Dear Editor:

Please find enclosed the edited manuscript in Word format (file name: 7201-edited-1.doc).

Title: Non invasive blood flow measurement in cerebellum detects minimal hepatic encephalopathy earlier than psychometric tests.

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Name of Journal: World Journal of Gastroenterology

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The manuscript has been modified taking into account all the suggestions of the reviewers, as described below. Changes have been highlighted in red to facilitate its localization.

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
Reviewer's comments:

(1) In this cross-sectional study, Felipo and colleagues report a moderate correlation between non-invasive cerebral blood flow, in the cerebellum and minimal hepatic encephalopathy as well as other psychometric tests in patients with cirrhosis.
Overall, this is a rigorous and well-conducted study, and the authors must be commended for all the hard work.

We thank to the referee for the nice comment on the interest of the manuscript.

(2) Causality can not be inferred from a cross-sectional study, but rather associations/correlations can be made. Hence, I would recommend modifying the manuscript throughout to remove any inference on causality - for example, between NO/cGMP levels and ASL; between cerebellar blood flow causing MHE etc.

According to the suggestion of the reviewer we have now modified the manuscript to remove any inference on causality. We now talk along the text about associations or correlations, not about causes. The changes have been highlighted in red.

(3) Since the current gold standard for defining MHE is PHES, I'm unsure how it can be inferred that cerebellar blood flow is detecting MHE earlier. Moreover, the correlations between cerebellar blood flow and all measures of cognitive function was moderate at best (Correlation coefficient, between 0.3-0.4).

This point is now discussed in detail on page 15, last 6 lines and page 16, lines 1-12.

Moreover, to get further insight on this matter, we sub-classified the patients showing a PHES of -3 (who are usually classified as without MHE) as "borderline" patients. There were 7 patients with PHES -3. BF in vermis was 60±12 ml/min/100g, which was nearly significantly different (P=0.055) from controls (Figure 1B). BF in cerebellar hemisphere of these "borderline patients" was 37±6 ml/min/100g which was significantly different ($p<0.01$) from controls and not different from patients with MHE (Figure 1B). This supports that altered BF in cerebellum detects some motor deficits earlier than the PHES battery in its present form.
This is now indicated on page 13, lines 1-13 from the bottom, and a new Figure 1B, including the data from these borderline patients has been added

(4) Is there a cut-off for abnormal blood flow? In the absence of such a cut-off, I don't think it can be used for "detection of MHE". It may be useful to create an AUROC curve how different psychometric tests and cerebellar blood flow perform in diagnosis of MHE.

As suggested by the reviewer, we have performed ROC curves for BF in cerebellar vermis. As AUC of the curve was less than 0.8, we have also included a logistic regression analysis. These results support an association of BF in cerebellar vermis and the presence of MHE. This is now included on page 13, lines 3-13.

(5) Was statistical analysis corrected for multiple comparisons, and do the p-values presented represent those corrected values?

Yes. We analysed the results by one-way ANOVA followed by post-hoc Bonferroni's multiple comparison test. Differences between groups were analyzed by Games-Howell test for multiple comparisons in the parameters with non-homogeneous variances, and adjusted p-values are shown. We have added some sentences regarding this topic in Statistical Analysis paragraph (page 9, last 6 lines) and in legends to Tables 2 and 3.

(6) Please simplify the abstract, and results should represent correlation coefficient between BF and global scores of PHES.

To fit with the Instructions for Authors, the Abstract can not be simplified. The Instructions for Abstract say that METHODS must be no less than 140 words for Original Articles. Our Methods section has 143 words and can not be further reduced to fit with the limit. RESULTS must be no less than 150 words for Original Articles. Our results section has 172 words.

Correlation coefficients between BF and global scores of PHES are now given on page 12, lines 5-7 from the bottom.

(7) The manuscript would benefit from simplification - the introduction can be shortened, too much data is presented and may be better condensed.

According to the suggestion of the reviewer, we have now shortened the Introduction

We wish to thank you and the reviewers for your suggestions which have improved the manuscript. We hope it will be now acceptable for publication in World Journal of Gastroenterology.

Yours sincerely

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