Research Article

Somatostatin and the pathophysiology of Alzheimer's disease

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Since early research on Alzheimer's disease (AD), it has been known that among the central features of its progression are altered levels of the neuropeptide somatostatin, and the colocalisation of somatostatin-positive interneurons (SST-INs) with amyloid-β plaques, leading to cell death. In this theoretical review, I propose a model for the pathogenesis of AD that coheres with the qualitative profile of its neuropsychological deficits and neurobiological progression. Namely, hypofunctional and hyperactive SST-INs struggle to control hyperactivity in mid-temporal regions in early stages, leading excessive presynaptic GABA-B inhibition, GABA-B1a-APP complex downregulation and internalisation, thereby boosting Aβ production. Concomitantly, excessive SST-14 release accumulates near SST-INs in the form of amyloids, known to bind to Aβ to form toxic mixed oligomers. This leads to differential SST-IN death through excitotoxicity, further disinhibition, SST deficits, and increased Aβ release, fibrillation and plaque formation. Aβ plaques, hyperactive networks and SST-IN distributions thereby tightly overlap in the brain. Finally, SST-IN disinhibition reportedly induces neuropsychological deficits that qualitatively agree with those found in AD cohorts, with pattern separation and encoding deficits, mnemonic indiscrimination, interference and reconsolidation.

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1. Introduction

Alzheimer's disease (AD) accounts for 60–80% of dementia cases worldwide (Prince et al., 2015), with a prevalence of 2.4–8.4% among individuals over 65 (Kasai et al., 2010; Querzfurth, 2010), ramping up to 1:3 past the age of 85 (Querzfurth, 2010; Hirtz et al., 2007). AD is also the sixth leading cause of death in adults older than 65 years in the United States (Skaria, 2022). Inasmuch as it is so prevalent,

disabling and poorly-responsive to treatment, it has understandably become the most costly disorder in current neuropsychiatry, with financial expenditure on the disease soaring around $321 billion a year and costs projected to exceed $1 trillion by 2050 (Skaria, 2022). Hence, it seems safe to proclaim that AD is the most pressing neuropsychiatric challenge of modern times.

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). Although some have spurred significant progress (e.g., the 1976 cholinergic hypothesis by Peter Davies and A. J. F. Maloney supported the first FDA approval of an acetylcholinesterase inhibitor for AD, tacrine, in 1993; Coyle et al., 1983; Waldholz, 1993; Ashford, 2015; Davies and Maloney, 1976), upon closer scrutiny each has unveiled several caveats (Liu et al., 2019). Even the origins and means by which the most recognisable signs of AD's progression - viz. extracellular Aβ plaques, intracellular tau neurofibrillary tangles and synaptic losses in mid-temporal regions (e.g., De Wilde et al., 2016) - ultimately cause the semiological syndrome itself are still a mystery. Moreover, a plethora of alternative biological disturbances, ranging widely from cholesterol transport to catecholaminergic deficits, can cast a smokescreen of confounders over the (presumably) more central mechanisms of AD's pathogenesis. Consequently, the precise neurophysiology behind disrupted memory and cognition in the disease remains a terra incognita.

Altogether, such lack of knowledge stands in the way of the development of effective treatments and prophylaxis. Our aim here will be to attempt to tackle these deficits by putting forth a novel theoretical model on the aetiology, progression, and neuropsychological profile of AD. In particular, mounting evidence points to a critical role of somatostatin-positive interneurons (SST-IN) in the disease, as well as the neuropeptide somatostatin (SST) that they release. Whilst the former prominently regulates, in associative cortices affected by AD, memory, learning, cognition and even sleep oscillations (e.g., Anderson et al., 2020; Almeida, 2022; Artinian and Lacaille, 2018; Riedemann, 2019; Gerashchenko et al., 2018, Gerashchenko et al., 2008, Zielinski et al., 2019; Cummings and Clem, 2020; Schmid et al., 2016; Scheggia et al., 2020; Lovett-Barron et al., 2014; Abbas et al., 2018; Dobrzanski et al., 2021), the latter has been shown to promote Aβ cleavage and clearance in the brain (Iwata et al., 2005; Hama and Saido, 2005; Solarski et al., 2017). My proposal is that AD's aetiology hinges mainly

on an early hyperactivity of SST-INs, associated with SST-IN hypofunction and increased network activity, which contribute to the formation of several alterations in the cortex and hippocampus. These include, for example, the formation of Aβ plaques (Solarski et al., 2017), dystrophic neurites (Tomidokoro et al., 2000; Tago et al., 1987; Su et al., 1993), overactive glial cells (Henriques et al., 2022), early cortical and hippocampal hyperactivity (Jimenez-Balado and Eich, 2021; Almeida and Radanovic, 2022), altered functional connectivity and oscillatory frequencies (Almeida and Radanovic, 2022; Nimmrich et al., 2015), indiscrimination and information loss in spatial, episodic and semantic memory (e.g., Almeida and Radanovic, 2022; Morales et al., 2021; Zhao et al., 2014; Caccuci et al., 2008; Ness and Schultz, 2021; Cheng and Ji, 2013; Cayzac et al., 2015), and the topographical progression of Aβ plaques and atrophy (e.g., Braak and Braak, 1991, 1995; Insel et al., 2020).

The manuscript is structured as follows. In section 2, we will cover the SST models of AD. In section 3, I will propose a novel model based on SST-IN hyperactivity and hypofunction. Finally, in section 4 I will conclude the manuscript with a discussion on the functional and cognitive implications of this model, and how they concur with AD's neuropsychological profile.

2. Somatostatin models of Alzheimer's disease

Somatostatin is a neuropeptide that, like others, is stored in dense-core vesicles that are only released upon sustained high-frequency firing (Liguz-Lecznar et al., 2016; Iversen et al., 1978). In particular, it is generally co-released with GABA from SST-INs in a Ca^{2}+-dependent manner during periods of intense network activity, so as to fine-tune inhibitory signals pre- and postsynaptically (Iversen et al., 1978; Solarski et al., 2018; Liguz-Lecznar et al., 2016). Importantly, due to the lack of selective reuptake mechanisms and the distance between SST receptors and release sites, SST's effects outlast GABA's, and the neuropeptide tends to accumulate and form amyloids extracellularly around SST-INs (Liguz-Lecznar et al., 2016; Solarski et al., 2018).

Since early research on AD, SST alterations have been considered a central feature of the disease (e.g., Davies et al., 1980, 1981; Rossor et al., 1980; Grouselle et al., 1998; Beal et al., 1986; Chan-Palay, 1987; Tamminga et al., 1987; Soininen et al., 1984; Arai et al., 1984), with SST neurons being consistently colocalised with Aβ plaques. Possibly the first model of AD to be mainly based on SST dysfunction was proposed by Hama and Saido (2005). The authors underscored how Aβ catabolism is primarily driven by a neutral endopeptidase, neprilysin, which is tightly regulated by SST release (Iwata et al., 2005; Saito et al., 2005). Therefore, they hypothesise that the natural decline of SST levels observed in

senescence (e.g., Florio et al., 1991; Hayashi et al., 1997; Saito et al., 2005) leads to the accumulation of Aβ in the brain and eventual development of AD (figure 1).

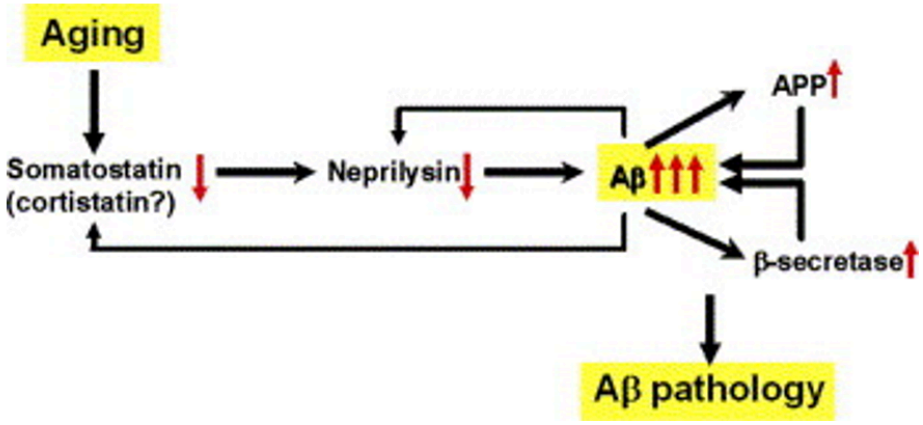

Figure 1. Aging, SST, neprilysin and Aβ accumulation. The aging-dependent reduction of SST causes a decrease of neprilysin activity, which then causes the steady-state Aβ levels in brain to increase. Chronic elevation of the Aβ levels may result in further downregulation of SST levels, oxidative inactivation of neprilysin, increased expression of APP and β-secretase. These events form a vicious circle leading to a catastrophic accumulation of Aβ in the brain. Reproduced from Hama and Saido (2005).

More recently, this model has been updated by Solarski et al. (2018) under the light of new evidence. Namely, their group noticed that SST can be protective also by preventing Aβ fibrillation, and that the proximity of SST-INs to senile plaques appeared incongruent with these interneurons' ability to promote neprilysin-dependent Aβ cleavage. Hence, the authors point out that whilst monomeric SST may be protective, in an aggregated form it could actually become pernicious. This is because the isoform SST-14 aggregates into amyloids near SST-INs, which can lead to the formation of toxic mixed oligomers with Aβ (Solarski et al., 2018; Anoop et al., 2013; Wang et al., 2017). That is, the same group found that the small cyclic SST-14 is the most selectively-enriched binder to oligomeric Aβ1-42, with preparations of Aβ1-42 alone giving rise to fibrillar structures, but when co-incubated with SST-14 it exclusively formed oligomers (Solarski et al., 2018; Wang et al., 2017). The formation of Aβ oligomers is highly toxic for SST-INs (Solarski et al., 2018), whose death results in SST deficits, fibrillar Aβ aggregation, and the formation of the senile plaques that set off AD progression. In what follows we will expand on this model.

3. Disinhibition in Alzheimer's disease

AD is associated with significant excitatory/inhibitory imbalances (e.g., Varela et al., 2019; Maestú et al., 2021; Bi et al., 2020; Almeida and Radanovic, 2022). Indeed, patients are 17 times more prone to epileptic seizures than age-matched healthy controls, for example (Vossel et al., 2017; DiFrancesco et al., 2017), with clinical observations further pointing to an even higher incidence of epileptic seizures in early-onset familial AD (Palop and Mucke, 2009). Such imbalances might arise from a conjunction of factors, including $Ca^{2}+$ dyshomeostasis (Mattson et al., 1992), aberrant synaptic scaling (Small, 2008), dendritic degeneration (Siskova et al., 2014), mitochondrial dysfunction (Swerdlow and Khan, 2004), ion channel dysregulation (Kagan et al., 2002), inter alia. However, the flagship pathogenetic mechanism appears to be more straightforward: disinhibition.

Early studies have concluded that GABAergic interneurons overall are resistant to AD pathology (e.g., Li et al., 2016; Rossor et al., 1982), but extensive reports have been accrued since then which point to an early and progressive loss of specific interneuron taxons (Jimenez-Balado and Eich, 2021; Ramos et al., 2006; Levenga et al., 2013). The most abundant evidence, in particular, has converged towards a highly selective loss of somatostatin-positive interneurons (SST-INs) as well as SST in both the cortex and hippocampus, which strikes earlier than in any other inhibitory or excitatory cell type and correlates tightly with memory deficits (e.g., Gabitto et al., 2023; Leung et al., 2012; Andrews-Zwilling et al., 2010, 2012; Ramos et al., 2006; Li et al., 2009; Almeida and Radanovic, 2022; Davies et al., 1980, 1981; Rossor et al., 1980; Solarski et al., 2018; Grouselle et al., 1998; Beal et al., 1986; Chan-Palay, 1987; Jimenez-Balado and Eich, 2021; Ramos et al., 2006; Levenga et al., 2013; Tamminga et al., 1987; Schmid et al., 2016; Soininen et al., 1984; Arai et al., 1984). Levels of the neuropeptide SST, which is released by these cells, decline disproportionately with disease progression, and correlate roughly with a 50% loss of SST-INs in multiple regions (Saiz-Sanchez et al., 2010, 2015), though it is noteworthy that mouse models report 50-60% loss of hilar SST-INs preceding histopathology in any other neuron type (Ramos et al., 2006), with further reports of a ca. 70% SST-IN loss in the human hippocampus (Hardy et al., 1987). Importantly, SST itself displays strong antiepileptic properties (e.g., Tallent, 2007).

Even as compared to pyramidal neurons, robust evidence indicates that SST-INs are highly vulnerable to Aβ as well, and again, affected earlier than other cell types (e.g., Gabitto et al., 2023; Ramos et al., 2006; as compared to PVs and CRs, Saiz-Sanchez et al., 2015; Ali et al., 2020; Sanchez-Mejias et al.,

2019; Saiz-Sanchez et al., 2015, 2020; Ramos et al., 2006; Moreno-Gonzalez et al., 2009; Albuquerque et al., 2015; Mahar et al., 2016; Giovannetti and Fuhrmann, 2019; Palop and Mucke, 2009). Specifically, Aβ greatly increases SST-INs' vulnerability to hyperactivity and Ca^{2+} overload, which leads to cell death by excitotoxicity (e.g., Algamal et al., 2022; Ramos et al., 2006; Mattson et al., 1992; Kimura and Schubert, 1993). In anaesthetised APP/PS1 mice, for instance, it was found that SST-INs (but not PV-INs or excitatory cells) are selectively and consistently hyperactive and found near Aβ plaques, and the level of this hyperactivity correlates with their proximity to those plaques (Algamal et al., 2022). This is due not only to oxidative stress and lipid peroxidation (with disruption of Na2+ and Ca2+ pumps, Mattson et al., 1992; Mattson, 2020), but likely the disinhibition of neighbouring pyramidal cells by Aβ itself, and the death of other SST-INs (e.g., Busche et al., 2008). Bai et al. (2017) also found that Aβ specifically disinhibits Ca^{2+} transient duration in the apical dendrites of supragranular neurons, whose very effective control is mainly exerted by SST-INs (e.g., Almeida, 2022). Thus, in tandem these data suggest that an early hyperactivity, related to SST-IN dysfunction, heralds AD.

Accordingly, early baseline hyperactivity in the medial temporal lobe is indeed a reliable finding among amnestic Mild Cognitive Impairment (aMCI) patients (and early AD), which has also been reproduced by a number of mouse models (e.g., Nuriel et al., 2017; in Anastacio et al., 2022; O'brien et al., 2010; Jimenez-Balado and Eich, 2021; Busche et al., 2008; Almeida and Radanovic, 2022; Najm et al., 2019; Levenga et al., 2013; Ramos et al., 2006; Celone et al., 2006; Petrache et al., 2019). This hyperactivity has been correlated with higher risk of clinical decline at a 2-year follow-up study (Jimenez-Balado and Eich, 2021; for subclinical epileptiform activity in AD, Vossel et al., 2016), for example, as well as hippocampal and cortical thinning in both aMCI and healthy ageing (e.g., Putcha et al., 2011; Stargardt et al., 2015), and epileptic activity has been associated with earlier cognitive decline (Vossel et al., 2013). Early losses of inhibitory cells have repeatedly been proven the most likely cause for these (e.g., Ramos et al., 2006; Levenga et al., 2013; Celone et al., 2006; Jimenez-Balado and Eich, 2021).

Importantly, the APOE4 gene is also tied to increased activity in temporal, parietal and frontal cortices of aged, cognitively-intact individuals (thereby preceding aMCI), and some evidence suggests this is also true for younger ages (Bookheimer et al., 2000; Burggren et al., 2002; Wishart et al., 2006; Filippini et al., 2009; Nuriel et al., 2017; Koelewijn et al., 2019). Although APOE4 partakes in the transport of lipids and cholesterol - which are important regulators of synaptic and ion channel functions and neuronal excitability (Anastacio et al., 2022; Wang et al., 2005) -, this hyperactivity is

already shown to stem primarily from a loss of SST-IN inhibitory tone (e.g., Filippini et al., 2009; Nuriel et al., 2017; Leung et al., 2012; Li et al., 2009, 2014; Tong et al., 2014; see also Martinez-Losa et al., 2018; Knoferle et al., 2014; Grouselle et al., 1988; Leung et al., 2012; Andrews-Zwilling et al., 2010; Leung et al., 2012). In fact, it has been linked to early SST-IN dysfunction independently of Aβ, possibly mediated by cholinergic deficits – which would concur with acetylcholine's critical role in SST-IN survival, function and morphology (Schmid et al., 2016; Fanselow et al., 2008; Grouselle et al., 1988; Leung et al., 2012; Andrews-Zwilling et al., 2010, 2012; Almeida and Radanovic, 2022). APOE4 genotype also reduces the number of SST-INs in temporal regions (Leung et al., 2012). Unsurprisingly, Petrache et al. (2019) found early hyperexcitability in the lateral entorhinal cortex in an APP model, which was ameliorated by GABA-αR agonism. Conversely, APOE4 knock-in mice restore learning and memory functions after transplantation of embryonic progenitor interneurons in the hippocampus which mostly grow into SST-INs (similarly, transplants of SST-IN and PV-IN interneurons from the medial ganglionic eminence overexpressing Nav1.1 levels, a voltage-gated sodium channel, normalised oscillatory aberrations) (Tong et al., 2014; see also Martinez-Losa et al., 2018; Knoferle et al., 2014).Hence, APOE4-positive subjects suffer from an intrinsic SST-IN hypofunction, itself inductive of learning and memory deficits and early hyperactivity; interestingly, as a side note, APOE4-carrying female rats are significantly more susceptible to AD, with SST-INs decreasing in an age-dependent manner mostly in females, which is accompanied by spatial learning deficits (Leung et al., 2012).

Relevantly as well, APOE4 was associated specifically with decreased miniature inhibitory postsynaptic currents, which measure the effectiveness of spontaneous, sustained background inhibition, which in turn regulates baseline network activity; this was observed in the entorhinal cortex of aged mice with no AD-related histopathology (namely, APP/AB and phosphorylated tau immunolabeling; Nuriel et al., 2017; see also Klein et al., 2014; Hunter et al., 2012). Additionally, the APOE4 gene most notably disinhibits the entorhinal cortex, the putative origin of AD pathology and a region that very selectively and densely expresses SST-INs (Nuriel et al., 2017; Filippini et al., 2009; Hunter et al., 2012; Anderson et al, 2020; Kim et al., 2017). Thus, early rhinal SST-IN hypofunction should affect to control of baseline excitatory activity and activity-dependent AD pathology.. All in all, both prodromal AD and APOE4 genotype are associated with hyperactivity and disinhibition, before AD pathology develops, due to SST-IN dysfunction and sparser SST-IN populations (e.g., Koelewijn et al., 2019; Leung et al., 2012; Li et al., 2009 Grouselle et al., 1988; Andrews-Zwilling et al., 2010, 2012).

Thus, early hypofunction pre-AD can force existing SST-INs into hyperactivity (as observed in multiple studies) to compensate for an original and milder disinhibition, giving rise to a pathological process that rendersthese cells particularly vulnerable to Ca^2 dyshomeostasis upon eventual contact with Aβ oligomers(e.g., Algamal et al., 2022; Koelewijn et al., 2019; Ruiter et al., 2020).

Supporting evidence comes alsofrom APP models. For example, an APP and PS1 double transgenic model of AD (APP23PS45 model) in which hyperactive neurons were found in the vicinity of amyloid plaques (less than 60 mm from their borders), with GABA-αR agonist diazepam normalising their activity but antagonist gabazine increasing it less than in other neurons; this scenario is, of course, indicative of impaired GABα-AR inhibition (Busche et al., 2008). Similarly, Ruiter et al. (2020) report reduced dendritic inhibition - whose leading source are SST-Ins - with paradoxical increased excitatory recruitment of interneurons in CA1 due to amyloidosis in an APP-KI model. Moreover, hyperactivity in APP models precedes the formation of plaques (e.g., Busche and Konnerth, 2015; Ruiter et al., 2020). For example, two-photon calcium imaging demonstrates that even in young APP23PS45 mice without plaques, over 25% of CA1 neurons experience sharp increases in activity levels (Busche et al., 2012), which is only later followed by plaque deposition (similarly, reducing soluble Aβ concentrations with one oral dose of a gammasecretase inhibitor could already normalise hyperactivity in APP transgenic mice, Abramowski et al., 2008). This is because even slightly increased endogenous Aβ already promotes network disinhibition and SST-IN toxicity (e.g., Algmal et al., 2022; Zott et al., 2019; Ruiter et al., 2020).

Finally, the stereotyped topographical progression of Aβ atrophy and tau deposition in AD and aMCI, as well as the development of overactive networks, all very crisply overlap with SST-IN distribution across the brain (Braak and Braak, 1991; Anderson et al., 2020; Kim et al., 2017; Jimenez-Balado and Eich, 2021; Gail Canter et al., 2019; see figures 1 and 2; see figure 2). Thus, AD pathology first develops in regions where SST-INs are densely and selectively expressed, only later encroaching into regions with sparser SST populations connected with them (see figure 2 for an idea of SST distribution in the cortex).

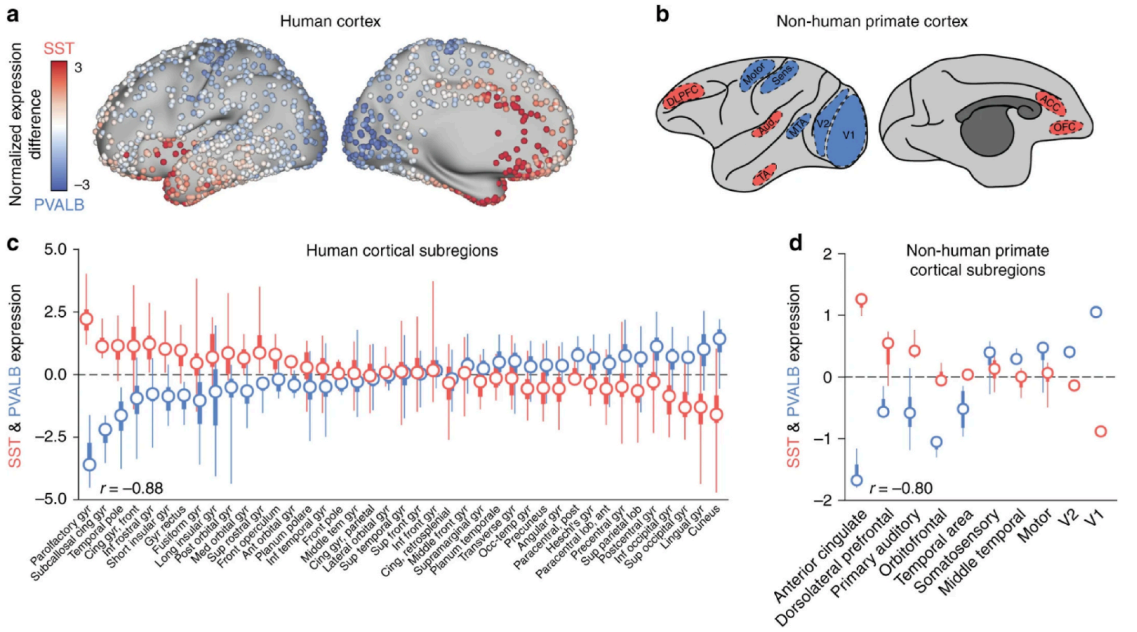

Figure 2. Anderson et al.'s (2020)'s data. SSTs are depicted in red, and parvalbumin-positive cells in blue. (a) Allen Human Brain Atlas (AHBA) tissue samples mapped to the human cortical surface, and (b) an illustration of primate tissue sample locations. Normalised expression difference reflects the sample-wise subtraction of z-transformed PV from SST. Reproduced from Anderson et al. (2020).

In conclusion, early hyperactivity caused by disinhibition from a hypofunctioning SST-IN inhibitory system drives SST-INs into hyperactivtiy in order to maintain homeostasis. This is conducive to the production of Ab in these interneurons, and their early and preferential degeneration upon contact with Ab oligomeres.

3.1. Activity-dependent pathology

Another crucial point to understand about the above pattern of disease progression is the following. Early-affected regions, as SST-INs themselves, are well-known for profuse recurrent spontaneous firing and long temporal receptive windows, i.e., sustaining activity for long periods of time (as opposed to sensory cortices, for example; Almeida, 2022). The medial temporal lobe is known to receive abundant projections from all over the cortex, which enhance recurrent firing; the DMN is famous for being consistently active during rest; and the mid-frontal cortices display wide temporal receptive windows to support working memory (e.g., Hasson et al., 2008; Huntenburg et al., 2018). Accordingly, SST-INs, which are densely-expressed in these regions, function with a

neurophysiological profile that is ideally-suited to control all this recurrent excitation (Almeida, 2022). Unlike PV-INs (the other major interneuron affected in AD), which are better-suited for controlling brief windows of spiking activity (typical of sensory regions, Almeida, 2022), SST-INs characteristically sustain recurrent firing for long periods of time to tonically inhibit spontaneous background activity (e.g., Jackson et al., 2016; Urban-Ciecko et al., 2015; Cichon et al., 2022; Fanselow et al., 2008). These cells portray non-depressing firing patterns and persistently high firing rates; further, they respond non-linearly to the accumulation of inputs from most surrounding pyramidal cells, providing sustained feedback inhibition specifically in periods of elevated activity (Almeida, 2022; Fanselow et al., 2008). The short-term facilitatory excitatory synapses onto SST-INs amplify postsynaptic potentials nonlinearly with temporal summation of inputs, insofar as greatly enhancing SST-IN recruitment in a cumulative manner (Almeida, 2022).

All of this means that for every small increase in network activity, there is a significantly larger, compensatory one in sustained SST-IN firing (which sets the stage for eventual Ca^{2}+ overload). This is particularly problematic in light of the fact that inhibitory neurons are already associated with marked metabolic demands, with SST-INs also already functioning at high spontaneous firing rates and developing distinctive metabolic vulnerabilities with the ageing process (Ibrahim and Llano, 2019). Indeed, a well-established fact is that SST-INs are preferentially and extraordinarily vulnerable to excitotoxic degeneration from epileptic seizures, for instance (Hofmann et al., 2016). Thus, this again indicates that chronic SST-IN hyperactivity and excitotoxicity are a risk factor for AD. Thus, even preceding Aβ accumulation and neuroinflammation, Shi et al. (2020) demonstrated that hippocampal SST-INs grow aberrantly hyperactive. Several consolidated risk factors for the AD are tied to hyperactive and/or hypofunctional SST-INs as well, including migraines (Marchionni et al., 2022), sleep loss (Delorme et al., 2021), chronic and acute alcohol abuse (Dao et al., 2021; Ochi et al., 2022; Lunden et al., 2019), sensory deprivation and loss (Richter et al., 2022; Herrmann and Butler, 2021; Ibrahim and Llano, 2019), ageing (Stanley et al., 2012; Brown, 1984; Ibrahim and Llano, 2019), Down Syndrome (Zorrilla de San Martin et al., 2020; Schulz et al., 2019), stress, depression and anxiety (Fee et al., 2017; Banasr et al., 2017), autism (Lunden et al., 2019), and others. Similarly, multiple neurodegenerative diseases that share a genetic basis with AD also suffer from some measure of SST-IN hyperactivity or dysfunction (Zhang et al., 2016).

Adding to this problem, Aβ/tau pathology are activity-dependent (Jimenez-Balado and Eich, 2021; Nuriel et al., 2017; Gail Canter et al., 2019; Yuan and Grutzendler, 2016; Cirrito et al., 2005; Yamamoto

et al., 2015; Pooler et al., 2013; Wu et al., 2016; Zott et al., 2019; Mattson et al., 1990; Bero et al., 2011; Elliott et al., 1993; Liu et al., 2010; Qing et al., 2008; Sanchez et al., 2012; Mark et al., 2015; De Haan et al., 2012; Kastanenka et al., 2019). In the TG2576 model, for example, in vivo microdialysis shows how Aβ concentrations in interstitial fluid covary with activity levels (as per the pharmacological manipulations, Bero et al., 2011). Overactivation of glutamate receptors drives tangle-like changes in Tau in cultured hippocampal neurons through a mechanism associated with $Ca^{2}+$ overload, for example, as well as synaptic losses, oxidative stress, and Aβ release (Mattson, 1990; Zott et al., 2019). Seizures can spur Tau pathology in the hippocampus (Elliott et al., 1993), and numerous anticonvulsants are shown to prevent Aβ-induced $Ca^{2}+$ dysregulation and tauopathy both in vitro and in vivo - drugs like levetiracetam, diazoxide and valproic acid can ameliorate as well as delay cognitive decline in mouse models as well as in humans (Liu et al., 2010; Qing et al., 2008; Sanchez et al., 2012; Mark et al., 1995). What all of this means is that regions inhabited by SST-INs, i.e. characterised by long-lasting neural activity (e.g., DMN and various cortical hubs and frontotemporal associative regions), are prone to develop AD pathology biassed towards SST-IN degeneration (De Haan et al., 2012; Buckner et al., 2009; Braak and Braak, 1991; Pini et al., 2016). Further, as Aβ (and tau) deposition begins, SST-IN degeneration and network disinhibition accelerate (e.g., Huang and Mucke, 2012; Verret et al., 2012). Eventually, this could lead, for example, to failures of DMN deactivation upon tak engagement as observed in AD patients and asymptomatic subjects with significant amyloid burden (e.g., Sperling et al., 2009).

Hence, with hyperactivity or disinhibition of mid-temporal networks prior to the onset of aMCI, AD pathology aggravates the heavy burdens laid on remaining SST-INs.. This pattern could be particularly accentuated in females, since recent findings with optogenetics indicate that there are sex-dependent variations in the distribution of SST-INs' targets; whilst being more selectively aimed at pyramidal cells in males, they are more evenly distributed between inhibitory and excitatory neurons in females, such that higher firing rates would be needed to control the same level of excitatory activity (Dao et al., 2020).

3.2. GABA-B receptor overstimulation

Crucially, the prodromal SST-IN hyperactivity itself spurs Aβ production not only from their own activity but even their presynaptic connections. That is, increased SST-IN spontaneous firing causes excessive stimulation of GABA-B1a receptors (e.g., Shen et al., 2022; Kanigowski et al., 2023; Urban-

Ciecko et al., 2015), with heterodimeric GB1a/2 and GB1b/2 receptors accumulating at excitatory terminals and in the somatodendritic compartment, respectively. Excessive SST-IN spontaneous activity targets and thus downregulates presynaptic GABA-B1a receptors, which is indeed observed in postmortem AD studies and animal models (Martín-Belmonte et al., 2020a, 2020b; Osse et al., 2023). On the other hand, APP is known to be transported to axons by GABA-B1a ligands (Rice et al., 2019; Dinamarca et al., 2019; Bi et al., 2020). GABA-B1a, specifically, acts as a receptor for secreted APP (Rice et al., 2019). Hence, this receptor is known to form GABA-B1a/APP complexes in the axonal surface of presynaptic SST-IN connections. In non-pathological conditions, these complexes restrict APP internalisation, and thus prevent BACE1-dependent recycling/endosomal processing to Aβ (which is mainly released by axons due to greater presence of BACE1, Buggia-Prevot et al., 2013; Dinamarca et al., 2019). Their downregulation/internalisation, however, translates into increased Aβ production; for example, mice lacking GABA-B1a consistently exhibit enhanced amyloidogenic processing (see Dinamarca et al., 2019). Interestingly as well, downregulation of GABA-B1a in AD should impair top-down spontaneous suppression of UP states and interareal synchronisation of DOWN states, which are mediated by this subunit (Craig et al., 2013); such disruption of slow-wave activity in NREM states is known to aggravate amyloidosis and disrupt memory consolidation as well (for a review, Lee et al., 2020).

Altogether, then, early SST-IN hyperactivity leads to GABA-B1a downregulation and internalisation, with increased availability of APP for Aβ release around these very same cells by the presynaptic terminals they inhibit. Given that SST-IN hyperactivity further causes accumulation of SST-14 amyloids nearby when hyperactive (e.g., Wang et al., 2017; Anoop et al., 2013; Solarski et al., 2018), the increased availability of extracellular Aβ and SST-14 is conducive to the formation of mixed amyloid oligomers, which finally result in even further biassed SST-IN death through Ca^{2+} overload (Solarski et al., 2017; Hector et al., 2021; Kimura and Schubert, 1993). For each dead SST-IN, there is a compensatory increase in surrounding SST-IN activity, further GABA-B1a downregulation and internalisation, and thus further Aβ release around these interneurons. This vicious cycle eventually leads to AD.

Finally, GABA-B downregulation can also be caused by NMDAR-dependent endocytosis and lysosomal degradation upon prolonged activation (e.g., Guetg et al., 2010; Terunuma et al., 2010; Maier et al., 2010). However, the primary pathogenetic mechanism is likely SST-IN hyperactivity due to the macroscopic overlap between Aβ deposition, SST-IN density and hyperactive networks in both

patients and animal models (e.g., Jimenez-Balado and Eich, 2021; Gail Canter et al., 2019; Edelman et al., 2017). Specifically, SST-INs exert powerful and highly effective inhibition of these receptors, such that SST-IN dysfunction should promote glutamatergic overstimulation of NMDARs and NMDAR-dependent GABA-B1a endocytosis and lysosomal degradation (Schulz et al., 2018; Homayoun and Moghaddam, 2007; Ali et al., 2020; Maier et al., 2010).

Blockade of NMDARs prevents downregulation of GABA-B1aRs (e.g., Maier et al., 2010), which could partly relate to the effectiveness of the NMDAR antagonist memantine in AD. Additionally, signalling pathways that increase cAMP levels (e.g., β-adrenergic receptors) can upregulate GABA-B expression as well as promote widespread network silencing, thereby helping prevent Aβ formation (though a multitude of biological processes are also involved, Lương and Nguyễn, 2013; Devilbiss and Waterhouse, 2000; Gu, 2002).

3.3. Slow waves and oscillatory slowing

Sleep is a critical factor to account for in the context of Aβ pathology. Slow-wave sleep (SWS) is known to support a clearance mechanism hinged on a 60% increase of cortical interstitial space during sleep, through modulation of the paravascular glymphatic system (Iliff et al., 2012; Xie et al., 2013); indeed, Aβ levels actually drop during sleep and are higher in wakefulness (Kang et al., 2009; Lucey et al., 2017; Lee et al., 2020). SWS has also proven time and again crucial for the consolidation of declarative memory, with its disruption causing memory deficits (Steriade and Timofeev, 2003; Marshall et al., 2006; Walker, 2009; Lu and Göder, 2012; Lee et al., 2020). Crucially, it is well-established that SST-INs modulation of GABA-BRs is essential for SWS; particularly, these cells are regulators and terminators of UP states, and capable of initiating and synchronising/sustaining DOWN states (Funk et al., 2017; Niethard et al., 2018; Lee et al., 2020; Gerashchenko et al., 2008, 2018; Craig et al., 2013; citar); conversely, the initiation of UP states relies on astrocytic stimulation of GABA-B receptors (Poskanzer and Yuste, 2011, 2016; Szabó et al., 2017; Lee et al., 2020).

In light of the model presented so far, it should be unsurprising that Aβ deposition directly correlates with sleep alterations in preclinical AD patients (Ju et al., 2013; Spira et al., 2013; Lee et al., 2020; Mander et al., 2015; Winer et al., 2020; Westerberg et al., 2012), which is aggravated by age-dependent SWS deterioration. For example, Mander et al. (2015) found that reduced SWS among older adults is associated with increased Aβ accumulation in the mPFC, accompanied by memory deficits; the relationship between Aβ load and memory deficits was mediated by SWS (Mander et al., 2015).

Conversely, Winer et al. (2020) reported that SWS disruption forecasts Aβ accumulation, AD development, and speed of disease progression. Another important study found that APP mice develop disrupted SWS, accompanied precisely by disinhibition and downregulation of GABA-BRs and GABA-ARs (and lower GABA levels), which accelerates Aβ accumulation and calcium dyshomeostasis; optogenetically-induced synchronisation of SWS, on the other hand, sufficed to restore calcium homeostasis and halt Aβ accumulation (Kastanenka et al., 2017). Moreover, it is noteworthy that there is a surge of orexin in the cortex that accompanies sleep loss, which itself is shown to depolarise SST-INs through blockade of K+ channels and enhance excess sustained activity both by inhibiting afterhyperpolarisation and increasing $Ca^{2}+$ influx in conditions of weak depolarisation through low-voltage activated T-type $Ca^{2}+$ channels (Luo et al., 2023).

Thus, early SST-IN hyperactivity may very well promote glymphatic dysfunction prior to AD, and increased amyloidosis as well as accumulation of various other toxins due to slow-wave disruption. The TDP-43 protein, for example, abounds in postmortem brains of AD subjects and is actually shown itself to drive even further SST-IN hyperactivity (this was observed in amyotrophic lateral sclerosis and frontotemporal dementia, Zhang et al., 2016), which caused excitotoxicity of layer V pyramidal neurons from SST-INs' over-inhibition of PV-INs (i.e., disinhibition of pyramidal cells' somatic compartment).

Finally, SST-INs are known to regulate slow oscillations, especially delta and theta. Both frequency bands are associated with mnemonic processing under SST-IN mediation (e.g., Almeida and Radanovic, 2022). For example, altering delta oscillations by knocking out nitric oxide synthase expression from SST-INs induces recognition memory impairments (Zielinski et al., 2019). Accordingly, delta oscillatory slowing during sleep is linearly correlated with cognitive impairment (Rempe et al., 2023), and regional oscillatory slowing reliably predicts Aβ burden in AD cortex (Wiesman et al., 2022).

3.4. Astrocytes and adenosine

The present model can also accommodate certain changes in astrocytes - namely their overactivity in AD, especially near Aβ (even if not in the form of plaques, Wisniewski and Wegiel, 1991). Indeed, there is a close correlation between astrogliosis and Ab/tau pathology (e.g., Coomaraswamy et al., 2010; Bodea et al., 2016).

SST-INs are known to recruit astrocytes through both SST release and GABA-B stimulation, with GABA-B-mediated cytosolic Ca^{2+} in astrocytes mostly being detected during periods of intense activity (Henriques et al., 2022; Mariotti et al., 2018). Matos et al. (2018) showed that CA1 hippocampal astrocytes sense GABA released by moderate SST-IN activity via GAT-3-mediated Ca2+ elevations, releasing ATP, which is immediately converted into adenosine. Through activation of A1 receptors (A1Rs; likely postsynaptic), this potentiates SST-IN's typical GABA-A5R inhibition of bursting activity. Presynaptic A1Rs inhibit neurotransmitter release through G-protein-coupled inhibition of voltage-dependent Ca2+ channels, while postsynaptic A1Rs induce neuronal hyperpolarisation through activation of inwardly rectifying K+ channels, which regulates burst firing (Matos et al., 2018). Thus, SST-IN hyperactivity can lead to astrocytic excitotoxicity, overstimulation and downregulation of A1Rs, and inhibition of neurotransmitter release, along with diffuse and long-lasting disinhibition of pyramidal neurons by SST.

Interestingly, chronic blockade of A1Rs leads to its upregulation and thus possibly enhanced SST-IN inhibition (Shi et al., 1993), whereas antagonism of A2ARs could help mitigate plaque formation by attenuating excitatory transmission from presynaptic terminals onto SST-INs and thus preventing SST-IN hyperactivity. This could help explain the protective effects of caffeine, for example (e.g., Arendash and Cao, 2010). Conversely, it has been shown that caffeine consumption during pregnancy may be a risk factor for the acceleration of the early stages of AD, which also agrees with findings that early A2A antagonist exposure delays migration of SST-INs, causing cognitive deficits during development (Zappettini et al., 2019; Silva et al., 2013).

3.5. Summary of the model (biology)

To recapitulate, the model assumes at least some measure of SST-IN sparsity of hypofunction as an aetiological feature of AD (though these deficits themselves can arise for a variety of reasons). Impaired SST-IN inhibition disinhibits multiple associative networks, leading to increased recurrent firing. Such increased excitatory activity in SST-dense associative regions thereby lays a burden on hypofunctional and sparse SST-INs to increase their firing rates so as to maintain excitatory/inhibitory balance. Sustained hyperactivity of SST-INs thus promotes overactivation of GABA-B1a/APP receptor complexes, leading to their downregulation/internalisation. Hence, increased intracellular APP availability in presynaptic terminals inhibited by SST-INs induces enhanced amyloidogenic processing and extracellular Aβ availability. Conversely, SST-INs' hyperactivity and

high-firing rates cause SST-14 aggregation in the surrounding extracellular environment. The upshot is that SST-14 and Aβ form toxic mixed oligomers, which result in SST-IN death, increased disinhibition and compensatory increases in firing rates of surrounding SST-INs. As such, this process stimulates a vicious cycle of Aβ production, SST deficiency and SST-IN death, ultimately resulting in the formation of Aβ plaques that set off aMCI and AD. Moreover, it should be noted that GABA-B downregulation enhances amyloidosis and memory dysfunction also through disinhibition - e.g., acceleration of cortical neurons' firing rates in a mouse model led to Aβ accumulation and dendritic spine loss specifically due to the development of inhibitory hypofunction and associated with downregulation of GABA-A and GABA-B receptors (Kastanenka et al., 2019). Net disinhibition, at some point, should also cross some threshold past which, and as with any exponential curve, it abruptly spikes upwards (which could coincide with the onset of aMCI). In Down Syndrome, this threshold would be expected to be crossed at a much earlier age, which can be partially explained by reports of overactive excitatory recruitment of SST-INs in this neurodevelopmental disorder (Zorrilla de San Martin et al., 2020; Schulz et al., 2019). Finally, women may be more susceptible to AD because of differences in the distribution of inhibition by SST-IN (which is more biassed towards other interneurons in females than in males) leading to heavier demands on firing rates to control excitatory activity, as well as sex-dependent accelerated SST-IN degeneration.

In regards to tauopathy, though it develops downstream of Aβ, it spreads trans-synaptically and thereby independently of SST-INs (Braak and Tredici, 2019). 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). Conversely, in APP23PS45 mice, the first plaques emerge in deep layers (Busche et al., 2008) - layer Vb pyramidal neurons being, accordingly, the chief targets of SST-IN inhibition, and highly prone to a distinctively sustained, high-frequency burst firing activity (Almeida, 2022).

In the following sections, we will weave considerations on the neurocognitive profile of AD based on this biological model.

4. Functional considerations

4.1. Engram destabilisation

Inhibitory engrams are "negative images" of actual memory traces - i.e., inhibitory connections potentiated along with excitatory ones, creating suppressive representations that safeguard learned information from reconsolidation, interference, and overexcitation (e.g., Koolschijn et al., 2019; Barron et al., 2017; Adler et al., 2019; Cichon and Gan, 2015; Chiu et al., 2015; Almeida and Radanovic, 2022; Canto-Bustos et al., 2022; Shrestha et al., 2020). Whenever information needs to be retrieved or learned, these tonic inhibitory blankets are transiently lifted off; this means engrams are destabilised, allowing for access as well as various forms of synaptic plasticity; following the transient instability, inhibition is reinstated and memories are stabilised once again (e.g., Barron et al., 2017; Letzkus et al., 2015; Almeida, 2021, 2022; Williams and Holtmaat, 2019; Garrett et al., 2020; Orlova et al., 2019; Ito et al., 2020; Baratta et al., 2002; Kato et al., 2015; Canto-Bustos et al., 2022). As such, inhibitory engrams can preserve learned information from being altered or lost through neuroplasticity by subsequent neural activity or coactivations (e.g., Barron et al., 2017; Adler et al., 2019; Cichon and Gan 2015; Chiu et al., 2015; Shrestha et al., 2020). For example, in zebra finches, it has been demonstrated that inhibition protects new learning from the interference of previously-acquired information by selectively suppressing the latter (Vallentin et al., 2016).

Evidence favours SST-INs as the protagonists for the implementation of inhibitory engrams. SST-INs preferentially suppress potentiated memory traces, such as familiar, habituated and other types of predictable stimuli (whereas PVs tend to show opposite patterns), whilst also distinctively promoting memory consolidation (Hayden et al., 2021; Silberberg and Markram, 2007; Berger et al., 2010; Natan et al., 2017a, Natan et al., 2017b; Kato et al., 2015; Garrett et al., 2020; Orlova et al., 2019; Almeida, 2021; Asgarihafshejani et al., 2022; Racine et al., 2021; Vasutta et al., 2015; Honoré and Lacaille, 2022; Shrestha et al., 2020). Furthermore, this inhibition is transiently silenced by vasoactive intestinal polypeptide-positive interneurons (VIPs) in conditions requiring memory destabilisation (disinhibition for access or learning, e.g., Letzkus et al., 2015; Almeida, 2021, 2022; Williams and Holtmaat, 2019; Garrett et al., 2020; Orlova et al., 2019; Ito et al., 2020; Baratta et al., 2002; Kato et al., 2015), such as reward and punishment (Szadai et al., 2022; Kim et al., 2016), unpredictability, mismatch and contextual novelty (Garrett et al., 2020; Orlova et al., 2019; Arriaga et al., 2019; Almeida, 2021), and attentional engagement (Garrett et al., 2020; Kato et al., 2015; Pi et al., 2013; Karnani et al.,

2016); interestingly as well, VIPs' responsiveness is reduced by activity-induced lgf1 enhancers, which are known to increase incoming GABAergic transmission (Roethler et al., 2023) when ensembles are potentiated - thus unleashing SST-IN firing with synaptic potentiation.

Indeed, SST-INs undergo a very distinctive synaptic potentiation near the long-term potentiation (LTP) of excitatory neurons; additionally, an NMDAR-dependent potentiation of excitatory synapses onto SST-INs accompanies learning, as does a relocation of extrasynaptic GABA-a5Rs to inhibitory synapses; and the intrinsic excitability of hippocampal SST-INs increases following learning, with reduced afterhyperpolarisation and increased baseline firing (e.g., Asgarihafshejani et al., 2022; Racine et al., 2021; Vasutta et al., 2015; Honoré and Lacaille, 2022; Cummings and Clem, 2020; Davenport et al., 2021; McKay et al., 2013; Oh et al., 2015). Accordingly, the inactivation of SST-IN inhibition destabilises dendritic branches coding for previously-acquired information, allowing for subsequent neural activity (associated with new learning in other tasks) to unduly recruit them; the indiscriminate activation of dendritic branches results in new learning overwriting old information through depotentiation of dendritic spines (i.e., interference), and an overall dedifferentiation of memory storage (e.g., d'Aquin et al., 2022; Chiu et al., 2015; Cichon and Gan, 2015; Adler et al., 2019; Schmidt et al., 2016). Indeed, SST-IN inhibition is highly precise even at a subcellular level, regulating selective activation of particular dendritic spines of individual pyramidal dendrites to promote functional selectivity (Chiu et al., 2015). Deletion of SST-INs leads to indiscrimination of context, stimulus-specific information and interference of previously-learned information by new learning specifically due to disinhibited, indiscriminate $Ca^{2}+$ activity in dendritic spines (which promotes the aforementioned depotentiation, Cichon and Gan, 2015). Furthermore, Adler et al. (2019) demonstrated that SST-IN inhibition is necessary to prevent novel motor information from altering pre-existing memories or erasing them. Inhibitory engrams of SST-INs are also associated with pattern separation (e.g., Nabavi et al., 2014; Morales et al., 2021), whose principal goal is to prevent interference and indiscrimination between memories. Thus, SST-INs are often not simply modulators but the leading source of stimulus-specificity and contextual sensitivity (e.g., see Keller et al., 2020; Adler et al., 2019; Almeida, 2021; Chiu et al., 2015; Morales et al., 2021; Nabavi et al., 2014; Cummings and Clem, 2020). SST-INs even increase mnesic computational capacity by providing compartmentalised inhibition (d'Aquin et al., 2022), and the neuropeptide SST stabilises representations by preventing LTP (whilst broadly hyperpolarising supragranular neurons, enhancing signal-to-noise ratios, and countering overexcitation, Tallent, 2007; Brockway et al., 2022).

All in all, representations in AD may become highly unstable (disinhibited) due to SST-IN degeneration (as discussed more in the following sections). This can lead to the progressive loss of information in cortical networks, and indiscriminate activation of memories upon retrieval attempts, triggering interference and reconsolidation (e.g., Almeida and Radanovic, 2022; Almeida et al., 2023; Morales et al., 2021; Cichon and Gan, 2015; Adler et al., 2019; Mabavi et al., 2014; Chiu et al., 2015).

Interestingly, cholinergic dysfunction should directly contribute to this indiscrimination, seeing that SST-INs are strongly modulated by muscarinic as well as nicotinic input (e.g., Fanselow et al., 2008; Urban-Ciecko et al., 2018; Obermayer et al., 2018; Hilscher et al., 2017; Xiang et al., 1998; Muñoz et al., 2017; Sugihara et al., 2016; Chen et al., 2015). For instance, SST-IN activity has been proven necessary for fear-memory acquisition and subsequent retrieval in a mouse model of AD, with these functions being impaired with development of AD pathology and subsequently rescued by treatment with the cholinergic agonist Cevimeline - particularly due to amelioration of SST-IN function (Schmid et al., 2016). Cholinergic input is also demonstrated to improve discrimination performance through SST-IN modulation, promoting decorrelation and desynchronisation of evoked cortical response (Chen et al., 2015). Accordingly, lesions to the nucleus basalis of Meynert entail a marked and multi-cortical loss of SST-INs (Zhang et al., 1998), with cholinergic modulation being protective and essential for healthy SST-IN function (e.g., Fanselow et al., 2008) and supporting its discriminatory functions in the cortex (e.g., Chen et al., 2015; Almeida, 2021). In the same vein, the antimuscarinic drug scopolamine increases interference between overlapping word lists, and word intrusions have been tied to reduced ChAT levels and increased Aβ plaques as well as scopolamine administration (e.g., Almeida and Radanovic, 2022, 2023; Fuld et al., 1982; Drachman and Leavitt, 1974; Caine et al., 1981). Both proactive and retroactive interference are marked features of aMCI and AD, and correlate with amyloid burden, itself associated with disinhibition of SST-INs (e.g., Almeida and Radanovic, 2022, 2023; Abulafia et al., 2019). Choline-deficient rats also exhibit high levels of proactive interference similar to SST-IN impairments and AD, whereas choline supplementation in prenatal development reduces it (Meck and Williams, 1999); AChEIs could thereby be beneficial for cognition in AD partly due to some improvement of SST-IN function.

Finally, SST-IN deficits should promote a loss of spine density, which seems to be an essential component of memory deficits in AD. Namely, Roy et al. (2016) demonstrated that optogenetic activation perforant path fibres to engrams in the dentate gyrus of AD mice led to an increase in LTP and dendritic spine density, which correlated with rescuement of long-term memory deficits. Ablation

of these engrams (with potentiated spine density) resulted in annulation of those effects. Accordingly, SST-INs are known to protect dendritic spines. For example, application of the neurotoxin MPTP reduces spine density, induces synaptic loss and increases aberrant dendritic $Ca^{2}+$ activity by impairing SST-IN function, all of which are rectified by activation of SST-INs (Chen et al., 2019); thus, SST-IN disinhibition and spine loss are colocalised with Aβ (Bittner et al., 2010, 2012; Algmal et al., 2022). Moreover, degeneration of SST-INs in AD hippocampus results in progressive synaptic loss, as well as deficits in memory and plastic rewiring (Schmid et al., 2016).

4.2. Functional dedifferentiation

SST-INs' most prominent function is to mediate interareal information transfer by suppressing the response of apical dendrites to cortical feedback, effectively either halting/gating or enabling top-down connectivity through synchronisation (e.g., Almeida, 2021, 2022; Delorme et al., 2021; Abbas et al., 2018; Karmani et al., 2016). Suggestively, stereotypical connectivity changes develop between early aMCI and late AD: much like early hyperactivity leading to late hypoactivity (e.g., Bass et al., 2015; Almeida and Radanovic, 2022; Anastacio et al., 2022; Stargardt et al., 2015), hyperconnectivity is observed in aMCI and early AD but followed by hypoconnectivity in late AD (e.g., Almeida and Radanovic, 2022; Koelewijn et al., 2019; Schultz et al., 2017). Thus, the present model explains this pattern with early hyperactivity caused by SST-IN disinhibition, whereas late hypoactivity could evolve due to tauopathy and disinhibition-related excitotoxicity - which is in accordance with the early Aβ-dependent acceleration of atrophy in AD, followed by late deceleration and hypoactivity (Sabuncu et al., 2011).

Indeed, SST-IN hypofunction has been shown to cause hyperconnectivity; that is, ethanol intake has been shown to ramp up functional connectivity between SST-sparse regions by dampening SST-IN inhibition (e.g., Ochi et al., 2022). Similarly, SST-IN degeneration in AD may ramp up connectivity between the affected regions (Almeida and Radanovic, 2022). This would agree with the findings that functional connectivity, particularly in the theta band, reflects hyperactivity in subjective cognitive impairment and MCI, whereas optogenetic normalisation of SST-IN function also normalises theta oscillations in AD (PV-INs ameliorating the gamma frequency, citar). Conversely, in another study, chronically reduced SST-IN inhibition through ablation of 30% of SST-INs in the auditory cortex ultimately led to a plunge in the levels of corticocortical transmissions - i.e., late hypoconnectivity (Seybold et al., 2012). Hence, chronic SST-IN hypofunction in aMCI could potentially drive

hyperconnectivity at first, only to eventually contribute to dampening corticocortical transmission in later AD due excitotoxicity and other complex neural processes (e.g., reshaping of receptive fields, Seybold et al., 2012).

Another interesting argument is that potentiated ensembles deprived of their SST-IN inhibitory engrams may be more susceptible to excitotoxicity due to overexcitation, which can lead to atrophy in specialised (potentiated) networks preferentially. Thus, a reduction of brain asymmetry is observed in AD patients, as well as cortical thinning of hyperactive regions (e.g., Putcha et al., 2011; Almeida and Radanovic, 2022). Hubs also tend to be overactive and exceptionally susceptible to Aβ deposition and atrophy, which later turns into hypometabolism - whether in AD or healthy ageing (Buckner et al., 2009; Stam et al., 2009; Lo et al., 2010; de Haan et al., 2012). These data are congruent with SST-IN-related NMDAR disinhibition and Aβ-driven Ca^{2+} dyshomeostasis (Mattson et al., 1992; Schulz et al., 2018).

Destabilisation of potentiated circuitry may thereby promote interference, depotentiation, and loss of functional selectivity. In terms of functional connectivity, disinhibition should notably promote functional dedifferentiation, with disinhibited regions being improperly recruited during task performance and interfering with specialised processes (e.g., language, face recognition). Thus, for instance, a loss of *functional* lateralisation is commonly reported with fMRI for language tasks (indicating impairments in lexical-semantic memory) (Almeida and Radanovic, 2022). Further, deficits in face recognition have been associated with functional dedifferentiation in AD, with authors suggesting that unrelated regions interfere with specialised face-processing networks (Kurth et al., 2015). Similar dedifferentiations are reported for memory tasks, whereby tau tangles induce mnemonic discrimination deficits (Kurth et al., 2015; Maass et al., 2019; Li et al., 2021). Loss of sensory dominance has also been demonstrated and tied to compromised inhibitory function in aMCI and older adults (e.g., Murray et al., 2018; Diederich et al., 2008; Laurienti et al., 2006). Shifts in the topography of certain oscillatory frequency bands as well as evoked-related potentials are observed among AD patients and seem suggestive of such a disarrangement of functional circuits (e.g., Spironelli et al., 2013; Almeida and Radanovic, 2022). Aβ/tau pathology have also been correlated with a loss of functional segregation between episodic-memory networks - namely, anterior-temporal and posterior-medial -, which itself correlated with memory decline in older adults (Cassady et al., 2021).

Finally, a loss of interareal inputs into SST-INs with hypoconnectivity may compromise top-down control of interference in lower regions (Almeida and Radanovic, 2022). This would agree with the fact

that deficits in recovering from proactive semantic interference have been correlated with diffuse loss of frontotemporal/limbic functional connectivity in asymptomatic offspring of late-onset Alzheimer's disease (LOAD) patients (Sánchez et al., 2017).

4.3. Spatial memory deficits

Hippocampal place fields are neural maps or cognitive representations of places in the real world, represented by well-defined and stable groups of place cells. Sets of such cells engage in high-frequency bursting whenever mice enter a known place, and remain fully active as place fields for the duration.

As a place grows familiar, place cells fire more selectively and specifically for that location, and assemble into increasingly-stable ensembles (Zhao et al., 2014; Caccuci et al., 2008; Ness and Schultz, 2021; Cheng and Ji, 2013; Cayzac et al., 2015; Yassa et al., 2010). The leading role of hilar SST-INs in spatial memory encoding, retrieval and representation are well-established, and multiple studies demonstrate how spatial memory deficits in AD correlate selectively with SST-IN degeneration (Andrews-Zwilling et al., 2010, 2012; Leung et al., 2012). Accordingly, in AD models place fields are represented in a lower-resolution state: familiar spatial representations fail to constrain the activation into a few well-defined set of place cells, displaying instability and conveying less location-specific information which codify distinctive features used to narrow down the identity of a particular location - and thus arise spatial memory deficits (which is observed even in tau models with hypoactivity, Zhao et al., 2014; Caccuci et al., 2008; Ness and Schultz, 2021; Cheng and Ji, 2013; Cayzac et al., 2015; Yassa et al., 2010); of note, ageing-related alterations also promote excessive hippocampal firing, poor encoding, interference and indiscrimination (Wilson et al., 2005, 2006; Busche et al., 2015).

Destabilisation by SST-IN hypofunction is quite eligible to induce such indiscriminate activation, interference, impaired encoding and unstable representations in AD. This would also concur with the fact that APOE4 mice show age- and sex-dependent (female-biassed) spatial learning deficits, and those in turn only correlate with APOE4-driven SST-IN loss but not other neurons (e.g., Leung et al., 2012; Andrews-Zwilling et al., 2010, 2012). Moreover, impaired GABA-B1a subunit function also is shown to permit unconstrained memory generalisation/indiscrimination (Lynch et al., 2016b).

Accordingly, Cayzac et al. (2015), for example, found neurons with larger place fields and lower spatial information in APP/PS1 mice. The authors reported a lower proportion of place cells as compared to

regular mice. Additionally, place fields did not decrease with learning in AD mice: the proportion of task-only cells decreased in WT mice, but not APP/PS1. This was, interestingly, accompanied by a slower theta frequency. The latter congrues with the fact that SST-INs tightly regulate theta oscillations, as well as reports that restoration of SST-IN function normalises theta oscillations in networks affected by Aβ oligomers (PVs, in turn, promote gamma activity; Chung et al., 2020). In a similar vein, Cheng and Ji (2013) found that, in a transgenic tau model, CA1 neural maps covered much wider areas and conveyed less spatial information (see figure 3). Further, these low-resolution maps correlated with interference of pre-existent firing patterns, coding for non-spatial information, which intruded during exploration of familiar as well as novel environments, and disrupted encoding of new data. These intrusions were characterised by well-formed sequences of patterned activity (Gelbard-Sagiv et al., 2008; Pastalkova et al., 2008), in line with the aforementioned SST-INs' role in protecting ensembles from proactive as well as retroactive interference. AD patients also display an inability to form new memories, as well as frequent intrusions of old ones (Cheng and Ji, 2013; Carlesimo and Oscar-Berman, 1992; Salmon and Bondi, 2009; Butters et al., 1987; De Anna et al., 2008), with SST-INs being known to support memory encoding and prevent these intrusions (Murayama et al., 2009; Almeida and Radanovic, 2022; Adler et al., 2019; Cichon and Gan, 2015).

As per the interpretation of Cheng and Ji (2013), "when the transgenic mice are placed in a space, instead of forming/retrieving the space's memory code, CA1 neurons are cued to activate those internally-driven activity patterns irrelevant to the current space". This implies that, just like proactive interference, "there exists a direct competition between external and internal inputs" (Cheng and Ji, 2013). Interestingly, interfering sequences were also evoked along with prominent theta oscillatory activity, again hinting at a link to SST-IN dysfunction - given SST-INs' prominent modulation of theta oscillations (Almeida, 2021; Chung et al., 2020).

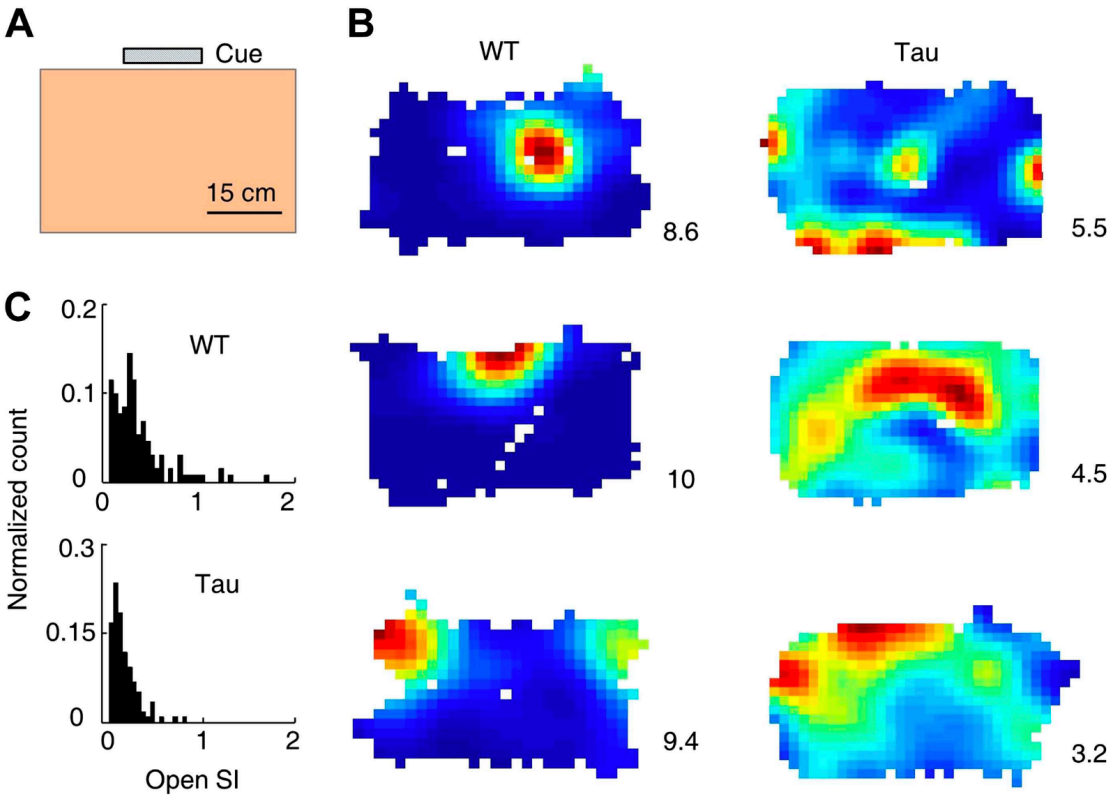

Figure 3. Tau neurons fired with low location-specificity in a familiar open box. (A) The open box with its interior colour and cue card (Cue) shown. (B) Color-coded firing rate maps of three WT and three Tau neurons, each from a different animal, in the open box. Numbers: peak (red/black) rates in Hertz. Note the broader firing areas of Tau neurons than those of WT neurons. (C) Distribution of open SI of WT and Tau neurons. Plots are histograms normalised by total numbers of samples, each computed for one neuron in one open box session. Reproduced from Cheng and Ji (2013).

Conversely, Mably et al. (2017) and Booth et al. (2016) failed to find increased place field size per se in 3xTg mice. Nonetheless, spatial information was still reduced in both studies, such that activation patterns were unspecific and low-resolution. In accordance with disrupted inhibitory engrams, place-map stability and firing rates were also impaired in both studies (Mably et al., 2017; Booth et al., 2016). In addition, theta-fast gamma coupling was impaired in Booth et al. (2016), indicating disrupted entorhinal-hippocampal communication (including of inhibitory nature, Cheng and Ji, 2013). Finally, a study with human subjects found that hyperactivity in aMCI is associated with discrimination (pattern separation) and spatial memory deficits (Yassa et al., 2010).

All in all, AD models fairly consensually depict how representations of memories of familiar places fail to look like so, because networks are unable to shape/refine them into specific and stable ensembles. This is fully congruent with the fact that inhibition, rather than excitation, shifts most prominently according to context, and is chiefly responsible for shaping excitatory activity in a context-dependent fashion (e.g., Besnard et al., 2019; Kuchibhotla et al., 2017). SST-INs, specifically, are known to control the size and specificity of memories, being highly sensitive to small contextual changes (e.g., Stefanelli et al., 2016; Scheggia et al., 2020; Besnard et al., 2016; Lovett-Barron et al., 2014; Dobrzanski et al., 2021; Arriaga et al., 2019; Cichon and Gan, 2015; Chiu et al., 2015; Asgarihafshejani et al., 2022; d'aquino et al., 2022; Adler et al., 2019; Kuchibhotla et al., 2017). Mounting evidence demonstrates that AD suffers from early and progressive worsening of pattern separation skills, which are conjectured to stem from AD pathology and cholinergic deficiency - both of which directly undermine SST-IN function; indeed, SST-INs are known to support pattern separation (Jun et al., 2020; Parizkova et al., 2020; Ally et al., 2013; Sinha et al., 2018; Zhu et al., 2018; Lee et al., 2020; Goetghebeur et al., 2019; Palmer and Good, 2011). Multiple other discriminatory cortical functions are carried out by SST-INs (e.g., Lepousez et al., 2010; Scheggia et al., 2020; Abraham et al., 2023; Adler et al., 2019). Accordingly, low-resolution spatial maps in AD have been proposed to stem from poor spatiotemporal control of excitatory activity due to disinhibition, specifically (Ness and Schultz, 2021).

SST-IN dysfunction and Aβ are proposed here to render spatial maps inaccurate, low-resolution, unspecific and unstable or destabilised. Loss of stimulus-specific responses and selectivity, as well as context-dependent modulation, are observed with Ca^{2+} disinhibition by Ab of dendritic spines (Kuchibhotla et al., 2008); these processes even precede neurodegeneration, synaptic and neural losses (Arbel-Ornath et al., 2017). Thus, in AD, detailed features of the environment are not narrowed-down into well-defined ensembles that can accurately distinguish and identify specific contexts due to poor inhibitory control. For instance, in the aforementioned studies, mice with APP overexpression and amyloidosis are shown to have an idea of the gist of a spatial map, but cannot home in on the precise location of a target in water-maze training - i.e., failing to narrow-down information according to context. Similarly, deficits in NMDAR-dependent plasticity - on which SST-INs rely heavily - of mice DG caused notable pattern separation deficits, and marked indiscrimination between contexts with overlapping features along with a reduction in context-dependent firing rate modulations (McHugh et al., 2007). Finally, spatial remapping, which most likely draws on plasticity and inhibitory mechanisms, is performed to discriminate between similar ensembles by reducing

their overlap, and this operation is also impaired in APP knock-in mice (Jun et al., 2020). Spatial remapping is accomplished by shifting activation and topographical patterns in response to even modest changes in the environment (e.g., ambience light, spatial size, geometry, and even itinerary and sequences of directions in a maze, which may result in shifts of firing rate, place-field locations and sizes, etc), thus making representations more distinctive and discriminable.

4.4. Declarative memory deficits

In AD, neurons in the temporal lobe may fail to respond selectively and coordinately to specific locations and contextual features which support episodic memory (Moser et al., 2008; O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978). Spatial indiscrimination in AD due to SST-IN disinhibition in fact already implies a disruption of episodic memory, given that place cells code also for episodic information such as time, context, or autobiographical features (Eichenbaum, 2013). For instance, hilar SST-INs in the DG were shown to discriminate between similar, partially-overlapping, episodic-like spatial-contextual memories (Morales et al., 2020). Similarly, studies on source or context memory, a subpartition of episodic memory involved in the remembrance of specific contextual features (e.g., where, when or how an event has come to pass), commonly show deficits in AD which are caused by interference of false memories and impaired retrieval of specific features (e.g., Irish et al., 2011; Pierce et al., 2008; Mammarella et al., 2012). For example, Pierce et al. (2008) found that AD patients had difficulty remembering which particular room studied items were encoded in. Mammarella et al. (2012) tested source memory for specific features of encoded words in AD, namely: perceptual, spatial, temporal, semantic, social, and affective details. The authors found that AD patients had difficulty remembering specific features, especially semantic and spatial details.

Further instances of interference in episodic memory can be found in the propensity for the formation of false memories in AD (El Haj, 2015; Budson et al., 2002; Plancher et al., 2009). Some patients are even known to confabulate over fictional memories that they claim to have lived. It is believed that this is driven by an inability to suppress intrusive irrelevant or fictional information and discriminate it from target memories (e.g., Plancher et al., 2009). Indeed, confabulations mainly consist of intruding salient and stable long-term memories, such as habits and personal semantic information (Burgess and McNeil, 1999; Dalla Barba, 1993, 2000; Dalla Barba et al., 1997, 1999). Multiple authors thereby conjectured that confabulation stems from an impaired ability to consciously retrieve weak long-term memories, whilst relatively sparing stronger representations (Dalla Barba et al., 1997,

1999, 2002; Dalla Barba, 2000). In concurrence, "over-learned information interferes with episodic recall, i.e., the retrieval of specific, unique past episodes" (De Anna et al., 2008), which are weaker representations.

Illustratively, De Anna et al. (2008) asked mild AD patients to recall different types of short stories: "one unknown story (similar to the Logical Memory test in the Wechsler Memory Scale-Revised, Wechsler, 1987), one well-known fairy-tale (Cinderella), and one 'modified' well-known fairy-tale (Little Red Riding Hood is not eaten by the wolf)". Whereas numbers of intrusions did not differ between conditions for healthy controls, patients produced most intrusions in the modified well-known fairy-tale - i.e., due to interference of overlearned elements of those stories. Hence, the "overlearned version of the fairy-tale interferes with the recall of the episodic representation of the elements of the modified version, which differ from the original version". Of course, this resonates well with the notion of disrupted inhibitory engrams of potentiated ensembles. Similarly, a decline in inhibitory ability in AD has been linked to difficulty telling whether previous actions were enacted or imagined (El Haj et al., 2012, 2013, 2015d). Finally, in concern to delayed verbal recall (a highly prevalent deficit among AD cohorts), it has been proposed to derive from a susceptibility to interference of distracting elements during the delay period - and minimising such interference does improve performance (e.g., Cowan et al., 2005). Accordingly, in vivo two-photon imaging of the hippocampus in a mouse model of AD during contextual fear conditioning demonstrated that recently-formed memories were not actually lost; namely, neighbouring, partially-overlapping ensembles near the engram precluded recall and induced forgetting, whereas optogenetic inhibition of the interfering ensembles produced recall (Poll et al., 2020). Engrams themselves proved intact. Similarly, Poll (2020) also applied two-photon imaging to APP/PS1 mice in a hippocampal-dependent memory test and discovered that although engrams were intact, they could not be retrieved due to superimposing of neighbouring ensembles. Hence, neural indiscrimination may best account for mnemonic impairments in AD.

Importantly, SST-IN disinhibition in the cortex may very well promote interference and reconsolidation of conceptual and semantic information in semantic memory as well (e.g., Colgin et al., 2008; Almeida and Radanovic, 2022). For example, cells in the lateral prefrontal cortex exhibit different representations for distinct stimuli with highly similar features (Freedman et al., 2001; see also Colgin et al., 2008; Donoghue et al., 2023). Cortical representations of events in close succession suffer pattern separation whenever abstract boundaries are detected between them, thereby

discriminating between different perceived events close in time through semanticisation or categorisation (Schapiro et al., 2013). Conversely, such deficits should apply not only to recently-encoded information like events, but also to long-term memories whose acquisition far precede the onset of aMCI - e.g., the meanings of words. For instance, semantic fluency in AD is impaired most notably in regards to cognitive switching between subcategories or clusters of semantically-related concepts, which has been associated with overwhelming interference and semantic competition as demonstrated by an fMRI study (Hirshor and Thompson-Schill, 2006;; Almeida and Radanovic, 2022). Furthermore, AD patients notably lose the ability to discriminate between exemplars or tokens of the same semantic category (e.g., specific animals such as "tiger" and "lion") due to impaired access to specific and distinctive features - as demonstrated by semantic priming and confrontation naming tasks -, which has been proposed to stem, among others, form disinhibition and cholinergic deficits (for reviews, Almeida and Radanovic, 2022; Almeida et al., 2023). Additionally, AD patients perform poorly at discriminating between confusable objects in recognition memory and conceptual matching tasks, which correlated mainly with damage to one of the very most SST-selective regions of the brain - namely, the perirhinal cortex (Frick et al., 2022). However, again, the fact that recently-encoded information in spatial and episodic tasks is also subject to the same pattern of indiscrimination strongly implies that it is not synaptic or neural loss that mainly causes memory deficits in AD, but disinhibition and indiscrimination.

Alternative instances of cortical discrimination deficits in AD patients include visual space (Nguyen et al., 2003), tone frequency and duration (e.g., Hellström and Almkvist, 1997; Caravaglios et al., 2010), colours (Salamone et al., 2009), visual objects (Gaynor et al., 2019), facial identity (Roudier et al., 1998), emotion (Kohler et al., 2005), semantic and contextual adequacy (Almeida and Radanovic, 2022), semantic categories and subordinates (Grossman et al., 2001; Almeida and Radanovic, 2022), visuo-semantic lures *versus* target picture memory (Leal et al., 2019), tactile angles (Yang et al., 2010), auditory-spatial information (Golden et al., 2015), word lists and events (Almeida and Radanovic, 2022), inter alia.

4.5. Summary of the model (cognition)

The fulcrum and main deduction of the model is that, chiefly in reason of hypofunctional SST-IN inhibition, spatial and declarative memory in AD suffer from harsh discriminatory deficits. In other words, it is not neural or synaptic loss per se that is most responsible for the qualitative

neuropsychological profile of AD patients, but widespread interference and indiscriminate neural activity due to impaired context-dependent inhibitory modulation of cortical and hippocampal networks. Hence, we discussed how this is reflected in spatial memory as low-resolution, unspecific and uninformative spatial maps which cannot narrow-down specific features of memories, but only access a low-resolution gist. The same fingerprint is observed in declarative memory. Semantic categories lose resolution, such that patients fail to discriminate between individual exemplars by accessing detail and distinctive features. Conversely, in episodic memory patients fail to home-in on weak or specific contextual features in autobiographical and source memory, exhibiting intrusions of overlearned information, whereas short-term memory suffers from the same deficits as reflected in proactive and retroactive interference studies and minimisation of interference during delay periods of verbal recall. Moreover, it is noteworthy that SWS impairment, GABA-B1a downregulation, cholinergic deficits, and amyloidosis: all of these are known to promote progressive memory generalisation over time, which may explain various discriminatory deficits in memory (Webb et al., 2020; Almeida et al., 2023).

Altogether, the present model concludes that memory in AD is not characterised mainly by loss of engrams, but unconstrained and indiscriminate neural activity that can ultimately lead to their disarrangement through interference and reconsolidation, in line with studies demonstrating rescuing of memory deficits and lost memories in animal models (e.g., Etter et al., 2019; Giovannetti et al., 2018). This neuropsychological profile directly reflects the biological model that was put forth, which postulates that SST-IN hypofunction is an ontological feature of AD.

Declaration of interest

None.

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