A Lipid-Raft Theory of Alzheimer's Disease

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Abstract. I present a theory of Alzheimer's disease (AD) that explains its symptoms, pathology, and risk factors. To do this, I introduce a new theory of brain plasticity that elucidates the physiological roles of AD-related agents. New events generate synaptic and branching candidates competing for long-term enhancement. Competition resolution crucially depends on the formation of membrane lipid rafts, which requires astrocyte-produced cholesterol. Sporadic AD is caused by impaired formation of plasma-membrane lipid rafts, preventing the conversion of short- to long-term memory and yielding excessive tau phosphorylation, intracellular cholesterol accumulation, synaptic dysfunction, and neurodegeneration. Amyloid β (Aβ) production is promoted by cholesterol during the switch to competition resolution, and cholesterol accumulation stimulates chronic Aβ production, secretion, and aggregation. The theory addresses all of the major established facts known about the disease and is supported by strong evidence.

Keywords. Alzheimer's disease; adaptive response plasticity; double-edged plasticity; short-term memory; cholesterol; lipid rafts;

1 Introduction

Alzheimer's disease (AD) is the main type of dementia, affecting dozens of millions of people [1]. Despite extensive research (215,000 papers indexed in PubMed, 1.9 million in Google Scholar) and many hypotheses [2], there is at present no coherent theory of AD. The dominant explanation is the amyloid β (Aβ) hypothesis, but it is not a complete theory and is widely criticized [3].

The minimal requirement for any theory of AD is to explain the following major facts. The main AD symptom is memory impairment, starting with anterograde memory and progressing

to retrograde memory. Other cognitive deficits are also present [1]. Olfaction and hearing problems occur very early, as do retinal abnormalities [4]. There are two disease variants, sporadic and familial autosomal dominant (FAD), with the former appearing only in relatively old age. The defining AD pathologies are intracellular neurofibrillary tangles (NFTs), which are associated with hyperphosphorylated tau (hyper p-tau), and extracellular plaques containing Aβ [1]. Tau pathology shows good spatial and temporal correlation with symptoms [5], but plaques are also commonly present in nondemented people during aging, and not all demented people exhibit them [3]. Several basic cellular components show dysfunctions that often precede NFTs and plaques, including in mitochondria and in lipid (especially cholesterol) and calcium homeostasis [6]. AD involves early synaptic damage and loss, followed by severe neurodegeneration [7]. Carrying the apolipoprotein (Apo) E4 isoform is strongly associated with AD, while ApoE2 is almost completely protective. There are other risk factors (female sex, viral infection, brain injury, insulin resistance (IR), inflammation, damaged brain blood vessels, and stress), and protective factors (education). Obesity and being underweight increase risk, but being overweight is protective.

This article presents a new theory of AD, the lipid-raft theory of AD (T*AD), which explains all of these facts. To do so, it first presents a new theory of brain plasticity; the theory of adaptive response plasticity (T*PL), which explains how neural activity yields memory formation; and the physiological roles of the main AD agents. The focus on plasticity is motivated by the fact that initial memory symptoms involve anterograde amnesia of benign everyday events [1]. This points to an early impairment in normal memory formation processes, i.e., in brain plasticity. Current descriptions of brain plasticity are incomplete and do not address AD agents, prompting the development of a new theory.

T*PL and T*AD address the major established facts known about brain plasticity and AD, methodically identified via a thorough examination of the scientific literature (hundreds of thousands of papers) done over more than 10 years. Both theories are supported by very strong evidence.

1.1 Overview of the Theory of Adaptive Response Plasticity

In T*PL, the organism can be in one of three states. The steady state involving neurons, their interconnections (synapses), and glia is supported by stable receptors and channels, the cytoskeleton, adhesion and scaffolding molecules, trans-synaptic nanodomains, extracellular matrix (ECM), myelin, and various constitutively active enzymes. Novelty-induced neural activity initiates a plasticity process consisting of two stages. First, a candidate generation (Cgen) stage involves the formation of elements competing for long-term enhancement. Candidates include existing synapses, new synapses, new neurite branches, and (sometimes) new neurons. This stage involves destabilization of the steady state, immediate potentiation of neurotransmission, and structural changes, and it is what underlies short-term memory (STM) (Figure 1). Second, competition resolution (Cres) consists of the enhancement of winning candidates, the elimination of losers, and restabilization (Figure 2). Winner enhancement starts early but involves a

relatively long process in which the evoked changes undergo consolidation to establish a new steady state (Figure 3).

Crucially, the switch from Cgen to Cres depends on the formation of plasma-membrane (PM) lipid rafts (LRs), ordered lipid nanodomains enriched in cholesterol, sphingomyelin (SPM), and phospholipids, which are essential for connecting the membrane to the cytoskeleton, the ECM, and synaptic partners and hence for receptor trafficking and signaling, winner enhancement, and stabilization. The role of tau is to promote cytoskeleton growth and stability in winning synapses. It is activated in a PM LR–dependent manner via dephosphorylation during early winner enhancement and inactivated during Cgen and loser removal. The role of amyloid precursor protein (APP) is to manage cholesterol during plasticity. APP has two mutually exclusive cleavage products, soluble APP α (sAPPα) and AβśAPPα is a major Cgen agent promoting cholesterol synthesis and transport. The incorporation of sufficient amounts of cholesterol in LRs triggers the production of Aβ, which terminates Cgen and removes losing candidates.

1.2 Overview of the Lipid-Raft Theory of Alzheimer's Disease

Once plasticity in health is understood, we can see what goes wrong in AD. T*AD provides a complete mechanistic account of AD symptoms, pathology, and risk factors. The central thesis is that AD is caused by impaired formation of PM LRs, mainly due to insufficient neural uptake of cholesterol, which is normally produced by astrocytes and transported to neurons via ApoE.

Reduced formation of PM LRs prolongs Cgen and prevents Cres (Figure 4), with three major consequences. First, STM is not converted to long-term memory (LTM), explaining AD anterograde amnesia. Second, the cytoskeleton is not linked to the membrane properly, leading to excessive p-tau, mitochondrial problems, impairment in all signaling triggered by PM receptors (including growth factor signaling), and eventual neurodegeneration. Tau phosphorylation is a direct consequence of the core mechanism of the disease, explaining the correlation between tau pathology and symptom severity.

A third consequence of impaired PM LRs is increased cholesterol production by neurons. In many cases, this is not sufficient to produce PM LRs and stimulates chronic Aβ production, leading to membrane Aβ cation channels that induce calcium toxicity and to Aβ aggregation. In other cases, neural cholesterol production does manage to establish PM LRs, with intact plasticity accompanied by excessive Aβ. This explains why Aβ plaques are associated only weakly with AD symptoms and why cognitively healthy people can exhibit them. They are neither causal nor essential for the disease.

Neurodegeneration is exacerbated by the fact that many plasticity agents obey a double-edged plasticity (DEP) principle, whereby an agent can support both Cgen and Cres, depending on the amount or cleavage. Crucially, Ca^{2+} is a DEP agent, with high Ca^{2+} marking winners and low Ca^{2+} inducing loser elimination. Since the LR impairment leads to chronic plasticity processes that involve relatively small calcium amounts, AD involves chronic loser elimination processes that yield degeneration.

Impaired formation of PM LRs can stem from several causes. In general, it occurs due to an

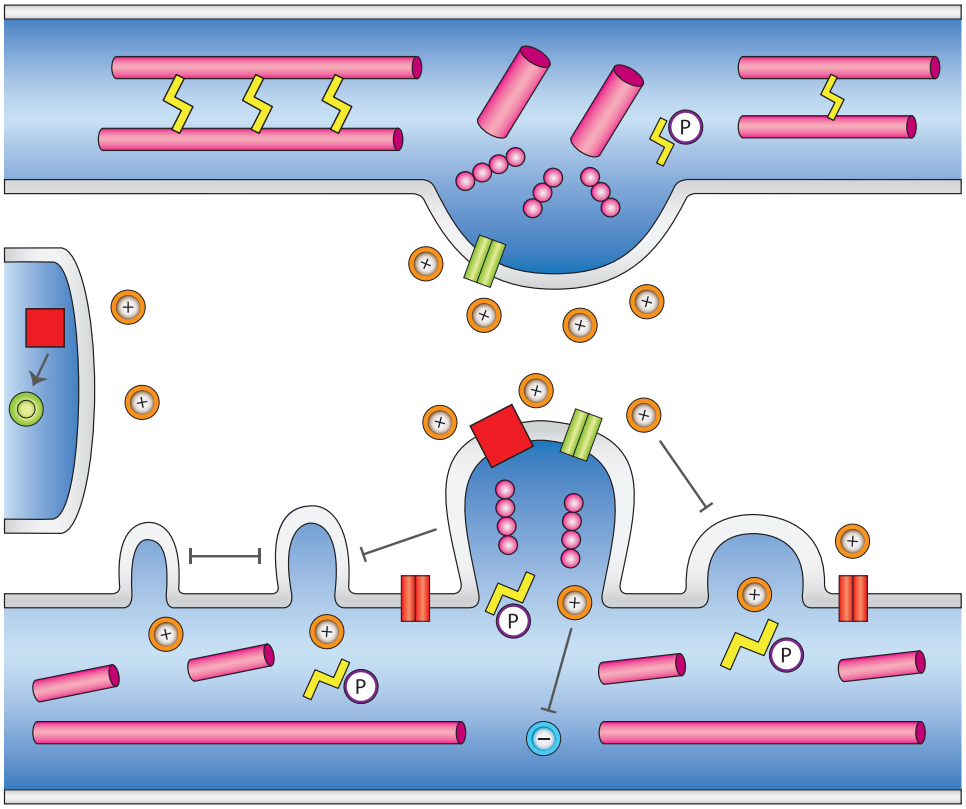

Figure 1: **Candidate generation (Cgen).** Candidate generation (Cgen). Neural activity triggers the release and activation of Cgen agents [e.g., tissue plasminogen activator, matrix metallopeptidase 9, brain-derived neurotrophic factor; circled plus symbols]. (a) These agents induce phosphorylation (P) of tau (yellow shapes), which destabilizes cytoskeleton microtubules (pink cylinders) to allow candidate generation; (b) induce the formation of competing candidates [four postsynaptic dendritic spines, one presynaptic axon bouton, and calcium-permeable glutamate receptors (red cylinders)] supported by dynamic actin (pink circles); (c) suppress competition-resolution agents (circled minus symbols); and (d) promote candidate growth. sAPPα (red square) is located outside lipid rafts (green cylinders) and promotes Cgen. In astrocytes, sAPPα promotes synthesis of cholesterol (green circle). The presynaptic neuron is shown at the top, and the postsynaptic neuron is shown at the bottom; an astrocyte is shown on the left. Abbreviation: sAPPα, soluble amyloid precursor protein α.

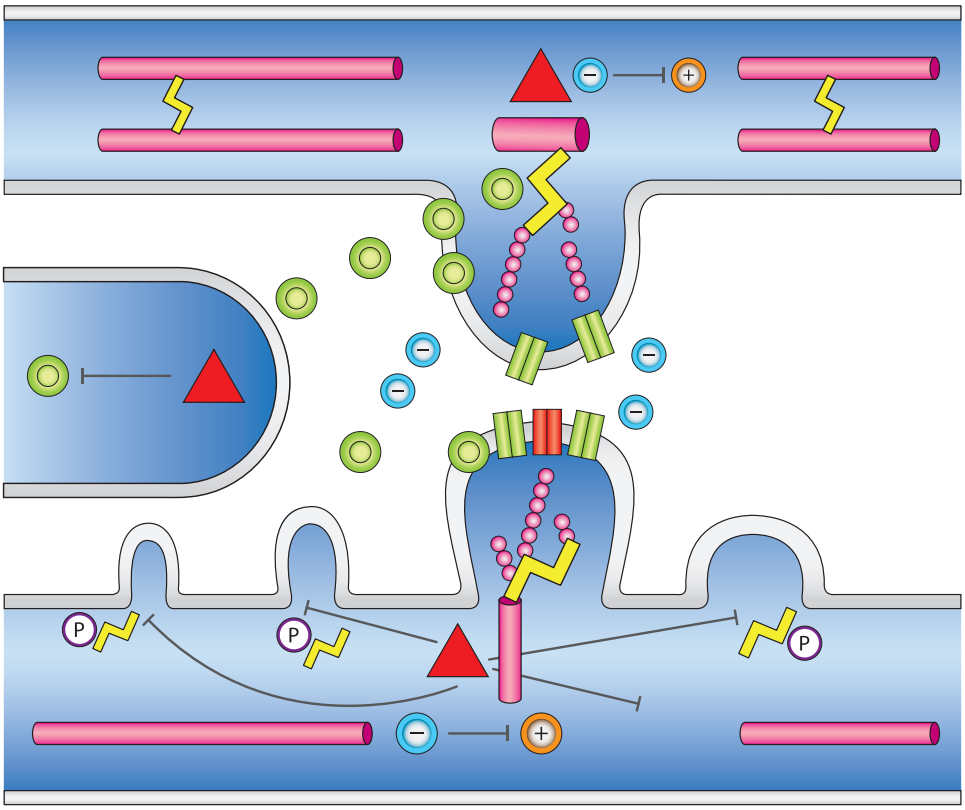

Figure 2: **Competition resolution (Cres)**. Astrocyte-produced cholesterol (green circles) transported by apolipoprotein E triggers the switch to Cres (circled minus symbols represent Cres agents), which includes production of amyloid β (Aβ) (red triangle) and formation of lipid rafts (green cylinders). Winning candidates are enhanced; active tau (yellow shapes; P indicates phosphorylation) supports growth by linking microtubules (pink cylinders) and active actin (pink circles); calcium-permeable glutamate receptors (red cylinders) translocate to synapses; and Aβ suppresses losing candidates, cholesterol, and candidate-generation agents (circled plus symbols). The presynaptic neuron is shown at the top, and the postsynaptic neuron is shown at the bottom; an astrocyte is shown on the left.

accumulation of risk factors, the strongest of which is aging. Other risk factors include ApoE4, infection by viruses that target LRs, brain IR (which impairs cholesterol synthesis), damaged brain vasculature, brain injury, stress, and chronic neuroinflammation.

The following sections detail T*PL, T*AD, the evidence for these theories, and AD risk factors.

2 The Theory of Adaptive Response Plasticity

Brain responses with any element of novelty trigger plasticity processes that alter the paths involved in response execution to facilitate the activation of this response in similar future situations. Plasticity can modify, create, or remove synapses, neurite branches, neurons, glia, and glial processes. The fundamental plasticity task is to identify or create the existing or new elements to be modified, perform the modification, and integrate the changes into the existing network. T*PL explains how this is done.

During the stable steady state, the brain uses a variety of mechanisms to achieve execution efficiency via structural and molecular stability. When plasticity is required, a two-stage process is initiated. The first stage, candidate generation (Cgen), involves destabilization of the steady state to allow modifications and generation of potential elements to be modified. These include synapses to be potentiated, new neurite branches, new boutons and spines, and new neurons. Candidates are generated in all areas in which there is novelty-related execution, as indicated by high calcium influx. A single neuron normally contains many synapse candidates, to provide a variety of options for optimal plasticity. The changes done at this stage promote high calcium influx via membrane insertion of calcium-permeable (CP) receptors.

Candidates compete for long-term persistence, the winners being those who have managed to gain sustained support from intracellular calcium. Competition occurs in a race-like manner, not directly, although candidates do compete indirectly over limited cellular resources.

In the second stage, competition resolution (Cres), winning candidates are enhanced, losing ones are eliminated, and the relevant structures are stabilized. Winner enhancement optimizes neurotransmission in terms of time and energy by creating spatially and temporally focused signaling and by replacing the CP receptors added during Cgen with receptors that allow the passage of less or no calcium. Winning spines are structurally supported via the formation of an actin cytoskeleton, which requires tau-mediated connectivity to cytoskeleton microtubules (MTBs) and the formation of trans-synaptic nanodomains. Losing spines and branches are retracted and removed, with appropriate modifications to the cytoskeleton. There is a relatively long consolidation process, much of it occurring during sleep, that involves protein synthesis to reestablish membranes, cytoskeletons, and the ECM.

There is overwhelming evidence that neural activity changes neurotransmission and induces new synapses, dendritic spines, axonal boutons, branching points, and (sometimes) neurons; that the neurons and neurites connected by new synapses participate in the inducing responses; that these changes undergo stabilization and consolidation; and that this process underlies mem-

ory [8]. There is also strong direct evidence for interspine competition [9]. Further evidence is given in Section 4.

The switch from Cgen to Cres is triggered by the formation of PM LRs, which are essential for connecting the membrane to the cytoskeleton, the ECM, and synaptic partners and thus for trafficking and anchoring receptors and scaffold proteins to winning candidates and for linking presynaptic and postsynaptic cells. The most sensitive element in LR formation is cholesterol, because it is produced by astrocytes and transported to neurons. Unlike other astrocyte-produced agents (e.g., glutamine, lactate), cholesterol has a large hydrophobic domain, and its transport requires relatively heavy machinery (ApoE). APP is a central plasticity protein whose major physiological role is to manage cholesterol during plasticity, with sAPPα promoting its synthesis and Aβ terminating it.

T*PL is a general theory in which plasticity consists of a single, well-defined process evoked in all plasticity-inducing contexts, including neonatal development, adult learning, and recovery after injury. It also operates in the same manner across all body tissues. These aspects are not detailed here due to my focus on the brain and AD.

2.1 Double-Edged Plasticity

The brain does not know in advance which candidates will win and which will lose, so both winners and losers are stimulated by the same agents. To distinguish between winners and losers, biology uses a mechanism that I call double-edged plasticity (DEP). In DEP, different agent amounts, rates, or cleavages can induce opposite effects. To induce amount-dependent effects, the agent binds different receptors or domains with different affinities. Usually, winners and losers use low and high affinities (high and low amounts), respectively. Brain agents are chemical and propagate through media, so only a focused execution path receives a high amount, defining where the winners are located.

Many important agents directly obey DEP. Calcium activates Ca^{2+}calmodulin-dependent protein kinase II (CaMKII) and protein phosphatase 2B (PP2B), promoting Cgen or Cres (see Section 2.6). Dopamine has two receptor families, the low-affinity D1R family that supports vigorous activity [via the G protein–coupled receptors (GPCRs) Gs and Gq] and the high-affinity D2R family that opposes it (via Gi/o) [10]. Similarly, high- and low-affinity serotonin 5-HT1 and 5-HT2 receptors suppress and promote effortful activity, respectively [11].

Another mechanism that supports DEP is different cleavages of a protein. To induce cleavage effects, the precleavage and various postcleavage agents activate different signaling pathways. This is the case with APP (see Section 2.4) and growth factors [brain-derived neurotrophic factor (BDNF) and neural growth factor (NGF)], whose mature forms support candidate and winner growth while their proforms support loser removal (see Section 2.6).

2.2 Long-Term Potentiation and Long-Term Depression

The notions of long-term potentiation (LTP) and long-term depression (LTD), which are ubiquitously used in relation to plasticity, are not used in T*PL. LTP occurs in both Cgen (all over) and Cres (in winners), and LTD occurs in Cres in both winners and losers. These terms are suitable for describing the local effects of specific experimental conditions but not for the high-level theory.

The following sections detail the steady state, Cgen, cholesterol and LRs, and Cres, with an emphasis on the T*PL aspects that are most relevant to AD.

2.3 The Steady State

The main relevant components of the steady state are the cytoskeleton, adhesion and scaffold proteins, the ECM, myelin, and constitutive enzyme activity.

Cytoskeleton. The cytoskeleton supports intracellular trafficking, including that of mitochondria and growth factors; exocytosis; and endocytosis and is crucial for neurotransmission and plasticity [12]. It has three main ingredients, MTBs, located mainly in axons but also in dendritic spines; intermediate filaments; and F-actin, located in spines. MTB and actin stability are mainly supported by Map1b and cofilin, respectively. Tau is discussed in Section 2.6.

Adhesion. A variety of synaptic adhesion proteins (e.g., neuroligin, neurexin, LRRTM) connect pre- and postsynaptic sites to improve physical stability and signaling [13]. An important role of these proteins is to establish trans-synaptic nanocolumns and cytoskeleton-connected synaptic nanodomains that restrict the spatial propagation of neurotransmitters to provide rapid and efficient activation of downstream signaling [13]. Stable localization of receptors at the PM is assisted by scaffold proteins such as PSD95 and GRIP1 [14].

Extracellular matrix. The brain's ECM is mainly arranged in perineuronal nets and the perinodal ECM [15]. It is synthesized following neural activity and provides stability. It closes the critical period of plasticity during development, opposes the lateral diffusion of some synaptic proteins to extrasynaptic sites, and augments synaptic adhesion [15]. Integrins are a family of cell surface ECM adhesion molecules that support cytoskeleton-based bidirectional trafficking [16]. Thus, the steady state includes a global skeleton that connects all cells to each other via cytoskeletons, adhesion molecules, and ECM.

Myelin. Oligodendrocyte (OLG) processes enwrap neural axons in a myelin sheath mainly made of OLG-produced cholesterol. Myelin protects axons and improves neurotransmission.

Constitutive activity. There are many proteins that are constitutively active to support the steady state. The ones most relevant here are CaMKII, protein kinase M zeta (PKMzeta), and glycogen synthase kinase 3 (GSK3β) (see Section 2.6).

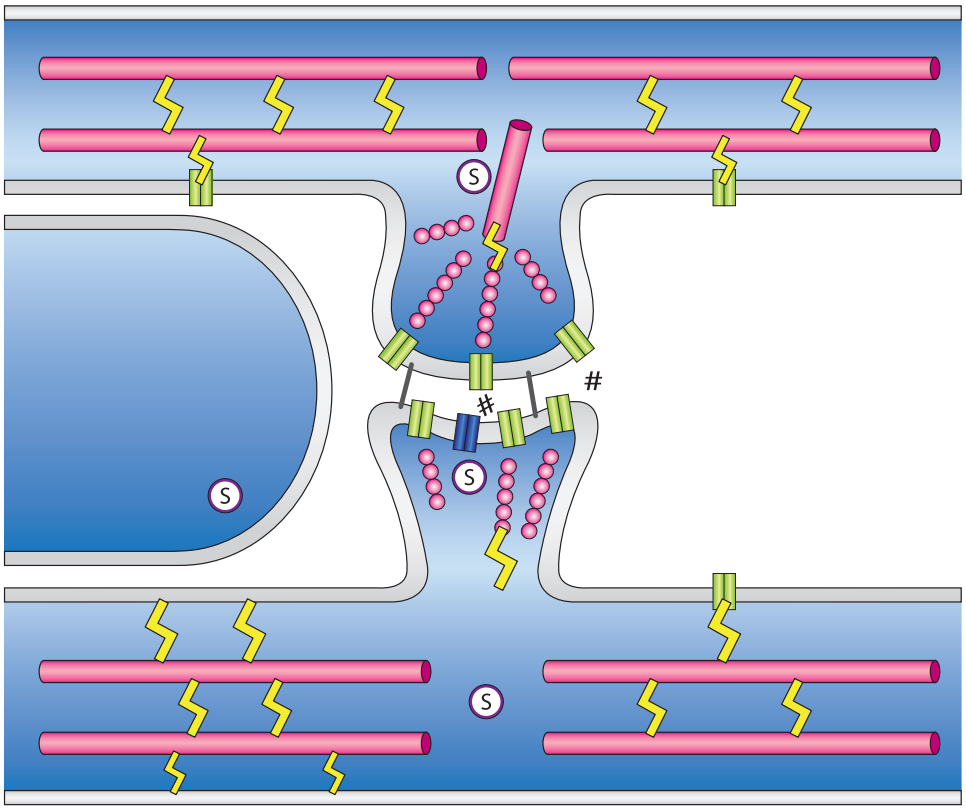

Figure 3: **The stable state**. Presynaptic and postsynaptic winners and the astrocyte processes supporting the new synapse complete their growth. Stability agents (S) maintain the stable state. Protein phosphatase 2A (PP2A) dephosphorylates tau (yellow shapes) to allow it to support structural elements. Lipid rafts (green cylinders) cooperate with the cytoskeleton (pink cylinders represent microtubules, and pink circles represent dynamic actin) to support receptor anchoring. Synaptic glutamate receptors are switched to be calcium impermeable (blue cylinders). Adhesion molecules (black lines) connect the two sides of the new synapse and form nanodomains, with protection from the extracellular matrix (hash symbols). The presynaptic neuron is shown at the top, and the postsynaptic neuron is shown at the bottom; an astrocyte is shown on the left.

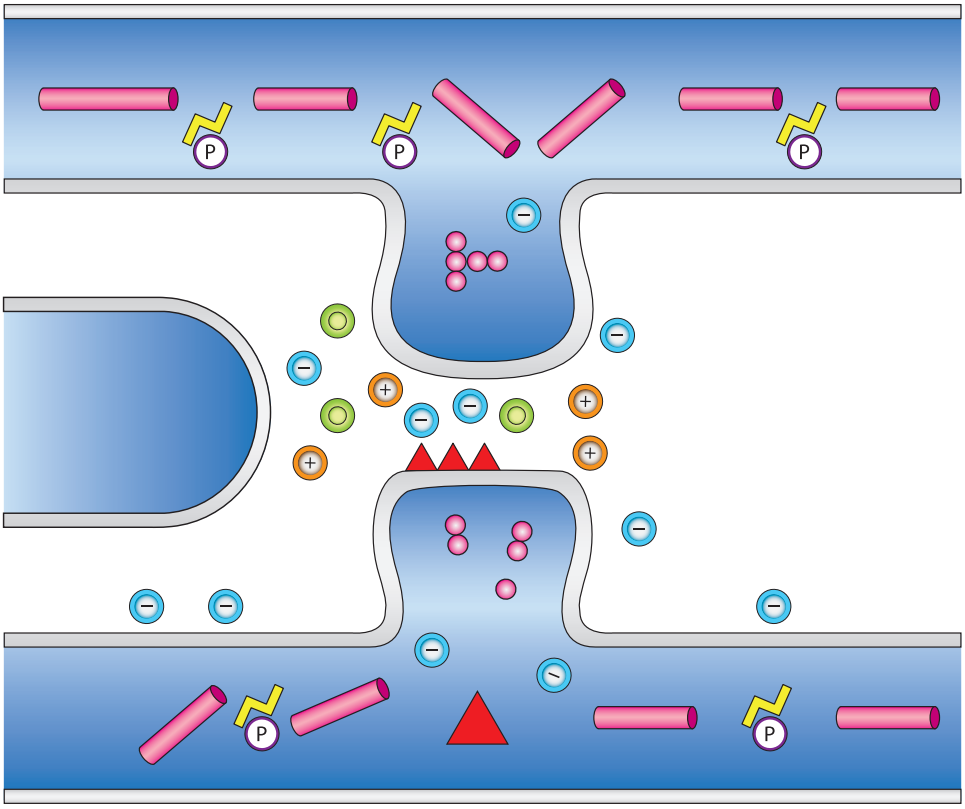

Figure 4: **Chronic plasticity and impaired competition resolution (Cres) in Alzheimer's disease (AD)**. In AD, cholesterol (green circles) is not incorporated sufficiently into plasma membrane lipid rafts (LRs) (e.g., due to reduced transport by apolipoprotein E4). As a result, synapse formation is not completed, manifesting as anterograde amnesia. LR deficiency impairs the switch from candidate generation (Cgen) to Cres (circled minus symbols indicate Cres agents) and results in a state of chronicity in which Cgen agents (circled plus symbols) remain present. Although chronicity starts with Cgen agents, the resulting state is biased toward Cres functionality due to the double-edged plasticity (DEP) principle. This yields hyper p-tau (yellow shapes; P indicates phosphorylation), neurite retraction, cytoskeleton collapse (pink cylinders represent microtubules, and pink circles represent dynamic actin), and eventually cell death, which manifest as retrograde amnesia. Chronic cholesterol production induces amyloid β (Aβ) (red triangles) plaques, and Aβ forms toxic cation pores. The presynaptic neuron is shown at the top, and the postsynaptic neuron is shown at the bottom; an astrocyte is shown on the left. Intracellular cholesterol and endosomal problems are not shown.

2.4 Candidate Generation

Cgen is triggered in acute states involving protein kinase A (PKA) activation and strong Ca^{2+} influx, depolarizing the cell and inducing action potentials. This is rapidly followed by the release of the growth factor proforms proBDNF and proNGF [17] (both pre- and postsynaptically); tissue plasminogen activator (tPA), which cleaves proforms to their mature forms, BDNF and NGF [18]; and matrix metallopeptidase 9 (MMP9), which digests ECM and adhesion molecules [19]. Cell detachment from the ECM activates integrin signaling and yields the endocytosis of LR components such as caveolin1, destabilizing the steady state [16].

PKA, MARK2, and high levels of Ca^{2+}activated CaMKII phosphorylate tau at S262, S356, and S214, and ERK phosphorylates tau at S199 and S202 [20]. Phosphorylation of tau inactivates it to destabilize the existing MTB–actin cytoskeleton and is essential for neurite formation. ERK also destabilizes myelin [21]. Thus, Cgen destabilizes both extracellular and intracellular stabilization mechanisms.

A central T*PL tenet is that Cgen is a state of cholesterol deficiency. In support, statins, which decrease cholesterol synthesis, increase expression of tPA and p11 (another agent that facilitates growth factor maturation) and BDNF maturation activity [22], and cholesterol deficiency induces hyperphosphorylation of tau, axonal degeneration, and MTB depolymerization (breakdown) [23]. NGF is a plasticity agent supporting winners. It cooperates with the Akt axis (see Section 2.6) to promote cholesterol synthesis and rapid axonal growth [24].

Silent synapses contain N-methyl-d-aspartic acid receptors (NMDARs; mainly the GluN2B subunit) but not α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) [25]. BDNF acts via tropomyosin receptor kinase B (TrkB) and enhances GluN2B currents to promote neurite branching [26] and trafficking of AMPARs (mainly the GluA1 subunit) to silent synapses, unsilencing them [25]. These unsilenced synapses are branching candidates. CaMKII binding to GluN2B is needed for spinogenesis [27]. Wnt protein, which promotes growth during development, also promotes axonal branching during Cgen [28].

GluA2-lacking AMPARs are calcium permeable. CP-AMPARs are located at extrasynaptic or synaptic sites, and mark synaptic candidates. During Cgen, PKA and CaMKII stimulate GluA1 surface expression via phosphorylation at S845 and S831 [29], with ERK promoting GluA1 trafficking to synapses [30]. Existing synapses are not degraded but are destabilized via the digestion of adhesion molecules, and their excitatory currents are enhanced by switching AMPARs to be calcium permeable via GluA2 endocytosis promoted by protein kinase C (PKC) phosphorylation at S880 [31].

Most PKC isoforms are activated by calcium. In addition to GluA2 endocytosis, PKC promotes membrane incorporation of GluA1 via pS181 [32] and activation of the Rho GTPase Rac1, which promotes spinogenesis via the actin cytoskeleton [33].

Reelin is an agent that promotes neural migration and growth during development, after which its expression diminishes. In the adult brain, it is expressed by excitatory neurons in entorhinal cortex (ETRC) layer 2 projecting into the hippocampus, GABAergic neurons in cortical layers 1/2, and retrosplenial cortex-projecting GABAergic hippocampus neurons [34]. All of

these neurons have axons in long-distance pathways. Reelin is a Cgen agent promoting APPα cleavage [35] and neurite branching [36]. In T*PL, its role is to promote the integration of new neurons and events into the network.

Amyloid precursor protein and soluble amyloid precursor protein α. Amyloid precursor protein (APP) is a transmembrane protein cleaved by α-secretase to yield sAPPα, with the remaining part later cleaved by γ-secretase, or by β-secretase (BACE1) followed by γ-secretase to generate AβḊespite extensive research on Aβ and APP [37], to my knowledge there is no coherent account of their physiological roles. T*PL provides such an explanation, in which sAPPα and Aβ are Cgen and Cres agents, respectively. A specific role of APP is to manage cholesterol, with sAPPα promoting its synthesis and transport and Aβ terminating its synthesis and promoting extrusion.

APP transcription is mainly promoted by Cgen agents, including BDNF [38] and ERK [39]. α cleavage (i.e., sAPPα production) is promoted by Cgen agents, including BDNF [40], NGF [41], tPA [42], MMP9 MMP9[43], and PKC [44]. Supporting the T*PL thesis that Cgen is a state in which membrane cholesterol is needed, α cleavage is stimulated by reduced membrane cholesterol [45] and occurs in non-LR domains [46]. sAPPα promotes cholesterol synthesis. The intracellular part created by sAPPα cleavage increases SREBP2, the main agent inducing cholesterol synthesis, in cells with low cholesterol, including human astrocytes [47]. sAPPα directly binds to and activates insulin receptors [48], which activate SREBP2 via the PI3K–Akt–mTOR axis and increase α-secretase expression [49].

sAPPα is a major Cgen agent. It rapidly increases surface extrasynaptic GluA1, decreases GluA2 and GluA3 and de novo GluA2 synthesis [50], and promotes neurite growth, branching, spine density, and spine volume [51]. It is an adhesion molecule that promotes axonal outgrowth and synaptogenesis [52].

Cgen directly opposes Cres by suppressing BACE1 via several Cgen agents, including sAPPα [53], NGF, TrkA [43], and BDNF (via SORLA) [54]. Cgen does not end until winners can stably grow, which requires PM LRs.

Short-term memory. Cgen is what supports STM. In particular, it has been repeatedly shown that GluA1 is essential for STM, with knockout animals showing normal spatial reference memory but markedly impaired spatial working memory and STM [55].

2.5 Cholesterol, Apolipoprotein E, and Lipid Rafts

Cgen is a cholesterol-deficient state, and the incorporation of cholesterol in LRs switches the cell from Cgen to Cres. Cholesterol is a vital element in all body tissues [56]. The brain is the most cholesterol-rich organ, containing over 20% of body cholesterol. Cholesterol is a major ingredient of LRs and myelin. It is also the precursor of steroids, which are major plasticity agents. Cholesterol does not cross the blood–brain barrier. Brain cholesterol is produced in astrocytes, transported to neurons in ApoE particles, and taken up via ApoE receptors [mainly the low-density lipoprotein receptor (LDLR) and LDLR-related protein 1 (LRP1)]. ApoE tran-

scription is promoted in growth situations via growth factors (BDNF and NGF) and estrogen [57, 58, 59]. It is normally produced by neurons only in small amounts, with production increasing in conditions of stress, injury, and resource deficiency [60].

Cholesterol synthesis is mainly stimulated by SREBPs [61], which also promote LDLR expression. SREBPs are activated by lack of PM cholesterol and by ERK and insulin–Akt signaling (see Section 2.6). The brain-specific cholesterol metabolite 24S-hydroxycholesterol (and its non- brain oxysterol counterpart 27-hydroxycholesterol) and intracellular cholesterol excess suppress SREBP and activate nuclear liver X receptors (LXRs), which promote ApoE and the transporters ABCA1 and ABCG1. These extrude cholesterol by lipidating ApoE and transporting it across the membrane.

Apolipoprotein E isoforms. Humans have three ApoE isoforms that differ in amount produced and transport capacity: ApoE2, ApoE3, and ApoE4, in order from greatest to lowest production and transport capacity [62]. ApoE4 has the highest receptor affinity, saturating receptors faster. These properties can have both positive and negative consequences. ApoE4 is more efficient in terms of speed and resources, explaining its various positive effects [e.g., improving cognition during youth [63]]. However, the fact that the neurons of ApoE4 carriers receive less cholesterol makes them vulnerable in aging, as discussed in this article.

Lipid rafts. LRs are dynamic membrane nanodomains enriched in cholesterol; sphin- golipids, mainly SPM; and glycerophospholipids such as gangliosides [64]. LRs were originally controversial due to technical difficulties but are now fully accepted. LRs increase local membrane rigidity and serve to anchor proteins and link the membrane to the cytoskeleton and the ECM, thereby supporting the connection between the intracellular and extracellular environments, specifically extracellular induced signaling [65, 16]. They are a major site of membrane proteins and are central cytoskeleton trafficking targets, interfacing with the actin cytoskeleton [64]. MTB proteins, mainly tau, associate with LRs, and impairing this association yields axonal retraction [66, 65].

Palmitoylation targets proteins to LRs and is required for stable membrane anchoring of many proteins, including synaptic density proteins, glutamate receptors and their recycling proteins, steroid receptors, GPCRs, and actin-regulating proteins required for spine growth [67]. Caveolae are LRs that contain caveolin1 and show as membrane invaginations. They are essential for membrane anchoring and trafficking of tyrosine kinase receptors such as TrkA (the NGF receptor) and the insulin receptor [68]. LRs and cholesterol are required for the activation of nicotinic receptors [69].

LRs are essential for plasticity. Synaptogenesis requires astrocyte-derived cholesterol [70]. Depletion of cholesterol or sphingolipids leads to gradual loss of hippocampus dendritic spines and synapses and to surface AMPAR instability [71]. Cholesterol depletion blocks winner enhancement in hippocampus CA1 [72], an area that shows specific vulnerability in AD (see Section 4.6).

LRs are present in intracellular membranes as well, including in mitochondria-associated endoplasmic reticulum membranes (MAMs), which are essential for mitochondria function

[73], and in the trans-Golgi network and recycling endosomes [74].

2.6 Competition Resolution: Winners and Losers

Cgen induces indiscriminate destabilization, candidate generation, and cellular calcium influx in the vicinity of active sites. Cholesterol induces a switch from Cgen to Cres in two ways. It allows winner enhancement through LRs and it stimulates the production of Aβ, which is the main loser- removal agent.

Cres has four main components. First, calcium influx is reduced in both winners and losers. Calcium must be restrained because it can be toxic. Most relevantly here, calcium activates calmodulin, whose continued binding to PSD95 rapidly (within 15 minutes) decreases its palmitoylation and synaptic location and increases AMPAR endocytosis, rendering synapses unusable [75]. This time frame is consistent with the duration of STM. Calcium is restrained by switching GluN2B to the GluN2A subunit [76], replacing CP-AMPARs with CI-AMPARs by adding GluA2 [77], and endocytosis of GluA1 via PP2B [78].

Second, the cytoskeleton is linked to the PM in winners to support trafficking, with tau being a major player (see Section 2.6.2). Third, winning synapses are stabilized, including through the formation of nanodomains for efficient neurotransmission [79]. Finally, the membrane is returned to a stable condition by removing losing candidates (see Section 2.6.3).

Winner determination. Ca^{2+} is a DEP agent, with large amounts (or rates) activating kinases (mainly CaMKII) that promote winners, and small amounts activating phosphatases (mainly PP2B) to eliminate losers [80]. It is not possible to restrain calcium before some persistent enhancement of winners occurs, because strong, focused, persistent calcium is what determines winner status. Once LRs are incorporated into the PM, Cres can enhance winning candidates and remove losing ones to establish a new steady state.

There are two main agents involved in winner enhancement, CaMKII and PKC. Both start their activity during Cgen (because winners need to be generated first (see Section 2.4) and continue during Cres.

CaMKII is activated by high calcium concentrations [27] during Cgen. It binds GluN2B, translocates with it to synapses, and promotes GluA1 channel conductance via phosphorylation at S831 [27]. It also induces spine growth via Rac1 [81]. When Cres starts, CaMKII undergoes autophosphorylation at T286, which allows it to continue activation without calcium. In this way, it can support synapse consolidation during Cres and possibly even the maintenance of synapses in the steady state. It promotes synapse stabilization and the formation of nanodomains via segregation of AMPARs and NLG from GluN2B [79] and the switch from GluN2B to GluN2A [76].

PKC is activated by sustained calcium release from intracellular stores. During Cgen, it promotes GluA1 synaptic delivery via S818 phosphorylation [32], structural growth via Rac1 [33], production of sAPPα over Aβ [44], and GluA2 endocytosis [14]. During Cres, it promotes the switch from GluN2B to GluN2A [76] and prevents winner damage due to Aβ (endocytosed APP undergoes β cleavage, unless this is opposed by PKC). At plasticity termination, its

constitutively active form, PKMzeta, supports LTM [82].

Candidate synapses that become large enough allow the invasion of MTBs and tau [83], an important factor in winner determination.

Tau. Tau binds cytoskeleton MTBs and was initially thought to support MTB stability. However, its detachment from MTBs does not destabilize them or impair axonal transport [84]. It is now viewed as a cross-linker of the MTB and actin cytoskeletons that promotes dynamic changes including axonal elongation, synapse formation, and stabilization of growing neurites [85].

During Cgen, tau is inactivated via phosphorylation (see Section 2.4) to oppose its stabilization effect. During Cres, it is activated in winners to promote their structural stabilization and cytoskeleton linking and inactivated in losers to allow their removal. Activation in winners is done by phosphatases, mainly PP2A [86]. Methylated (stronger) PP2A is enriched in LRs and decreases p-tau [87]. Inactivation in losers is mainly done by GSK3b and cyclin dependent kinase 5 (Cdk5), assisted by p75 [88].

As noted in section 2.5.2, active tau requires LRs to achieve its effects [66, 65]. Reducing cholesterol (which induces a loser-like, non-LR state) yields hyperphosphorylation of tau at the GSK3 and PKA sites [89]. Excess tau is secreted via direct translocation through the PM, and this action is supported by cholesterol and SPM [90]. Thus, extracellular tau is a normal by-product of plasticity-inducing activity.

Amyloid β. Aβ is a major Cres agent whose main role is to remove losers. The switch from α to β cleavage of APP, and thus initiation of Aβ production, occurs when LRs have been formed. Cholesterol clearly stimulates Aβ production and is needed for it, as its depletion inhibits BACE1 and γ-secretase additively [91, 92]. In turn, Aβ provides negative feedback on cholesterol synthesis [93], supporting the T*PL view that cholesterol synthesis occurs in Cgen but not Cres.

BACE1 operates in intracellular compartments (endosomes and Golgi), so Aβ can be produced without the formation of PM LRs [94] (as described in Section 3.3, this has important implications in AD). PM LRs are a feature of winners, while the main role of Aβ is to remove losers, which are spatially segregated from winners.

Aβ production is also promoted by the Cres agents p75 and JNK [95, 96]. Aβ promotes Cres by enhancing GSK3β [88, 48], PP2B [97, 78], proNGF [98], p75 [88], PTEN [99], JNK [96], and RhoA (which opposes Rac1) [100]. Aβ's loser removal functionality is obtained via three main mechanisms, involving RhoA; p-tau, via GSK3b, JNK; and p75, which is a high-affinity receptor for proBDNF and proNGF and a low-affinity receptor for NGF. p75 stops neurite growth and induces apoptosis [26]; with Aβ, p75 activates sphingomyelinase to remove SPM from the PM [93], thereby cleaning losing candidates from LR components and restoring membrane integrity.

Aβ opposes Cgen through these agents (e.g., GSK3β opposes Akt and thus insulin signaling, PP2B opposes BDNF, and PTEN opposes mTOR) and other mechanisms [e.g., it inhibits NGF [48] and nicotinic acetylcholine receptors (nAChRs), mainly the CP α-7 subunit [101]].

The ECM, which promotes the stable postplasticity state, contains several agents (e.g., heparan sulfate proteoglycan) that are contained in LRs and bind and take up Aβ [102].

Aβ is a DEP agent, possibly to prevent it from impairing winners. Aβ oligomers readily insert in membranes to form cation-selective pores [101, 103]. At low (picomolar) concentrations, the resulting calcium influx promotes the function of the α7 subunit of nAChRs [101], explaining the positive effect that low Aβ concentrations can have on LTP and growth [104]. At higher (nanomolar) concentrations, Aβ inhibits nAChRs and decreases plasticity [101, 104].

In summary, Aβ terminates Cgen, promotes Cres, especially loser removal, and terminates cholesterol synthesis. The common view of Aβ as a negative agent stems from the fact that loser removal involves reduced spine density and LTD. However, loser removal is essential for cellular health, and Aβ has a crucial healthy role in plasticity. Indeed, Aβ disruption prevents the consolidation and stabilization of memory [105].

Consolidation. This stage takes place after activity termination and involves protein synthesis and trafficking to the winning candidates, completion of loser removal, cytoskeleton stabilization, ECM and myelin production, and other actions needed to establish a stable steady state. Consolidation is one of the major processes taking place during sleep [106].

2.7 Summary

Brain plasticity starts with destabilization of the stable state, coupled with indiscriminate increases in neural excitability and the generation of structural candidates competing for enhancement. Winners are determined by sustained calcium signaling. Incorporation of cholesterol in PM LRs triggers a switch to restabilization, which involves winner enhancement and loser removal. The major agents in these processes are the AD-associated agents tau, APP, and cholesterol (with other lipids). sAPPα promotes the initial Cgen stage. Cholesterol induces a switch to the production of Aβ, which promotes loser removal. The formation of PM LRs allows activated tau to extend the cytoskeleton and link it to the enhanced winning synapses. Both Aβ and tau phosphorylation are crucial for normal, healthy plasticity.

3 The Lipid-Raft Theory of Alzheimer's Disease

Provided with a theory of brain plasticity that explains the roles of the main AD agents, it is now possible to understand what goes wrong in AD. This section presents the LR theory of AD (T*AD) and shows how it accounts for AD symptoms and pathology. Risk factors, protective factors, and strong evidence supporting the theory are given in subsequent sections. Unless explicitly noted, the discussion is about sporadic AD, not FAD.

3.1 Mechanisms Underlying Symptoms and Pathology

My starting point for explaining AD consists of the following three clues. First, the strongest genetic risk factor in AD, carrying ApoE4, points to reduced transport, neural uptake, or neural trafficking of cholesterol. Second, the characteristic symptom of AD, impaired anterograde memory with functioning STM, points to a problem in the initiation of Cres or in winner enhancement. Third, the main AD pathologies, hyperphosphorylated tau and Aβ, point to chronic Cgen or excessive loser removal. Neurodegeneration is a natural consequence of these pathologies and of chronic loser removal.

The main role of cholesterol in short-term plasticity is in LRs. Thus, the first clue leads to the hypothesis of impaired LR formation. Impaired LR formation impairs the switch from STM to LTM and from Cgen to Cres, explaining memory symptoms (the second clue). LRs and Cres are essential for tau dephosphorylation, explaining the tau part of the third clue (see section 3.3 for the Aβ part). Neurons can produce cholesterol in response to stress to support Aβ production, but they cannot supplant astrocyte-derived cholesterol for PM LRs [70]. Thus, we reach the following hypothesis: AD symptoms and pathology are caused by impaired formation of PM LRs, which is in turn caused by reduced neural uptake or trafficking of astrocyte-produced cholesterol.

3.2 Chronicity

The formation of PM LRs triggers the switch from Cgen to Cres. When this process is impaired, we can expect both Cgen and Cres to be active at the same time but with smaller agent amounts than those involved in healthy plasticity and with a prolonged duration. I use the term chronicity to refer to this state throughout this article (Figure 4). In early disease stages, chronicity should yield an increase in both Cgen and Cres agents. With disease progression, brain resources get depleted, so Cres should increase and Cgen decrease. This is exactly what the evidence shows (see Section 4.4).

Many plasticity agents obey DEP and are present in smaller amounts during chronicity. As a result, their effects are tilted toward Cres. Specifically, chronic calcium presence induces loser removal and neurodegeneration. Thus, the continued activation of Cgen, which could compensate for cholesterol deficiency by promoting its synthesis, actually exacerbates the situation. Moreover, because biological systems extensively rely on negative feedback, chronicity desensitizes receptors and pathways, impairing many cellular signaling pathways.

3.3 Cholesterol and Amyloid β

A straightforward explanation for reduced PM LRs is that cholesterol synthesis is decreased. Indeed, there are data indicating that ApoE4 is associated with reduced cholesterol synthesis capacity [107], and there is evidence for reduced cholesterol in AD (see Section 4.2). However, chronic synthesis is at least as likely, since cholesterol synthesis continues as long as it does not

get incorporated properly in the PM. Thus, AD can involve both cholesterol deficiency (in PM LRs) and excess. Chronic synthesis happens in both astrocytes and neurons, which increase cholesterol production under stress. Neural production may be able to counter membrane damage incurred by injury [60], but it generally does not compensate for cholesterol deficiency during plasticity [70, 108].

Cholesterol stimulates Aβ production, yielding two types of neurons associated with chronic cholesterol in AD. In the first type, chronic neural cholesterol production eventually manages to form PM LRs. Such neurons form synapses and do not show tau pathology but do show excessive Aβ production, causing Aβ secretion and aggregation. This explains why Aβ is common in aging and why Aβ plaques are not strongly correlated with AD symptoms and tau pathology. In the second type, chronic cholesterol production does not compensate for reduced PM LRs, and these neurons show plasticity impairment and both tau and Aβ pathology. Since Aβ binds cholesterol [103], Aβ plaques are expected to contain cholesterol in both neural types, as is indeed the case [109].

3.4 Tau

LRs are crucial for cytoskeleton-PM linking, neurite growth, and neurite stabilization, and tau has a major role in these functions [66, 65]. LRs promote the switch to Cres and allow tau dephosphorylation in winners. LR impairment promotes the cytosolic localization of tau and p-tau, and tau–membrane disconnect may facilitate the helical tau conformation found in NFTs [110]. Propagating p-tau is hypothesized to spread AD pathology [5], and tau is indeed secreted as a normal consequence of neural activity [90] (see Section 2.6.2). T*PL explains this tau secretion as a way of clearing excessive inactive tau generated during Cgen, but it is possible that it occurs in AD, which involves excessive inactive tau. Nonetheless, gradual spreading is not well supported by the evidence [111].

3.5 Core Cause

The mechanisms of AD can be explained by impaired PM LRs, and these can be explained by reduced uptake or trafficking of cholesterol. Why does this happen? Although the link with ApoE4 is very strong, there are people carrying this isoform (even homozygotes) who do not get the disease. In addition, there are ApoE3 carriers with AD.

The parsimonious answer to this question is that cholesterol metabolism, and specifically LRs, are normally reduced in aging [56, 83] (which incidentally explains why memory is reduced in normal aging), and a variety of risk factors can push this reduction beyond the damage threshold. Some viruses enter cells via LRs and impair lipid metabolism (this includes COVID-19, which might explain its long-lasting cognitive symptoms). IR and impaired vasculature affect all plasticity stages and can specifically induce cholesterol deficiency. Sleep problems, chronic inflammation, and chronic stress promote a state similar to chronic destabilization. Brain injury involves acute destabilization that can become chronic. Polyunsaturated

fatty acids (PUFAs) are also present in LRs and reduced in aging. These risk factors are expanded upon in Section 5. In addition, lipid metabolism is supported by many genes, providing ample opportunity for small gene changes to predispose a person to less efficient metabolism, especially in aging. Such changes can manifest as sporadic AD even in ApoE3 carriers.

Gonadal steroids are major plasticity agents and are reduced abruptly and relatively early in women (versus a gradual loss in men), explaining why women have an increased AD risk at younger ages and a faster cognitive decline after diagnosis [112].

3.6 Autosomal Dominant Alzheimer's Disease

The core cause of autosomal dominant AD (which approximately overlaps with FAD) is different from that of sporadic AD, and involves decrease-of-function mutations in the PSEN1 gene, whose protein (presenilin 1) is a major component of γ-secretase, or mutations in the γ-secretase APP cleavage site [113]. Such mutations affect both sAPPα and Aβ, which are central plasticity agents. Hence, these mutations can seriously damage plasticity, explaining the earlier age of onset of the disease. The reason that the brain manages to support plasticity until middle age is probably the large functional redundancy between the various Cgen and Cres agents.

4 Evidence

In addition to the salient evidence regarding tau, Aβ, and ApoE4, many other lines of evidence provide support for T*AD, including evidence concerning LRs, cholesterol, PUFAs, plasticity agents, synapse issues, the brain areas of earliest damage, genetics, and other diseases. These lines of evidence are presented in this section. Risk factors also provide support for the theory and are discussed in Section 5.

4.1 Lipid Rafts

LRs are reported to be reduced or abnormal in AD. In mixed ApoE3/ApoE4 carriers, membrane cholesterol was decreased by 36%, with abnormal LRs [114]. Neuronal LRs are strongly altered in frontal cortex and ETRC from the earliest stages of the disease (before NFTs) [115]. The changes include lower cholesterol, SPM, and PUFAs [115]. These neurons show increased sterol esters, which may indicate excessive cholesterol synthesis with impaired incorporation into LRs. Patient temporal cortex contains significantly lower numbers of LRs, with those remaining being depleted of cholesterol [116]. Frontal and temporal cortex LRs contain significantly higher levels of the gangliosides GM1 and GM2 [116]. Flotillin and gangliosides, strong LR markers, show marked abnormalities in patient brain, cerebrospinal fluid (CSF), and serum [117, 118, 119]. In most cases, these abnormalities also occur in patients with mild cognitive impairment, showing that it is an early event in the disease. Flotillin accumulates in lysosomes

in NFT-positive neurons, showing the link between LRs and tau pathology [120]. A recent review summarized strong evidence that Aβ plaques contain cholesterol and gangliosides [109].

4.2 Cholesterol

Dysregulated lipid metabolism, especially accumulation of lipids in glia, was noted as a third major AD pathology right from the start, over 100 years ago [121]. Cholesterol and lipid dysregulation is a strong characteristic of AD [121]. As predicted by T*AD, both lower and higher cholesterol are reported. Lower cholesterol is reported in temporal cortex [122] and CSF [123, 124], especially in patients with severe disease [125]. Seladin1, an enzyme that mediates the conversion of desmosterol to cholesterol, is reduced in AD, specifically in vulnerable regions [126]. ETRC and hippocampus show lower cholesterol synthesis, which is significantly associated with AD pathology (however, cholesterol levels themselves were normal, which might indicate chronicity) [127].

Most of the evidence points to chronically increased cholesterol synthesis. Neurons with NFT tau show higher levels of unesterified cholesterol [128]. Cholesterol and ceramides accumulate in AD brain in a vulnerable region (frontal cortex) but not the cerebellum [129]. ETRC shows elevated cholesterol esters, SPM, and ganglioside GM3 [130]. Patients with AD show higher brain cholesterol levels and decreased levels of LXR (cholesterol extrusion) [131]. Increased ABCA1 (sterol extrusion) expression correlates strongly with dementia severity in AD hippocampus [132]. Cholesterol is increased in patient astrocyte mitochondria [133]. Sensitive imaging shows significantly higher (34%) cholesterol in cortical layers 3 and 4 [134]. AD pyramidal neurons in the hippocampus show no nucleus translocation (activation) of SREBP2, indicating sterol excess. 40–50% of NFT neurons express nonnuclear SREBP2 [135]. Total cholesterol is increased in a CHO cell line with the FAD-causing presenilin1 mutation [136]. CSF levels of cholesterol correlate with p-tau [137] and secreted APP (both α and β) [138] in patients but not controls. PCSK9, which downregulates LDLR and thus ApoE uptake, was reported to be increased in AD, indicating excess. However, one study reported no changes [139].

Fibroblasts from sporadic AD and FAD patients show markedly higher levels of free cholesterol and cholesterol esters [140]. MAMs, which contain LRs, show a higher number of contacts and upregulated activity (cholesterol esterification and phospholipid synthesis) in sporadic AD and FAD fibroblasts and in mouse models [73]. Patient skin fibroblasts show increased levels of cholesterol esterification enzyme and decreased levels of SREBP2 and ABCA1 mRNA [141]. In addition to showing cholesterol excess, these results are important because they show that the problem can be present in cells other than glia and neurons, shedding light on the core cause and allowing practical biomarkers to be identified.

In many cases, the core of the problem may be lipid trafficking rather than uptake. ApoE4 (and, to a lesser degree, ApoE3) tends to aggregate in and damage endosomes [142], which are crucial for cholesterol homeostasis. Indeed, endosomes are dysregulated in AD, and endosome-related genes such as Bin1, TREM2, PICALM, and SORLA have been highlighted in genome-

wide association studies (GWAS) [142].

4.3 Polyunsaturated Fatty Acids

Docosahexanoic acid, the main omega-3 PUFA, is reduced in AD serum and postmortem brain [143]. PUFAs are the main target of lipid peroxidation by reactive oxygen species produced during oxidative stress, and AD brains show higher levels of PUFA oxidation products and oxidative stress (which can stem from chronicity, e.g., chronically high levels of calcium) [143]. Although PUFAs are mainly located outside LRs, some are located inside LRs, and PUFA levels are reduced in LRs in frontal cortex and ETRC in AD [115].

4.4 Plasticity Agents

Virtually all important plasticity agents are dysregulated in AD, including Ca^{2+} [2], ERK, p38, JNK, Akt, PKA, PKC, GSK3β, PP2B, PP1, PTEN, Cdk5 [144], BDNF, TrkA (the NGF receptor), tPA, MMP9 [145], and PAI-1 (a tPA inhibitor) [18]. Of the listed agents, tau phosphorylation agents (ERK, p38, JNK, GSK3, PP2B, and Cdk5 but not PKA) are chronically increased [144], while PP2A, the main tau dephosphorylation agent, is reduced in AD [86].

Notably, PKC [144] and GluA2 [146], the hallmarks of winner enhancement and stabilized winners, are reduced in AD. In the hippocampus, the greatest decrease in GluA2 occurs in the most vulnerable areas (subiculum, CA1) [146]. Note that PKC is activated by moderate levels of calcium, so chronically high calcium levels (e.g., those induced by membrane Aβ cation channels) should activate it, which would explain the reduction in GluA2 (PKC promotes its endocytosis; see Section 2.4). The fact that PKC is reduced and not increased indicates a fundamental non-Aβ problem with winner enhancement processes.

4.5 Synapses

Synaptic damage is a well-known early event in AD [7]. This shows that synapses are not formed correctly or are degraded early. Both cases support T*AD.

4.6 Brain Areas

The earliest areas that show tau pathology in AD are the ETRC, hippocampus, and locus coeruleus (LC) [5]. Among hippocampus fields, the subiculum and CA1 are much more vulnerable than the dentate gyrus (DG) and CA3 [147]. Among thalamic nuclei, the nucleus reuniens, connecting the ETRC, subiculum, CA1, and the medial prefrontal cortex, is one of the most heavily affected nuclei [148]. ETRC and hippocampus represent scenes and events, which due to their richness, present continuous novelty that requires plasticity. The LC, the main norepinephrine center in the brain, is also active in all novel situations. The fact that the areas that

show the largest plasticity requirements are those most vulnerable in AD supports T*PL. Moreover, CA1 and subiculum support familiar scenes, while DG and CA3 support the encoding of new ones [149]. Most of our life experiences involve familiar scenes with some element of novelty, explaining why CA1 and subiculum are relatively more vulnerable. ETRC supports both familiar and novel scenes, explaining its central role in early AD.

Early auditory [150], olfactory [151], and retinal [152] sensory cells contain LRs, explaining the early loss of hearing and smell and retinal abnormalities in AD [4]. Of note, statin use is associated with sudden hearing loss in an all-Taiwan insurance database [153], statins are among the drugs that can impair olfaction [154], and cholesterol depletion causes hearing loss in cats and severe cochlear hair cell loss in mice [155].

4.7 Genetics

Cholesterol and lipid pathway genes are repeatedly identified as leading clusters in AD GWAS [156]. So are endosome-related genes, as mentioned in Section 4.2.

4.8 Other Diseases

Niemann-Pick disease type C (NPC), which involves dementia and neurodegeneration, is caused by mutations in the NPC1 or NPC2 genes, which support transport of cholesterol from late endosomes and lysosomes [157]. NPC brains show tau-rich NFTs with paired helical filaments identical to those found in AD [157].

Down syndrome patients usually carry three copies of the APP gene and manifest AD-like pathology [158].

5 Risk and Protective Factors

Here, I discuss various factors affecting AD. Many of these factors are associated with aging, increasing the aging-related risk.

5.1 Viral Infections

Increased human herpesvirus 6A and 7 infections were reported in AD [159], and herpesvirus infection was found to induce a threefold increase in dementia risk [160]. Moreover, in a highly controlled all-Wales setting, herpes zoster vaccination was shown to decrease risk of dementia (all cause except vascular) by 20% [161].

In T*AD, viral infection is a direct AD risk factor because many viruses (including herpesvirus and COVID-19) highjack lipid metabolism to persistently weaken lipid homeostasis, especially LRs [162]. Incidentally, this may explain the long-lasting cognitive symptoms of COVID-19.

5.2 Traumatic Brain Injury

Traumatic brain injury (TBI) can induce a physical disconnect of the ECM, which triggers LR endocytosis [16]. Moreover, it involves strong release and prolonged presence of Cgen agents in the brain [163], which can induce chronic loser removal due to DEP. Indeed, TBI is an AD risk factor and is associated with synaptic dysfunction [163].

5.3 Diabetes and Obesity

Type 2 diabetes and obesity are AD risk factors [1], and the notion that AD is a third type of diabetes is gaining support [164]. In my view, this notion is not justified. T*AD explains this risk factor via the fact that the synthesis of lipids, including cholesterol and PUFAs, needs PI3K–Akt signaling, which is impaired by IR. Thus, IR can impair LRs and promote chronic cholesterol.

Although IR can exacerbate the situation of people who are at risk of AD, brain IR is just one of many risk factors that can yield LR damage, which is the core mechanism in AD. Note that cholesterol homeostasis is more fundamental in AD than IR, since if IR were the core cause, it should affect ApoE2 homozygotes, who are virtually protected. I conclude that IR is definitely a serious AD risk factor, and it may even suffice for causing dementia, but the dementia classified as AD requires additional factors.

It should be noted that the association between AD and obesity is not that simple, since low body-mass index (BMI) is also associated with increased risk [165]. This supports T*AD, since a low BMI may indicate a tissue-wide problem in lipid synthesis and/or uptake, which can impair LRs.

5.4 Vascular Impairment

Vascular dementia is the second most common dementia after AD, accounting for 5–10% of cases, and cerebrovascular disease is commonly shown in AD [1]. Cardiovascular disease is also associated with increased AD risk [1]. Vascular impairment can increase AD risk via a reduction in the raw materials needed for lipid synthesis. However, it can also be a consequence of the AD core mechanism, since impaired cholesterol homeostasis yields vascular damage.

Statins suppress cholesterol synthesis and are regularly taken by people at perceived risk of cardiovascular disease. They do not cross the blood–brain barrier, so they should not directly affect AD, but they might reduce risk via the other risk factors. They can also be detrimental in AD in the event of barrier damage.

5.5 Immunity

Neuroinflammation is common in AD and is associated with activation of microglia [2, 1] and their TREM2 receptors [166]. TREM2 is activated by lipids, and different mutations have been

identified that increase AD risk or decrease TREM2–ApoE binding [166]. Microglia might be activated by cholesterol excess and have an initial protective role in AD. However, chronic neuroinflammation promotes neurodegeneration.

5.6 Stress

Early-life and lifetime stress are associated with earlier AD onset and faster disease progression [167]. This is consistent with the fact that chronic stress is associated with neurodegeneration in memory-related areas [9]. The mechanisms of damage due to chronic stress may be related to LRs (e.g., cortisol induces endocannabinoid synthesis from PUFAs, which can impair LRs) or be independent of LRs (e.g., calcium excitotoxicity). As a neurosteroid, cortisol requires cholesterol for its synthesis, so chronic cortisol synthesis may promote brain cholesterol depletion.

Oxidative stress and its lipid peroxidation effect are higher in AD (see Section 4.3).

5.7 Smoking

Smoke exposure and smoking are associated with increased AD risk AZ2023. This can occur via several mechanisms. For example, nicotinic agonists increase p-tau [168].

5.8 Education and Bilingualism

Formal education is a clear protective factor against AD [1], and so is (less clearly) bilingualism [169]. T*AD explains these data as follows. Both involve memory-related learning, which creates synapses. A denser synaptic space might reduce the number of candidates, which is a function of novelty. It should facilitate the formation of new synapses, because synapse candidates are closer to each other and are thus easier to connect. Therefore, the growth needs of the educated brain are smaller, so smaller amounts of cholesterol are needed for plasticity. Indeed, bilinguals have a larger gray matter volume [170] and increased connectivity [171].

5.9 Exercise

Most (not all) data indicate that exercise weakly reduces AD risk [172]. Exercise has positive effects on many of the risk factors discussed here, including brain vasculature, blood flow, brain clearance from chronic agents, obesity, sleep, and cardiovascular disease.

6 Discussion

This article presents the first theory of AD that is complete, in the sense that it mechanistically explains all of the major AD phenomena, including etiology, symptoms, pathology, and risk

fac- tors. To do this, the article presents a new theory of brain plasticity (T*PL) that explains memory formation and the roles in health and disease of sAPPα, Aβ, tau, growth factors, kinases, phosphatases, cholesterol, and other agents. T*PL enables the development of a coherent theory of AD.

6.1 Related Theories

Cholesterol has been repeatedly recognized as an important factor in AD [173, 121]. However, this was based on its promotion of Aβ, its link with cardiovascular disease, and evidence of lipid dysregulation in AD. I found only one paper that points to cholesterol as the central agent in AD [158], but it focuses only on chronically high cholesterol as the driving force behind neurodegeneration, without addressing anterograde memory symptoms and plasticity agents and processes. All of this work presents a negative view of cholesterol (opposite to T*PL) and does not explain the disease mechanisms and pathological process.

Likewise, tau has long been known to be the main pathological factor correlated with symptoms, but no coherent story for why it is phosphorylated in health and disease has been presented. T*PL, which proposes that Cgen requires destabilization and Cres removes losing candidates, naturally explains p-tau and its chronicity-induced accumulation. Many hypotheses have been raised in AD research, including the cholinergic, Aβ, tau propagation, mitochondria, calcium, neurovascular, inflammation, microbe, metal ion, and lymphatic hypotheses [2], and the type 3 diabetes hypothesis [164]. As discussed in Section 5, these are factors that affect AD risk but are not fundamental to the disease.

6.2 The Theory of Adaptive Response Plasticity

Brain plasticity is one of the most heavily researched areas of neuroscience. Competition between spines and the elimination of losing ones is an established idea in plasticity research, with strong evidence supporting it [9]. T*PL is the first theory of plasticity that presents a coherent mechanistic story explaining how initial potentiation switches to consolidation and the first that seamlessly integrates structural plasticity with neurotransmission plasticity and explains the roles of cholesterol, APP, tau, and other agents.

Strong high-level support for T*PL comes from its structural similarity to other biological theories. Notably, candidate generation followed by competition is the cornerstone of the theory of evolution. In immunity, clonal selection of B and T cells can be viewed as candidate generation, while memory T cells result from consolidation. The principle of DEP has some superficial resemblance to the notion of hormesis in toxicology [174]. While the opposite effects of CaMKII versus PP2B and of TrkB and TrkA versus p75 are clearly known, as far as I know, this article is the first in which DEP is phrased as a general biological principle. Note that DEP applies to neuromodulators as well (see the examples involving dopamine and serotonin in section 2.1). It also applies to the immune system, with mechanisms that are not described in this article.

This article focuses on the main notions relevant to plasticity and AD, to show the forest rather than a huge number of trees. Additional topics are left for future texts, including the difference between LDLR and LRP1, other LRPs, gangliosides and SPM, Src and Fyn kinases, prion protein, reelin, amyloid precursor protein intracellular cytoplasmic domain, smoking, myelin, metabotropic glutamate receptors, Cdc42, Arc/Arg3.1, adenosine, p38, cofilin and other non- tau cytoskeleton proteins, specific adhesion molecules, α-synuclein, TGF-β, NFkB, homeostatic plasticity, the difference between different Aβ species, etc.

A topic that is of particular importance is the timeline of winner enhancement. For example, CaMKII is autophosphorylated to keep it active without calcium. Does PKC (which is calcium dependent) switch to PKMzeta (which shows constitutive activity) at the same time? It seems that it should, otherwise it would continue to promote sAPPα and inhibit GluA2. In addition, is GluN2A eventually removed from winners, like GluA1? More research is needed on these topics.

Additional research is also needed with respect to LR homeostasis. How precisely does cholesterol get incorporated in PM LRs? One possibility is that it is transported by caveolin1, but the precise mechanisms are still not clear.

6.3 Sleep

AD is associated with impaired sleep. Sleep is crucial for memory and plasticity, and the most upregulated genes in sleep support lipid synthesis and transport and LRs [106]. There is some controversy around the synaptic homeostasis hypothesis, in which the goal of sleep (or at least of slow-wave sleep) is to globally downscale synapses. In T*PL, sleep supports the late part of Cres, which indeed involves massive loser removal and reduced calcium entry in winning synapses. However, sleep also strengthens winning synapses.

6.4 Neurogenesis

Adult neurogenesis is crucial for memory [175] and occurs in the hippocampus DG, which receives inputs from ETRC reelin neurons; these neurons show specific vulnerability in AD. In T*PL, new neuron candidates are generated during Cgen. New cells require substantial resources to mature, so we expect adult neurogenesis to be impaired in AD, which is indeed the case [176]. Unlike synaptogenesis, which is a ubiquitous process, neurogenesis-related evidence is small. However, its impairment may well be important in AD.

6.5 Dementia

This article focuses on AD, but T*PL and T*AD also provide a reasonable explanation for other types of dementia, in particular vascular dementia. In addition, zinc, iron, and copper are fundamental in cellular processes and are dysregulated in AD [2]. Metals interact with ApoE, and the link to LRs and to other types of dementia should be further investigated.

Frontotemporal dementia (FTD) has a major variant that shows tau pathology. Nonetheless, in my view, both the core cause and the disease mechanisms of FTD are different from those of AD. A detailed theory of FTD will be presented elsewhere.

6.6 Theory Predictions

T*PL and T*AD are supported by very strong evidence, including evidence from patient data and a large number of animal models developed for AD and brain plasticity. This evidence pertains to the details underlying the theories. The main prediction resulting from these theories is that the cause of the human disease diagnosed as AD is reduced cholesterol in neural PM LRs during plasticity. This has not been directly shown yet. One way of showing it would be via clinical trials with the participation of people diagnosed with AD or known to be at a high risk, which is obviously a very long and risky process.

The theory presented here points to several promising directions for treating AD, for example, enhancing the ApoE receptor LDLR by inhibiting PCSK9. I hope that some of these will be taken to help patients, families, and caregivers.

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