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

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Potential competing interests: No potential competing interests to declare.

This is a very complete review that tackles AD etiology from a most interesting point of view, one that has been somehow overlooked during the last decades. The proposed model is well explained, the manuscript is very complete, easy to read and to follow.

I only have a couple of suggestions:

1. "Unsurprisingly, multiple hypotheses have been pursued in an attempt to elucidate AD's aetiology, including dysfunctions in the cholinergic system (Davies and Maloney, 1976), the Aβ cascade (Hardy and Allsop, 1991), tau propagation (Frost et al., 2009), calcium dyshomeostasis (Mattson et al., 1992), mitochondrial cascade and oxidative stress (Swerdlow and Khan, 2004), metal ion toxicity (Bush et al., 1994), among others (for reviews, Du et al., 2018; Bekdash, 2021; Coyle et al., 1983; Ashford, 2015; Liu et al., 2019)." Perhaps more recent literature could be cited regarding some of these theories.
2. What would make these STT-INs neurons more vulnerable to Aβ or to neurodegeneration in general? Is there any literature on their redox/metabolic capacity? The author mentions oxidative distress and lipid peroxidation. Can these features and their action on STT-INs vulnerability be explained with more detail?
3. "Accordingly, several studies attest the preferential colocalisation of SST-INs with Aβ even though the earliest signs of tauopathy showing at SST-INs two main presynaptic connections (viz., pyramidal neurons in layers III and V), but later spreading trans-synaptically and irrespective of SST-INs (Braak and Tredici, 2019)." This sentence is confusing. Furthermore, Figure 3 highlights the importance of tau in AD, however its relevance is not emphasized in this proposed model. Can the author explain more in detail how tauopathy fits in this model, if so?
4. Can the author provide more evidence (on previous works) of AD not being particularly characterized by loss of engrams?
5. A figure summarizing the present model would be most interesting. Figure 1 points to the relation between aging, STT and Aβ, but it would be interesting to see a figure depicting the STT-INs vulnerability, its proposed origins, the relation with Aβ, tau and oxidative distress, how this generates changes in inhibition (including cell populations, neurotransmitters and receptors involved) and thus affects engram stability, spatial memory, etc, leading to the AD phenotype.