# Review of: "Somatostatin and the pathophysiology of Alzheimer's disease"

Greg Sutherland[1]

1 University of Sydney

Potential competing interests: No potential competing interests to declare.

The Author has produced a various interesting review of the literature supporting the loss of somatostatin expressing interneurons (SST-IN) as an early event in the neuropathology of Alzheimer's disease. Refreshingly they have used their disciplinary knowledge to relate the basic biology e.g., neuropathological findings to psychological (functional) phenotypes. As discussed in a pre-print and referenced here (Gabitto et. Al 2023) the latest single nuclei RNA-sequencing studies, in combination with multiplex immunohistochemistry, are providing strong evidence in support of the treatise here.

In terms of issues:

1. There are quite a few typographical errors (e.g., Page 5, line 2) or meaning is slightly ambiguous given the choice of words employed (e.g. Page 6, paragraph 2, line 7).
2. This is a single Author review, but it refers continually to 'we' and 'our'
3. The current manuscript could be shortened – several messages are repeated.
4. A major part of the treatise is that there is SST-IN hypofunction followed by hyperactivity:
    a. It is not always clear if the Author is referring to SST-IN per se or brain hyperactivity (after SST-IN hypofunction)
    b. The reason behind the initial hypofunction is not well-explained (ie) why are SST-IN more susceptible to Abeta?
    c. It is implied that hyperactivity of SST-IN is the major issue, but it is not clear whether the Author thinks that hypoactivity could be more of an issue pre-symptomatically – augmentation of SST-IN inhibition is thus required therapeutically as opposed to attenuation.
5. The Author doesn't discuss evidence against an early pathogenic role for SST-Ins. Notwithstanding the manuscript length issue, the Author could reinforce his hypothesis by hypothetically testing the evidence for PV-Ins (or VIP-Ins) as an alternative hypothesis and presumably noting that the data doesn't fit psychological and fMRI data as well.
6. The Author cites his own 2022 paper (Almeida and Radanovic, 2022) on several occasions e.g., bottom of Page 2 – "*indiscrimination and information loss in spatial, episodic and semantic memory*". This Reviewer assumed given the adjacent references that this was a primary data paper. However, this was a review, and the content was extremely like the current manuscript. Indeed, Figure 2, which itself is reproduced from Anderson et al (2020) is the same. In the 2022 paper, the Authors refer to a 2021 paper again alongside primary data papers, making it appear that this paper is again reporting original findings.
    a. In the first instant, the Author should make it clear that previous papers are also a (theoretical) review.

b. It is not clear to this Reviewer that the current manuscript offers anything new in terms of themes here compared to the 2022 paper.
c. The Reviewer has not done a thorough check of the two papers, but the use of the same figure (particularly when it is reproduced) in two papers seems lazy, at best, or ‘double dipping', at worse.

Overall, I think the Author should consider a different tack for this manuscript where they build on the 2022 paper explicitly but then take a new angle like how the snRNA-seq data is supporting this idea or how early loss of SST-Ins fits the functional data better than loss of PV-Ins (as mentioned above). Otherwise, I don’t think the paper is novel enough to justify publication.