Author’s response to reviews

Title: The impact of attack frequency and duration on neurocognitive processing in migraine sufferers: evidence from event-related potentials using a modified oddball paradigm

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Author’s response to reviews:

Dear Editor,

Thank you and the reviewers for considering our paper and pointing out some important modifications needed in the manuscript. We believe that the comments have been highly constructive and very useful to reconstruct the manuscript, and we have carefully taken these critiques into account and improved our paper. Moreover, we have answered the reviewers’ questions and revised our manuscript. All revisions in the manuscript are indicated by track changes and are in red, and the explanations of what we have changed in response to the reviewers’ concerns are given point by point in the following pages.

We hope that all these changes could fulfill the requirements to make the manuscript acceptable for publication in BMC Neurology.
Responses to reviewers

To Marla J.S. Mickleborough (Reviewer 1)

2. Abstract

Comment:

Page 2, line 22. The authors say, "In this study, we aimed to reevaluate cognitive processing via event-related potential (ERP) examinations and explore further correlations between ERP data and migraine characteristics." This underlined portion could be more specific as to what you are actually looking for here (i.e., visual spatial attention).

Response:

We much appreciate your suggestion. Accordingly, we have replaced several descriptions of "(neuro)cognitive processing" with "visual spatial attention" in the abstract and throughout the manuscript (page 2, line 1, lines 14-15, lines 19-20; page 15, line 7 and page 18, lines 2-3), in order to better explain the specific cognitive domains involved in this ERP experiment.

Comment:

Page 2, line 8. The authors say, "We found that migraine patients were more anxious and depressed than healthy controls." I was surprised the results started with this as it was not the focus of the study. I was expecting ERP results. Perhaps this can be an "Of note..." statement later in results, as it is not the central focus of the study. The connection between migraine and mental illness is further explored on page 3, lines 3-4, but this topic still seems out of place with the rest of the study, especially because the authors seem to contrast mental disorders with cognitive impairment on page 3, line 4 ("In addition...")

Response:

We are sorry for the inappropriate descriptions. We have deleted descriptions related to this topic in the sections of abstract (page 2, line 8), background (page 3, lines 6-7) and discussion (page 14, lines 10-11).

Comment:

Page 2, line 9. Why does P3 exist twice in the following statement? "As for P3/difference P3 components".
It would be appropriate to tell us off the start what the P3, N1, and N2 components represent in your study, as not everyone reading BMC Neurology knows all the ERP components.

Response:

We are sorry for the confusing statement in the abstract. We have better explained the modified oddball paradigm used (page 2, lines 5-6) and difference P3 components (target minus standard and novel minus standard) (page 2, lines 10-11).

Thank you for your suggestion. Considering the simplicity and generalization of the abstract section, we do not provide the explanations of what the P3, N1 and N2 components represent here. However, the time windows selected for measurements of these ERP components are described in the method section and the electrophysiological/psychological representations are included in the discussion section, which are more detailed.

Comment:

Page 2, line 15. "cognitive processing deficits should be highlighted during clinical practice". While this data and other ERP studies are building to suggest that these visual-spatial attentional abnormalities in migraineurs seem to be reproducible, it is important to note that we still do not have a full picture of how they play out in day-to-day life as a symptom for migraineurs, so this is perhaps not quite ready to be translated into something we can "highlight" during clinical practice.

Response:

Thank you for your constructive comment. According to your suggestion, we have deleted the inappropriate description containing “should be highlighted during clinical practice” in the abstract (page 2, lines 16-18).

3. Background

Comment:

Page 2, line 21: "mainly impacting individuals in their prime, between the third and fourth decades." I can appreciate the authors' attempt at emphasizing the impact of migraines on migraineurs, but I'm not sure if it is their place to be qualifying an individual's "prime".

Response:
We are sorry for the improper statement here. We have rewritten this sentence (page 3, line 2) for the purpose of emphasizing the impact of migraine on migraineurs’ quality of life, and changed the reference [2].

Comment:
Page 3, line 6. Why does is say "Several studies…” and then only reference one study?
Response:
We are very sorry for the mistake. We have replaced “Several studies” with “a nationwide retrospective cohort study” (page 3, lines 9-10).

Comment:
Page 4, line 4. I think this should state specifically that you are looking at attentional ERP components.
Response:
Thank you for providing this idea. Accordingly, we have replaced several similar descriptions like “ERP data” with a more specific statement “attentional ERP components” in the background section (page 4, lines 7-8) and throughout the manuscript (page 13, line 5, line 15; page 16, line 4 and line 22).

4. Methods
Comment:
Page 5, lines 6-7: Could the authors please provide a citation or rationale as to why 49 and 52 were chosen as the cut-offs? Is this an accepted level for the SAS and SDS or did the authors choose these values themselves—and if so, why?
Response:
Thank you for your comment. We have added a reference [21] (page 5, line 17) in the manuscript concerning the cutoff scores. The Zung Self-rating Anxiety Scale (SAS) and the Zung Self-rating Depression Scale (SDS) are widely used evaluative tools in China with good reliability and validity. The clinical threshold of SAS is 50, and scores in the ranges of 50-59, 60-69 and 70-100 correspond to mild, moderate and severe anxiety, respectively. As for SDS, the
clinical threshold is 53, and scores in the ranges of 53-62, 63-72 and 73-100 correspond to mild, moderate and severe depression, respectively.

Comment:
Page 4, Line 11. "Besides" - Authors are not using "Besides," correctly (page 4, line 11; page 7, line 1; page 9, line 11; page 12, line 17; page 15, line 21)

Response:
We are sorry for the mistakes. We have changed “Besides” into “In addition” (page 4, line 14 and page 13, line 10), “Additionally” (page 7, line 11), “Furthermore” (page 10, line 2) or just delete it (page 16, line 18).

5. Results

Comment:
Page 8, line 10: "As for emotional characteristics, migraine patients tended to be more anxious and depressed compared with healthy controls." This is a bold statement and I'm not convinced it is adequately justified, especially because the authors only used two self-report scales (one for anxiety and one for depression; page 5, lines 5-6). The emotional characteristics of migraine doesn't seem to fit with the ERP/cognitive processing focus of the paper. It would be helpful to include a rationale for this dimension, and whether or not it has any implications for the results (does it possibly undermine the results? Why or why not.) (Also see page 13, lines 13-14.)

Response:
We greatly appreciate your efforts to carefully review the paper and the valuable suggestions offered. We are sorry for the inappropriate statements used here. According to your comments, we have combined the two paragraphs in the “Sample characteristics” section and added a more accurate description “assessed by SAS and SDS” (page 9, line 1). We wish you will accept our revisions.

Furthermore, we appreciate your constructive opinion that emotional characteristics of migraineurs are not the focus of this study, so we have deleted the results of emotional evaluation in the first paragraph of the discussion because these results may not be associated with the main topic of this study (page 14, lines 10-11).

In this study, we performed routine emotional assessment (SAS and SDS) in outpatients with migraine, together with the collection of demographic and migraine characteristics, so emotional
characteristics tend to be regarded as a part of clinical variables here. We further explored the correlations between attentional ERP components and clinical characteristics (including SAS and SDS). Since it has been demonstrated that emotional disturbances (even subclinical levels of anxiety and depression) may impact cognitive processing (see references [39] and [40] in the manuscript), we aim to rule out the influence of emotion on electrophysiological data (see page 17, lines 1-3 for revisions).

6. Discussion

Comment:

I'm not sure why you are leading with the information that migraine patients are more anxious and depressed than controls, as that doesn't seem to be the focus of the ERP study (visual spatial attention). While you report cognitive ERP "abnormalities" that are correlated with frequency and duration of migraine attacks, the first paragraph does not tell me why that might have any meaning to a migraineur or clinician.

I think if you combine the following two statements and put them at the end of the first paragraph of the discussion (as well as in the conclusion), you will have a clear take-home message for the reader, then you can go on to explain the components as you do.

Page 14, line 11. This statement, "our findings indicated that migraineurs might have interictal impairment in attentive neurocognitive processing, such as target processing and orienting responses"

Page 14, line 20. This statement, "...that migraineurs might suffer from deficits in the speed of visual information processing, especially when triggered by infrequent or unfamiliar stimulus."

Response:

We much appreciate your valuable comments provided. As illustrated above, we have deleted the descriptions concerning emotional evaluation (page 14, lines 10-11) since it is not the focus of this study and should not be stated here. In addition, according to your suggestions, we have added the meaning of correlation analysis (page 14, lines 17-18), which we believe is more comprehensible.

Moreover, we are sorry for the lack of explanations of ERP results in the first paragraph of the discussion. We have combined the two statements you recommend and put them at the end of the first paragraph of the discussion (page 14, lines 14-17), as well as in the conclusion (page 18, lines 3-4). Thank you for your great suggestions.
7. Conclusion

Comment:

Page 16, line 11. I think "P3/difference P3 amplitudes" needs to be reworded.

Response:

We are very sorry for the confusing description here. We have reworded it (page 17, line 22 and page 18, line 1) and we hope the revisions will be easier to understand.

Comment:

Page 16, Line 12. "suggesting the existence of impairment in cognitive processing, which was usually neglected in clinical practice." Again, I think the statement about "impairment in cognitive processing" is TOO general. This will be quoted in other studies and therefore should specifically reflect the impairment you are suggesting, such as abnormalities in attentive neurocognitive processing such as target processing, orienting responses, and speed of visual information processing, especially in response to infrequent stimuli. Further, I don't think we can make specific statements about this being neglected in clinical practice when it is not yet clear what it means to have this abnormal attentional processing.

Response:

Thank you for providing this idea. As stated above, we have carefully revised the statement (page 18, lines 3-4) in order to specifically reflect the impairment that migraineurs suffer from. Additionally, we have also deleted the inappropriate description “which was usually neglected in clinical practice” (page 18, lines 4-5) according to your suggestion. We hope you will agree.

8. Overall

Comment:

Overall, I think this is a great paper. I think this furthers previous work using ERP to look at very specific attentional processing in migraineurs, showing that variations of this effect of abnormal visual spatial attention in migraineurs is consistent and reproducible. I think the findings are valuable and definitely worth publishing. The fine-tuning that I would like to see is specific to the message that it gives.

For example, are we certain this abnormality is an impairment? Can you specify more clearly what the abnormal brain wave amplitude means? I think the authors could explore this a bit further for the audience. For example, could a decreased attentional response to target and novel stimuli sometimes be an advantage or is it always a disadvantage?
The other key changes (described in my review) were to consider how the anxiety and depression scales were included, as they do not seem very relevant to the ERP research in the study. If they are relevant, then it needs to be more clearly explained (how do depression and anxiety affect these ERP components?). Finally, the statements claiming how this can be translated into clinical practice need to be either tamed down or better justified on how exactly this information could be used clinically.

Response:

We greatly appreciate your approval of this manuscript, and we wish the revisions will make the paper more acceptable.

We think we use “impairment” because this phenomenon exists in migraine patients, which may have negative impact on daily life of patients. It can also be regarded as an “alteration” compared with healthy controls, and the underlying mechanisms need further elucidation. In addition, as described in the limitations, we wish to perform source localizations, perhaps also including morphological evaluation (like fMRI), to better uncover the possible network pathology in the near future. We hope that further evidence will make us more confident in explaining our findings, like the disease-specific meaning of the abnormal brain waves to migraine sufferers, even considering their different periods (interictal period and attack period) and clinical manifestations (with or without aura), and brain regions involved in these processes and their pathological alterations may also be illuminated. Moreover, based on previous literatures with similar results (like [25] and [34] cited in the manuscript), a decreased attentional response to target and novel stimuli is usually considered a “disadvantage”, since these changes will negatively impact the interpersonal communication, productivity and social functioning of migraine patients, but we think further studies are needed before the definitions of “always disadvantageous”, perhaps by recruiting more patients and using different paradigms for validation.

Moreover, as illustrated above, we are very sorry for the inappropriate descriptions concerning “emotional evaluation” since it is not the main topic of this study. According to your valuable suggestions, we have deleted corresponding statements in the abstract (page 2, line 8), background (page 3, lines 6-7) and discussion (page 14, lines 10-11) sections. In this study, emotional characteristics tend to be considered as a part of clinical variables (like frequency and duration of migrainous attacks). It has been reported that even subclinical levels of anxiety and depression may have a negative impact on cognitive processing (see references [39] and [40] in the manuscript), thus, correlation analysis was performed in order to rule out the effect of emotional characteristics on attentional ERP components. We aim to demonstrate that the visual spatial attention impairment in migraineurs may be due to the pathological alterations (such as constant brain lesions caused by recurrent attacks) rather than emotional disturbances, which will make the results more convincing. Finally, we have also deleted corresponding descriptions about “clinical significance” in the sections of abstract (page 2, lines 16-18) and conclusion.
Although ERP examinations have been widely used in clinical studies, in order to exactly illuminate how these electrophysiological data can be used in clinical practice, we think further investigations containing larger cohorts and many distinct paradigms are still warranted before concluding. Thank you for your constructive suggestions.

To Marco Lisicki (Reviewer 2)

Comment:

* Given that attack frequency and duration were quantified by asking the patient about the last year, which is enormously affected by recall bias, I would not suggest you to focalize your manuscript on these variables.

Response:

We greatly appreciate your efforts to carefully review the paper and the constructive suggestions offered. Accordingly, we have carefully added your comments in the limitations of this study (last paragraph of the discussion, page 17, lines 4-9). In this study, migraine characteristics (such as frequency and duration of migrainous attacks) were obtained by a standardized interview using a structured questionnaire, and we interrogated migraine patients and their family members (usually spouses) who were familiar with their sufferings and complaints simultaneously. In order to diminish the effect of recall bias on Pearson’s correlations to the minimum extent, we excluded patients with incomplete or ambiguous clinical characteristics (including patients who were unclear about them and had disagreement with their family members on these questions) (page 5, lines 10-11). Moreover, we think the main finding of this study is the phenomenon that the visual spatial attention is impaired in migraineurs. As for the results of correlation analysis, we aim to further validate them in our future investigations, perhaps with larger cohorts and by using other analytical methods (like regression analysis). Thank you again for providing us this extremely valuable idea and we believe it is instructive for our future studies.

Comment:

* How was the sample size calculated?

Response:

We are very sorry for the lack of how the sample size was calculated in the method section, and we have added it in the section of “subjects and criteria” (see page 5, lines 8-13). Initially, 33 migraine patients (19 females) and 23 age-matched healthy controls (14 females) fulfilling the inclusion and exclusion criteria were recruited in this study. However, 8 patients (3 females) had to be excluded due to excessive blink and electromyographic artefacts, as well as incomplete or
ambiguous clinical characteristics. So only 25 migraineurs (16 females, 7 with aura and 18 without aura) were included. As for controls, 2 participants (1 female) were excluded due to technical problem during recording. Thus, 21 healthy controls (13 females) were finally included for further analysis. Moreover, the medium sample size (25 migraineurs and 21 healthy controls) is believed to be appropriate for ERP examinations, which has certain representativeness. Thank you for raising this valuable question to make the manuscript more comprehensible.

Comment:

* Why would you choose Self-Rating Anxiety Scale, which includes items about headache, fatigue, spells, gastrointestinal symptoms and so on, to evaluate anxiety on a cohort of migraine patients?

Response:

Thank you for your question. We have added a reference [21] (page 5, line 17) in the manuscript in order to better explain these two scales used for emotional evaluation. The Zung Self-Rating Anxiety Scale (SAS), with good reliability and validity, is widely used in China to evaluate anxiety. It contains 20 items based on the daily life of Chinese people, including headache, fatigue, gastrointestinal symptoms and so on. The clinical threshold of SAS is 50, and scores in the ranges of 50-59, 60-69 and 70-100 correspond to mild, moderate and severe anxiety, respectively. In addition, it is commonly employed for routine anxiety assessment in Chinese outpatients, and we think SAS results may be representative for Chinese patients. Furthermore, SAS has also been widely applied to evaluate anxiety in migraine patients (Guerzoni et al., 2015; Lieba-Samal et al., 2009).

Comment:

* P3a and P3b are first mentioned in the results section. The methods used for identification and statistical analyses should be clarified earlier.

Response:

We much appreciate your constructive comment. We are sorry for the lack of explanations of P3a and P3b prior to the results section, and we have added corresponding statements in the methods section (page 8, lines 5-7) according to your suggestion offered. In this study, target-elicited P3 and novel-elicited P3 were defined as P3a and P3b, respectively. The amplitudes and latencies of P3 were also subjected to repeated-measures ANOVA, with stimulus (standard, target (i.e. P3b) and novel (i.e. P3a)) and electrode (Fz, Cz and Pz) as within-subject factors, while with group (migraine patients vs. healthy controls) as a between-subject factor, which was
same as other original ERP components (N1, P2 and N2). We hope the revisions will make our manuscript easier to understand and more acceptable.

Comment:

* From the 66 correlations performed in the study, only the columns of SDS score and SAS score are reliable. Migraine history is somewhat affected by recall bias, but to a lesser extent compared to the remaining variables; I would also leave it.

Response:

Thank you for providing these instructive ideas. As illustrated above, we have added your comments in the limitations of this study (last paragraph of the discussion, page 17, lines 4-9). We greatly appreciate your opinion that SAS and SDS scores objectively reflect emotional state of migraineurs, while other clinical variables (including migraine history) are affected by subjective recall bias. In this study, we worked hard to diminish the impact of recall bias to the minimum extent. For instance, during the standardized interview, we asked outpatients with migraine and their family members (usually spouses) who were familiar with their sufferings and complaints simultaneously to obtain more reliable clinical characteristics, and 6 patients (about 18%) with incomplete or ambiguous clinical characteristics (including patients who were unclear about them and had disagreement with their family members on these questions) (page 5, lines 10-11) were also excluded from further analysis. Thank you again for the great suggestions.

Comment:

* The spatial resolution of electrical fields on figures 2 and 4 is very limited. Has baseline activity been subtracted on these plots? Have you tried by applying any spatial filters? Have you considered running ICA and plotting independent components?

Response:

Thank you for your constructive comments. According to your suggestions, we have rechecked the scalp topographical maps in Figure 2 and Figure 4. We have all finished the processes you mention during data preprocessing, including subtracting baseline activity (baseline correction), applying spatial filters, as well as running independent component analysis (ICA) for artefact correction and plotting independent components. The topographies of voltage distribution have been plotted in accordance with the detailed manufacturer’s instructions, so we think they are rather standardized. The spatial resolution may be limited by the 32-site montage, and we hope to record EEG signals by 64 or 128 channel amplifier in the future study to improve spatial resolution of topographical maps.
Comment:

* Page 13 line 42 reads: "In this study, we discovered that migraine patients were more anxious and depressed than their control counterparts." I would suggest changing the word -discovered- for -corroborated- and make reference to prior studies addressing this issue.

Response:

We much appreciate your valuable suggestion provided. According to the comments of the other reviewer, we have deleted this sentence in the first paragraph of the discussion section (page 14, lines 10-11), as well as similar descriptions in the abstract (page 2, line 8) and background sections (page 3, lines 6-7). In this study, we think the emotional characteristics of migraineurs tend to be regarded as a part of clinical variables, thus the results of emotional evaluation should not be stated here since they are not the focus of this study (the main topic is ERP results). Thank you for your extremely constructive comment and we sincerely hope you will accept our revisions.

Comment:

* For the discussion, smaller P300 amplitudes in migraine patients could also be due to a higher baseline degree of activation. This phenomenon is known as the ceiling theory.[1]


Response:

Thank you for your incisive and constructive comment. We have carefully read the literature you cite and added your valuable comment together with our explanations in the limitations of this study (last paragraph of the discussion, page 17, lines 9-16). In this study, post-hoc analysis revealed that, compared with healthy controls, the amplitudes of P3b elicited by target stimuli and P3a elicited by novel stimuli were both attenuated in migraineurs, while not for standard stimuli (to some extent reflecting baseline excitability). These phenomena were further validated in difference P3 components (P3dT and P3dN) which could better rule out the influence of baseline activity. Thus, we think the smaller P3 amplitudes in migraine patients were more likely due to the visual spatial attention impairment rather than the higher activity for baseline. This issue needs to be further investigated in the future.
Comment:

* The presence of brain lesions was not evaluated in this study, yet results seem to be interpreted as if they were present.

Response:

We greatly appreciate your instructive idea. Accordingly, we are very sorry for the lack of brain lesion evaluation in the manuscript and we have added corresponding explanations in the second paragraph of the “subjects and criteria” section (page 4, line 22 and page 5, line 1). In this study, after necessary neurological examinations by two specialized neurologists (XL and XH) and routine MRI examinations, we excluded patients with abnormal findings on neurological examinations or brain morphology indicating other potential neurological diseases. So the migraineurs selected for further analysis were verified to have no observable brain morphology abnormalities and brain lesions, at least indicated by MRI examinations. Moreover, we have used “more serious cerebral dysfunction” (page 16, lines 14-15) which we believe is more accurate. Thank you again for your constructive comment.

Comment:

Bottom line is there are some interesting findings, but try to focus on the more reliable data (both positive and negative results). For the introduction and discussion, I would suggest you to emphasize functional over structural conjectures and hypotheses as imaging analyses were not performed on this electrophysiological experiment.

Response:

We much appreciate your very constructive and valuable comments on this manuscript and we have learned a lot from these suggestions. We have thoroughly revised our paper according to your comments and provided explanations concerning data reliability. Since only electrophysiological experiments were performed in the present study, our main finding was limited to the visual spatial attention impairment in migraineurs, a kind of specific “cognitive dysfunction”. Thus, we cite numerous references emphasizing functional alterations (like [4-6] and [36] in the manuscript) as well as ERP abnormalities (such as [16-17] and [24-26]) in the background and discussion sections to illustrate “cognitive dysfunction” in migraine patients. We have also cited several references concerning structural alterations (such as [11] and [35]) in order to explain this main topic more clearly and profoundly. Moreover, further investigation is underway to uncover the possible structural pathology by performing source localizations and other morphological evaluation. Thank you for providing so many instructive suggestions which are very beneficial for our future studies, and we hope our revisions will make the manuscript more acceptable.
References


Again, we appreciate all of your insightful comments. We work hard to be responsive to them, and we thank you and the reviewers for your time to help us improve the paper.

With best regards,

Yunliang Guo; Qiang Tian; Song Xu; Mimi Han; Yue Sun; Yan Hong; Xunyao Hou; Xueping Liu*

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