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OPEN PEER REVIEW

Qualitative Assessment of Perfusion Maps Derived from Pulsed Arterial Spin Labeling Magnetic Resonance Imaging (PASL MRI) in Patients with Cognitive Disorders

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1 Original submission

3 comments · 25 Apr 2021 – 12 Jun 2021

Referee 1 Reviewer

MAJOR REVISION 25 Apr 2021

1. The objectives you mentioned in the abstract of the article differ from those in the title and main text. Please correct them.

2. What do you mean by reproducibility in the manuscript? Please clearly explain this sentence: "Also, reproducibility may be affected by long-term colleagues working together for years."

3. The article suffers from several errors in grammar and syntax (e.g., sentence 62).

4. Three main features are associated with the aging process and cognitive impairment, and all are visible on a T1 MRI sequence.
• Atrophy
• Leukoaraiosis
• Ventricle dilation
It is suggested that you compare the ASL images with the mentioned qualitative features and add the analysis to the results.

5. Given the lack of comparison with the control group, what is the rationale for the correct qualitative assessment? Please explain the CBF map qualitative evaluation criteria in the MRI technique and evaluation section.

6. Depending on the labeling method, ASL may be classified into four broad types: CASL, pCASL, PASL and VSASL. Please explain them in the discussion section of the article.

Referee 2 Reviewer

MINOR REVISION 29 Apr 2021

In general, the manuscript is relatively appropriate in terms of the structure of scientific writing, but from a methodological point of view, it requires the following modifications:
1. PSL must be written out in full in the title.
2. The total number of cognitive patients is reported as 134 in the abstract Methods section but as 129 in the full-text Methods section?
3. The study has a cross-sectional design, which must be stated in the abstract and the Methods section of the full text.
4. Table 2 does not provide any significance levels, but p-values are presented in the abstract Results section and the second paragraph of the full-text Results section? Group differences can be compared statistically using confidence intervals. When the confidence intervals of the two groups do not overlap, it can be said that they have a statistically significant difference at the 95% confidence level. According to the results of Table 2, the first two rows are not significantly different from each other, but the last group is significantly different from both. The results need to be corrected.
5. The first sentence of the statistical analysis section is ambiguous. First, we have to describe the descriptive index and then each test used for each variable.
6. Table titles should be written above the tables.

Editor-in-Chief MAJOR REVISION 12 Jun 2021

Dear authors,
Your article needs Major Revision.
Regards

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Reviewer,

Following ammendments have been made based on your precious opinions and legitimate critics.

Reviewer 1:
In general, the manuscript is relatively appropriate in terms of the structure of scientific writing, but from a methodological point of view, it needs to be modified, which include:

1. PSL must be written in full format in the title.

Manuscript Full Title: Qualitative Assessment of Perfusion Maps Acquired with Pulsed Arterial Spin Labelling MRI in Patients with Cognitive Problems (changed)

2. The total number of cognitive patients was written in the abstract method 134 but in the complete method 129?

3.1 Subjects Out of 134 (corrected) patients with cognitive problems, we included 85 patients

3. The study is a cross-sectional design that must be written in the abstract and the full text method.

Abstract

Methods: Out of 134 patients with cognitive problems, 85 patients were included in this cross-sectional study

3. Methods
3.1 Subjects
This retrospective cross-sectional study has been approved by institutional ethical committee. (corrected, added)

4. Table 2 did not provide any significant level, but in the abstract results and the second paragraph of full-text results, p value was presented? Group differences can be compared

statistically using the confidence interval. When the confidence intervals of the two groups do not overlap, it can be said that they have a statistically significant difference in the 95% confidence level. According to the results of Table 2, the first two rows are not significantly different from each other, but the last group is significantly different from both. The results need to be corrected.

Results:

Analysis results showed that the bilateral parietal hypoperfusion pattern was statistically significant (p <0,01) in AD and MCI (95% confidence interval 61,22-95,05 and 44,68-84,37 respectively) compared to combined group of patients of depression and SMI patients (95% confidence interval 4,41-28,09). The hypoperfusion rates were higher in the AD group (83%) compared to in the MCI group (67%). The hypoperfusion rate was significantly low in depression group (%13) while it was null in SMI group. (changed, ammended, and added)

5. The first sentence of the statistical analysis part is ambiguous. Firstly, we have to explain about the descriptive index and then about each test that was used for each variable.

3.4 Statistics

Statistical tests were utilized on the qualitative data of CBF maps after dichotomization of perfusion patterns such as normoperfusion and hypoperfusion. (added)

6. Table titles should be written above of them

Done

Dear Reviewer,

Following ammendments have been made based on your precious opinions and legitimate critics.

Reviewer 2:

1.The concept of objectives that you mentioned in the abstract of the article is different from the title and the objectives of the text. Please correct them.

2. Objectives

In this study, we inspected the feasibility and variability of perfusion maps derived from pulsed arterial spin labeling (PASL) MRI in a heterogeneous group of patients with cognitive impairment. (corrected and added)

2. What do you mean reproducibility by that in the manuscript? pls clear explain this sentence "Also, reproducibility may be affected by long-term colleagues working together for years."

Abstract

We inspected the feasibility and variability of cerebral perfusion maps… (ammendment)

Discussion

Besides, reproducibility and variation in measurements of the test, specifically interobserver variability here, may be affected by long-term colleagues working together for years. (ammended and added)

3.The article suffers from several errors in grammar and syntax. (eg sentence 62)

…including permission for using using the images pertaining the patient anonymously were (corrected and all text rechecked thoroughly)

4.Three main features are associated with the aging process, cognitive impairment, and all are visible on a T1 MRI sequence.

• Atrophy

• Leukoaraiosis

• Ventricle dilation

It is suggested to compare the ASL images with the mentioned qualitative features and add analysis to the results.

Structural MRI was used to rule out other causes of memory problems (hydrocephalus, tumor, stroke or vascular dementia, etc.) and as a support for AD diagnosis according to structural clues like hippocampal or global atrophy. As stated in the flow chart, three patients with vascular dementia and 11 with hydrocephalus were excluded from this study based on this morphologic assessment. All AD patients had MTA scores higher than two, while it is not a specific finding for diagnosis. Mesial temporal atrophy was not statistically evaluated in this study as it is out of the scope of this study. (This statement has also been added in 4. Results the text)

5. Given the lack of comparison with the control group, what is the rationale for the correct qualitative assessment? Please explain about CBF map qualitative evaluation criteria in section MRI technique and evaluation.

5. Discussion

In this veritable clinical study we had no healthy control group but depression group and subjective memory impairment group diagnosed with clinical tests. Aforementioned clinical tests were accepted as the reference standard test. (Response to reviewer 2, it has also been added as an ammendement in the limitations).

After acquiring two control and two tagged images, inline calculated CBF maps (128 x 128 matrix, 3.6 x 3.6 x 4 mm voxel plane) were derived automatically using subtraction with a t-test. These qualitative perfusion images were first analyzed by optimal windowing and were then

coregistered with MPRAGE images on the vendor’s work station (Syngo, Siemens AG, Berlin, Germany) for further evaluation. Both colored perfusion maps inspected through all brain sections. (ammended and added)

6.Depending on the labeling method, ASL may be classified into four broad type: CASL, pCASL, PASL and VSASL. Please explain about them in the discussion section of the article.

5. Discussion

There are different labeling methods such as continuous, pulsed, and velocity-selective ASL. In continuous ASL, a constant gradient is applied in the direction of flow along with a constant RF pulse, while pseudo continuous ASL uses a long series of short RF and gradient pulses. In PASL a single RF pulse, or short train of pulses, is used to rapidly invert the magnetization of a slab. Magnetization of the blood is inverted proximal to the brain in the former techniques, while in velocity-selective ASL, the labeling pulse is without spatial selectivity and includes whole the brain imaging volüme (added).

Dear Reviewer,

Following ammendments have been made based on your precious opinions and legitimate critics.

Reviewer 4:

1-How did the author exclude the patients with recent stroke and vascular dementia from the study?

As stated in Methods section (3.3 MRI technique and evaluation) structural scales were used to measure atrophy and white matter densities, such as the global cortical atrophy scale, Fazeka white matter scale, mesial temporal lobe scale, Koedam parietal lobe scale, NINDS-ARIEN criteria for vascular infarct and white matter lesion. With this, the above pathologies are ruled out that may affect the perfusion patterns. (response to reviewer 4)

Patients with a concern of cognitive impairment, as reported by participants or close family members, were included in this study. Exclusion criteria included the followings: any contraindication for MRI, presence of a known neurologic disease that may affect cognitive functions; baseline MRI findings indicating multi-infarct dementia, normal pressure hydrocephalus or brain tumor; history of psychotic disorders or major depression; alcohol or substance abuse or dependence; abnormal laboratory findings that might interfere with the study. (The inclusion and exclusion criteria above have been added in the text for the sake of clarity).

2-On figure 3, we have only a small part of parietal lobes. Author should replace it with ones that show most of the parietal lobes. If it is all the hypo-perfused area, show it on whole brain 3D volumetric perfusion maps of brain.

Figure 2. Inline calculated CBF map images shows bilateral parietal hypoperfusion (A) derived from two control-two tagged images (B). (added)

3-Referring to similar published articles, what is new in this study?

This study has been performed with easily accessible PASL method; it has been shown that PASL MRI perfusion maps in clinical settings in patients with cognitive problems is reliable and feasible. (Response to Reviewer 4, besides conclusion revised as following)

In conclusion, PASL MRI may offer a valuable method for evaluating patients with cognitive impairment with qualitative assessment of perfusion maps. ASL perfusion might serve as a noninvasive, swift, and reliable biomarker that may help diagnosis of patients with cognitive problems. Although considered as a research tool previously, it has become easily accessible and feasible for clinical use, thanks to recent technological advances. However, translating ASL into clinical practice still requires development and validation of standardized guidelines. (revised)

4-Review the article to correct the grammatical mistakes.

Text rechecked thoroughly

2 Revision 1

4 comments · 2 Aug 2021 – 22 Nov 2021

Referee 2 Reviewer

ACCEPT 2 Aug 2021

Hi
Thanks to the authors for addressing the comments in the manuscript.
It is now acceptable from a methodological perspective.

Associate Editor

ACCEPT 25 Oct 2021

Dear Editor in Chief,
This article is accepted for printing in IJR.

Associate Editor

MINOR REVISION 22 Nov 2021

1-The authors have written in line 15: "In AD and MCI, bilateral parietal hypoperfusion (83% and 67% respectively) were statistically significant (p <0,01) on CBF maps". It is unclear what the comparison groups are in this sentence. In fact, is hypoperfusion in AD compared with hypoperfusion in MCI, or are both compared separately with another group? Please clarify and write more clearly. If this is a comparison of these two groups, the authors can write: "Bilateral parietal hypoperfusion on CBF maps was statistically higher in AD compared to MCI (83% vs. 67%) (p <0,01)"
2-Another sentence in the abstract is incorrect and unclear, as in the previous question: "In depressive patients was hypoperfusion was significantly low (13%)". Please clarify.
3-Please add the full terms for abbreviations at first use in the abstract and the paper separately [for example, CI].
4-This sentence in the abstract seems unclear: "Qualitative assessment used in clinical settings
21 when a quick judgment needed for perfusion is reproducible."
5-In line 46, it would be better to replace inspected with investigated.
6-In line 64, it would be better to replace "measured" with "obtained" or something similar.
7-The authors mentioned: "MMSE scores were calculated for each group and were found to be 28, 4 for MCI, 26, 3 for AD, and 29, 5 for depression and SMI groups". This sentence is somewhat unclear, as there are two numbers for each disease [for example, 28, 4 for MCI]. Please clarify.
8-Please add the full terms for abbreviations at first use in the text.
9-This part is unclear: "Chi-square % Defective".
10-Please correct this part: "with a kappa value above 0.75, which is accepted as excellent agreement according to Fleiss."
To: " …… in which, according to Fleiss, kappa values above 0.75 were considered as excellent agreement."
11-It seems the authors have used a comma [,] as the decimal separator in numbers, whereas they should use a period [.] for this purpose. Please correct this throughout the paper [for example, 61,22-95,05 should be 61.22-95.05].
12-In lines 134 and 136, the authors have mentioned 95% CIs, but it is unclear for which variable these 95% CIs have been calculated. Are they for the mean difference? Or are they for the mean? Please write more clearly.
13-In addition, it is questionable how a hypoperfusion pattern could be expressed as a real number [lines 133-136].

14-In line 137, please delete the word “in”.
15-Why and how did the authors calculate a post hoc test for kappa? [lines 142-145] [A post hoc test is applied in group comparisons, not in a comparison of three numbers.]
16-In line 162, what is the SCF biomarker? Please add the full terms for abbreviations.
17-Please move the abbreviation explanations in the legends of tables 1 and 2 to the footnotes of the tables. Explain all abbreviations in the footnotes.
18-Table 3 is a crosstab for the assessment of agreement, but both raters are labeled observer 2.
19-The figure 1 legend is: patients’ enrollment flow chart. In addition, add explanations of the abbreviations in this figure [AD, MCI,. . ..].

Editor-in-Chief

MINOR REVISION 22 Nov 2021

Dear authors,
Your article needs Minor Revision.
Regards

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Associate Editor 2,

Following amendments have been made based on your precious opinions and legitimate critics. Thank you very much for your extensive review.

1-The authors have written in line 15: "In AD and MCI, bilateral parietal hypoperfusion (83% and 67% respectively) were statistically significant (p <0,01) on CBF maps" it is unclear what are the comparison groups in this sentence? In fact, hypoperfusion in AD and MCI are compared together or they are both compared separately with another group? Please clarify and write clearer. If this is comparison of these two groups, they can write: "Bilateral parietal hypoperfusion on CBF maps was statistically higher in AD compared to MCI (83% vs. 67%) (p <0,01)".

In Abstract

In AD and MCI groups, the proportion of patients who had bilateral hypoperfusion (83% and 67% respectively) were statistically significant (p <0,01) on CBF maps compared to combined group of patients of depression and SMI. In depressive patients it was significantly low (13%) and SMI group demonstrated no hypoperfusion.

2-Another sentence in abstract is wrong and unclear, same as previous question: "In depressive patients was hypoperfusion was significantly low (13%)" please clarify.

(corrected as in the preious comment)

3-Please add full term of abbreviations for the first time usage in abstract ans paper separately [for example, CI].

In Abstract

Interobserver agreement 18 evaluated by kappa value showed good agreement (0.78 with 95% confidence interval = 0.65–0.91). (sentence re-written without abbreviation)

4-This sentence in abstract seems unclear: "Qualitative assessment used in clinical settings 21 when a quick judgment needed for perfusion is reproducible."

In Abstract

Qualitative assessment of CBF maps derived with this technique is reproducible and feasible in routine clinical settings. (sentence re-written)

5-in line 46, it seems better inspected be replaced by investigated.

In this study, we investigated the feasibility and variability of perfusion maps derived from pulsed… (changed in abstract and text)

6-in line 64, it seems better to replace "measured" by "obtained" or something like this.

… including permission for using the images pertaining the patient anonymously were obtained.

7- The authors mentioned: "MMSE scores were calculated for each group and were found to be 28, 4 for MCI, 26, 3 for AD, and 29, 5 for depression and SMI groups" this sentence is somehow unclear as there are two numbers in each disease. [for example 28, 4 in MCI]. Please clarify.

There are not two numbers, the decimal numbers were wrongly had a blank; the blank has been deleted (corrected) as followings;

Avarage MMSE scores were calculated for each group and were found to be 28,4 for MCI; 26,3 for 78 AD; 29,5 for depression and SMI groups.

8-please add full term of abbreviations in first usage in text.

Whole text has been for abbreviations checked thoroughly.

9-This part is unclear: "Chi-square % Defective"

Chi-square was used to compare association of bilateral parietal hypoperfusion among the groups. (corrected no need to indicate % defective, sentence restructures)

10-Please correct this part: "with a kappa value above 0.75, which is accepted as excellent agreement according to Fleiss." To: "…… in which, according to Fleiss, kappa values above 0.75 were considered as excellent agreement."

The degree of agreement among observers was expressed by kappa statistics, in which, according to Fleiss, kappa values above 0.75 were considered as excellent agreement. (corrected)

11-It seems the authors have used kamma [,] for decimal place of numbers while they should use dot [.] for this purpose. Please correct in all paper. [for example, 61,22-95,05 should be 61.22-95.05]

Whole text has been checked for it thoroughly.

12-in lines 134 and 136, the authors have mentioned 95% Cis but it is unclear for which variable, these 95% CIs have been calculated? Are they for mean difference? Or are they for mean? Please write in a clearer form.

The sentence has been restructured as followings;

The ratio of patients who had bilateral parietal hypoperfusion were the highest in the AD group (83%) and lowest in depression group (%13) while it was null in SMI group. Analysis showed that this proportion was statistically significant ($p < 0,01$) in AD and MCI groups compared to combined group of patients of depression and SMI patients (CI 61,22-95,05; 44,68-84,37 and 4,41-28,09 respectively). There was no statistically significant difference between the AD group and MCI group in terms of the rate of bilateral parietal hypoperfusion patients. (67%).

95 % confidence interval (CI) was used to represent the effect size. (added to the statistics section).

13- In addition, it is questionable how hypoperfusion pattern could be mentioned as a real number? [lines 133-136]

The above sentences in previous comment have been restructured as the numbers represent the ratios.

14-in line 137, please delete the word "in"

…deleted and sentence restructured

15-why and how the authors did calculate post hoc test for kappa? [lines 142-145] [post hoc is applied in group comparison not in comparison of three numbers????]

Tukey's HSD post hoc test was used to analyze assesing agreement of observers. (also added to the statistics section)

Complete agreement was found in 89% of the total sample, expected agreement was 0.50, 141 interobserver agreement as expressed by kappa values was 0.78, and CI was 0.65–0.91. A post hoc analysis revealed that agreement was highest in the Depression and SMI groups and lowest in the MCI group, 92% and 83%, respectively. Observed agreement was 88% in the AD group, reflecting similar results of overall complete agreement (Table 3).

16-in line 162, what is SCF biomarker? Please add full term of abbreviations. SCF biomarker (corrected, full term for abbreviation has been added in the introduction)

17-Please move abbreviation explanation in table 1 and 2 legend to the footnote of table. explain all abbreviations in footnotes.

In Table 1 and and Table 2 abreviations are moved to the footnote as Abbreviations:

18-Table 3 is a crosstab for assessment of agreement but two raters are both observer 2.

First one is changed to Observer 1

19-Figure 1 legend is: patients' enrollment flow chart. In addition add abbreviation explanation in this figure [AD, MCI,]

Figure 1. patients' enrollment flow chart (AD Alzheimer's disease; MCI Minimal cognitive impairment; SMI subjective memory impairment).

3 Revision 2

1 comment · 13 Dec 2021

Editor-in-Chief

ACCEPT 13 Dec 2021

Dear authors,
Your article is acceptable for publication in IJR.
regards