Reviewer's report

Title: Higher atherosclerotic burden and disturbed subcortical blood flow related to mild depressive symptoms in a population-sample of octogenarian men.

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Reviewer: Rita Bella

Reviewer's report:

The authors address an exciting research field, that of the relationship between peripheral artery disease, cerebral hypoperfusion and depressive symptoms in the elderly. The main finding is that depression in late life correlated with more persistent smoking habits, worse lower limbs vascular burden and perfusion changes in cerebral area involved in mood and cognition regulation and in movement control. The strength of this paper is the support of the “vascular depression hypothesis” and that even mild depression in the elderly is associated not only with impaired cerebral perfusion but with a widespread vascular pathology. The question posed by the authors is well defined, the data seem to be consistent and the limitations are clearly stated. Nevertheless, there are some major and minor issues that should be addressed before publication.

Major revisions:

1. In the Results section of the abstract, please specify which part (or parts) of the “subcortical area” ($r = -0.42^*$) was the most involved and which side of the basal nuclei ($r = -0.35^*$) was affected.

2. The Methods are described but there is unclear about the appropriateness. Why the authors defined systolic hypertension as brachial blood pressure $\geq 160$ mmHg? Do they have a specific reason? I wondered whether the obtained results might be influenced and, perhaps underscored, given that patients with systolic brachial blood pressure i.e. of 140 or 150 mmHg were not considered as affected by hypertension according to this study. As stated, circulation in lower extremities was estimated using ankle-brachial pressure index (ABPI). Although is a popular tool for the non-invasive assessment of peripheral vascular disease, the use of ABPI raises some issue, since ABPI is known to be unreliable on patients with arterial calcification (especially in elderly patients and patients with other vascular risk factors), resting ABPI is insensitive to mild peripheral artery stenosis, there is no standardized protocol and skilled operators are required for consistent and accurate results. Did the authors consider this point in the analysis and comment of their results? Did they perform a lower limbs Doppler ultrasound evaluation?

3. In the Discussion section, the authors should comment more the results. For instance, the role of impaired perfusion of specific cerebral areas in the late life depression, as well as the effect of laterality (e.g., the correlation between
ZSDS-scores and CBF with depression is statistically significant on the left basal nuclei only. An asymmetric reduced perfusion at the level of the basal ganglia is commonly observed in parkinsonian syndromes. Is there evidence of extrapyramidal features in the patients? The relevant findings from general and neurological examination should be reported. The term “subcortical” used in the text and in the Table 2 is quite generic. Did the authors find an involvement of the prefrontal subcortical areas? This aspect would be appropriate given the relevance of the depression-executive dysfunction of the late life according to the “disconnection syndrome”. Is there a correlation between the observed results and the psychopathological profile of the examined sample, such as executive dysfunction or other affected prefrontal cognitive functions? The MMSE used in the study is a screening test for global cognitive assessment and its sensitivity for executive functions is very low. Finally, a brief comment on the persistent smoking habit and depressive symptoms in the elderly could be added.

Minor revisions:

1. Why and how did the authors choose the age groups of 58, 68 and 82?
2. In the Introduction (line 2), cognitive decline is not a “somatic symptom”.
3. Lastly, language of this manuscript could be improved at several points throughout the body of this manuscript (e.g. in the Title, “disturbed”).

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.