Format for ANSWERING REVIEWERS

September 1, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 21760-Review.doc).

Title: Amyloid positron emission tomography and cognitive reserve

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Name of Journal: *World Journal of Radiology*

ESPS Manuscript NO: 21760

We thank both the Reviewers for appreciating our work and for their punctual observations that we believe have increased clarity and scientific value of the manuscript. Given both reviewers' remarks calling for more information about "models, validation and quantification". We have decided to include a figure (Figure1) summarizing the different hypothesis proposed for explain the effects of Cognitive Reserve in AD as well as the expected results of both AMY-PET and 18F-FDG (considered a neurodegeneration biomarker).

Revewer1

This is an interesting area of research with huge clinical application potential. The manuscript will be strengthened with any guidance to current or future application with regard to available models including quantitative data for those models

We thank the Reviewer for this important comment. Quantification of Amyloid PET data is a meaningful issue indeed. Furthermore we believe that quantification of different "grade" of Amyloid PET positivity may further elucidate some issues related to positive AMY-PET in cognitively intact subjects (such as in the case of patients with greater cognitive reserve).

Given the Reviewer's remark the following sentences and references have been added:

"Besides underlying the importance of integrating Amy-PET with neurodegeneration biomarkers, the issue of positive Amy-PET in cognitive normal subjects further supports the need of a standardized approach to Amy-PET quantification. In fact, to date there's still considerable variability in the numbers reported as quantitative outcome measures of tracer retention. Many international efforts are ongoing to address the problem of Amy-PET quantification[49]. Besides the increased accuracy and consistency potentially provided by tracer binding quantification, a further possible benefit would be related to the possibility of defining three ranges of amyloid deposition: (1) the amyloid-negative range; (2) the "AD-like" range and (2) the "just-positive" range[49, 50]. A greater comprehension of this latter range may be of interest to better differentiated 'incidental' amyloid load from amyloid load in the AD-like range in cognitively intact subjects with greater CR"

Klunk WE, Koeppe RA, Price JC, Benzinger TL, Devous MD Sr, Jagust WJ, Johnson KA, Mathis CA, Minhas D, Pontecorvo MJ, Rowe CC, Skovronsky DM, Mintun MA. The Centiloid Project: standardizing quantitative amyloid plaque estimation by PET. *Alzheimers Dement* 2015; **11**: 1-15 [PMID: 25443857 DOI:

10.1016/j.jalz.2014.07.003].

Mormino EC, Brandel MG, Madison CM, Rabinovici GD, Marks S, Baker SL, Jagust WJ. Not quite PIB-positive, not quite PIB-negative: slight PIB elevations in elderly normal control subjects are biologically relevant. *Neuroimage* 2012; **59**: 1152-60 [PMID: 21884802 DOI: 10.1016/j.neuroimage.2011.07.098].

Reviewer2

Well written, good narrative review. Some quantitative information would be welcome, such as incidence or prevalence of AD

Given the Reviewer's remarks the following sentences and reference have been added to the introduction.

"AD is the most common neurodegenerative cause of dementia and affects around 10% of individuals over age 65 and up to 40% of individuals over age 85[1]. In 2010 it has been estimated that 4.7 million individuals aged 65 years or older were affected by AD in the United of States with the total number of people with AD dementia projected to be 13.8 million in 2050[1]."

Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology. 2013 May 7;80(19):1778-83.

Include information about validation data of AmyPET. It might be useful to mention whether PET is recommended or is considered investigational in the workup of AD.

Information and pertinent references have been provided as follows:

"The oldest and more extensively studied PET tracer for Amy-PET is the Carbon11 labeled Pittsburgh compound B (PiB)[15]. More recently three fluorine18 labeled compounds have been developed. Following multicenter Phase 3 trials, they were all approved both in the United States and Europe to in vivo image amyloid plaques[19-21]. Accordingly, appropriate use criteria have been now proposed for the use of Amy-PET[22]. Although obtaining in vivo information about the presence of amyloid pathology allowed a greater accuracy in the work up of patients with suspected AD, the clinical repercussions of PET-assessed Aβ load are certainly mediated by CR."

Clark CM, Schneider JA, Bedell BJ, Beach TG, Bilker WB, Mintun MA, Pontecorvo MJ, Hefti F, Carpenter AP, Flitter ML, Krautkramer MJ, Kung HF, Coleman RE, Doraiswamy PM, Fleisher AS, Sabbagh MN, Sadowsky CH, Reiman EP, Zehntner SP, Skovronsky DM; AV45-A07 Study Group. Use of florbetapir-PET for imaging beta-amyloid pathology. JAMA. 2011 Jan 19;305(3):275-83

Curtis C, Gamez JE, Singh U, Sadowsky CH, Villena T, Sabbagh MN, Beach TG, Duara R, Fleisher AS, Frey KA, Walker Z, Hunjan A, Holmes C, Escovar YM, Vera CX, Agronin ME, Ross J, Bozoki A, Akinola M, Shi J, Vandenberghe R, Ikonomovic MD, Sherwin PF, Grachev ID, Farrar G, Smith AP, Buckley CJ, McLain R, Salloway S. Phase 3 trial of flutemetamol labeled with radioactive fluorine 18 imaging and neuritic plaque density. JAMA Neurol. 2015 Mar;72(3):287-94;

Sabri O, Sabbagh MN, Seibyl J, Barthel H, Akatsu H, Ouchi Y, Senda K, Murayama S, Ishii K, Takao M, Beach TG, Rowe CC, Leverenz JB, Ghetti B, Ironside JW, Catafau AM, Stephens AW, Mueller A, Koglin N, Hoffmann A, Roth K, Reininger C, Schulz-Schaeffer WJ; Florbetaben Phase 3 Study Group. Florbetaben PET imaging to detect amyloid beta plaques in Alzheimer's disease: Phase 3 study. Alzheimers Dement. 2015 Aug;11(8):964-74.

Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, Karlawish JH, Rowe CC, Hedrick S, Pappas V, Carrillo MC, Hartley DM; Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. Update on appropriate use criteria for amyloid PET

imaging: dementia experts, mild cognitive impairment, and education. Amyloid Imaging Task Force of the Alzheimer's Association and Society for Nuclear Medicine and Molecular Imaging. Alzheimers Dement. 2013 Jul;9(4):e106-9

-Minor typo's: Abstract: define abbreviations Aβ, CSF. Text: age onset -> age of onset. "frame" or "Framework"? Check dictionary definitions of frame and framework, "framework" would be more appropriate. Contribute of ... --> contribution of ... Page 6: "and fMRI" --> a fMRI. page 7: pAD: define. page 12: Accordingly is still a... -> accordingly it is still a...

We thank the Reviewer for these remarks. Abbreviation have been defined and typos have been corrected.

Thank you again for publishing our manuscript in the *World Journal of Radiology*

Sincerely yours,

Silvia Morbelli