Thank you for your valuable feedback on our manuscript titled "Estimating Brain Age Gap and Cognitive Profiles using MRI and FDG PET." We appreciate your time and effort in reviewing the paper. We have carefully considered your comments and have made revisions to address your concerns. Please find our rebuttal and responses below. In the manuscript, changes are indicated in red.

**Reviewer 1 Comments for the Author...**

Doering et al. estimated brain age gap (BAG) in cognitively normal individuals, persons with subjective and objective cognitive impairment, using MRI and FDG PET. They report a number of findings, concluding that brain age can be reliably estimated from MRI and FDG PET.

**While the results might be interesting for the readership of the JNM, major clarifications are needed. Overall, the manuscript reads very difficult. Many terms seem to be used interchangeably, complicating understanding; it is not clear if the interchangeable terms are used as synonyms or have a different meaning. For instance, brain age and BAG; cognitive profile, cognitive variance, cognitive scores, cognitive status and so on. Some terms are used inaccurately. For instance, directly in the title: What are “pathological profiles”? Can the cognitive progression or non-progression be called “prognostic profile”? What are “different brain ages”? It is really hard to understand the title of the manuscript. Further, I don’t think it is correct to talk about the “Alzheimer’s disease continuum”. According to Table 1 many study individuals are amyloid-negative. Alzheimer’s disease is not an “intracereberal abnormality”. Overall, the language of the whole manuscript including the title and abstract should be carefully revised.**

We apologize for the confusion caused by the interchangeable use of terms in the manuscript. We have now revised the language to ensure consistent and accurate terminology throughout. We clearly define "brain age" as the estimated age from either MRI or FDG-PET and "brain age gap" (BAG) as the difference between estimated brain age and chronological age (p. XX):

“XX”

Moreover, we have summarized the concepts “cognitive profile”, “cognitive variance” and “cognitive scores” to cognitive performance and added an explanation for “cognitive status” on p. XX:

“XX”.

We refrained from referring to our sample as “Alzheimer’s disease continuum” and instead now call it “non-demented individuals.” and we removed the term “intracerebral abnormality”. We carefully revised the title to accurately reflect the study's objectives and findings more accurately.

**Is it known if the CN individuals had any cognitive complaints?**

As mentioned in the supplementary materials, CN individuals had no cognitive complaints. We have moved the distinction between CN and SCD to the main manuscript to avoid confusion.

**What is the rationale of the study? Why is the comparison of MRI- and PET-BAG meaningful?**

We appreciate your suggestion to further clarify the rationale behind comparing MRI-derived BAG and PET-derived BAG. We have revised the manuscript to provide a more explicit explanation. Specifically, we highlight that MRI and PET provide complementary information about brain structure and function, and comparing their respective BAG values allows for a comprehensive evaluation of accelerated brain aging and its association with cognitive outcomes on p. XX:

“XX”

**Surprisingly, MRI-BAG predicted cognitive decline more accurately than PET-BAG. In the discussion section, the authors explain “our algorithms were trained to estimate age, and regions relevant for aging on FDG-PET were not typical of early AD, thus explaining the lack of prognostic potential.” I cannot agree. In fact, the authors studied not age, but BAG, i.e., accelerated brain aging. This acceleration is supposed to be realised by inclusion of subjects at the early stages of AD. In fact, the lack of AD typical regional pattern in PET supports my previous remark about the AD continuum. That is, many study individuals do not have AD. Hence, the authors should propose another explanation of this unexpected finding.**

Accelerated brain aging (BAG) was studied by estimating brain age with models trained on a CN cohort and subsequently comparing individuals’ brain age to their chronological age. Different brain regions display susceptibility to ageing when observed with MRI or FDG-PET, and those regions susceptible to normal aging on MRI are also typically more associated with AD-proneness.

“*Our study's finding that MRI-BAG predicted cognitive decline more accurately than PET-BAG may be attributed to the algorithms primarily trained to capture age-related changes and regions relevant to normal aging. The lack of typical early Alzheimer's disease patterns observed in FDG-PET-based models suggests that PET-based BAG may not be specific to early-stage Alzheimer's. The diverse cognitive profiles in our study, including individuals without Alzheimer's pathology, may have influenced the attenuated predictive potential of FDG-PET-BAG in our cohort.”*

**The above findings about the cognitive status are based on results in the combined sample of cognitively normal and subjectively impaired “decliners”. This approach doesn’t fit into the current praxis of clinical settings or clinical trials. To be useful, MRI should be performed in cognitively normal individuals without any objective or subjective cognitive impairment.**

We provided an analysis on the prognostic potential of MRI or FDG-PET BAG conducted only in CN or only in SCD. Results were presented in the supplementary materials due to limitations on Figure and word count.

**The predictive value of MRI-BAG is not superior to the established AD biomarkers including memory tests. So, why should MRI-BAG be preferred over the established biomarkers? How can the MRI-BAG be incorporated into a diagnostic algorithm?**

While it is true that the predictive value of MRI-BAG may not be superior to established AD biomarkers, such as memory tests, it is important to note that MRI-BAG provides additional information about brain aging and cognitive profiles. By incorporating MRI-BAG into a diagnostic algorithm, we can enhance the accuracy and comprehensiveness of the diagnostic process. MRI-BAG can capture age-related changes and provide insights into accelerated brain aging, which may complement the information provided by traditional biomarkers. In the revised version of the manuscript, we additionally present the superior prognostic potential of MRI BAG and memory tests for the prediction of cognitive decline.

**Irrespective of that, sensitivity and specificity below 70% don’t promise a clinical application. Do the authors wish to propose another value of the results?**

Regarding the sensitivity and specificity of below 70%, we acknowledge that these values may not meet the threshold for direct clinical application. However, our study aims to contribute to the field by providing valuable insights into the potential utility of MRI or FDG-PET BAG as a potential complimentary tool to describe cognitive health. Our results, even those where we present low sensitivity and specificity, can guide future research and help refine the algorithms used in BAG estimation to improve sensitivity and specificity. Note that not only MRI BAG, but all AD biomarkers had low sensitivity and specificity when corrected for age and sex in our analyses. For better comparison to previous literature, we now also present (significantly higher) metrics when omitting covariate correction:

Methods (p. XX)

“XX”

Results (p. XX)

“XX”

**Reviewer 2 Comments for the Author...**

**In this new version of the manuscript authors answered most of the requirements**

**made by reviewers and now the manuscript is clearer and better understood. At**

**the SCI stage, MRI-derived BAG is significantly related to CSF AB1-42 and p-**

**tau/AB1-42; and FDG-PET derived is related to ADNI-MEM. On the other hand, at**

**the MCI stage both are significantly related to global cognitive scores and CSF**

**AB1-42, but only MRI-derived BAG is related to p-tau/AB1-42 measures. Finally,**

**only BAD estimated by MRI is prognostic of cognitive decline. In my opinion the**

**abstract conclusions and the summary included at the end of the manuscript are**

**not clearly reflecting these findings.**

We appreciate your positive feedback on the revised version of our manuscript and your acknowledgment that the changes have improved its clarity and understanding. We have carefully reviewed the abstract conclusions and the summary included at the end of the manuscript in light of your comments, and we agree that they may not accurately reflect our findings. We will ensure that the abstract conclusions and the summary are revised to more clearly and accurately reflect the relationships observed in our study.

**Additionally, it will be important to clarify some issues more in detail:**

**- AD pathology: you use this term to refer to CSF biomarkers results.**

**Surprisingly, some associations were significant only when comparing to CFS but**

**not to amyloid PET. However, you didn’t discuss this issue. Please discuss the**

**lack of related associations with amyloid-PET while you found associations with**

**CSF biomarkers. This is quite surprising finding particularly in MCI patients in**

**whom differences between CSF and PET are not frequent. Did you check any**

**difference between CSF and amyloid-PET in your cohorts?**

CHECK THIS

**Moreover, MRI-derived BAG was related to CSF biomarkers but FDG-PET-Derived BAG**

**was related to CSF Aβ1-42 too (at least in the MCI stage). However, you asserted**

**in the abstract conclusions that only MRI-derived BAG is reflecting neurologic**

**indications of AD. Besides, this assertion is not correct: “… whereas FDG-PET**

**BAG, derived from various regions throughout the brain, reflected cognitive**

**variance unspecific to AD.”**

**As introduced above, a similar comment can be said to the global cognitive**

**dysfunction.**

CHECK THIS

**- Prognostic biomarkers: you are comparing the results obtained using MRI-**

**derived BAG with standard methods (hippocampal volume and amyloid-PET), but it**

**doesn´t include FDG-PET (a well stablished biomarker of AD progression).**

XX

**The comment “The notion that FDG-PET BAG holds no prognostic utility is in**

**apparent contrast to existing literature showing that cognitive decline can be**

**predicted from FDG-PET” can be misunderstood. BAG is a measure that might be a**

**possible marker in the evaluation of AD, but you only make this statement by**

**comparing directly in your cohort as you did with hippocampal volume and**

**amyloid-PET. FDG-PET is reflecting neuronal or synaptic activity and different**

**that BAG. Have you considered possible reasons of the difference between the**

**calculation of BAG by means of MRI and FDG-PET?**

XX

**- Methodological issues: It is not clear if you are using a reference region to**

**calculate the SUVR, and this is the case which region were you using.**

We previously mentioned that SUVr was generated using the pons as a reference region only in the supplementary materials. This information was moved to the main manuscript (p. XX) for better readability:

“XX”

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