Author's response to reviews

Title: Quantification of vision by visual evoked potential in visual disability assessment

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Author's response to reviews: see over
Thank you for the comments on our paper, “Quantification of vision by visual evoked potential in visual disability assessment”. We are grateful to the reviewers for their helpful suggestions. We have adopted them in this revised manuscript.

Title: Quantification of vision by visual evoked potential in visual disability assessment

Reviewer 1

1. In abstract, Please clarify the subject used in the study in the method section.
We changed the method section in abstract. We also added table 1((Clinical characteristics and visual evoked potentials results in 18 amblyopic eyes and 20 normal eyes)

A retrospective chart review was conducted of patients diagnosed with normal vision, unilateral amblyopia, optic neuritis, and visual disability who visited the university medical center for registration from March 2007 to October 2009. The study included 20 normal subjects (20 right eyes: 10 females, 10 males, ages 9–42 years), 18 unilateral amblyopic patients (18 amblyopic eyes, ages 19–36 years), 19 optic neuritis patients (19 eyes: ages 9–71 years), and 10 patients with visual disability having visual pathway lesions.

2. In material and method, on line 7, please explain this sentence:”subjects presumed to be malingering with amblyopes were excluded from the study.”
We changed this sentence.

Subjects presumed to be malingering with amblyopia were excluded from the study at the time of diagnosis by repeated fogging and stereopsis tests [13].

3. On results section, please explain how do you get this average 0.47±0.57 log MAR. is it the average of normals and amblyopic eyes of amblyops or this is the average of normal eye of normal with normal eyes of amblyops. And how do you get the amplitude of 10.52±5.36uv …
We changed the result section.

It is the average of right eye in normal and amblyopic eyes in unilateral amblyops. We changed table 1 (we showed VEP amplitude data and logMAR acuity of 20 right eye of normal and 18 unilateral amblyopia )

We convert snellen visual acuity of 20 normal right eye and 18 amblyopic eyes to log MAR acuity. Then we calculate the average of logMAR acuity.
Retrospective clinical data from 20 normal subjects and 18 amblyopic subjects were obtained (Table 1). The average logMAR Snellen acuity of 20 normal subjects (20 normal right eyes) and 18 amblyopic subjects (18 amblyopic eyes) was 0.47±0.57 logMAR. The average pattern amplitude of 20 normal subjects (20 normal right eye) and 18 amblyopic subjects (18 amblyopic eyes) was 10.52±5.96 µV.

4. In page 4, in the heading title of comparison of subjective and predicted objective visual acuity in disability assessment using pattern VEP, how can predict from an interrelation of \( y = -0.0722 + 1.221 \) (-0.072) the reliable VA of optic neuritis?

We changed and added these on the result section of Predicting visual acuity using function in optic neuritis

First, we compared the difference between two groups by \( t \) test that is already shown at the paragraph.
Second, the comparison between two linear regressions, one is \( (y = -0.072x + 1.22 \) normal/amblyopia) and the other is \( (y = -0.108x + 1.55 \) optic neuritis)

1) \( t \) test is the test used for significant difference between two groups.
The average value calculated by substituting the amplitude value of patients with optic neuritis into the function was 0.93±0.30. The difference in the average between actually measured visual acuity and function value was 0.18±0.4, indicating no statistically significant difference (\( t \) test, \( P = 0.07 \); Fig. 3).
2) Linear regression with Comparing slopes and intercepts was performed using GraphPad Software. The slope and intercepts are not significantly different.

The average amplitude values of 19 optic neuritis eyes was 4.09±4.20 µV, and correlation coefficient between amplitude and visual acuity relationship was -0.762, \( p = 0.0002 \) \( (p<0.01) \), indicating a significant interrelationship (Figure 2). Linear regression analysis of pattern amplitude and visual acuity (logMAR acuity) in optic neuritis subjects indicated an interrelation of \( y = -0.108x + 1.55 \), which was statistically significant.
The average value was calculated by substituting the amplitude value of patients with optic neuritis into the function \( y = -0.072x + 1.22 \) was 0.93±0.30. The difference in the average between actually measured visual acuity and function value was 0.18±0.4, indicating no statistically significant difference (\( t \) test, \( p = 0.07 \); Figure 3).
Another way to determine if the function \( (y = -0.072x + 1.22) \) is fitted to predict visual acuity in optic neuritis is to perform a comparison of linear regression. We compared function of normal /unilateral amblyopia \( (y = -0.072x + 1.22) \) vs optic neuritis\( (y = 0.108x + 1.55) \). The slopes were not significantly different. The pooled slope equals -0.0789258 (GraphPad Prism).
5. On discussion, in last paragraph, it was mentioned the estimation of visual acuity in visual disability assessment through correlation of absolute amplitude values rather than comparison between the two eyes of the same subject. It was very difficult to use this assessment, the VEP amplitude for confirming visual acuity assessment with real disability because the amplitude reduction may be due to other abnormalities related to disabled subjects. The consequences of visual impairment affect many aspects visual system which affect the amplitude and latency of VEPs.

We have changed paragraph in the discussion. We delete “rather than comparison between the two eyes of the same subject”.

In conclusion, estimation of visual acuity in visual disability assessment through correlation of absolute amplitude values in pattern VEP might be useful for giving reference visual acuity associated with malingering vs real disability in some ranges (>5.77 µV).

We agree with you. The VEP amplitude for confirming visual acuity assessment with real disability is difficult because it is affected by other disability. This study is to give reference of visual acuity prediction using absolute values in one tertiary clinic, in order to evaluate disability for registry. We select the disability patients with visual pathway lesion for register with no obvious brain lesion. The disability assessment with brain lesion will be decided not by ophthalmologists. Therefore we add only eye disease affecting VEP amplitude.

We changed the method and discussion.

Visual disability having visual pathway lesion was evaluated at the time of diagnosis by examining visual field, extraocular movement, color vision tests, VEP test, multifocal electroretinogram (mfERG), fluorescein angiography, and retina and optic nerve appearance. Visual disability with retina disease was excluded if a multifocal electroretinogram (mfERG) and fluorescein angiography (FAG) were abnormal. Visual disability with obvious brain lesion was excluded.

Second, VEP amplitude will be affected by other causes of visual acuity loss because the pattern reversal visual evoked response (PVER) mainly represents the function of the macula and optic nerve [20-22]. However, we tried to exclude patients with disability registry with retinal disease by reviewing the results of multifocal ERG and FAG.

6. References are not up to date.

We updated the references.
Reviewer 2

Major compulsory revisions:
1) The manuscript is very difficult to follow in its current form and requires significant editing for grammar and structure throughout, including a revision of all subheadings and a much clearer explanation of the methods and results. Errors are also present in the title and abstract.

We edit and revise all manuscript.

Title: Quantification of vision by visual evoked potential in visual disability assessment
Subheading: Predicting visual acuity-using function in optic neuritis
Subheading: Predicting visual acuity-using function in disability assessment

2) The assumption that VEP amplitude will be affected in the same way by all causes of visual acuity loss needs to be clearly justified within the manuscript.

We have added the paragraph in the discussion.

Second, VEP amplitude will be affected by other causes of visual acuity loss because the pattern reversal visual evoked response (PVER) mainly represents the function of the macula and optic nerve [20-22].

3) The sample size is rather small for a study with the aim of providing a protocol for detecting malingers. In addition, it is not clear how the authors selected the cases that were used to derive their correlations. It is stated that the cases were collected over a 2.5 year period but the inclusion criteria are not clearly presented. Also, what were the criteria for presuming that a patient was malingering with regard to amblyopia (“clinical evaluations section”)? These details are important as excluding patients will affect the correlations reported.

We changed the method section. We also added table 1((Clinical characteristics and visual evoked potentials results in 18 amblyopic eyes and 20 normal eyes)

A retrospective chart review of patients diagnosed with normal vision, unilateral anisometric/strabismic amblyopia, optic neuritis, and visual disability, who visited the university medical center for registration from March 2007 to October 2009, was conducted. We selected 20 normal subjects (20 right eyes: 10 females, 10 males, ages 9–42 years), 18 unilateral amblyopic subjects (18 amblyopic eyes, ages 19–36 years), 19 patients with optic neuritis (19 eyes: ages 9–71 years), and 10 patients with visual disability having visual pathway lesion. A total of 67 patients with VEP recordings were selected.
Subjects with Snellen VA of 20/20 and normal ophthalmoscopic exams were defined as having normal vision. Unilateral amblyopia was defined as a visual acuity difference of more than two lines between the
two eyes. Anisometropic, strabismic amblyopia, or both, were included. **Subjects presumed to be malingering with amblyopia were excluded from the study at the time of diagnosis by repeated fogging and stereopsis tests** [13]. Patients with organic eye disease, a history of intraocular surgery, history of cataract, glaucoma, retinal disorders, or laser treatment were excluded from the amblyopia group. Optic neuritis was diagnosed by examining VA and visual field, color vision tests, VEP test, optic nerve appearance, and/or by magnetic resonance imaging (MRI). Visual disability having visual pathway lesion was evaluated at the time of diagnosis by examining visual field, extraocular movement, color vision tests, VEP test, multifocal electroretinogram (mfERG), fluorescein angiography, and retina and optic nerve appearance. Visual disability with retina disease was excluded if a multifocal electroretinogram (mfERG) and fluorescein angiography (FAG) were abnormal. Visual disability with obvious brain lesion was excluded.

4) It is not clear to me why both pattern and flash VEPs were collected and where these different types of VEPs fit into the analyses presented later in the manuscript. This should be clarified.

We analyze all VEP data after collecting from retrospective chart review. So we want to show the results. But it makes the reviewers confused. We delete “Comparison of subjective and predicted objective visual acuity in optic neuritis using flash VEP” section

5) There is no need to present results in the text and in a table. It would also be informative to present the VEP data for the amblyopic and normal groups separately and provide clinical characteristics for the group with amblyopia including types of amblyopia and the range of visual acuity.

We agree with you. We substitute table 1. (Clinical characteristics and visual evoked potentials results in 18 amblyopic eyes and 20 normal eyes)

6) There appear to be large differences in the age ranges of some of the different groups of patients. It would be useful for the authors to comment on whether this might influence their results.

We agree with you. We added it on the discussion.

Third, there has been controversy about the relationship between amplitude of VER and age [23, 24]. The unilateral amblyopia group in our study consisted of patients requiring exam for entering the army. Therefore, they were all about 20 years of age. We should consider age differences affecting VEP in future studies.
7) The results section is very difficult to follow, however it would appear that the linear fit to the combined control and amblyopia data allows for a prediction of VA in the optic neuritis group based on their VEP amplitudes.

The authors point out that the predicted VAs do not significantly differ from the measured VAs for this group. Although this is true, there is still only a 7% probability that the difference between these two measures is due to chance.

This is important in the context of using the predicted values to determine malingering and suggests that while the correlations are statistically reliable, they may not be strong enough to predict VA in individual cases. A suggestion of a different way to interpret the data is provided in the next comment.

We added the linear regression comparison (between normal/amblyopia and optic neuritis) by GraphPad Prism.

1) We already suggested the t test. This is the test used for significant difference between two groups.

The average value calculated by substituting the amplitude value of patients with optic neuritis into the function was 0.93±0.30. The difference in the average between actually measured visual acuity and function value was 0.18±0.4, indicating no statistically significant difference (t test, P=0.07; Fig. 3).

2) We added more analysis: the comparison between two linear regression, one is \( y = -0.072x + 1.22 \) and the other is \( y = -0.108x + 1.55 \) (optic neuritis).

Linear regression with **Comparing slopes and intercepts** was performed using GraphPad Software. The slope and intercepts are not significantly different.

The pooled slope equals -0.0789 and intercept equals 1.34 between amblyopia and normal groups and optic neuritis.

The average value was calculated by substituting the amplitude value of patients with optic neuritis into the function \( y = -0.072x + 1.22 \) was 0.93±0.30. The difference in the average between actually measured visual acuity and function value was 0.18±0.4, indicating no statistically significant difference (t-test, \( P = 0.07 \); Figure 3).

Another way to determine if the function \( y = -0.072x + 1.22 \) is fitted to predict visual acuity in optic neuritis is to perform a comparison of linear regression. We compared function of normal/unilateral amblyopia \( y = -0.072x + 1.22 \) vs optic neuritis \( y = 0.108x + 1.55 \). The slopes were not significantly different. The pooled slope equals -0.0789258 (GraphPad Prism).

8) An inspection of figure 1 seems to show two clusters of data, one with VEP amplitudes in the 8-22uV range that contains all of the observers with a LogMAR of 0 and one with much lower amplitudes. If the authors plot the distribution of the VEP amplitudes, is the distribution bimodal?

If so then from the data shown in figure 1, it seems likely that one of the lobes of the distribution would include only patients with reduced VA. Therefore rather than trying to use a linear fit to determine VA the authors could consider using a cutoff VEP amplitude.
to detect malingerers. Either way the authors should comment on the wide spread VEP amplitudes associated with normal visual acuity in Figure 1.

In normal group with 20/20, the range of VEP amplitude was 8-22 µV
In amblyopic groups, the visual acuity and amplitude of the data we collected from 2007 to 2009 were much lower and not evenly distributed. Thus, a causal distribution of the data was in two clusters. However, the relation between amplitude and logMAR has linear relation. We apply the linear relation to predict in disability patients (Table 2)

We also try to find reliable cut off to detect malingering by ROC curve. The interrelationship of \( y = -0.072x + 1.22 \) will be useful to >5.77 µV (<0.8 logMAR). Suspicious malingering with no obvious pale disc appearance can be ruled out if the amplitude is below 5.77 µV

We changed result section

**Predicting visual acuity-using function in disability assessment**

Linear regression analysis of pattern amplitude and visual acuity (logMAR) in normal and amblyopic patients was useful in predicting visual acuity in optic neuritis. Therefore, we calculated the pattern VEP-estimated VA of 16 eyes of 10 patients to evaluate for registry using interrelationship of \( y = -0.072x + 1.22 \)

\( (x: \text{amplitude}, y: \text{logMAR acuity}) \) (Table 2). We input the amplitude (N1-P2) of the disability patient in \( x \) and obtained \( y \) as pattern VEP-estimated VA (logMAR), which was converted to Snellen acuity.

We attempted to determine a cutoff value for the function that could be applied because the data were limited to very low amplitude. To assess the diagnostic validity of the test, plots of sensitivity vs. specificity, as a Receiver Operator Characteristic (ROC) curve, were made. The most useful cutoff points were found to be at sensitivity (92%), specificity (60%), and accurate screening measure when using cutoff VEP amplitude of 5.77 µV (Table 3). The interrelationship of \( y = -0.072x + 1.22 \) will be useful to >5.77 µV (<0.8 logMAR).

The severe low amplitude (<5.77 µV) will not provide objective visual acuity measurements. However patients with VEP amplitude < 5.77 µV would be compatible with legal blindness [< 20/200 (1logMAR) VA] required for disability registration.

9) It is not clear to me how the case studies relate to the VA measurements. They all seem to have very poor VA so it is not surprising that their VEP amplitude is low. This should be clarified. I also found the discussion very difficult to follow. Highlighting the key conclusions from the study at the start of the discussion would be useful.

In table 2, we use the relation \( y = -0.072x + 1.22 \). We input the real amplitude(N1-P2) of the disability patient in \( x \) and obtain \( y \) as logMAR. This logMAR value is calculated logMAR value. Then we convert it to Snellen acuity.
We found that regression relationship will not be reliable below 5.77uV amplitude. The severe low amplitude (<5.77 µV amplitude) will not give us objective visual acuity. However, we think the patient with VEP amplitude below 5.77 µV would be compatible to legal blindness (visual acuity below 20/200(1logMAR)) that required for disability registry.

There was no disagreement for evaluating cases 1 to 11 and 14 as legally blind because of obvious pale optic disc and VEP amplitude ranging from 0.27 µV to 5.39 µV (Table 2).

In case 12, 13: The amplitude was below cutoff (4.25 µV, 5.71 µV) in this case. The VEP-estimated VA was estimated as < 20/120 Snellen VA (corresponding to amplitude 5.77 µV). He was diagnosed as legally blind in his both eyes. He was not malingering.

Case 15, 16: The reliable pattern VEP-estimated VA of the left eye (7.61 µV) from the correlation was 0.67 logMAR (20/94) O.S because the amplitude was above cutoff (Table 2). Pattern VEP-estimated VA of his right eye (2.58 µV) was <20/120 Snellen VA (corresponding to amplitude 5.77 µV). He was diagnosed as legally blind in his right eye. He was not malingering.

We also revise the discussion section.

10) Some of the references used are rather obscure. There is a large literature on VEPs and visual function that could be cited more widely to support the arguments made by the authors.

We changes reference.

Minor essential revisions

1) I’m not sure what “secondary gain” means in relation amblyopia. This should be clarified.

That means “malingering with amblyopia”. We delete “secondary gain” because of amblyopia criteria is already shown.

Subjects presumed to be malingering with amblyopia were excluded from the study at the time of diagnosis by repeated fogging and stereopsis tests [13]