Dear Editor,

Thank you for your great effort in handling our submission (Manuscript NO.: 82160, entitled Functional near-infrared spectroscopy in elderly patients with four types of dementia: a retrospective study). We also thank the reviewer for his/her comments. In response to the comments and suggestions made by the referees, we have made a number of changes and additions to the manuscript. We believe that these changes, together with the detailed response to the reports given below, clarify all the points made by the referees. We would like to resubmit it. Thank you in advance for your further consideration of our contribution. We look forwards to your response in due course.

Sincerely yours,
Xi Mei

**Reviewer(s)' Comments to Author:**
Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: The study demonstrated the use of functional near-infrared spectroscopy (fNIRS) during two tasks and a resting state to differentiate four types of dementia (FTD, LBD, PDD, AD). The presentation of the main results is clear and concise. The results are valuable and worthy of being published taking into account their possible applications in the clinical diagnosis of different types of dementia using fNIRS. However, there are some issues that need to be addressed first to improve the quality of the manuscript. Some comments are detailed below.

The description in the Introduction chapter is too brief, and some descriptions about the application of past studies are mixed in the Discussion chapter. It is recommended to supplement and take stock of the evidence of fNIRS applied to various dementias (at least the four mentioned in this study) and the advantages and disadvantages of this method.

We added several sentences and relevant references in section of Introduction.

"While PET and MRI studies have generated insights into the pathological changes in brain oxygenation and activity associated with mild cognitive impairment (MCI) and dementia, these methods have some limitations involving the injection of radioactive compounds and motion artifacts (5)."

"fNIRS is used to monitor hemodynamic changes evoked by neural activity by taking advantage of the fact that biological tissues are relatively transparent to near-infrared light 700-1000nm (6). Recent studies on fNIRS detection of dementia focused on MCI and Alzheimer's disease (AD) (7). Amnestic MCI is more predictive of AD than nonamnestic MCI, and nonamnestic MCI is more predictive of other types of dementia including Lewy bodies dementia (LBD) and frontotemporal dementia (FTD) (8, 9). To measure cortical activation in patients with behavioral variant of the frontotemporal dementia (bvFTD), fNIRS was used while performing the verbal fluency task (VFT) (10). The flexible of fNIRS makes the

possibility of measurement of the neurology of gait in cognitive dysfunction or dementia during dual-task gait assessment (11)."

Although the Data analysis chapter describes the tools and analysis methods used, it is a general description without too much in-depth explanation. Please add explanations or cite appropriate literature to help readers obtain relevant information or have the opportunity to reproduce the steps of the experiment.

We added a section of fNIRS experiment and relevant reference before Data analysis.

"fNIRS experiment The participants were guided to the experimental room, and seated on a wooden stool with a wooden table. During the experimental preparation phase, the participants were asked to wear an electrode cap. The experimenter repeatedly adjusted the electrode cap to maximize the signal channel gain. When the experiments begin, participants performed the task by listening to the instruction (verbal fluency task) or using an ipad (working memory task), as our previous work (12)."

The Case Report chapter clearly and completely describes the condition of the case and the relevant examination results. However, the LBD and AD cases do not mention the findings obtained by MRI or CT imaging examination. It is suggested that in addition to the results of the fNIRS examination, the results of other routine examinations should be added for comparison and discussion in each case, so as to achieve a more correct and objective interpretation of the results of the fNIRS examination.

We found the patient's records and added the CT imaging of LBD and AD cases.

"A brain MRI showed localized atrophy in the temporal, frontal and parietal lobes."

"A brain MRI showed reduced hippocampal volume and internal olfactory cortex volume bilaterally (MTA-score>2)."

Regarding the description of the fNIRS results (only brief figures), there is no description of the fNIRS results in the Case Report chapter and the Discussion chapter. It is difficult to understand the degree of activation of these 4 cases and the status of resting state functional connections. It is recommended to first introduce the interpretation level and key points of the inspection results, and then supplement the results obtained in these cases and their significance in detail.

We added description of fNIRS results in detail and relevant references in section of Case Report and Discussion.

"In Figure 2A, fNIRS showed global lower activation in frontotemporal lobe when the patient performed the verbal fluency task. This was consisted with his clinical manifestation of poor verbal function."

"Frontalpolar and temporopolar area showed most activation than other regions. The overall pattern was different from other three subtypes of dementia."

"As shown in Figure 1C, the dorsolateral prefrontal cortex (DLPFC) was activated strongly (symmetrical pattern; in red color region) during the working memory task."

"The contrast of the two demented subjects (PDD v.s. AD) was characterized by a nearly symmetrical pattern in both task contrasts: prefrontal lobe was more activated in verbal fluency task in the AD than in PDD, while the frontotemporal lobe was more activated in working memory task in the PDD than in AD (Figure 2C and D). Regarding to the working memory task, the activation of brain in AD was the

weakest of four dementias."

"The results of this study indicate that cortical activation measured with fNIRS while performing a verbal fluency and working memory task differs in patients suffering from four types of neurodegenerative dementia including FTD, LBD, PDD and AD. Furthermore, this activation differs between the four types of neurodegenerative dementia, a result shown for the first time using fNIRS in antidiastole of dementia subtypes.

A reduction in cortical activation during verbal fluency task performance in FTD patient compared to other three dementias has been shown in this study. FTD disorders include behavioral variant FTD (bvFTD), nonfluent/agrammatic variant primary progressive aphasia (nfvPPA), and semantic variant PPA (svPPA) (16). PPA patients showed differential linguistic features of verbal fluency from bvFTD (17). In this FTD case, the patient showed the poor verbal function. The fNIRS pattern showed low activation during the verbal fluency task."

"The AD pattern is weaker and more similar to the healthy pattern, whereas the bvFTD pattern is qualitatively different, namely more frontopolar and without frontoparietal compensation activation (10). Our results showed the AD patient have lower and slower activation in the bilateral PFC and left parietal cortex during working memory maintenance. This was consisted with previous study on moderate to severe AD (1). aMCI patients, as early stage AD, were reported a larger reduction in frontal deoxy-Hb during the memory task (22)."

"Regarding to prefrontal cortex, primarily DLPFC, activation has a positive correlation with working memory load and performance until the working memory load exceeds the capacity (26)."

Due to the 4 types of dementia cases selected by the author, complex issues such as individual severity (MMSE score), onset conditions, whether they are mixed with other mental problems, and whether they are typical of the type of dementia are mixed together, which is not easy understand the essential impact from the test results.

Thank you for your advices, we added these conditions in each case. The format of case description was also adjusted as "Clinical manifestation, Examinations, and fNIRS results".

"Considering to his education level of high school, the severity of dementia was moderate. The patient was diagnosed as FTD accompanied by mild depression."

"The degree of dementia was severe. The patient was diagnosed as primary neurodegenerative disease LBD."

"The degree of dementia was severe. The patient was diagnosed as typical PDD accompanied by sleep disorders."

"The degree of dementia was moderate to severe due to her education level of 1 year. The patient was diagnosed as typical AD accompanied with mild depression."

Although the author put forward some proof that some activation areas are consistent with the symptoms of individual cases, it is still not enough to enable readers to fully understand and grasp the application and interpretation of fNIRS for dementia detection. For example, why are the MMSE scores of PDD and AD similar, but the functional connection strength is much different? What can be learned from the results of Figure 3? It is recommended that the author make a complete description of the conditions of these cases and the results of fNIRS.

We discussed the reason why are the MMSE scores of PDD and AD similar, but the functional connection strength is much different in section of Discussion.

"Regarding to the functional connection reflected by fNIRS, connections between different brain regions, as well as synergies between them, work together to provide comprehensive cognitive functions. As shown in Figure 3, the total scores of MMSE of patient with PDD and AD were similar in our study, but the functional connection strength is much different. The MMSE scale included six cognitive domains of orientation, immediately recall, attention, delayed recall, language and executive, and visual function (23). Although the total MMSE scores of PDD and AD patients are close, they have different sub-scores in different cognitive domains, which reflect different brain area functions. In this aspect, the functional connectivity reflected by fNIRS can distinguish these differences, and enhanced the diagnostic accuracy as an auxiliary method."

Reviewer #2:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: 1 February 2023 The review report on the manuscript titled 'Functional near-infrared spectroscopy in elderly patients with four types of dementia: Case reports', submitted to World Journal of Psychiatry Manuscript ID: 82160 Dear Authors, The present research article entitled 'Functional near-infrared spectroscopy in elderly patients with four types of dementia: Case reports' is a well-written and useful summary of the current status of knowledge on the possible implementation of functional near-infrared spectroscopy (fNIRS) technique in identifying symptoms of dementia and this neurodegenerative's progression. For this purpose, here authors presented four cases of patients with different types of dementia: with the use of fNIRS, different hemodynamics characteristics of prefrontal cortex were identified, providing evidence that this imaging tool might be very useful for the differential diagnosis between dementia subtypes. In general, I think the idea of this manuscript is really interesting and the authors' fascinating observations on this timely topic may be of interest to the readers of World Journal of Psychiatry. However, some comments, as well as some crucial evidence that should be included to support the author's argumentation, needed to be addressed to improve the quality of the manuscript, its adequacy, and its readability prior to the publication in the present form, in particular reshaping parts of the Introduction and Methods sections by adding more evidence and theoretical constructs.

Please consider the following comments:
1. Abstract: Please proportionally present background, purpose, methods, results, and conclusion. Also, in my opinion, a lack of explanation of the fNIRS imaging technique and of its clinical application in Neuroscience makes the reader unable to grasp the key aspects of this paper by consulting the abstract. I suggest reorganizing the abstract, making sure to include an explanation of this concept.

We reorganized the Abstract according to the Reviewer's advice.

2. Keywords: Please list five keywords and use them as many as possible in the first two sentences of the abstract.
We listed five keywords and use then in front part of the abstract.

3. A graphical abstract is highly recommended.
We added a graphical abstract as a supplementary.

4. In general, I recommend authors to use more evidence to back their claims, especially in the Introduction of the article, which I believe is currently lacking. Thus, I recommend the authors to attempt to deepen the subject of their manuscript, as the bibliography is too concise: nonetheless, in my opinion, less than 50/60 articles for a research paper are really insufficient. Therefore, I suggest the authors to focus their efforts on researching more relevant literature: I believe that adding more studies and reviews will help them to provide better and more accurate background to this study.
Thank you for your advice. We added more evidence and relevant references in our Revision.
"It was shown that resting-state fNIRS recordings from prefrontal regions can provide a potential methodology for detecting MCI and its progression (10). The sensitivity and specificity increase as the cognitive impairment worsens (11)."
"Similar studies focused on old people with risk of dementia, such as those with subjective memory complaints, were reported to be examined by fNIRS in dual-task gait (16)."

5. The objectives of this study are generally clear and to the point; however, I believe that there are some ambiguous points that require clarification or refining. In my opinion, authors should be explicit regarding how they assessed the reliability of fNIRS in estimating global cerebral function and how it could be a critical tool to investigate frontal lobe oxygenation in patients with different types of dementia.
We added the sentences on how to assess the reliability of fNIRS in estimating global cerebral function and how it could be a critical tool to investigate frontal lobe oxygenation in patients with different types of dementia.
"The reliability of fNIRS in estimating global cerebral function was supported by previous studies (21). fNIRS measurements are reproducible and can be reliable used in single subjects for neuroscientific research and clinical applications (22). It could be a critical tool to investigate frontal lobe oxygenation in patients with different types of dementia and age-related decline of neurovascular coupling responses (23-25)."

6. Introduction: I suggest the authors to reorganize the Introduction section, which seems inhomogeneous and dispersive, and specifically, not enough informative as an Introduction should be. For this reason, I believe that a general overview about the use of optical techniques, specifically fNIRS, to study brain hemodynamics and to assess

prefrontal cortex's activity of older adults for detection of certain types of seizures and cortical spreading deactivation in cognitive tasks, would provide a more defined background here. In this regard, I believe that it could be useful to focus on 'Dissecting Neurological and Neuropsychiatric Diseases: Neurodegeneration and Neuroprotection' and on representation of altered prefrontal mechanisms reflected by fNIRS imaging (https://doi.org/10.17219/acem/146756; https://doi.org/10.1111/psyp.14122). This additional information may help in understanding how fNIRS stimulation could have the potential to develop accessible neuroimaging biomarkers for different neurodegenerative disorders (https://doi.org/10.3390/cells11162607; https://doi.org/10.3390/biomedicines9040340), as 'Accuracy of Biomarkers in the Detection of Clinical Outcome in Disorders after Severe Acquired Brain Injury: Preliminary Results of a Pilot Study Using a Machine Learning Approach'.

Thank you for your advice. We added more evidence and relevant references in our Revision.

"The use of optical techniques, specifically fNIRS, to study brain hemodynamics and to assess prefrontal cortex's activity of older adults for detection of certain types of seizures and cortical spreading deactivation in cognitive tasks is also important. fNIRS can be useful to investigate the altered prefrontal mechanisms of neurological and neuropsychiatric diseases and discover neuroimaging biomarkers for different neurodegenerative disorders (17-20)."

7. Case reports: I suggest the authors to better explain and further describe data about the subject and provide full information about their clinical assessment (i.e., severity of disorder, pharmacotherapy duration etc.). Moreover, I suggest the authors to use more references to back their claims, especially when describing the laboratory tests used. Moreover, I suggest the authors to use more references to back their claims, especially when describing the laboratory tests used.

Thank you for your advice. We added more evidence and relevant references in our Revision.

We added the references "as described in our previous study (27)"

"During the task period, participants were instructed to generate as many words as possible, they continuously named different words beginning with a specific letters for 20 seconds (trials for three letters totaled 60 seconds); 3) Participants repeated step 1 for 70 seconds to return to baseline. The task took less than three minutes total. Other matters needing attention were described in previous studies on verbal fluency task of fNIRS (28-30)."

"Working memory performance was used to reflect the cognitive function in many studies (32-34)."

8. I think the 'Conclusions' paragraph would benefit from some thoughtful as well as in-depth considerations by the authors, because as it stands, it lists down all the main findings of the research, without really stressing the theoretical significance of the study. Authors should make an effort, trying to explain the theoretical implication as well as the translational application of their research.

We modified the Conclusion to explain the theoretical implication as well as the translational application of this research.

"In the future, as a non-invasive tool, multichannel fNIRS technology can provide high spatial and

temporal resolution signals to continuously assess regional cerebral oxygenation. The sensitivity of fNIRS increased its use as a wide-spread clinical tool for the robust assessment of brain function."

9. In according to the previous comment, I would ask the authors to better define a 'Limitations and future directions' section before the end of the manuscript, in which authors can describe in detail and report all the technical issues brought to the surface.

We modified the Limitations and future directions.

"Although our fNIRS recording technique was a multichannel flexible tool to detect the brain function in patients with different type of dementia, it focused on the frontal and temporal lobe of the brain, not the global brain region. This can be improved by using whole brain detection of fNIRS in the future."

10. Regarding the Figures: Please provide an explanatory caption for each figure within the text. I hope that, after these careful revisions, this paper can meet the Journal's high standards for publication. I am available for a new round of revision of this paper. I declare no conflict of interest regarding this manuscript.

Best regards, Reviewer

We modified the figure captions in the article.

"Figure 1 Diagrammatic sketch of localization of the fNIRS probe set over left and right frontotemporal cortex."

"Figure 2. Comparison of fNIRS patterns and task performances during the verbal fluency task (left) and the working memory task (right) between four types of dementia patients."

"Figure 3 Resting state functional connections were calculated by conducting Pearson's correlation analysis between the time series of every pair of measurement channels."