lesions leading to very similar motor deficits. All of the children participating at our study were diagnosed with unilateral CP, indicating that all of these children had unilateral brain lesions affecting the motor areas of the brain. Furthermore, the control group used in the current study did not differ in terms of hand capacity, side of affected hand or cognitive ability. These findings give further indications that the associated brain lesions were comparable between both groups.

   We do however still agree with the reviewer that the ERP differences between children with unilateral CP with and without DD might reflect a subtle differences in affected brain areas between the two groups. We do nevertheless think that both hypotheses (DD as result initial injury vs. DD as result of developmental delay) are not mutually exclusive. We propose that especially the reduced N1 component might be a reflection of the initial injury to different brain networks. We have elaborated on this subject in the revised manuscript. (page19, last paragraph, & and 20, first paragraph)

2. It would be helpful to know what the N1, P2 etc components are measuring in biological terms i.e. what is it in the structure or function of the brain that makes the waveforms. With this information it will be easier to make inferences on the biological relevance of the data presented.

   # 2: We thank the reviewer for pointing this out and agree that we did not add sufficient information about the underlying brain mechanisms related to the different ERP components in our initial manuscript. In the revised manuscript we did add this information.

   In our revised introduction we added information about the meaning of every component typically observed in go/nogo-experiments (N1, P2, N2, & P3). In addition, information about the brain structures related to the N2 and P3 components was added (page 7, second
paragraph). In our Discussion section we added more information about the meaning as well as about the underlying brain mechanisms of the N1 component (page 19, first paragraph).

3. a) The second major issue relates to the age of the participants. The age range is from 5-12 years and it is possible that there is maturation of the ERP across that age range. This should be explored.

# 3a: Please see reaction to comment number 9 of the first reviewer (Dr Dido Green).

b) In addition, if DD is a function of cognitive development then one might expect that the children with DD show little change over time whilst those without DD show a marked change. It appears that these data are available and could be analyzed using regression methods.

# 3b: Thank you for this very interesting comment. We fully agree with the reviewer that if DD is a function of cognitive development, we should explore the influence of age as soon as we find group differences. We therefore added these analyses to our revised manuscript (page 12, second paragraph). As a result of these adaptations we are convinced that the manuscript has greatly improved and provides an even more in depth analysis of DD.

As shown in the Result section, age is actually predicting the amplitude of the go-P3 in the DD group, but not in the control group (page 15, last paragraph). This finding indicates that in the control group there are no developmental changes with respect to cognitive load and response preparation. This indicates, that even in the youngest children of this group, this cognitive function had already been fully developed. In the DD group however, the P3 amplitude of the go-P3 decreased as the children got older. This finding gives a strong indication that the enhancement of the P3 following go-stimuli (increased mental effort related to response preparation in the DD group) indeed seems to be related to a developmental delay in this group.

However, no effects of age were observed with respect to the N1 component. The reduced N1 component (spatial attention deficits in the DD group) does not seem to be related to a developmental delay. The interpretation of these finding have been added to the discussion. (page 20, first paragraph)

4. It is interesting that the behavioral and ERP data show a bilateral deficit despite an apparently unilateral lesion. This suggests that in children with DD the ‘normal’ side of the brain is either itself injured in which case the child would have bilateral DD, or that the abnormal hemisphere is somehow influencing the normal side in a way that leads to a decrease in performance. This needs to be addressed in the manuscript.

# 4: Thank you for pointing this out. A possible explanation for this finding has been added to the revised manuscript. (page 20, second paragraph )

5. It is very difficult to see the different lines in Fig 2. I wonder whether it is possible to either separate out the groups or to use lines that are more distinguishable
# 5: We think that the reviewer is commenting on figure 3 instead of figure 2.

We do agree with the reviewer that the lines used in Figure 3 were not easy to distinguish. However, if we separated the groups, we would lose the visual representation about the group differences. We therefore choose to use colored lines instead of black and grey lines in our revised manuscript and hope that they now easier to distinguish.

Additional changes
1. Correction with respect to demographic information in unilateral CP group

# 1: One of the participants of the unilateral CP group (children without DD) that was indicated to be a female was actually a male. This has been changed accordingly.