Reviewer's report

Title: Alzheimer's disease: structural and cognitive basis of odor identification deficits

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Reviewer: Martijn Muller

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Major Compulsory Revisions

Impaired olfaction has been well-documented in both prodromal and disease stages of Alzheimer disease (AD) and Parkinson disease (PD); especially the impaired ability to identify various odors. Frequently used methods to test for odor identification impairment include the University of Pennsylvania Smell Identification Test (UPSIT) and the 'Sniffin Sticks' Identification Test (SSIT). The authors note that some AD and MCI patients have relatively intact odor identification abilities. This observation forms the premise of this paper. Cognitive and brain volumetric measures are compared between patients with intact vs. impaired odor identification function. My main concern revolves on the criteria of "intact" and "impaired". For example, for the brief version of the UPSIT (B-SIT) the authors base the cutoff on criteria used by Westervelt et al. (2007), who applied a 'median split' on the possible score range of the test (0-12); i.e. 7 or better ("intact") vs. 6 or less ("impaired"). In my opinion, this is an incorrect and arbitrary approach and the cutoff should really be based on the median scores of the normal control population. Figure 1 of this paper provides some insight in the performance of patients on the two odor identification tests. The median scores of the normal controls for the BSIT and SSIT appear to be at 10 and 13, respectively. Based on these cutoff criteria there are only 2 "intact" odor identification patients. I believe that my estimate is more in line with previous literature (for example Gray et al (2001) and Westervelt et al (2008) which both were cited by the authors) than the estimate based on the current cutoff. Actually, Gray et al. show complete separation between AD patients and normal control subjects based on this approach (figure 1 of their paper).

It can be a lengthy and perhaps impossible discussion to decide on criteria for 'normal' odor identification performance in an older population. However, the authors should provide a better justification for the cutoff criteria that they used and especially make clear why they do not base this on their own normal control data. On this note, it should also be noted that there are 2 'normal' controls with extremely low odor identification scores (figure 1). If peripheral factors can be excluded as an explanation for these low scores, the authors should consider that these two subjects may have (prodromal) synucleinopathy. With a small group this may skew the results.

In conclusion, if the approach laid out in this paper would not be changed, the results and conclusions presented in this paper appear to be valid although
underpowered overall. However, as explained, I see problems with the criteria used for defining impaired and intact odor identification, especially since it is not based on cutoff of their own normal control data. If the authors would follow my recommendations, a larger group would be needed to find more "intact" MCI/AD subjects to achieve appropriate statistical power.

Level of interest: An article whose findings are important to those with closely related research interests

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