Tipping the scales: Peptide-dependent dysregulation of neural circuit dynamics in Alzheimer's Disease

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SUMMARY

Identifying effective treatments for Alzheimer's disease (AD) has proven challenging and has instigated a recent shift in AD research focus towards the earliest disease-initiating cellular mechanisms. A key insight has been an increase in soluble Aβ oligomers in early AD that is causally linked to neuronal and circuit hyperexcitability. However, other accumulating AD-related peptides and proteins, including those derived from the same amyloid precursor protein, such as Aη or sAPPα, and autonomously, such as tau, exhibit surprising opposing effects on circuit dynamics. We propose that the effects of these on neuronal circuits has profound implications for our understanding of disease complexity and heterogeneity, and the development of personalized diagnostic and therapeutic strategies in AD. Here, we highlight important peptide-specific mechanisms of dynamic pathological disequilibrium of cellular and circuit activity in AD and discuss approaches in which these may be further understood, and theoretically and experimentally leveraged, to elucidate AD pathophysiology.

MAIN TEXT

1. INTRODUCTION

It is now well established that there is a prolonged delay, of the order of decades, between the onset of Alzheimer's Disease (AD) (i.e. the abnormal accumulation of amyloid-beta, Aβ, in the brain) and subsequent neurodegeneration and cognitive decline (for review see Sperling et al., 2014). This 'asymptomatic' period suggests that the deleterious effects of peptide accumulation in AD (**Box 1**; the term peptide is used here in a generic sense to include peptides, polypeptides and proteins) are not immediate but instead occur cumulatively over long timescales, ultimately overwhelming the brain's homeostatic mechanisms and leading to the emergence of clinically measurable deficits (for review see Frere and Slutsky, 2018). However, a mechanistic framework linking the abnormal accumulation of peptides to the onset of dementia has remained, to date, elusive, and represents a critical hurdle to be overcome in order to make real progress in our understanding and treatment of AD. This knowledge gap persists as a result of multiple factors, including the inherent, and increasingly appreciated, complexity and heterogeneity in AD, as well as the limitations of current theoretical and experimental methodologies to study the disorder. Importantly, AD differs from several other neurodegenerative disorders in that it is a multi-proteinopathy where several peptides accumulate, and where newfound species (e.g. Aη, see Willem et al., 2015) continue to be detected. Moreover, emerging evidence suggests that these peptides are not only comprised of many species variants and aggregation states (e.g. Aβ monomers and oligomers, pyroglutamate modified-Aβ, N-terminal elongated Aβ, plaques, etc.), but that these also synergistically, competitively, and dynamically interact during disease progression (e.g. Aβ-tau interaction, see Busche et al., 2019). This represents a shortcoming of typical preclinical research approaches which often model the effects of one peptide species in isolation (e.g. using either APP or tau mice which are incomplete models of AD). Further complexity arises from observations that at least some of these peptides exhibit differing cellular and regional specificity as well as propagatory patterns (e.g. vulnerability of excitatory neurons to tau pathology, see Fu et al., 2019), and genetic investigations that continue to reveal a host of risk genes/loci and pathophysiological pathways, including those pertaining to the innate immune system, lipid metabolism and synaptic transmission (for review see Verheijen and Sleegers, 2018).

AD patients consequently exhibit multiple genotypes and phenotypes, with heterogeneity in clinicopathologic presentation (e.g. language or frontal variants, posterior cortical atrophy), age of onset, and rate of patho-progression.

The above complexity underscores the challenges faced by AD research today, and questions the validity of the established, yet somewhat simplistic, view that AD is a single disorder determined by a linear causal relationship between the accumulation of Aβ (and tau), and cognitive decline and dementia. How, then, can we understand why specific neurons degenerate and explain the heterogeneity in AD? How can we trace the historical patho-progression in each patient, and predict the subsequent course of the disease? What is the most effective scale for intervention (molecular, genetic, circuit-level, or cognitive-behavioral) and which is the most promising biological target(s) for therapy in AD? These fundamental questions, and others, have recently come into sharp focus due to the mixed clinical outcomes of anti-Aβ therapies, ranging from potentially beneficial effects in specific patient populations (i.e. Aducanumab, unpublished) to reports of null and even negative effects on cognition (such as in the case of β-secretase inhibition, for review see Panza et al., 2019). Perhaps in an effort to mitigate these findings, in light of the formidable investment and support for the amyloid hypothesis of AD, it has been suggested that therapeutic interventions have historically been administered too late in the disease process and, rather, should be levelled at disease-initiating cellular processes (De Strooper and Karran, 2016), as well as targeted to patient subgroups most responsive to therapy. Nevertheless, a critical question yet again emerges from this proposition: How can we identify, phenotypically stratify and assess therapeutic efficacy in patients with early preclinical AD, at a stage of the disease in which neuropathological changes are only beginning to emerge and clinical signs and symptoms remain absent?

Here we propose an alternative, 'center-out' approach and suggest that the above themes critically converge at the level of neuronal circuits. Circuits are the intermediary linking microscopic changes in molecular and genetic characteristics to macroscopic, 'real-world', changes in cognition and behavior (e.g. symptoms), and are uniquely positioned to integrate, compensate and modulate effects at both ends of the scale. Moreover, by virtue of their mesoscopic nature, circuits are amenable to interrogation using current non-invasive neuroimaging techniques that balance the trade-off between spatial and temporal resolution and which, although lacking the granularity of molecular approaches, can monitor

longitudinal circuit changes in real-time. We surmise that each stage of AD, including the 'asymptomatic' period, is in fact associated with quantitative changes in the activity of circuits and their constituent brain cells. These changes represent homeostatic and maladaptive circuit alterations and the dynamic integrated effects of underlying genetics and neuropathological changes. Remarkably, recent evidence suggests that circuits in AD show common modes of dysfunction (i.e., hyper- and hypoexcitability) that can arise from the neuronal effects mediated by different peptide species and their associated cellular pathways. We therefore propose that the roles of individual peptides and associated pathologies, molecular signalling cascades, and cell-specific vulnerability in AD pathogenesis is best understood in the context of neuronal circuits. Accordingly, in this review, we will summarize the current state of the field regarding the role of AD peptides in modulating neuronal circuit activity in AD, and suggest that reconceptualizing AD as a circuit-based disorder, beyond the classical syndromal or recent protein-biomarker based definitions, offers a promising new framework to understand the complexities of AD.

2. NEURONAL CIRCUIT PATHOGENESIS AND HETEROGENEITY IN AD

2.1 Biphasic changes in circuit excitability during AD progression

Our understanding of neuronal circuit behavior and deterioration in AD has grown substantially over the past few years and has been driven by advances in sophisticated non-invasive neuroimaging techniques (**Box 2**), alone and in combination with electroencephalography (EEG) and magnetoencephalography (MEG). A key clinical insight that has emerged is that of pathologically disrupted cortico-hippocampal circuits in AD, in which a dynamic disequilibrium in neuronal excitation and inhibition (E/I balance) manifests biphasically as hyperactivity in pre-clinical (i.e. asymptomatic) stages of AD and hypoactivity in later phases of the disease (Alexander et al., 2002; Busche and Konnerth, 2016; Dickerson et al., 2005). Indeed, increased resting-state and task-related activations of the default-mode network (DMN) and the hippocampus in asymptomatic and very mildly impaired individuals with AD can be observed relative to controls (Dickerson et al., 2005; Sperling et al., 2009), and transitions to hypoactivation with subsequent clinical decline (Celone et al., 2006). Hyperactivity of the hippocampus is of particular diagnostic and prognostic value, since it is coupled to the degree of clinical impairment, and predicts a greater extent and rate of

subsequent cognitive decline (Dickerson et al., 2004; Miller et al., 2008; O'Brien et al., 2010). Importantly, hippocampal hyperactivity, which has also been described in asymptomatic familial AD (Quiroz et al., 2010) and carriers of the Ɛ4 allele of the apolipoprotein E gene (APOE4, the strongest genetic risk factor for AD) (Bookheimer et al., 2000), is significantly related to the deposition of Aβ in the brain (Leal et al., 2017). Therapeutically targeting this hyperactivation phenotype with the antiepileptic levetiracetam notably resulted in normalization of hippocampal activity levels and an improvement in memory performance in mildly impaired individuals with AD (Bakker et al., 2015; Bakker et al., 2012). These findings thus suggest that pathological hippocampal activation is linked to the emergence of Aβ pathology, contributes to memory impairment, and is a dysfunctional, rather than a compensatory, mechanism that may be a valuable biomarker of individuals in prodromal AD (Corriveau-Lecavalier et al., 2019).

On the other hand, hypoactivation in other connected brain regions has also, albeit less frequently, been reported, such as a reciprocal relationship between hippocampal hyperactivation and hypoactivation within parietal regions forming part of the DMN in mildly impaired individuals with AD (Celone et al., 2006; Corriveau-Lecavalier et al., 2019). Moreover, hypoactivation has also been observed in entorhinal cortex (where tau pathology is initiated, see below) alongside hippocampal hyperactivation, and normalized by levetiracetam administration (Bakker et al., 2015). These data indicate that hyperactive and hypoactive circuits can co-exist to varying degrees in early AD, although it should be noted that there is ongoing debate regarding the neurophysiological underpinnings of functional magnetic resonance imaging (fMRI) deactivation/hypoactivation signals, where such perfusion-related responses may reflect feedforward inhibition and/or 'vascular steal' effects, and be differentially affected by pathological states.

2.2 Enhanced seizure susceptibility in early AD

The existence of hyperactive circuits in early AD is supported by observations that a substantial proportion of individuals with AD exhibit epileptiform and seizure activity which exceeds normal population levels (Cretin et al., 2016; Palop and Mucke, 2009; Scarmeas et al., 2009; Vossel et al., 2013). Heterogeneity in seizure susceptibility in AD is high, with reports of rates between 10-64% (for review see Vossel et al., 2017), and also regarding subclinical

epileptiform activity, with a reported prevalence of approximately 40% (Vossel et al., 2016). Seizures in AD can emerge several years prior to cognitive symptoms/decline and may persist into the dementia phase, albeit less prevalently, where they may contribute to behavioral symptoms and cognitive deficits (Cretin et al., 2016; DiFrancesco et al., 2017; Vossel et al., 2013). It is important to note that the prevalence of seizures in AD groups is likely underestimated, due to many of these being subclinical in nature (i.e. without motor symptoms) and more prevalent during sleep and within hippocampal circuits, thus being imperceptible to clinicians and electrophysiological surface recordings (Lam et al., 2017). Epilepsy is a key feature associated with an earlier onset of cognitive decline in individuals with AD (Vossel et al., 2013), and is more prevalent in dominantly inherited familial forms of AD (Voglein et al., 2019). Notably, clinically significant differences between *PSEN1* and *APP* mutation carriers have been reported, including increased seizure incidence and a younger age at symptom onset in the former (Ryan et al., 2016; Shea et al., 2016). Moreover, mutation positions may also differentially influence clinical phenotypes, with *PSEN1* mutations before codon 200 being associated with earlier ages of onset and increased seizure prevalence than those occurring after this codon (Ryan et al., 2016; Shea et al., 2016). Taken together, these reports not only indicate that hyperactivity and epilepsy in early AD are oft-observed phenomena associated with a more severe clinical presentation, but also emphasize complex phenotypic heterogeneity in AD, where neuronal circuit excitability is dependent on the clinico-genetic status of the individual.

3. PEPTIDE SPECIFIC MODULATION OF NEURONAL ACTIVITY IN AD

The literature described above depicts a state change in cortico-hippocampal circuits during AD which has the potential to be exploited as a personalized diagnostic and prognostic tool. What, then, are the mechanistic drivers of long-term circuit changes in AD? Here, crucially, recent work has revealed novel mechanisms by which AD-related peptides directly and dynamically modulate neuronal and circuit activity during AD progression. These findings, described below, underscore the physiological relevance and importance of in-vivo methodologies to elucidate the functional effects of AD-related peptides, many of which would not have been possible to predict from molecular work nor evinced from in-vitro preparations which lack intact circuits.

3.1 Amyloid beta

Burgeoning evidence indicates that soluble Aβ oligomers are key players in driving neuronal hyperactivity in AD (Brorson et al., 1995; Busche et al., 2008; Sanchez-Mejia et al., 2008; Ye et al., 2003) (**Figure 1A,B**). Evidence for such has been extensively reviewed elsewhere and will only be briefly described here (Busche et al., 2015; Busche and Konnerth, 2016; Zott et al., 2018). Neurons in areas with high Aβ plaque burden, e.g. frontal cortex or hippocampus, demonstrate tonic hyperexcitability in multiple mouse models of AD (Busche et al., 2008; Busche et al., 2015). While many of the initial studies were performed in lightly anesthetized animal models, a recent study has independently confirmed the occurrence of neuronal hyperactivity in plaque-bearing awake-behaving mice (Korzhova et al., 2019). Importantly, administration of Aβ oligomers in the absence of plaque pathology can also induce neuronal hyperexcitability in hippocampus (Busche et al., 2012) and cortex (Keskin et al., 2017), indicating that soluble Aβ oligomers, as opposed to Aβ plaques, are a critical driver of neuronal dysfunction (Zott et al., 2019) (but see also Section 4.5 on methodological considerations of acute versus chronic experimental preparations). Interestingly, there is a direct correlation between brain Aβ concentration and number of hyperexcitable cortical cells (Keskin et al., 2017). β- and γ-secretase inhibition (**Box 3**) rescues the aforementioned neuronal hyperexcitability in mouse models of AD, and, in the case of former, is also re-established following superfusion of soluble Aβ oligomers (Busche et al., 2012; Keskin et al., 2017). This finding, together with results of acute Aβ applications, provides critical evidence that hyperactivity is causally linked to Aβ, rather than the potentially confounding overexpression of APP seen in such mouse models.

The mechanism by which Aβ exerts its effects remains an area of active research with several recent advances. Earlier evidence that Aβ disrupts the excitation/inhibition balance, and that hyperactivity may result from reduced synaptic inhibition, was evinced when application of the benzodiazepine diazepam enhanced inhibition and rescued neuronal hyperactivity in APP23xPS45 mice (Busche et al., 2008). In addition, hyperactivity-mediated disruption of slow wave activity and resultant deficits in spatial memory were also rescued by increasing $GABA_A$ergic neurotransmission through administration of low-doses of the benzodiazepines midazolam or clonazepam (Busche et al., 2015). These studies are broadly consistent with other reports of reduced GABAergic terminals on cortical neurons

proximal to Aβ plaques both in mice and humans (Garcia-Marin et al., 2009) and beneficial effects of GABA enhancement on cognitive function and Aβ toxicity in young APP/PS1 mice which exhibited reduced GABA levels (Sun et al., 2012). In addition, restitution of impaired Nav1.1 channels in parvalbumin-positive GABAergic neurons, including through Nav1.1-overexpressing interneuron transplants, was shown to improve cognitive and behavioral deficits in hAPP-J20 mice, and to rescue impaired gamma oscillations and the seizure phenotype in this model (Martinez-Losa et al., 2018; Verret et al., 2012) (**Figure 1A**). Impaired glutamate homeostasis has also been proposed as a mechanism for Aβ-mediated neuronal hyperactivity. Recent in-vivo evidence has indicated that Aβ induces hyperactivity in neurons exhibiting ongoing baseline activity, but not inactive neurons, and is initiated by Aβ-mediated suppression of glutamate reuptake, presumably by astrocytes (Zott et al., 2019). This result reinforces the notion that AD is a multi-cellular disorder, and that non-neuronal cell types including astrocytes and microglia, where in fact most AD risk genes are expressed (Kunkle et al., 2019), fundamentally impact the disease process. Moreover, in combination with the activity dependent production of Aβ (Kamenetz et al., 2003), this data closes the circle on a positive feedback loop, and provides an explanation for why Aβ induced hyperactivity might not always be observed in-vitro, where spontaneous activity is usually absent (Zott et al., 2019) (**Figure 1B**).

Supporting evidence for the above has also emerged from recent work in human induced pluripotent stem cell (hiPSC)-derived neurons, cerebral organoids and three-dimensional (3D) culture models. AD hiPSC-derived neurons, manifesting mutations in presenilin-1 (PS1) or the amyloid precursor protein (APP), were found to exhibit reduced neurite length, increased excitatory synaptic transmission, as well as decreased inhibitory neurotransmission and a reduced number of inhibitory GABAergic neurons, relative to isogenic wild-type neurons (Ghatak et al., 2019). In addition, AD cerebral organoids, similarly to AD hiPSC-derived neurons, were associated with increased vesicular glutamate transporter (VGLUT1) and decreased vesicular GABA transporter (VGAT) levels, as well as increased action potential firing, indicating that the observed hyperactivity in AD hiPSCs and cerebral organoids occurs as a result of an imbalance between excitatory and inhibitory influences (Ghatak et al., 2019). Notably, γ-secretase and BACE1 inhibition also rescued the hyperexcitability phenotype in hiPSC-derived AD neurons, as previously reported in-vivo, providing further support for a critical role for Aβ in driving neuronal hyperexcitability (Busche

et al., 2012; Ghatak et al., 2019; Keskin et al., 2017). Finally, abnormal neuronal hyperexcitability was also observed using calcium imaging in a 3D human cell tri-culture system that incorporates neurons and astrocytes expressing mutant APP, together with immortalized microglia (Park et al., 2018).

It is well established that Aβ impairs synaptic plasticity mechanisms including long-term potentiation (LTP) (e.g. Shankar et al., 2008; Walsh et al., 2002), and that this impairment is imparted by Aβ oligomers and not monomers (Li et al., 2018). At first sight, Aβ-mediated increases in net excitatory drive at the circuit level, and impairment of LTP, as well as other reports of facilitation of long-term depression (LTD) by Aβ (Hsieh et al., 2006; Li et al., 2009), might seem paradoxical. These effects, however, may be reconciled by Aβ-mediated modulation of synaptic glutamate mechanisms inducing a shift in E/I balance towards excitation (for example, by augmenting presynaptic glutamate release and/or blocking glutamate reuptake) (Lei et al., 2016; Wang et al., 2017). Impaired synaptic glutamate handling might then subsequently lead to increased synaptic activation of NMDA receptors and their subsequent desensitization, followed by internalization of NMDA and AMPA receptors (as shown to be promoted by Aβ, Hsieh et al., 2006; Snyder et al., 2005; Um et al., 2012), and also activation of extra-synaptic NMDA and metabotropic glutamate receptors due to glutamate spillover (implicated in Aβ-mediated facilitation of LTD, Hsieh et al., 2006; Li et al., 2009). In addition, Aβ-induced activation of the calcium-dependent phosphatase calcineurin (CaN) (Wu et al., 2010), as a corollary of neuronal excitability-related increases in calcium influx, might also be expected to result in NMDA and AMPA receptor endocytosis (Hsieh et al., 2006; Snyder et al., 2005) and lead to impairment of LTP and facilitation of LTD, as well as spine loss. In contrast, it is more difficult to reconcile accounts of Aβ-mediated reductions in glutamatergic transmission at the synaptic level (Kamenetz et al., 2003; Snyder et al., 2005) to circuit-level hyperexcitability, and this remains a topic of intense research. Since it is improbable that Aβ mediates differential influences at the synaptic and circuit scales, further work is necessary to diambiguate the complexity of Aβ-effects, and clarify whether the apparent divergence in observations lay in methodological differences (e.g. in-vitro versus in-vivo, maturity status of neurons studied, or Aβ-concentration dependent effects - see Puzzo et al., 2008) or may be explained by an as yet undetermined mechanistic link.

It is also interesting to remark that the effects of Aβ may not be exclusively neurocentric (**Supplementary Figure 1**). For example, Aβ has been suggested to act as an antimicrobial peptide and to inhibit replication of influenza and herpes simplex viruses (Bourgade et al., 2015; White et al., 2014). Aβ-overexpressing 5xFAD mice showed enhanced Aβ-seeding and plaque deposition following intra-cerebral injection of microorganisms (e.g., *Salmonella typhimurium and herpes simplex virus*) and, intriguingly, displayed increased survival and increased resistance to infection compared to non-transgenic littermates (Eimer et al., 2018; Kumar et al., 2016). In turn, there is also long-standing evidence that Aβ exerts vasoactive effects (Thomas et al., 1996), with more recent work indicating that Aβ induces pericyte-mediated capillary constriction (Nortley et al., 2019) that may underpin the large decreases in cerebral blood flow often observed in early in AD (e.g. see Iturria-Medina et al., 2016; Kisler et al., 2017). Given that the expected consequence of Aβ-mediated neuronal hyperactivity would be that of functional hyperemia, the opposing vasoconstrictive effect of Aβ suggests a toxic dual-hit of increased metabolic demand and reduced perfusion. Notably, hypoxia may also lead to upregulation of BACE 1 and increased Aβ production (**Box 3**) (Sun et al., 2006) suggesting a possible mechanism for a self-enhancing feedback loop contributing to patho-progression.

3.2 Tau

Emerging in-vivo work has indicated that tau, another major hallmark of AD, is associated with dysfunctional neuronal activation and hypoexcitability, in direct contrast to Aβ-mediated effects (**Figure 1A, C**). Suppression of in-vivo cortical neuronal activity was observed in rTg4510 mice overexpressing and aggregating human-tau^{P301L} and neurofibrillary tangles (NFTs), and notably also in rTg21221 mice that overproduce similar levels of non-aggregating wild-type human tau but with the absence of NFTs, indicating neuronal suppression is driven by soluble forms of tau (Busche et al., 2019). Moreover, suppressing tau transgene expression reversed neuronal silencing in both mouse models (Busche et al., 2019). These results are consistent with other recent in-vivo reports of reduced functional connectivity in transgenic mouse strains expressing mutant variants of the truncated tau four-repeat domain (TauRD), which was rescued by switching-off tau expression (Green et al., 2019), and tau-mediated neuronal hypoactivity in awake P301S mice independent of the

presence of NFTs, providing further evidence of increased bioactivity of soluble tau species (Marinkovic et al., 2019). In the rTg4510 mouse model, pathological tau was found to reduce the activity within the neocortical network due to suppression and disruption of neuronal firing patterns (Menkes-Caspi et al., 2015), and network activity impairment, reduced grid cell firing, and destabilized grid fields, were also observed in a transgenic mouse model expressing mutant human tau (EC-tau model) (Fu et al., 2017). Additionally, in-vitro studies have reported the suppression of hippocampal excitability in two tau^{P301L} mouse lines (rTg4510 and pR5) due to tau-mediated distal relocation of the axon initial segment (AIS) (Hatch et al., 2017) (**Figure 1A**), and an increase in the threshold for action potential firing and the amplitudes of inward-rectifying potassium currents, as well as a significant reduction in LTP, indicative of reduced excitability in pR5 mouse hippocampal neurons (Müller-Thomsen et al., 2020). Mislocalization and accumulation of hyperphosphorylated tau in dendritic spines disrupts glutamate receptor trafficking and anchoring, thereby impairing synaptic function (Hoover et al., 2010), and pathological tau also disrupts presynaptic vesicle mobility and release in fly and rat neurons, leading to reduced neurotransmission (Zhou et al., 2017) (**Figure 1C**). Interestingly, tau induces a profound downregulation of neuronal and synaptic genes, which is consistent with the hypoactivity phenotype (Castanho et al., 2020; Sierksma et al., 2020). In addition, the toxic effect of tau appears to preferentially target excitatory neurons and leads to downregulation of genes involved in glutamate receptor signaling (including several AMPA and NMDA receptor subunits) (Fu et al., 2019; Fu et al., 2017; Pickett et al., 2019).

Notwithstanding the evidence for tau-mediated neuronal hypoactivity, it is also important to note there have been opposing reports of tau mediating hyperexcitability phenotypes. For example, in-vitro patch clamp recordings of rTg4510 mouse frontal cortical pyramidal neurons were reported to exhibit a depolarized resting membrane potential and increased action potential firing in response to depolarizing current injections (although notably with a conserved synaptic excitation/inhibition balance) relative to non-transgenic controls (Crimins et al., 2012; Crimins et al., 2011; Rocher et al., 2010). Such results are, however, at variance with other findings utilizing in-vivo intracellular and extracellular recordings in the same mouse model, which found spontaneous action potential firing rates to be markedly reduced, relative to control animals, with no differences in membrane potential (Menkes-Caspi et al., 2015). That tau may play a pro-excitable role has also been inferred from studies reporting increased seizure susceptibility to pentylenetetrazol

administration in Tau58/4 (Van Erum et al., 2020) and Tau^{VLW} (Garcia-Cabrero et al., 2013) mice, or in which tau reduction in genetic mouse ($Kcna1^{-/-}$) and Drosophila models of epilepsy was associated with seizure suppression (Holth et al., 2013). Similarly, antisense reduction of tau in mice was reported to be protective against chemically induced seizures (DeVos et al., 2013), and tau ablation in a mouse model of Dravet syndrome (a severe form of childhood epilepsy) was associated with a reduction in the susceptibility of mice to spontaneous and heat-induced seizures, and a decrease in inter-ictal spike frequency, the latter also found in acute hippocampal slices following application of chemoconvulsants (Gheyara et al., 2014). Tau nullification was also found to protect against Aβ-mediated hyperexcitability and epileptiform activity in APP mice (Ittner et al., 2010; Roberson et al., 2011; Roberson et al., 2007). Interestingly, rTg4510 mice show an increased susceptibility to amygdala kindling-induced seizures relative to wild-type animals, although tau knockout mice exhibited no difference in rates of kindling epileptogenesis relative to controls (Liu et al., 2017). An increased incidence of spontaneous electrographic epileptic spikes in awake A152T-variant (hTau-A152T) mice was also reported relative to non-transgenic controls whereas, notably, transgenic mice expressing wild-type human tau exhibited the opposite effect (Maeda et al., 2016).

Since epileptic activity has traditionally been thought to reflect a synchronous escalation of neuronal firing in a large ensemble of local cells, the correlation between tau and epileptic activity has been taken to reflect a pro-excitable effect of the protein, and to be consistent with clinical observations of increased seizure incidence in tauopathy (e.g. see also in frontotemporal dementia with parkinsonism linked to chromosome 17, Sperfeld et al., 1999). Recent evidence, however, indicates that epileptiform events in humans are associated with profound heterogeneity in single unit spiking activity, including decreases in firing, across excitatory and inhibitory cell classes, and that the complex network interaction of these manifold firing behaviors at the single-neuron level are essential to the emergence of interictal and ictal discharges at the macroscale (Keller et al., 2010; Truccolo et al., 2011). Such seizure activity, when gauged using population measures such as EEG, may therefore not faithfully reflect the activity of underlying excitatory cells, and may also emerge from the contribution of several other non-neuronal mechanisms, including glial (i.e. astrocytes and microglia) dysfunction, blood brain barrier breakdown and extracellular matrix remodeling (for reviews see Farrell et al., 2019; Patel et al., 2019). This suggests that the manifestation of

macroscale epileptiform activity may not be incompatible with hypoactivity in a fraction of neurons expressing pathological tau, and thus that seizure suppression through tau reduction need not necessarily implicate tau as a direct mediator of neuronal hyperactivity. Nevertheless, other reports supporting tau-mediated hyperexcitability have also emerged, including increased neuronal burst frequency in a double-mutant iPSC line (IVS10+16/P301S) (Verheyen et al., 2019), increased levels of extracellular glutamate and epileptiform activity in A152T-variant slice preparations (Decker et al., 2016), and impairment of activity-dependent plasticity of the AIS cytoskeleton in human neurons by the V337M tau mutation (which leads to frontotemporal dementia, FTD), resulting in aberrant increases in neuronal activity in response to chronic potassium chloride induced depolarization (Sohn et al., 2019). The A152T-variant was also suggested to modulate the power of brain oscillations in the 0.5-6Hz frequency range, with suppression of hTau-A152T expression and levetiracetam treatment reported to reverse tau-dependent network dysfunction (Das et al., 2018), although, in this context, it is interesting to note that seizure-like low frequency activity may be naturally linked to cellular hypoactivity in the network, with a recent report of a similar effect resulting from hypoxia-induced spreading depolarization (Revah et al., 2019). Lastly, it is important to emphasize that two recent human studies have independently reported an association between measures of tau pathology and increased hippocampal activity during task-related fMRI in clinically normal older subjects (Berron et al., 2019; Huijbers et al., 2019).

It is evidently difficult to reconcile the findings obtained using in-vivo circuit-level techniques with single cell/unit resolution, which have indicated a hypoexcitability phenotype of tau under resting state conditions (Busche et al., 2019; Marinkovic et al., 2019; Menkes-Caspi et al., 2015), to those in which macroscale measures of epileptiform activity suggest otherwise, and to square the contrasting data yielded by in-vitro preparations. Differences in recording modalities, species, models, and tau isoforms or mutations provide a potential, if unsophisticated, explanation, and it is therefore clear that additional work is required to disambiguate the direct and indirect role(s) of tau on neurons and the circuits in which they are functionally and reciprocally embedded. In the following text, and in light of the aforementioned in-vivo evidence for tau-mediated cellular hypoactivity under resting state conditions in the intact brain, we work off the premise of a tau-related hypoexcitability phenotype, albeit with the ongoing consideration that much remains to be elucidated on this topic.

3.3 Amyloid Beta and Tau Interaction

The above in-vivo literature demonstrates how the two hallmark peptides in AD may exhibit opposing effects on neuronal circuits in AD, with Aβ promoting hyperactivity and tau inducing hypoactivity. However, what are their combined effects? Recent work, involving the crossing of APP/PS1 and rTg4510 or rTg21221 mouse lines to generate an AD mouse model overexpressing Aβ and tau, has revealed that tau effects dominate and counteract Aβ-related hyperactivity thus inducing neuronal silencing and hypoactive neuronal circuits (Busche et al., 2019). Notably, suppression of the tau transgene did not recapitulate the restoration of circuit impairments in the crossed mice which was observed in tau mice (rTg4510 or rTg21221), suggestive of a synergetic interaction between Aβ and tau that conspires to disrupt the functional integrity of neuronal circuits (Busche et al., 2019). These findings are consistent with other reports that Aβ and tau conspire to disrupt synaptic and circuit function, enhance behavioral deficits and promote neuronal loss (Ittner et al., 2010; Roberson et al., 2011; Roberson et al., 2007). In addition, other recent studies involving the APP/PS1-rTg21221 mouse line, reported that these animals exhibited less and smaller Aβ plaques compared to the APP/PS1 strain, and diminished expression of genes involved in synaptic function relative to the parental strains, providing further evidence of a co-pathogenic effect of Aβ and tau (Jackson et al., 2016; Pickett et al., 2019).

3.4 A simplified theoretical model of Aβ-tau effects during AD progression

Based on the above translational and clinical data, we propose a framework which encompasses the changes in the neuronal circuits during AD progression through the prism of the development of Aβ and tau pathology. During early pre-clinical stages, Aβ begins to accumulate and predisposes neuronal circuits towards hyperexcitation. Neuronal hyperexcitability subsequently results in increased production and release of Aβ and tau (Cirrito et al., 2005; Pooler et al., 2013; Wu et al., 2016) leading to a feedback increase in peptide accumulation and deposition. In concert, deposition of Aβ plaques, which has outspread sequentially from the neocortex and finally to the cerebellum (Thal et al., 2002), begins to plateau. Subsequently, tau accumulation results in a progressive counterbalancing of Aβ effects and eventual tilting of neuronal circuits towards hypoactivity, with NFT

deposition progressing from entorhinal cortex to primary sensory areas, via the hippocampus, in later stages of the disease (Braak and Braak, 1991), and correlated with cognitive decline and neuronal loss (Arriagada et al., 1992).

These effects can be represented by a basic model where the temporal evolution of Aβ and tau levels during AD progression are characterized by sigmoidal functions, and where the onset of tau pathology is temporally delayed with respect to Aβ (**Figure 2A**) (as suggested by experimental and theoretical evidence, for review see Jack et al., 2013). Assuming that Aβ-mediated hyperactivity and tau-mediated hypoactivity have equal and opposing effects on neuronal circuit excitability, that track the level of these peptides in the brain, the combined effects of Aβ and tau on circuit excitability results in transient hyperactivity that arises due to the temporal lag between the onset of both pathologies (**Figure 2B**). However, when tau-mediated effects are further conceptualized to include a gain parameter, representing the potentiating/synergistic interaction between Aβ and tau, and such that tau effects ultimately dominate over those of Aβ (e.g. Busche et al., 2019), the combined effects of Aβ and tau on circuit excitability produces a biphasic response, reflecting an early increase in hyperactivity which transitions to hypoactivity in later stages of the disease **(Figure 2B)**.

Alternatively, in the event that tau effects might mediate neuronal hyperexcitability (see Section 3.2), the combined dual-hit of Aβ and tau alike on circuits would be expected to lead to a markedly greater increase in net hyperexcitability as the disease course unfolded (**Figure 2C**). A moderating effect (e.g. mediated by homeostatic mechanisms) can also be conceptualized within this model through the introduction of a simple arbitrary negative-feedback term. Under these conditions, varying efficacy of this countering effect, conceptually reflecting a spectrum of adaptive and maladaptive (e.g. deficient or excessive) feedback responses by intact and/or pathologically dysregulated compensatory processes (Styr and Slutsky, 2018), produces a diverse series of circuit-level effects, including runaway excitation (i.e. unregulated), renormalization, and over-regulation, the latter consisting of a biphasic change with early hyperexcitability subsequently evolving into hypoexcitability (**Figure 2C**).

It is important to note, however, that the above models do not make specific predictions as to the clinical disease stage at which these biomarker and circuit changes occur, since these will vary across individuals due to differing genetic profiles, cognitive reserve, comorbidities, age of onset as well as disease course (see Jack et al., 2013). In addition, it

should be highlighted that the predicted Aβ/tau-related circuit dynamics represent net changes in circuit activity. As such, it does not preclude constituent microcircuits from being hyperactive or hypoactive, such as hyperexcitability proximal to Aβ plaques, while the overlying network may, overall, be in a seemingly paradoxical state of excitability. Indeed, seizure risk in AD increases around the time of onset of cognitive decline and begins to decrease with AD progression, but remains at a somewhat elevated level (Vossel et al., 2013) (**Figure 2B**, top trace). It is therefore possible that brain microdomains, which are in of themselves able to generate microseizures and ultimately large-scale clinical seizures (Stead et al., 2010), continue to have a propensity towards ictogenesis in later stages of AD, despite the overlying circuit being potentially hypoactive due to tau dominating effects. A further limitation of this model is that it does not incorporate the contribution of non-neuronal cell types (e.g., microglia), and elucidating their potentially complex role in modulating neural circuit activities will not only enhance our understanding of disease mechanisms but also provide more broader insights into how emerging genetic observations can be incorporated into the proposed pathophysiological model. Nevertheless, these simple models emphasize how the delay between onset of Aβ and tau pathologies and Aβ/tau cooperation can illustrate the overall neuronal circuit changes in translational and clinical data described previously.

3.5 The amyloid precursor protein and other peptides

In addition to the effects of the hallmark peptides in AD on neuronal function, recent evidence has also surprisingly emerged suggesting that the amyloid precursor protein (APP) processing pathway comprises of several components able to modulate neuronal function and circuit activity. APP itself has been suggested to play an important role in several biological processes within the central nervous system, including synaptic transmission and plasticity, and is strongly expressed in cortical and hippocampal excitatory and GABAergic neurons (Ludewig and Korte, 2016; Rice et al., 2020). Notably, APP (and interestingly APLP1/APLP2, see Cousins et al., 2015) associates with N-methyl-d-aspartate (NMDA) receptors and affect NMDA receptor trafficking and cell surface expression (Cousins et al., 2009), suggesting that APP may actively regulate post-synaptic excitatory processes. Furthermore, APP also affects hippocampal GABAergic transmission (Wang et al., 2014) through presynaptic modulation of Cav1.2 L-type calcium channels (Yang et al., 2009), and

aged APP null mice exhibit (subtle) LTP deficits (Seabrook et al., 1999). Of particular note, APP binds to $GABA_B$ receptors thereby enhancing receptor trafficking and cell surface expression, and promoting pre-synaptic inhibition (Dinamarca et al., 2019). Furthermore, complex formation with $GABA_B$ receptors stabilizes APP at the cell surface and reduces amyloidogenic processing of APP to Aβ (Dinamarca et al., 2019). These findings implicate APP as contributing to the regulation of E/I balance in the brain, with several of its cleavage products also being recently implicated in modulating excitatory and inhibitory processes.

3.51 Secreted forms of APP

Cleavage of APP by α and β-secretase (**Box 3**) is activity dependent (Kamenetz et al., 2003; Nitsch et al., 1992) and competitive, with the former protease cleaving within the Aβ sequence thus preventing Aβ-generation (Skovronsky et al., 2000) and liberating sAPPα into the extracellular space. Until recently, sAPPα had been mostly associated with neurotrophic and neuroprotective properties and implicated in synaptic plasticity as well as learning and memory. For example, exogenous sAPPα administration was reported to rescue behavioral deficits in learning and memory as well as LTP in aged rodents (Xiong et al., 2017), and APP knockout mice (Hick et al., 2015), and facilitate LTP through an increase in NMDA receptor activation (Moreno et al., 2015; Taylor et al., 2008) and promoting glutamate receptor trafficking (GluA2-lacking AMPARs and NMDARs) and synthesis (Mockett et al., 2019). In addition, AAV-mediated expression of sAPPα was observed to rescue synaptic and LTP deficits in the APP/PS1 mouse model of AD and reduce soluble Aβ levels and plaque load (Fol et al., 2016). The same AAV technique was also used to show that the augmenting effect on LTP by sAPPα may derive from its action as a allosteric positive modulator of excitatory α-7 nicotinic receptors (a7-nAChR) (Richter et al., 2018). In this context, the C-terminal 16 amino acids (CT16) of sAPPα mediated this effect on LTP, with activation of α7-nAChR potentially promoting pre-synaptic glutamate release and post-synaptic Ca^{2+} influx leading to membrane depolarization, and supporting synaptic plasticity via glutamate receptor trafficking and synthesis (Mockett et al., 2019; Richter et al., 2018). It is interesting to note that sAPPβ, which lacks the C-terminal 16 amino-acids (CT16) region, failed to modulate LTP in several of the above studies (Hick et al., 2015; Mockett et al., 2019; Richter et al., 2018; Taylor et al., 2008).

The results thus engendered a great deal of interest in the community since enhancing sAPPα presented itself as an attractive pathway through which to therapeutically target synaptic and cognitive deficits in AD. However, the mechanism of action of sAPPα is likely more complex that the reports discussed above suggest. sAPPα activates cyclic GMP-mediated K^+ channel activation and suppression of neuronal activity, with sAPPβ inducing less significant effects (Barger et al., 1995; Furukawa et al., 1996). More recently, after identifying that both sAPPα and sAPPβ bound to the sushi-containing γ-aminobutyric acid type B receptor subunit 1a ($GABA_BR1a$), Rice et al. (2019) showed that this binding could be restricted to the APP extension domain (ExD) common to sAPPα, sAPPβ, and sAPPη (**Figure 1B**). Accordingly, all three sAPP forms bound to $GABA_BR1a$, and it was further shown that nanomolar concentrations of sAPPα and sAPPβ reduced the frequency of excitatory and inhibitory postsynaptic currents in cultured hippocampal neurons. In turn, Rice et al. (2019) revealed that a 17 amino acid sequence truncation of the ExD was sufficient to tightly bind with the $GABA_BR1a$ sushi 1 domain, and that application of a corresponding synthesized 17–amino acid peptide (APP 17-mer), both in hippocampal slices and in-vivo, recapitulated a $GABA_BR1a$-dependent reduction of synaptic vesicle release probability, enhanced paired-pulse facilitation and reduced ongoing neuronal activity in the hippocampus as measured by in vivo two photon calcium imaging, respectively (Rice et al., 2019).

3.52 Aη-α and Aη-β

Aη-α and Aη-β are supplementary, and only very recently discovered, fragments derived from APP processing (Willem et al., 2015) (**Box 3**). In fact, the proteolytic pathway leading to these soluble, non-aggregating, peptides is more productive than the 'canonical' Aβ-generating pathway, with Aη being five times more abundant than Aβ in human CSF (Willem et al., 2015). Aη-α, but not Aη-β, markedly diminishes LTP in hippocampal slices and, intriguingly, this impairment is comparable to effects typically observed with Aβ. However, in striking contrast to the effects of Aβ on neuronal excitability (see above), Aη-α strongly suppresses ongoing neuronal activity in-vivo, and thus could antagonize Aβ neuronal effects (Willem et al., 2015). The strong effect on LTP, and the observation that Aη-α exerts its activity-blocking effect within milliseconds following local application to neurons in-vivo, indicate a rapid synaptic mechanism, possibly involving postsynaptic glutamatergic receptors

(**Figure 1B**). Whilst the mechanistic underpinning and difference in bioactivity between both species remains to be elucidated, it is interesting to note that Aη-α and Aη-β peptides were found to differ structurally by 16 amino-acids, with the former being the longer species. This sequence is, remarkably, also common to the C-terminal domain (CT16) of sAPPα. Notwithstanding, while this sequence has been considered to confer LTP-facilitating effects on sAPPα (see above), this appears not to be the case for Aη-α in light of its significant reduction in LTP. Willem et al. (2015) further demonstrated that blockade of β-secretase activity (BACE1 inhibition) increased production of CTF-η and Aη-α, at the expense of the shorter BACE1-generated Aη-β, and η-secretase APP processing products accumulated in dystrophic neurites near Aβ plaques. This suggests that the action of BACE inhibitors may have unexpected downstream effects on the modulation of neuronal circuit activity and lead to enhancement of hypoactivity and perhaps even cognitive impairment. This may also contribute to the negative outcomes of clinical trials employing BACE inhibition for treatment of AD (for review see Panza et al., 2019).

3.6 APOE4

In parallel, there is also a direct link between APOE4, an isoform of the APOE lipoprotein, and impairment or death of GABAergic interneurons (**Figure 1A**). Somatostatin expressing interneurons are particularly susceptible, such that APOE4-knockin mice exhibit learning and memory deficits which are rescued by application of the $GABA_A$ receptor agonist pentobarbital, or inhibiting APOE4 expression in neurons (Andrews-Zwilling et al., 2010; Knoferle et al., 2014). These data thus indicate that APOE4 also contributes to neuronal hyperactivity by diminishing inhibitory tone (Nuriel et al., 2017).

4. LESSONS, CHALLENGES AND PERSPECTIVES

4.1 Functional hierarchy of soluble peptides in AD

Several important insights have thus emerged from the investigation of AD related peptides on neuronal function while also, inevitably, raising further questions (**Box 4**). A key lesson pertains to evidence that soluble forms of the peptides often exert stronger effects on circuit dynamics than aggregated or insoluble forms, reinforcing the view that in-vivo markers

of these soluble forms are critical targets for future research. Moreover, there is a 'functional hierarchy' of these peptides that is dynamic during the progression of AD and underpins the biphasic progression and biomarker data seen in human patients. In APP overexpressing mice, which lack tau pathology and where Aβ is overexpressed, Aβ-related hyperactivity ostensibly dominates, and is consistent with clinical data in early AD. In turn, at later stages of the disease in which Aβ and tau pathology are co-established, and modelled using APP-tau models, tau effects dominate of those of Aβ, thereby blocking hyperactivity and leading to net hypoactive circuits. Importantly, however, there is also a synergistic interaction since tau reduction does not normalize activation levels in the presence of Aβ, and the presence of Aβ accelerates tau-related hypoactivity (Busche et al., 2019). Due to the inherent design of current APP mouse models which favor Aβ production, it is unclear where Aη and sAPPα sit in this functional hierarchy at different stages of the disease, although the clinical evidence supporting hyperactivity (but not hypoactivity) strongly implicates these to be subservient to Aβ, at least in early AD. As the sensitivity and selectivity of CSF and blood biomarkers for AD-related peptides improve, a key target for future studies will be to chart the temporal evolution of other AD-related peptides, beyond simply Aβ and tau, and determine whether the prevalence, proportion and broad interaction effects of these are correlated to the neuronal circuit status of the individual and underpins heterogeneity across patients. For example, although prevalent, not all individuals with AD have epilepsy – do these cases have variant biomarker signatures that parallel the phenotypic differences?

4.2 The undefined functional role of neuronal circuit state changes in AD

It is surprising that Aβ-mediated neuronal hyperactivity can be present in the absence of overt cognitive or behavioral symptoms, both in animal models and human patients. It is also puzzling that neurodegeneration or cell loss is not observed in APP mouse models which exhibit neuronal hyperactivity and seizures, since such aberrant activity modulates sensory processing (Harris et al., 2013), causes instability of neuronal features such as orientation or direction selectivity in the primary visual cortex (Grienberger et al., 2012), and is inherently associated with increased metabolic demand (Harris et al., 2018; Hillary and Grafman, 2017). Interestingly, a recent study utilizing repeated in-vivo multiphoton imaging in mice demonstrated that the same neurons can remain hyperactive for at least 4 weeks, and this

surprising steady-state of hyperactivity is elevated around plaques (Korzhova et al., 2019). Outstanding questions therefore remain; does neuronal hyperactivity negatively impact on other regionally specific neuronal features, for example place cell coding in the hippocampus, and what, if any, are the clinical correlates of neuronal hyperactivation? To address these directly, we anticipate that a theory-guided computational approach to understand circuit level vulnerability in AD will be crucial. This will help to provide valuable insights into why some stages and models of AD are asymptomatic, or accompanied by only subtle cognitive impairments, while abnormal circuit states are already established. States of circuit excitability leading to hyperactivity, for instance, may comprise a mixture of loss and gain of function that are partially compensatory. Quite generally, in population coding theories, higher firing rates and spike counts improve encoding quality both of stimulus or action features (Babadi and Sompolinsky, 2014; Brunel and Nadal, 1998; Sompolinsky et al., 2001) as well as of temporal information (Fourcaud-Trocme et al., 2003; Puelma Touzel and Wolf, 2015; Tchumatchenko and Wolf, 2011; Wei and Wolf, 2011). The loss of stimulus selectivity found in visual cortical populations in APP/PS1 models (Grienberger et al., 2012) that reduces sensory information content, *per se,* might thus be partially compensated by beneficial effects of a higher spike count and bandwidth of population coding. Computational decoding from densely sampled populations as well as simultaneous recording from subsequent processing stages will enable to experimentally test such compensatory mechanisms. Beyond this, current evidence also suggests that, while hyperactivity may not be directly related to symptoms, it may also render neuronal circuits more vulnerable to subsequent pathological changes. Hyperactivity may enhance spatiotemporal disease progression by accelerating release and accumulation of AD-related peptides, possibly leading to enhanced Aβ plaque deposition and driving the synaptic propagation of tau across connected brain areas (Cirrito et al., 2005; Pooler et al., 2013; Wu et al., 2016). In addition, the hypersynchronous nature of seizures may also lead to the functional recruitment of distributed brain regions and predispose these to downstream, peptide-mediated, pathological changes, consistent with the observation that increased functional connectivity is associated with existing and future tau accumulation (Franzmeier et al., 2020).

A related question pertains to whether neuronal hypoactivity is a harbinger of impending cell death as typically assumed, possibly as a consequence of preceding hyperexcitability and the excessive metabolic demands this imposes, or whether this may also

play a quasi-homeostatic role that could help protect other brain processes (through a reduced metabolic requirement) that would otherwise fail in a stressed network. In this context, it is interesting to note that excitability is only one of many neuronal properties, and that normalizing activity in a neuron that has experienced prolonged dysfunction may restore some, but not all, of its functional intrinsic properties. Indeed, it has been shown that while hypoactive neurons in the APP/PS1 mouse model were reactivated following $GABA_A$ receptor antagonism, these same neurons subsequently failed to respond to visual stimuli (Grienberger et al., 2012). It thus remains to be elucidated to what extent hypoactive neurons, even in a functionally decoupled state, can contribute to the maintenance of circuit integrity and information processing.

4.3 Towards an improved theoretical framework of circuit-level changes in AD

The literature above also raises several notes of caution since circuits are far too complex to be accurately described through the simple prism of excitation/inhibition imbalance. Indeed, there are several, unrepresented, components integrated within this simplistic model, which are often experimentally overlooked since they are not intuitively understood. For example, inhibition is particularly multifaceted (e.g. different classes of interneurons targeting different neuronal sites) and there are several additional circuit motifs including feedforward inhibition, feedback inhibition, recurrent excitation and counter inhibition that are not appropriately modelled. In the APP/PS1 mouse model of AD, feedforward inhibition, presumably mediated by parvalbumin expressing interneurons, is impaired (Viana da Silva et al., 2019), and somatostatin expressing interneurons, implicated in feedback inhibition, are also compromised (Schmid et al., 2016). Both types of impaired inhibition will thus interact differentially with also-modified glutamatergic synaptic transmission between principal neurons, making it a challenge to ascribe the resulting net change in circuit excitability to individual contributing factors. Indeed, computational modeling work has revealed that emergent features of circuit dynamics are not simply related to cellular excitability thresholds or average synaptic strengths, but depend on subtle features of the neuronal populations' physiology, e.g. their speed and bandwidth (Brunel and Hakim, 1999; Geisler et al., 2005; Lazarov et al., 2018; Revah et al., 2019; Tchumatchenko et al., 2011;

Wei and Wolf, 2011), and critically on the speed of feedback inhibition (Monteforte and Wolf, 2010, 2012; van Vreeswijk and Sompolinsky, 1996; Wolf et al., 2014). In addition, microcircuit models predict that relatively small differences in the overall strength of local circuit motifs can strongly affect computational function. Small changes in the strength of recurrent excitation, for example, are sufficient to shift a local cortical circuit from input driven sensory processing to a functional regime of persistent activity, potentially subserving working memory functions (Compte et al., 2000). Thus, at the local cortical circuit level, similar molecular phenotypes, depending on microcircuit structure, are expected to cause qualitatively different levels of functional impairment. A circuit neuroscience methodology founded on multi-level computational modeling, multimodal imaging, and theory-guided circuit diagnostics is therefore essential to dissect the complexity of circuit level excitability and information flow in AD. Future work, in addition, should go beyond local circuitry and elucidate long-range circuit dynamics. Long-range forebrain circuitry, such as cortical processing hierarchies or the circuitry of the cortico-hippocampal loop, underlie high-level functions such as object recognition, action planning or systems memory consolidation. Accumulating evidence from chronic imaging studies indicate that hippocampal and cortical representations are subject to a lifelong turnover (Lutcke et al., 2013; Schlesiger et al., 2015; Ziv et al., 2013) that is locally regulated, driven by activity-dependent neuroplasticity, and potentially universal, even affecting primary sensory areas (Clopath et al., 2017). Local circuit hyper- and hypo-activity are predicted to alter the representational turnover in downstream circuits by mechanisms of activity-dependent plasticity. Assessing and modeling long-range circuit dynamics will thus be required to understand whether and how impairment of representational stability and turnover are involved in disease progression and whether they may differentiate between benign changes and functional breakdown. Such studies, in addition, will also provide a fine-grained spatiotemporal picture of the spread of pathological changes across large-scale forebrain circuitry. In this context, it is interesting to note that a recent clinical study combining magnetoencephalography (MEG) and positron emission tomography (PET) with Aβ and tau tracers, has revealed neurophysiological signatures of AD associated with Aβ and tau pathology, and cognitive decline (Ranasinghe et al., 2020). Specifically, hypersynchrony in the delta-theta frequency band was found to be colocalized with both Aβ and tau load and modulated by both tracers' uptake, with alpha band hyposynchrony being strongly associated with tau deposition and tracer uptake, correlated

to cognitive dysfunction, and remarkably able to differentiate between neurobehavioral phenotypes (Ranasinghe et al., 2020).

A related target for future research is to examine neuromodulatory influences such as those expressed during circadian variations. AD patients exhibit disrupted sleep and circadian rhythm patterns (for review see Musiek et al., 2015) and are predisposed to hyperexcitability during sleep (Lam et al., 2017; Vossel et al., 2016). Importantly, sleep disruption, in particular impaired slow-wave (non-REM) sleep, is associated with increases in Aβ and tau burden (Ju et al., 2017; Lucey et al., 2019), possibly due to impaired clearance and/or enhanced neuronal activity (Busche et al., 2015) and reduced cellular restoration (Vyazovskiy and Harris, 2013). Finally, while certain circuit changes dominate at different stages of the disease, it is important to note that this does not implicitly suggest that the underlying deficits fail to persist. For example, the impairment of inhibition by Aβ at earlier stages of AD may still persevere into later phases of the disease, during which tau pathology functionally and regionally dominates, leading to a net decrease in neuronal activity alongside a paradoxical, albeit reduced, susceptibility to seizures (Vossel et al., 2013).

4.4 Treatment opportunities

The model of biphasic alteration in the E/I balance of neuronal circuits during the progression of AD, while simplistic, suggests windows of opportunity during which to leverage the action of different interventions to alter circuit activity. For example, peptides and other tools promoting hypo-excitability might be exploited during early stages of AD when Aβ-mediated hyperactivity dominates, while approaches to counter hypo-excitability might be beneficial at later stages of the disease when tau pathology becomes more established. Further work will need to elucidate whether hyperactivity is in fact constrained by possibly compensatory hypoactive effects of sAPPα and Aη, and whether the reduction of these peptides further enhances hyperexcitability, and even leads to increased seizure susceptibility, or vice versa. Given the possibility of a neurotrophic and neuroprotective role of sAPPα, as well as its ability to modulate β-secretase activity and suppress Aβ production, it is unsurprising that it has been considered as a potential therapeutic target in AD (Obregon et al., 2012). A method by which to enhance sAPPα is via BACE inhibition, which would have the additional benefit of suppressing Aβ production (De Strooper et al., 2010; Keskin et al.,

2017) albeit with an increase in Aη-α production (Willem et al., 2015). The combined suppressive influence on neuronal activity might therefore go beyond a balanced effect, leading to cognitive impairment. Interestingly, this cellular mechanism might underpin recent failures of BACE inhibition in clinical trials in which cognitive deficits were worsened (for review see Panza et al., 2019) and might suggest that directing such interventions at patients at pre-clinical stages of AD, where hyperactivity is particularly pronounced, might be more effective, were accurate biomarkers of this staging, such as at the circuit level, be developed. It also remains to be elucidated whether administration of the synthesized APP 17-mer which binds to the $GABA_BR1a$ and suppresses neuronal activity in mice (Rice et al., 2019) is able to counteract hyperactivity in humans. Repurposing of anti-epileptic compounds to treat hyperexcitability in AD has also garnered increased attention since levetiracetam was found to normalize hippocampal hyperexcitability and improve memory performance in MCI patients (Bakker et al., 2015; Bakker et al., 2012). Nevertheless, recent work suggesting that Aβ and tau conspire to intensify impairment of synapses and neuronal circuits may underpin the disappointing failures of clinical trials targeting Aβ (for review see Panza et al., 2019), and emphasizes the need to develop combination therapies that target the synergistic effects of AD-related peptides.

On the other hand, as a more viable alternative to correcting alterations at the molecular level or the rebalancing of peptide species, which is fraught with complexity given the above inter-relationships, several promising circuit-level approaches for the treatment of AD are fortunately now emerging. This includes the use of temporal interference which non-invasively modulates neuronal circuit activity in deep brain regions (Grossman et al., 2017), or the induction of gamma band (40Hz) oscillations through multi-modal sensory stimulation which has been reported to reduce phosphorylated tau, Aβ plaque burden and improve cognitive performance in multiple mouse models of neurodegeneration (Adaikkan et al., 2019; Iaccarino et al., 2016). While these approaches require further confirmation of their efficacy in human participants, they suggest a burgeoning role for stimulation-based circuit modulation in AD therapy. Finally, because neuronal dysfunction can be widespread, and thus difficult to target without affecting non-diseased areas, the notion of focusing instead on ‘chokepoints’ of pathological activity has also been proposed. For example, ongoing clinical studies are testing the effects of deep brain stimulation of the fornix (i.e. the major output

fiber bundle of the hippocampus) on neuronal dysfunction and cognition in mildly impaired individuals with AD (Leoutsakos et al., 2018).

4.5 Methodological Considerations

Finally, on a methodological note, it is important to highlight that many of the experimental studies reviewed above have relied on acute application of peptides, or mice that overexpress one of the peptides (e.g. APP and tau models). As such, it is unlikely that these models fully mimic peptide-mediated effects in the human brain, in which the disease evolves over several years and decades, and where several pathologies develop in a time and brain-region dependent manner. In this regard, the emergence of knock-in mouse models is an important first step, but even these are incomplete models of the disease and are currently only established for APP and APOE4, but not yet for tau. An additional limitation concerns the limited outlook of many studies, which often only examine isolated brain regions of interest, despite the fact that multiple brain areas undergo a differential rate, extent and mode of patho-progression in AD. Development of a single model that faithfully recapitulates AD pathology and technologies that enable quantitative brain-wide monitoring at the cellular level are thus of utmost priority, in order to ensure that the translational research we conduct is of tangible clinical value and yields a definitive disease modifying treatment in AD.

5. CONCLUSION

In conclusion, the recent discovery of a suppressive effect of tau on neuronal network activity (Busche et al., 2019; Marinkovic et al., 2019) parallels emerging evidence that APP processing in AD gives rise to a myriad of cleavage products (**Box 3**) that exhibit an equally remarkable breadth of functional properties, including the promotion of neuronal hyperactivity (Aβ, Busche et al., 2012; Busche et al., 2008; Zott et al., 2019) and hypoactivity (sAPPα and Aη-α, Rice et al., 2019; Willem et al., 2015). We now understand that these AD-related peptides, while not directly degenerating neurons, have substantial competing and synergistic functional effects on neuronal circuits, and can tip neuronal circuits towards hyperactive and hypoactive states dynamically during disease progression (**Figure 3**). These circuit-level effects, crucially, provide valuable diagnostic and prognostic information and,

considering the recent failures of clinical trials in AD, offer a unique framework to understand AD and deliver treatments that are targeted to the individual. Disambiguating which peptide species are perpetrators or bystanders of neuronal impairment, and which underlie disease and symptom progression, is now a critical next step to identify credible therapeutic targets in AD and deliver optimal treatments at the right time to the most responsive individuals.

The challenge for future AD research will be to devise and implement the necessary inter-disciplinary approaches, likely consisting of sophisticated circuit-level neuroimaging techniques and multi-level computational modelling, that are able to provide the 'big-data' and analytical tools that are deserving of the intricacies of AD. Only then can we finally hope to turn what has felt akin to a Sisyphean challenge into a not insurmountable Herculean endeavor.

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COMPETING INTERESTS

The authors declare no competing interests.

AUTHOR CONTRIBUTIONS

S.S.H and M.A.B conceived the original idea. S.S.H, F.W, B.D.S and M.A.B wrote the paper.

TEXT BOXES

Box 1: Clinico-pathological perspective on AD

Alzheimer's disease (AD) is histopathologically characterized by the presence of widespread amyloid beta (Aβ) plaques and a hierarchically arrayed pattern of neurofibrillary tangles (NFTs) in limbic and association areas. Plaques are composed of the Aβ peptide, itself a cleavage product of the much larger amyloid precursor protein (APP), while tangles constitute paired helical filaments (PHFs) of the microtubule-associated protein tau. Glial activation and neuroinflammation accompany plaques and tangles in the brain. Histopathological changes emerge many years before the symptom onset and, as a result, the field has shifted away from a dichotomous diagnosis of "Alzheimer's Disease versus normal aging" towards the current concept of a long preclinical period and a continuum of changes that ultimately lead to clinical symptoms and decline. In the rare familial cases of AD, genetic mutations in *APP, PSEN1, or PSEN2* genes lead to enhanced APP processing that can promote aggregation of Aβ (for review see De Strooper, 2010; Hardy and Selkoe, 2002), and are often associated with an earlier symptom onset in their 40s or 50s. Emerging evidence also indicates the presence of rare protective APP mutations which hamper production of Aβ and protect carriers against developing AD (Jonsson et al., 2012), as well as APOE variants that modify the risk of developing dementia (Arboleda-Velasquez et al., 2019; Medway et al., 2014).

Box 2: Non-invasive brain mapping techniques

The development of non-invasive brain mapping techniques has revolutionized our understanding of the structure and function of the brain. Electroencephalography (EEG) and magnetoencephalography (MEG) measure electrical potentials generated by post-synaptic currents across neurons and the magnetic fields that these give rise to. Although possessing high temporal resolution, enabling the examination of neuronal oscillations and synchrony, these techniques have poor spatial resolution. They are thus often combined with perfusion related neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), to merge the spatiotemporal resolution of both modalities and to obtain perfusion related correlates of neuronal activity. The primary form of fMRI uses the blood-oxygen level dependent (BOLD) signal which relies on a complex interplay between cerebral blood flow (CBF), metabolism and hemoglobin oxygenation. BOLD fMRI is commonly used in resting-state paradigms to examine the functional connectivity between distributed brain regions

during spontaneous activity, and which may be used as a biomarker to differentiate between disorders. This method differs from conventional MRI and diffusion-weighted MRI which can be used to examine anatomical structures and abnormalities of the brain. In turn, positron emission tomography (PET) is a nuclear medicine technique that involves the injection of a radioligand that binds to a receptor of choice. It is sometimes combined with fMRI to link functional activity to radiotracer metabolism, although it is important to note that both perfusion-based modalities rely on an accurate understanding of neurovascular coupling. More recently, MEG and PET have been used to study neuronal rhythms and their association with underlying Aβ and tau deposition.

Box 3: APP and tau biology

Within the amyloidogenic pathway, Aβ is produced following a two-step process, firstly by β-secretase (β-site APP cleaving enzyme 1, BACE 1) cleavage of APP, during which a soluble sAPPβ fragment is jettisoned and a membrane-bound C-terminal fragment (CTFβ) remains tethered (**Box Figure B1**). CTFβ is then successively cleaved by presenilin (PS) containing γ-secretase (De Strooper et al., 1998), thereby releasing Aβ into the extracellular space and unbinding the residual APP intracellular domain (AICD) into the cytoplasm (Takami et al., 2009). Analogously, in the non-amyloidogenic pathway, APP may be competitively cleaved by α-secretase (mainly disintegrin and metalloproteinase domain containing protein 10, ADAM10) (Kuhn et al., 2010) or η-secretase (matrix metalloproteinases such as MT5-MMP) (Willem et al., 2015), liberating two additional soluble fragments, sAPPα or sAPPη, and leaving behind two membrane bound C-terminal fragments, CTFα or CTFη, respectively (**Box Figure B1**). In turn, CTFα, similarly to CTFβ, undergoes secondary cleavage by γ-secretase, leading to extracellular release of an N-terminal truncated form of Aβ, known as p3. Little is known about the p3 peptide, although recent intriguing work has suggested that it may also possess amyloidogenic properties (Kuhn et al., 2020). CTFη on the other hand, can be further cleaved by α- or β- secretase, resulting in the extracellular release of amyloid-eta-α (Aη-α) or amyloid-eta-β (Aη-β), respectively (Willem et al., 2015) (see figure). Several additional proteases in ancillary APP processing pathways have recently been described, including cleavage by caspases, the zinc metalloprotease Meprin-β, and, interestingly, delta-secretase (asparagine endopeptidase) that is not only able to cleave APP (Zhang et al., 2015) but also tau (Zhang et al., 2014). In turn, tau, another major hallmark of AD, is a highly soluble protein which

promotes the stability and assembly of microtubules, that resides primarily in the intracellular compartment (in contrast to Aβ), and is aberrantly phosphorylated in AD (Braak et al., 1994; Goedert et al., 1988; Grundke-Iqbal et al., 1986). The extent to which tau is phosphorylated governs its efficacy, such that hyperphosphorylation diminishes the ability of tau to assemble and bind to microtubules (Lindwall and Cole, 1984). Prior to hyperphosphorylation and aggregation as neurofibrillary tangles (NFTs) in AD, tau pathologically translocates from axons to somatodendritic compartments, and accumulates in pre- and post-synaptic domains.

Box 4: Open questions

- Despite much insight and supporting evidence, in what manner, and to what extent, do different peptides play a physiological role in delicately regulating synaptic and neuronal activity?
- Soluble proteins exhibit increased 'bioactivity' relative to insoluble aggregates, however which species are the most toxic and to what extent are they present in the human brain?
- In what manner, and to what extent, do non-neuronal cell types such as microglia contribute to dysregulation of neural circuits?
- How can the direct action of AD-related peptides be leveraged to understand neurodegeneration and dementia that appears much later in the disease? More specifically, how can we connect the dots from peptides to circuits to neurodegeneration/dementia?

FIGURE LEGENDS

Figure 1: Key mechanisms of AD-related peptide modulation of neuronal and circuit function. A) Illustration of simplified microcircuit composed of multiple susceptible neuronal and non-neuronal cell types. Two forms of dysfunction in the vicinity of the axon initial segment (AIS) are highlighted; impairment of Nav1.1 channels in parvalbumin (PV)-positive GABAergic neurons leading to hyperactivity (in APP models), and relocation of the AIS (a key target for tau-mediated modulation of excitability) in pyramidal neurons in the presence of hyperphosphorylated tau leading to hypoactivity. There is a reduction in the numbers of somatostatin (SOM) interneurons in APP and APOE4 KI models, and upregulation of Nav1.6 in primary neurons in APP models. How activated microglia and neurons interact remains unknown although neuronal silencing is associated with microglial activation (Brawek et al., 2014). **B)** sAPPα contributes to neuronal hypoactivity through binding to the sushi containing $GABA_BR1a$ resulting in reduced synaptic vesicle release probability (1), the neuronal suppressing mechanism of action of Aeta is unclear but is likely to affect post-synaptic glutamate receptors (GluR) (2). In contrast, Aβ contributes to neuronal hyperactivity through an impairment of glutamate reuptake (3) and a reduction in inhibitory tone (e.g. see Nav1.1 channel reduction in panel A). **C)** Pathological tau binds to presynaptic vesicles leading to their reduced mobility and release, while relocation of tau to somatodendritic compartments leads to reduced post-synaptic GluR trafficking and anchoring. Both mechanisms result in neuronal hypoactivity.

Figure 2: Simplified models of the temporal evolution of Aβ and tau biomarker levels during AD progression and the effects of both peptide species on neuronal circuit activity (see main text). A) Temporal evolution of Aβ (red) and tau (blue) levels follow a putative sigmoidal shape in which tau pathology is delayed. **B)** Aβ-mediated effects on circuit hyperactivity are modelled as tracking changes in Aβ biomarker levels (red solid line), while tau-mediated effects on circuit hypoactivity are modelled using two approaches: Firstly, as tracking changes in tau biomarker levels (blue line), and secondly, with an additional gain parameter representing the synergistic interaction between Aβ and tau, (blue dashed line). The combined effects of Aβ and tau, when equal and opposing, predict a transient early increase in circuit excitability due to the temporal lag between both pathologies (green dashed line).

However, the effect of an interaction between Aβ and tau results in a biphasic change in circuit excitability (hyperactivity → hypoactivity) which is consistent with translational and clinical data (green solid line). **C)** In the case where tau might mediate neuronal hyperexcitability, as suggested by some reports, the additive effects of Aβ (red solid line) and tau (blue solid line) would be expected to lead to a marked monotonic increase in circuit-level excitability (green solid line). A range of moderating influences on the net change in circuit excitability (*E*), as a result of potential adaptive and maladaptive regulatory processes counteracting the combined effects of Aβ and tau (*R*), can also be simulated through the introduction of a simple, albeit somewhat arbitrary, adjustable negative feedback parameter (*B*), where $E = R/B$, $B = (1–kR)^{-1}$ and *k* spans the range [0,1]. Under this framework, a spectrum of circuit-level changes can be replicated (dashed lines) including runaway excitation (i.e. absence of regulation, *k*=0, green solid line), renormalization, and over-compensation (*k*=1, consisting of early hyperexcitability followed by hypoexcitability).

Figure 3: Summary schematic representing key effects of AD-related peptides on neuronal circuit function in the context of the excitation/inhibition (E/I) balance. AD-related peptides have single or multiple modes of action. For example, Aβ mediates neuronal circuit hyperactivity through both an increase in excitation and decrease in inhibition (upper left quadrant), while tau mediates hypoactive effects through a decrease in excitatory drive (center-bottom). These effects, in combination, tilt neuronal circuits away from normal activity levels (center-point), and balanced excitation/inhibition (along the counter-diagonal), towards hyperexcitability or hypoexcitability. Aeta (Aη-α) induces neuronal suppression (hypoexcitability) although the mechanism of action is currently unknown.

Figure B1 (Text Box 3): Schematic of main amyloid precursor protein (APP) processing pathways and cleavage products.

Supplementary Figure 1: Schematic summarizing reported Aβ-mediated effects. This list is not exhaustive, with Aβ reported to exert manifold and bidirectional effects outside of the scope of the current text, and which are the focus of several other reviews (e.g. see Cline et al., 2018; Crouch et al., 2008; Mao and Reddy, 2011). Asterisk denotes that picomolar

concentrations of Aβ can augment LTP, with high nanomolar concentrations resulting in the oft-seen reduction in LTP (Puzzo et al., 2008).

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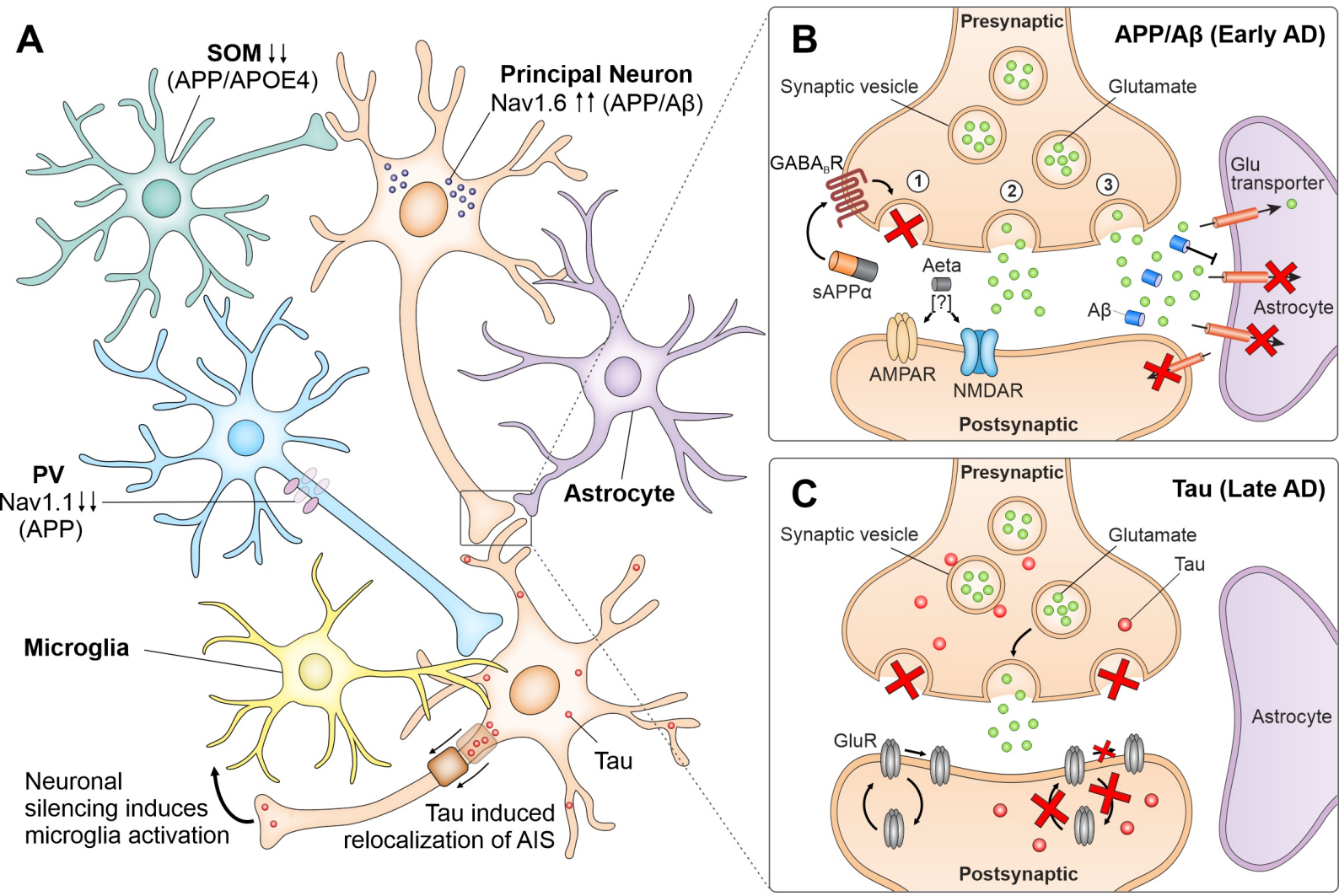
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SOM ↓↓
(APP/APOE4)
Principal Neuron
Nav1.6 ↑↑ (APP/Aβ)
PV
Nav1.1↓↓
(APP)
Astrocyte
Microglia
Tau
Neuronal
silencing induces
microglia activation
Tau induced
relocalization of AIS
B
Presynaptic
APP/Aβ (Early AD)
Synaptic vesicle
Glutamate
GABA$_B$R
1
2
3
Glu
transporter
sAPPα
Aeta
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Aβ
Astrocyte
AMPAR
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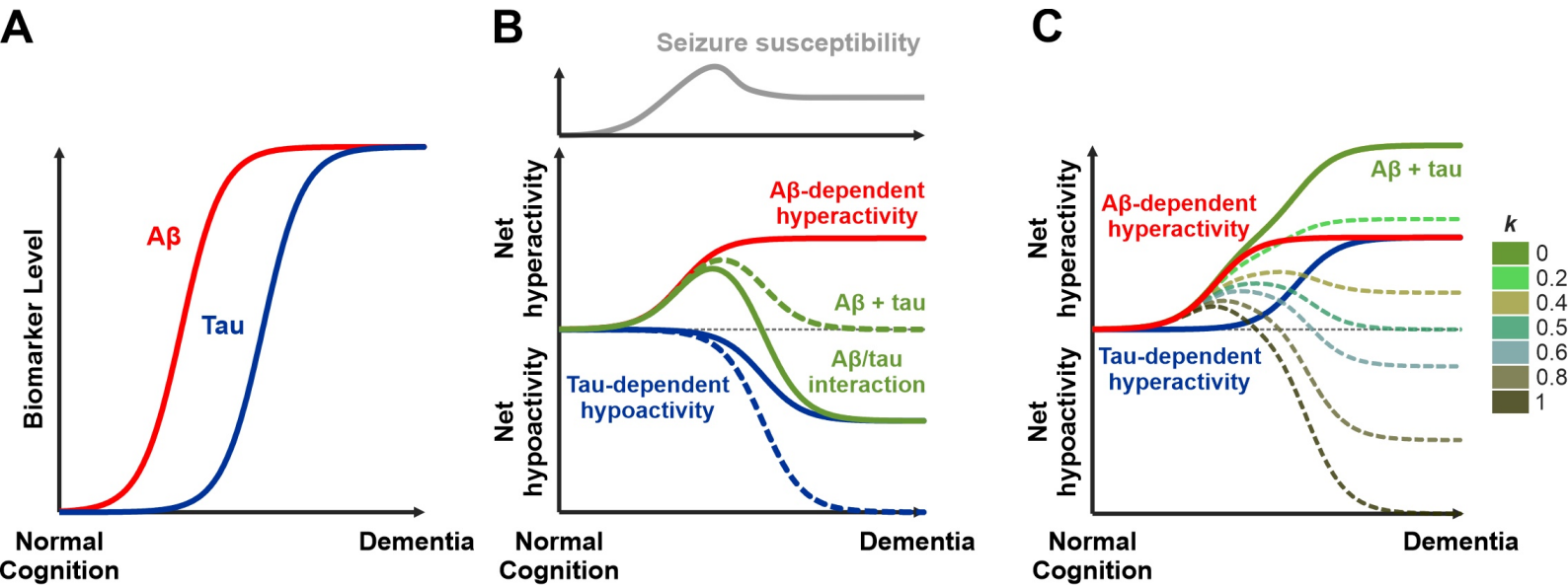
Glutamate
Tau
Astrocyte
GluR
Postsynaptic


A
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Normal Cognition
Dementia
B
Seizure susceptibility
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Aβ-dependent hyperactivity
Aβ + tau
Aβ/tau interaction
Net hypoactivity
Tau-dependent hypoactivity
Normal Cognition
Dementia
C
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Aβ-dependent hyperactivity
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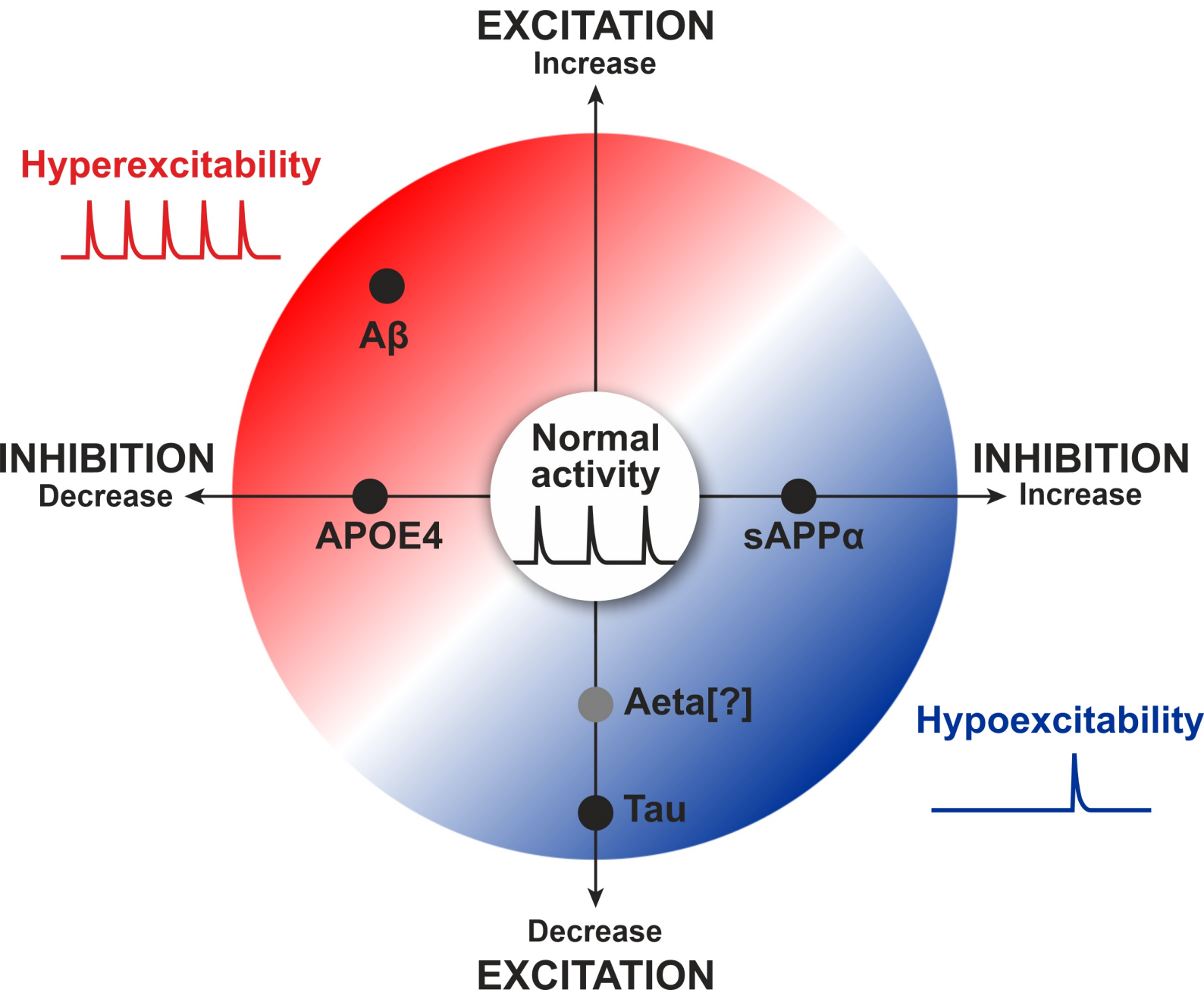
Normal Cognition
Dementia


EXCITATION
Increase
Hyperexcitability
Aβ
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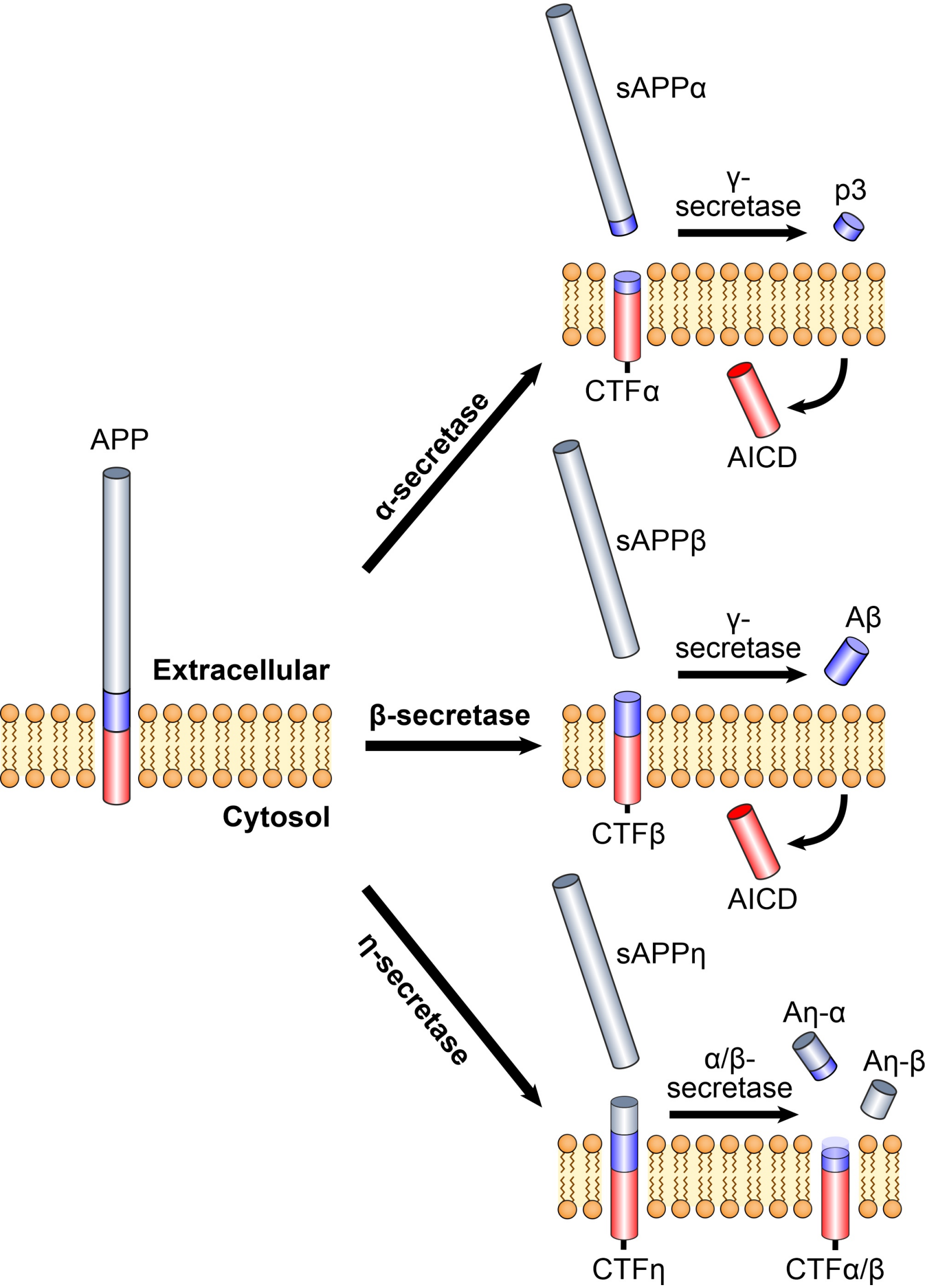
sAPPα
γ-
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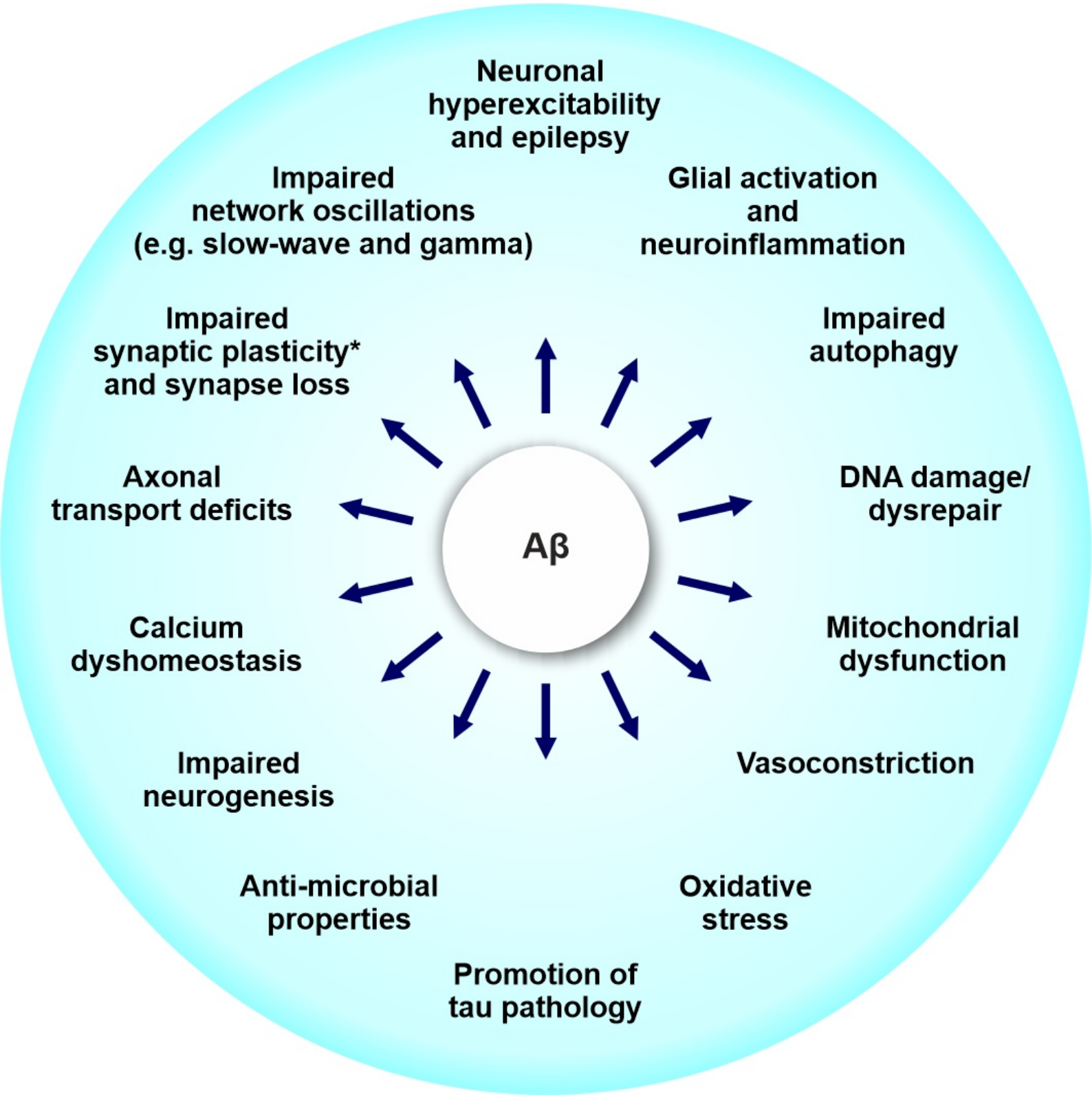
Neuronal hyperexcitability and epilepsy
Glial activation and neuroinflammation
Impaired autophagy
DNA damage/ dysrepair
Mitochondrial dysfunction
Vasoconstriction
Oxidative stress
Promotion of tau pathology
Anti-microbial properties
Impaired neurogenesis
Calcium dyshomeostasis
Axonal transport deficits
Impaired synaptic plasticity* and synapse loss
Impaired network oscillations (e.g. slow-wave and gamma)
Aβ