



## UvA-DARE (Digital Academic Repository)

### At the crossroads of epilepsy and Alzheimer's disease

*Investigating the role of LRP1 in the cerebral vasculature*

Rozeboom, A.

#### Publication date

2025

[Link to publication](#)

#### Citation for published version (APA):

Rozeboom, A. (2025). *At the crossroads of epilepsy and Alzheimer's disease: Investigating the role of LRP1 in the cerebral vasculature*. [Thesis, fully internal, Universiteit van Amsterdam].

#### General rights

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

#### Disclaimer/Complaints regulations

If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: <https://uba.uva.nl/en/contact>, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.

# Chapter 1

## **General introduction**

## **1. Epilepsy**

Epilepsy affects over 65 million people worldwide [1], making it one of the most prevalent brain disorders. According to the International League Against Epilepsy (ILAE), epilepsy is defined as “a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, social, and psychological consequences of this condition” [2]. These seizures result from synchronized or excessive neuronal activity that causes transient symptoms [2]. A clinical diagnosis of epilepsy can be made when any of the following conditions is met: diagnosis of epilepsy syndrome; occurrence of at least two unprovoked seizures more than 24h apart; or one unprovoked seizure and a probability of further seizures of more than 60% over the next ten years [3]. Epilepsy can impact individuals of any age, but its prevalence peaks in both children and the elderly [4-8]. Unfortunately, a considerable number of people with epilepsy feel stigmatized [9, 10] and experience social exclusion [11]. Additionally, neurological and psychiatric comorbidities, including dementia, depression and anxiety disorders, have a negative impact on the quality of life [12].

### **1.1 Epileptogenesis**

Epileptogenesis refers to the process by which epilepsy develops and progresses after the first occurrence of spontaneous seizures [13]. This complex phenomenon can arise from various underlying factors such as genetic factors, structural abnormalities, metabolic disorders, immune responses, infections, or sometimes the cause remains unknown [14]. A key aspect of epileptogenesis involves a disturbed balance between excitatory and inhibitory neurotransmission. Various factors contribute to this imbalance, including the loss or dysfunction of inhibitory interneurons [15-17], resulting in hyperexcitability, as well as brain inflammation and blood-brain barrier dysfunction.

#### *1.1.1 Brain inflammation and gliosis*

Astrocytes and microglia play crucial roles in maintaining brain function and responding to neuroinflammation or injury [18-21]. Reactive gliosis can significantly contribute to immune responses in epilepsy [19, 22]. In epilepsy, pronounced activation of astrocytes and microglia triggers the release pro-inflammatory molecules, such as cytokines [19, 22-24]. For instance, IL-1 $\beta$  is a proinflammatory cytokine implicated in epilepsy pathogenesis [22] released by activated astrocytes and microglia [25] that can increase the glutamatergic tone [26]. Activation of astrocytes and microglia involves an increased expression of astrocytes and microglia markers, as has been shown after status epilepticus [27, 28] and in patients with temporal lobe epilepsy (TLE) [29-31]. Astro- and microgliosis can play a role in epileptogenesis. For example, when astrocytes and microglia become activated, they can release pro-inflammatory cytokines and other mediators

that alter neuronal excitability and promote epileptogenesis [32-34]. Vice versa, increased neuronal activity can trigger neuroinflammation [35]. This bidirectional relationship highlights a complex feedback loop: while glial activation can facilitate the onset and progression of epilepsy, increased neuronal firing can also stimulate inflammatory responses in the brain. This neuroinflammatory response may further exacerbate the imbalance between excitation and inhibition, perpetuating the cycle of seizure activity and contributing to the overall pathophysiology of epilepsy.

### 1.1.2 Blood-brain barrier

The blood-brain barrier (BBB) serves as a critical protective mechanism that strictly regulates the entry of substances from the bloodstream into the brain, as well as the removal of potential harmful substances from the brain into the bloodstream, helping to maintain brain homeostasis [36]. The BBB is composed of an endothelial cell monolayer, firmly connected by tight junctions which restrict paracellular transport. There are specific conditions under which some substances can cross this barrier, e.g., lipid-soluble molecules with a molecular weight under 400 Da can enter the brain via passive diffusion through endothelial cells (transcellular transport). Other ways of transcellular transport are receptor-mediated transcytosis, cell-mediated transcytosis, transporter-mediated transcytosis, and adsorptive mediated transcytosis. Ions and small solutes can cross the BBB via paracellular transport using concentration gradients. To provide the brain with essential nutrients and remove waste substances, endothelial cells contain membrane specific transporters such as solute carriers (SLC transporters) for the transport of various solutes, including glucose, amino acids, and electrolytes into the brain and ATP-binding cassette (ABC) transporters (including P-glycoprotein, the most commonly studied ABC transporter) for effluxing potentially harmful substances out of the brain [37].

The endothelial cells are enclosed by the basal lamina embedded with pericytes and astrocytic end foot processes. The basal lamina consists of a vascular basement membrane secreted by endothelial cells and pericytes, and a second parenchymal basement membrane produced by astrocytes [38]. Astrocytes can regulate cerebral blood flow in response to neuronal activity [19, 39]. Pericytes regulate the function, integrity and permeability of the BBB [40, 41] and play a role in regulating neuroinflammation [42]. Together these cells are collectively known as the neurovascular unit [43].

BBB dysfunction has been observed in the epileptogenic brain [37, 44-46], leading to the entry of blood borne substances into the brain (e.g., albumin) promoting hyperexcitability, brain inflammation [47-49], as well as perivascular fibrosis (scarring) in accordance with damaged or reactive pericytes that may contribute to further cerebrovascular dysfunction [50-52]. Furthermore, the entry of albumin

into brain activates the transforming growth factor-beta (TGF- $\beta$ ) pathway [53], a critical signaling mechanism involved in various cellular processes, including cell growth, differentiation, immune response, and tissue homeostasis, leading to downregulation of inward-rectifying potassium (Kir 4.1) channels in astrocytes, reduced extracellular potassium buffering, and neuronal hyperexcitability [54].

## **1.2 Temporal lobe epilepsy**

Temporal lobe epilepsy (TLE) is the most frequent diagnosis among the elderly with new-onset epilepsy [55] and in about 40% of the cases hippocampal sclerosis (HS) is evident [56, 57], which is characterized by neuronal loss and gliosis in the hippocampus [58]. Distinct subtypes of HS can be identified based on a histopathological classification system [58]: HS type 1 (the most common type of HS) with severe neuronal loss (majority of neurons lost) and fibrillary astroglia in both CA1 and CA4 regions, and variable neuronal loss and gliosis in CA2, CA3, and the dentate gyrus (DG); HS type 2 with predominant neuronal loss and gliosis in CA1 and HS type 3 with predominant neuronal loss and gliosis in CA4. When only gliosis is present without neuronal loss, it is classified as no HS. The degree of HS is associated with factors such as the presence of an initial insult, seizure frequency, and the duration of epilepsy [59]. Furthermore, granule cell dispersion, characterized by the widening of the granule cell layer within the dentate gyrus of the hippocampus, is observed in approximately 50% of patients with TLE [60].

## **1.3 Anti-seizure therapies**

Current anti-seizure medication (ASM) does not adequately suppress seizures in 30% of epilepsy patients [61-63]. Moreover, for 21% of individuals with dementia and epilepsy, the administration of anti-seizure medications does not lead to seizure freedom or a reduction in seizure frequency of more than 95% [64]. There are several treatment options for patients with drug-resistant epilepsy. For example, surgical resection of the epileptic focus yields favorable outcomes for TLE patients [65], with approximately 50% of refractory focal epilepsy patients achieving seizure freedom [66]. However, only a limited number of individuals are eligible for this treatment, as the epileptogenic focus must be clearly delineated and should not overlap with functional regions, such as areas important for language. Additionally, this treatment is invasive and drastic, carrying potential risks including issues with memory [67]. Vagus nerve stimulation (VNS) results in a  $\geq 50\%$  reduction in seizure frequency in more than half of the patients [68]. However, seizure freedom is achieved in only 8% of patients [68], and the treatment has disadvantages such as the need for invasive surgery and regular battery changes. Moreover, the mechanism of action VNS are complex, diverse, and not well understood [69]. A non-invasive therapy is dietary treatment, such as the ketogenic diet, a high-fat, low-carbohydrate diet designed to induce ketosis, a metabolic state in which the body burns fat for energy instead of carbohydrates, and works through multiple

mechanisms to reduce neuronal hyperexcitability [70, 71]. The ketogenic diet shows a 50% seizure reduction in more than half of this patient population [72]. However, compliance issues stemming from adverse effects and the strict dietary requirements often render this treatment option unfavorable [73]. Since none of the above mentioned treatment options accomplish complete seizure freedom in all epilepsy patients, there is a pressing need to find novel treatment targets for the development of new therapeutic treatments.

#### **1.4 Late-onset epilepsy (LOE)**

Late-onset epilepsy (LOE) refers to the development of epilepsy *de novo* later in life. Since the world population is steadily growing, the number of older adults with epilepsy is set to rise substantially and the burden of epilepsy for society is expected to rise tremendously and should be an important public health concern [4]. The prevalence of epilepsy among the elderly is likely underestimated because it is often underdiagnosed or misdiagnosed [63]. Common causes of epilepsy in older people are degenerative conditions such as dementia, stroke, brain injury and brain tumors [8, 74-76]. Aging is also associated with an increased risk of developing status epilepticus (SE) [77, 78], a condition characterized by prolonged or repetitive seizures lasting for more than 5 minutes [79] that requires immediate medical intervention as it can lead to serious complications, including brain damage and even death if not treated promptly [80]. Cognitive impairments are observed in (aged) epilepsy patients compared to healthy controls [81-84], which is associated with inflammatory and vascular risk factors [83, 85]. Lower cognitive scores are also found among patients with late-onset epilepsy of unknown aetiology (LOEU) as compared to controls [86].

## **2. Alzheimer's disease: a bidirectional relationship with epilepsy**

Alzheimer's disease (AD) is a neurodegenerative disease characterized by the deterioration of cognitive function [87]. As the disease progresses, individuals may experience difficulties with language, reasoning, and behavior, eventually requiring full-time care. It is the most common form of dementia affecting millions of people [88]. While treatments can help manage AD symptoms, there currently is no cure. The neuropathological hallmarks of AD are deposition of extracellular amyloid- $\beta$  (A $\beta$ ) plaques, intracellular neurofibrillary tangles (NFT), dendritic spine loss and neurodegeneration [89], which may lead to disruptions of neural networks [90]. The incidence of AD is higher in women compared to men [91]. Aging is a prominent risk factor for AD and after the age of 65 the prevalence rate increased exponentially affecting up to 47% of individuals over 85 years old [92, 93]. When the initial symptoms emerge before the age of 65 years, it is classified as early onset AD (EOAD), while after the age of 65 years it is termed late onset AD (LOAD). The familial form of AD (FAD), that accounts for the minority of all AD cases,

is linked to various genetic mutations in genes related to amyloid metabolism, including amyloid precursor protein (APP) and presenilins (PSEN1 and PSEN2 [94]. The more prevalent sporadic form from AD may arise from interactions between genetic and environmental factors [94]. Mild cognitive impairment (MCI) is a prodromal stage of AD that denotes a condition involving noticeable cognitive decline beyond typical age-related changes but not severe enough to disrupt daily activities [95]. Numerous therapeutic interventions aimed at modifying the progression of AD have been subjected to clinical trials, but ultimately demonstrate lack of success [96]. The first FDA-approved disease-modifying drugs that could slow down the progression of AD are two anti-amyloid monoclonal antibodies that enhance the clearance of brain A $\beta$  aggregates: aducanumab targets aggregated forms of A $\beta$ , including insoluble fibrils and soluble oligomers [97], while lecanemab targets soluble A $\beta$  protofibrils, which are intermediate forms between soluble monomers and insoluble fibrils [98]. However, adverse events including amyloid-related imaging abnormalities (ARIA), characterized by edema (ARIA-E) or hemorrhages (ARIA-H) have been a major concern. The drug development pipeline is investigating novel therapies aimed at different facets of AD biology beyond solely addressing A $\beta$  accumulation, encompassing targets such as tau accumulation, inflammation, and altered cell metabolism [99].

## **2.1 Increased risk of dementia in epilepsy**

People with epilepsy have a 2.5 times greater risk of developing dementia compared to people without epilepsy [100]. Individuals with LOE face a two to three times greater risk of developing dementia in later life compared to adults of similar age without epilepsy [101, 102], which is confirmed by two recent meta-analysis studies [103, 104]. LOEU patients have a similar risk factors for developing dementia [105]. Among LOEU patients, the prevalence of dementia development within 5 years ranges from 10% [106] to 16.7% [107], with 22% developing dementia within 10 years [108], and with 40% within 13 years [106]. After the first seizure is reported the average time to dementia diagnosis is 5 years in LOEU patients [108]. Moreover, the age of dementia onset in LOEU patients is 6 years earlier compared to that in the control patients [106]. In a recent meta-analysis study in which it is found that there is a 2-fold higher risk of developing AD among epilepsy patients [109]. Similarly, LOE is linked to a 2.4-fold increased risk of developing AD [104]. Among LOEU patients, 17.5% converts to AD within a follow-up period of 3 years [110]. Moreover, multiple studies reveal that a significant proportion of LOEU patients met the criteria for MCI, with rates ranging from 54.2% [107] to 56% [111], and even reaching 59% [112]. Interestingly, LOEU-MCI patients have worse cognitive performance compared to non-epileptic MCI patients [112]. Therefore, the risk of progressive cognitive impairment emphasizes the necessity for a deeper understanding of the mechanisms underlying cognitive dysfunction associated with epilepsy.

## 2.2 Epilepsy and seizures in dementia

Dementia patients face a twofold increased risk of developing epilepsy [102] and a 2.5-fold increased risk of developing LOE [113]. It is estimated that 1 in 10 AD patients encounters at least one seizure [114] and the prevalence of active seizures in AD dementia increases by 0.64% per year of disease duration [115]. Among AD patients, the incidence of seizures is 2-6 times higher than in non-demented controls [116]. In two recent meta-analyses, it is further confirmed that AD patients have a threefold increased risk of seizures or developing epilepsy compared to controls [109, 117].

Seizures occur especially frequently in autosomal familial dominant AD [118], in almost 50% of the cases [119], even prior to the onset of cognitive symptoms [120]. The risk of developing of epilepsy at 10 years following diagnosis is higher in early onset (9.4%) compared to late onset (2.5%) AD patients [121]. In another study, a similar prevalence of epilepsy (8.8%) is reported in mostly young-onset AD patients [122]. Moreover, younger AD patients (age 50-59) face a 87-fold increased risk of seizures, whereas the older AD population (age 85+) has a threefold increased risk [123]. These studies highlight that an earlier age of AD onset is associated with a more rapid progression of the disease, including an elevated risk of seizures.

High prevalence rates are reported in neuropathologically confirmed AD cases: seizures in 31% [124] and a history of epilepsy in 17% [125]. Furthermore, in 18% from AD patients with confirmed AD CSF biomarkers a seizure is reported within a period of 5 years [126]. Lower prevalence rates are reported retrospective studies, likely due to reliance on medical records for diagnoses: at diagnosis 2% [127], within five years 4% [128], and 14% within ten years [129] have epilepsy. Also, the prevalence of seizure in patients with AD dementia is 5% at 11.0 years of disease course based on medical records, observation and an interview [115].

Since in over half of the cases seizures in AD patients present as non-convulsive [130], and therefore are easily missed and go unrecognized, high prevalence rates of seizures are reported in a study in which it is reported that 28% of those patients exhibit features suggestive of epilepsy [131]. When specific seizure detection methods are employed for an extensive time period in addition to the assessment of medical history a relatively high prevalence of seizures is observed, as it is found using a 24-hour EEG that a total of 24% of AD patients experience seizures [132]. Lower prevalence of seizures (13%) is found in AD patients when seizure diagnosis primarily based on medical records and merely a minority of patients had undergone EEG recordings [133]. In an AD patient, a subclinical silent seizure can be detected using foramen ovale electrodes aimed at the mesial temporal lobe region, while it is not visible on scalp EEG [134]. This observation implies that silent seizures may occur even when scalp EEG findings remain unchanged, likely due to

subcortical epileptogenic foci, and thus the prevalence of seizures in many studies might be underestimated since they lack proper intracranial seizure detection.

Cognitive decline in AD patients with seizures suggests a potentially faster disease progression, as seizures are linked to an earlier onset of cognitive symptoms [115, 130, 135], a younger age at AD onset [126] and more severe cognitive impairment [115, 126, 136, 137]. In LOEU patients who progress to AD, cognitive decline begins 3.6 years earlier than in those without an epilepsy history [138]. AD patients with epilepsy also experience a longer disease duration and are diagnosed at a younger age [125]. The recurrence of seizures in 70% of AD patients within 7.5 months [115] underscores the need for effective seizure management in this population.

### **2.3 Hyperexcitability in dementia patients without seizures**

Since (sub)clinical seizures are infrequent or absent in AD patients, screening for other markers of epileptiform activity may yield valuable insights. For instance, an epileptiform spike is a brief electrical discharge resulting from hypersynchronous neuronal firing [139]. Spikes are typically observed in epilepsy patients detected via EEG or other diagnostic tools [140]. Subclinical epileptiform activity, in AD patients without a history of seizures, is observed in 19.8% of awake individuals during a 13-minute scalp EEG [141] and in up to 22% of early-stage patients during a 24-hour ambulatory scalp EEG [142]. In a recent meta-analysis study, it is found that the incidence of subclinical epileptiform activity among AD patients is 21% [117]. Other studies report that the prevalence of subclinical epileptiform activity is detected in more than 40% of AD patients without a documented history of seizures [132, 143-145]. Additionally, 11.6% of MCI patients without a history of seizures have subclinical epileptiform activity using a full-night video-polysomnography including EEG recording [146].

The prevalence of pathological hyperexcitability in AD may be considerably higher, as epileptiform events often escape detection due to multiple reasons described hereafter. First, more sensitive detection methods targeting deeper brain regions are needed, given that 95% of spikes detected by intracranial electrodes go undetected by scalp EEG in AD patients and predominantly originate in the temporal lobes [130, 134, 141-143, 145]. Second, extended monitoring is essential, as routine short EEG sessions do not detect epileptiform activity in 60% of MCI or AD patients with a seizure history, while long-term video EEG monitoring detects it in 83% [130]. Third, monitoring during sleep is crucial, as in AD patients without seizures, epileptiform activity occurs predominantly (90-92%) during sleep [142, 143, 145]. In AD patients with epilepsy, such activity also appears during wakefulness, though primarily (80%) during sleep [142, 147].

Controlling epileptiform activity is essential to prevent further cognitive decline, as AD patients with subclinical epileptiform activity experience faster deterioration than those without [141, 143, 145]. Additionally, subclinical epileptiform activity is linked to an earlier onset of AD [130, 132] and increases with disease severity, affecting 16.7% of patients with very mild, 19.8% with mild, 23.4% with moderate, and 33.3% with severe dementia [141]. Hippocampal spikes also impair cognition in epilepsy patients [148, 149] and in rats with recurrent seizures [150]. Furthermore, spikes are observed in various AD animal models [151-158]. For example, transgenic hAPP-J20 mice, which overexpress human APP with two familial AD-linked mutations (Swedish and Indiana), exhibit spikes [156] originating in the hippocampus [158] as early as 4 weeks of age [155]. Furthermore, in Tg2576 mice, which overexpress human APP with the Swedish familial AD mutation (APP<sup>Swe</sup>), spontaneous epileptiform activity is observed from the age of 6 weeks [154] with especially large amplitude spikes in the dentate gyrus (DG) granular cell layer [153], and are detected primarily during rapid-eye movement (REM) sleep [151]. In APP/PS1 mice, which carry the APP<sup>Swe</sup> mutation and mutant human presenilin 1 (PS1<sup>dE9</sup>), epileptiform spikes [157] and giant spikes originating in the hippocampus [152] are observed. Treatment with ASM ameliorates cognition and aberrant network activity in a prodromal stage of AD [159], in AD patients [160] and in a mouse model of AD [161].

### **3. Pathophysiological mechanisms underlying epilepsy and dementia**

The important clinical bidirectional link between epilepsy and dementia [162, 163] suggests overlapping pathophysiological mechanisms [164]. A wide range of potential neurobiological mechanisms that drive these persistent effects of seizure induced cognitive dysfunction may play a role, ranging from neuroinflammation to structural brain alterations. TLE and AD share several neuropathological features, such as the fact that especially the hippocampal circuitry is damaged in both neurodegenerative diseases [165], possibly caused by excitotoxic neuronal death [166]. Smaller hippocampal volumes are found in TLE patients compared to controls [82], and in the AD brain the hippocampus is one of the affected regions [167]. Similar proteomic differences are found in epilepsy and AD hippocampal tissue [168]. Furthermore, brain glucose hypometabolism manifests early in the clinical course of AD [169], and has also been found in LOEU patients compared to controls [86, 170].

#### **3.1 The role of A $\beta$**

According to the amyloid cascade hypothesis, A $\beta$  is assumed to be a key factor behind the development of AD [171]. A $\beta$  buildup in the brain begins more than a decade before clinical symptoms of AD appear [172]. In the non-amyloidogenic

pathway, APP is cleaved by  $\alpha$ -secretase that prevents the formation of A $\beta$  [173]. In the amyloidogenic pathway, the processing of APP by beta-site APP cleaving enzyme 1 (BACE1) [174] and  $\gamma$ -secretase [175] leads to the generation of A $\beta$  peptides of various lengths. A $\beta_{40}$  consists of 40 amino acids and constitutes approximately 80% of all A $\beta$  peptides, while A $\beta_{42}$ , with 42 amino acids, is produced less frequently (about 5–10%) but is more hydrophobic making it more prone to aggregation into diffuse parenchymal plaques [173, 176]. A $\beta_{40}$  is more commonly deposited in vascular walls, as observed in cerebral amyloid angiopathy (CAA) [177]. Physiological concentrations of the A $\beta$  peptide are important for memory formation [178, 179]. However, at higher concentrations A $\beta$  monomers self-assemble into oligomers, fibrils and ultimately deposit into plaques. The intermediate forms are thought to be more toxic compared to mature aggregates [180]. Brain amyloid deposition does not correlate with worse cognitive function in elderly individuals [181]. Soluble A $\beta$  levels can rise in the brain before the formation of amyloid plaques, and increase exponentially with age when plaques are present [182]. Instead of amyloid deposits, the concentration of soluble A $\beta$  significantly distinguishes AD patients from non-demented controls who meet the criteria for AD neuropathology [183]. In AD patients, disease severity strongly correlates with soluble A $\beta$  levels, whereas the presence of insoluble A $\beta$  merely indicates the existence of the disease [184]. Furthermore, soluble A $\beta$  extracted from human AD cortex has been shown to impair memory function in rats [185].

### 3.1.1 Abnormal A $\beta$ levels in epilepsy

A reduction in A $\beta$  cerebral spinal fluid (CSF) levels serves as a biomarker for pathological A $\beta$  buildup in the brain [186] and is increasingly used to support the diagnosis of AD [187]. Interestingly, AD patients with epilepsy exhibit lower CSF A $\beta_{42}$  levels compared to those without [188]. Similarly, AD patients with seizures show a trend towards lower CSF A $\beta_{42}$  levels compared those without [126]. LOEU patients show lower CSF A $\beta_{42}$  levels compared to controls [86], with pathological A $\beta$  CSF levels identified in nearly 40% of LOEU patients [110]. Moreover, LOEU patients with MCI show lower CSF A $\beta$  levels than those without cognitive impairments [112]. Finally, a notable proportion of drug-resistant TLE patients, aged 25 to 55 years, exhibited abnormal CSF A $\beta_{42}$  levels [189].

A subset of TLE patients have increased brain A $\beta$  expression [190-196]. Likewise, hippocampal expression of levels of APP are higher in a subset of TLE patients compared to controls [192, 197, 198]. Furthermore, in models of epilepsy and seizures accelerated or increased levels of A $\beta$  or pro-amyloidogenic changes are found in a subset of animals compared to controls, such as in kainic acid mouse [199] and rat [200] models, pilocarpine mouse model [201], and after pentylenetetrazol kindling [202]. For instance, adult rats treated with kainic acid show elevated hippocampal levels of A $\beta_{40}$  and A $\beta_{42}$  from day 2 onward compared to control rats

[200]. Kainic acid treatment in mice elicits pro-amyloidogenic changes [199]. In the triple transgenic AD mouse model (3xTg-AD), which expresses mutant human APP<sub>swe</sub>, PSEN1 M146V, and microtubule-associated protein Tau (MAPT P301L), pilocarpine-induced chronic epilepsy prompts extracellular brain A $\beta$  expression to appear several months earlier than the typical age of A $\beta$  plaque formation [201]. In the five times familial AD mouse model (5xFAD), which overexpresses human APP with the Swedish (K670N/M671L), Florida (I716V), and London (V717I) mutations, along with human PSEN1 carrying the M146L and L286V mutations, pentylentetrazol-kindled seizures intensified A $\beta$  neuropathology, including plaque deposition and increased levels of soluble A $\beta_{42}$  [202]. In hippocampal brain extracts from mice that are exposed to repetitive mild traumatic brain injury, which is a risk factor for LOE [75], increased levels of soluble A $\beta_{1-40}$  en A $\beta_{1-42}$  are reported [203].

### 3.1.2 The role of A $\beta$ in brain excitability

A role for A $\beta$  in epileptogenesis is highlighted by studies showing epileptiform activity, including seizures and spikes, in AD animal models overexpressing A $\beta$  in the brain [158]. Furthermore, neuronal hyperactivity near A $\beta$  plaques is observed in APP/PS1 mice [204]. Additional evidence comes from studies demonstrating increased susceptibility to spontaneous or induced seizures in mice overexpressing A $\beta$  [157, 202, 205], as well as enhanced susceptibility to corneal kindling in mice with elevated soluble A $\beta_{1-42}$  levels [206, 207]. Similarly, the lowered threshold for pentylentetrazole-induced seizures at a young age before A $\beta$  plaque formation in an AD mouse model suggests that soluble A $\beta$ , rather than plaque formation, significantly contributes to hyperexcitability [208]. This is supported by findings that neutralizing soluble A $\beta$  species with antibodies reduces seizure occurrence induced by intrahippocampal kainate injection in pre-plaque AD mice [209]. Similarly, hippocampal neurons exhibited hyperactivity *in vivo* at a young age before plaque formation in an AD mouse model, which is alleviated by reducing soluble A $\beta$  levels with a  $\gamma$ -secretase inhibitor [210]. Moreover, application of soluble A $\beta$  oligomers in hippocampal slices from wild-type mice results in heightened neuronal excitability [211]. Neuronal hyperactivity has been demonstrated to contribute to A $\beta$  deposition in the hippocampus [212]. Together, these findings suggest a reciprocal relationship where soluble A $\beta$  can induce hyperexcitability, and in turn, hyperexcitability or seizures can exacerbate soluble A $\beta$  accumulation, creating a detrimental cycle.

Although the precise mechanisms through which soluble A $\beta$  induces hyperexcitability in the brain are not fully elucidated, there are several indications that soluble A $\beta$  directly affects neurons. Soluble A $\beta$  depolarizes the membrane potential of hippocampal granule cells and enhances the activity of excitatory neuronal populations in rodent brains [157]. Additionally, A $\beta$  promotes glutamate

release from astrocytes [213] and neurons via activation of  $\alpha 7$  nicotinic acetylcholine receptors [214], while it may also inhibit astrocytic glutamate reuptake [215]. Furthermore, oligomeric  $A\beta_{42}$  can induce glutamate release from astrocytes, leading to NMDA receptor activation [213]. Notably,  $A\beta$  increases cell surface expression of NMDA receptors and enhances NMDA-induced calcium levels, which coincide with excitotoxicity [216]. Moreover,  $A\beta$  induces neuronal hyperexcitability by upregulating the expression of voltage-gated sodium channels [217] and reducing potassium channels at the neuronal membrane [218]. Finally, in response to  $A\beta$  the release of interleukin 1 beta (IL-1 $\beta$ ) [219] from astrocytes is triggered. Thus, changes in the expression of  $A\beta$  are found in epilepsy might potentially contribute to epileptogenesis, but its role is not well understood.

### **3.2 The role of tau**

Tau is a microtubule-binding axonal protein expressed in neurons that plays a role in microtubule stabilization [179]. Despite the fact that tau deposition is a better predictor of cognitive decline than  $A\beta$  [220], mutations in the tau gene cause frontotemporal dementia without the presence  $A\beta$  pathology [221]. Several preclinical studies support the evidence that  $A\beta$  drives tau alterations. For example, crossing Tg2576 mice, which overexpress human mutant APP, with JNPL3 mice, which overexpress mutant tau, results in increased NFT load without affecting  $A\beta$  depositions [222]. Further evidence comes from a study in which it is shown that that soluble  $A\beta$  oligomers isolated from the cortex of AD patients is able to induce hyperphosphorylation of tau and neuritic degeneration in cultured rat neurons [223].

#### *3.2.1 Abnormal tau levels in epilepsy*

In several studies, neuropathological tau alterations have been identified in epilepsy. Increased CSF levels of total tau and phosphorylated tau (p-tau) are a biomarker for AD pathology [187, 224]. In AD patients with epilepsy CSF total tau and p-tau levels are higher compared to AD patients without epilepsy [188]. Furthermore, seizures development is associated with higher CSF total tau protein levels in AD patients [126], although CSF p-tau levels does not differ from AD patients without seizures. Similarly, higher total tau and p-tau proteins are found in LOEU patients compared to controls [86]. CSF p-tau levels were associated with poorer cognitive performance in drug-resistant TLE patients, aged 25 to 55 years [189]. Hyperphosphorylated tau is found in epilepsy patients and animal models [168, 192-196, 199, 225-231]. Transgenic mice overexpressing human mutant tau exhibit spontaneous seizures and epileptic activity [232] and increased susceptibility to induced seizures [233, 234]. Tau reduction lowers seizure latency and duration in an  $A\beta$  overexpressing mouse model for AD [235]. Neuronal hyperactivity enhances tau pathology [236].

### 3.3 Clearance of A $\beta$ and tau

A $\beta$  can be cleared through multiple pathways, including degradation either extracellularly or intracellularly following phagocytosis by various proteins [237-242]. A $\beta$  is cleared by various A $\beta$ -degrading enzymes, including matrix metalloproteinases (MMPs), serine and cysteine proteases, thiol-dependent metalloendopeptidases, zinc metalloendopeptidases, and others [242]. For example, the thiol metalloprotease insulin-degrading enzyme (IDE) [239, 240] and the plasma membrane glycoprotein zinc metalloendopeptidases neprilysin (NEP) [243] degrade A $\beta$ . Activated astrocytes and microglia are involved in clearing accumulated A $\beta$  from the brain [244, 245]. Intracellular degradation of A $\beta$  relies on systems such as the ubiquitin–proteasome system (UPS), endosomal/lysosomal pathways, and autophagy [246]. Intriguingly, the efflux of A $\beta$  from the brain into the bloodstream via the BBB contributes to approximately 25% of its clearance [247]. In the periphery, A $\beta$  is cleared systemically through the liver, kidneys, and spleen [242]. The receptor for advanced glycation end products (RAGE) mediates the influx of A $\beta$  into the brain [248]. The neurovascular hypothesis of AD posits that compromised efflux of A $\beta$  at the BBB is the cause for increased levels of brain A $\beta$  and neurovascular dysfunction [249]. Impaired brain A $\beta$  clearance is shown in late-onset AD patients rather than increased production when compared to controls [250]. A dysfunctional BBB with impaired clearance function can result in the accumulation of harmful substances in the brain, as has been described for AD [251].

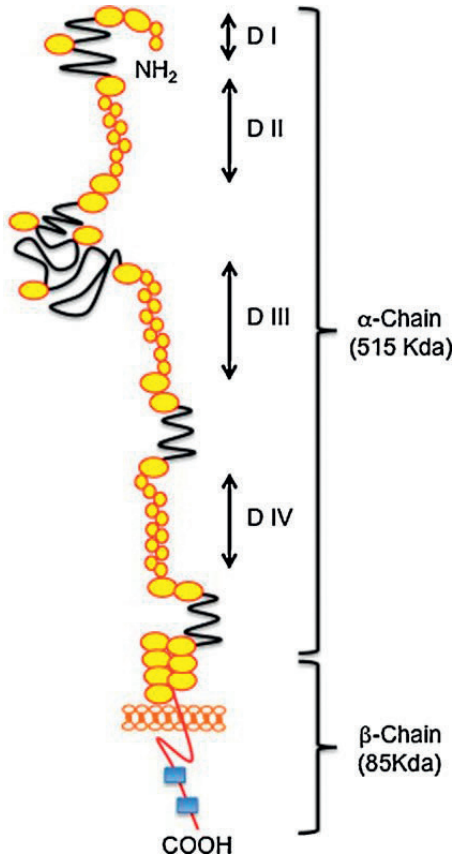
## **4. The role of low-density lipoprotein receptor-related protein 1 in the brain**

Low-density lipoprotein receptor-related protein 1 (LRP1) is a multifunctional transmembrane receptor that has an endocytic and signaling function and is a member of the low density lipoprotein receptor (LDLR) gene family [252]. The LDLR family is a well-conserved family of receptors that bind a diverse array of ligands, including A $\beta$  [241, 253]. LRP1 has a more rapid endocytosis rate compared to other members of the LDLR family [254]. It functions primarily as a scavenger receptor and mediates the endocytosis of various ligands, including lipoproteins, hormones, and proteases. LRP1 is expressed in various tissues including liver, lungs, adipose tissue and brain [255]. In the liver, LRP1 is involved in lipoprotein metabolism [256]. The extracellular domain of LRP1, the heavy  $\alpha$ -chain (515 kDa), contains four ligand-binding clusters (I–IV) that bind over a 100 ligands (**Figure 1**). The intracellular domain, the light  $\beta$ -chain (85 kDa), consists of transmembrane segment and the cytoplasmic domain, that control endocytosis or serves as a docking site for cytoplasmic adaptor proteins. The importance of LRP1 is demonstrated by the fact that it is essential for embryonic development, due to vascular defects in mice lacking it [257-259]. Conditional LRP1 forebrain knockout mice show reduced brain

cholesterol levels, highlighting LRP1's role in brain cholesterol metabolism [260, 261]. LRP1 is located at the abluminal side of the brain endothelium [262]. LRP1 is an important protein for A $\beta$  efflux at the BBB [249, 262-268]. LRP1 at the BBB has a higher affinity for A $\beta$ <sub>1-40</sub> than for A $\beta$ <sub>1-42</sub> [269]. After A $\beta$  is internalized by LRP1, it is subsequently transferred to P-glycoprotein (P-gp) for transcytosis across the BBB [270]. P-gp is expressed at the luminal side of the brain endothelium and is important for mediating A $\beta$  efflux from the brain [271, 272]. LRP1 also mediates A $\beta$  clearance in brain vascular smooth muscle cells [273] and pericytes [274]. LRP1 expression decreases in the human brain with age and in AD patients [275]. Brain A $\beta$  deposition is linked to a LRP1 polymorphism in AD patients [276]. Membrane-bound LRP1 can be cleaved by  $\alpha$ -secretase and  $\beta$ -secretase [277]. Subsequently, the  $\alpha$ -chain is released into plasma as soluble LRP1 (sLRP1) [278], where it sequesters approximately 70% A $\beta$  in the bloodstream [279].

LRP1 also plays an important role in the inflammatory response modulation [281-283]. For example, LRP1 deletion in macrophages *in vitro* strongly increases the expression of proinflammatory cytokines [281]. Moreover, silencing LRP1 causes the activation of microglia and astrocytes [284] and the release of proinflammatory cytokines, such as IL-6, IL-1 $\beta$  and TNF- $\alpha$  [261]. This process is mediated by Toll-like receptor 4 (TLR4) activation, which triggers the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) and mitogen-activated protein kinase (MAPK) [285, 286].

The expression of brain capillary LRP1 is studied during aging and in AD by several studies [265, 266, 287-290]. The gene mRNA expression of LRP1 from isolated cerebral microvessels is reduced during aging in rats [288]. Furthermore, at protein expression level there is a similar loss of capillary LRP1 during aging in rats and this is also shown by immunostainings [289]. Moreover, its loss during aging correlates with A $\beta$ <sub>42</sub> accumulation [289]. During aging, the number of LRP1 positive vessels decreases from 94% in 2 month old mice to only 52% in 9 month old mice [265]. In human frontal cortex, LRP1 immunostaining in vessels of AD patients reduces when compared to age-matched controls [265]. Moreover, the number of LRP1-positive cerebral vessels reduces from 45% in age-matched controls to ~12% in AD [266]. Similarly, a reduction of LRP1 levels of 74% is found in brain endothelial cells in AD patients when compared to controls [290]. Finally, in AD hippocampal microvasculature LRP1 immunoreactivity decreases compared to age-matched controls [287].



**Figure 1. Structure of low-density lipoprotein receptor-related protein (LRP1) (Figure adapted and reprinted from [280]).** The extracellular domain of LRP1, the heavy  $\alpha$ -chain (515 kDa), contains four ligand-binding clusters (I–IV) that bind over a 100 ligands. The intracellular domain, the light  $\beta$ -chain (85 kDa), consists of transmembrane segment and the cytoplasmic domain, that control endocytosis or serves as a docking site for cytoplasmic adaptor proteins.

At pathological concentrations, A $\beta$  promotes the proteasomal degradation of brain capillary LRP1 [266]. Moreover, the reduced expression of capillary LRP1 can be attributed to conditions that are known to play a role in the pathophysiology of epilepsy, such as the natural aging process [4, 265, 288], but also hypoglycemia [291, 292] or hypoxia [293, 294]. Furthermore, LRP1 is found to be oxidized in the hippocampus of AD patients [295], that results in even more impaired binding of LRP1 to A $\beta$  [279]. Oxidative stress is implicated in the pathophysiology epilepsy [296, 297], aging and AD [298]. However, the role of brain endothelial LRP1 in epilepsy has not been studied in detail.

Reduced expression of LRP1 in brain endothelial cells exacerbates brain A $\beta$  accumulation, leads to cognitive impairment in a mouse model of AD [263, 264] and has a detrimental effect on BBB permeability [299]. Similarly, higher levels of brain endogenous mouse A $\beta$  and impaired cognition are observed in mice using i.c.v. injection of antisense directed against LRP1 [300]. Furthermore, ankyrin repeat and SAM domain containing 1 A (ANKS1A) facilitates the transport of LRP1 from the endoplasmic reticulum towards the membrane, and its endothelial deficiency in an AD mouse model results in aggravated A $\beta$  pathology and cognitive decline [301].

In neurons, LRP1 facilitates the clearance of A $\beta$  from the extracellular space through LRP1-mediated endocytosis followed by lysosomal degradation [302]. However, LRP1 is capable of internalizing APP and promoting its subsequent amyloidogenic processing into A $\beta$ , resulting in a situation where the net production of A $\beta$  surpasses its clearance function [303]. LRP1 expressed in neurons also regulates the endocytosis and propagation of tau protein [304]. Neuronal LRP1 expression may contribute to the spread of harmful substances in the brain that may further disrupt brain network excitability. Thus, neuronal LRP1 may play a role in the spread of harmful substances within the brain, potentially contributing disruptions in brain network homeostasis.

In glia, LRP1 clears A $\beta$  by cellular uptake and degradation [305]. Furthermore, depleting LRP1 in astrocytes leads to diminished levels of several A $\beta$ -degrading enzymes, including insulin-degrading enzyme and matrix metalloproteases MMP2 and MMP9 [305], underscoring the significant involvement of astrocytic LRP1 in modulating extracellular A $\beta$  degradation. Mice lacking LRP1 in radial glial cells and their progeny, including both hippocampal astrocytes and neurons, experience seizures shortly after birth and exhibit hyperexcitability in hippocampal neurons [284], implying the involvement of astrocytic LRP1 in modulating neuronal excitability. In an animal model for epileptogenesis an upregulation of LRP1 expression was found that was likely due to astrogliosis [306], indicating an important function of astrocytic LRP1 after SE.

## **5. Research in animal models**

### **5.1 Epilepsy animal models**

Further research on the mechanisms of epilepsy in humans is necessary, though it comes with certain limitations. As a result, studies are often conducted using animal models of epilepsy, which also have their own limitations but offer distinct advantages over human research. These animal models allow for the investigation and manipulation of specific processes during epileptogenesis, which allows for probing causal relationships and gaining mechanistic insights [13]. During epileptogenesis, various circuit and molecular changes occur in the animal

brain resembling human epilepsy neuropathology, including gliosis, synaptic reorganization, BBB dysfunction, and neurodegeneration [13]. Several chronic models of epilepsy share a common feature: an initial chemically or electrically [307] induced insult, known as status epilepticus (SE). This is followed by a latent period characterized by neuropathological changes such as cell loss, gliosis, synaptic reorganization, and inflammation [308], leading to a chronic stage during which spontaneous recurrent seizures occur. To chemically evoke SE several convulsants are used, such as pentylenetetrazole (PTZ) that antagonizes the inhibitory GABA<sub>A</sub> receptors [309], or kainic acid and pilocarpine that are used to stimulate the brain by activating ionotropic kainate receptors and muscarinic receptors [310], respectively. In the electrically induced post-SE rat model, SE is induced by electrically stimulating the hippocampus through the angular bundle [311-313]. The initial stimulus elicits periodic epileptiform discharges (PEDs) that last for several hours. Starting from the acute phase (1 day after SE) neuronal loss is observed and this is most extensive in rats with a progressive seizure development [16]. Following a latent period (1 week after SE) characterized by hippocampal spikes, spontaneous recurrent seizures develop during the chronic phase. Furthermore, the post-SE model develops gliosis, and BBB dysfunction [46, 314] and synaptic reorganization, such as mossy fiber sprouting [28, 311]. Cognitive dysfunction is observed in several epilepsy animal models [315]. Additionally, greater cognitive impairment is linked to an increasing number kindled seizures [316, 317].

## 5.2 AD animal models

Various animal models of AD are currently available that reproduce at least several aspects of AD and allow for a more mechanistic approach to study AD etiology [318-320], see **Figure 2** for phenotypes of widely utilized AD mouse models. The aggregation of endogenous mouse A $\beta$  into plaques is unlikely due to differences in its amino acid sequence compared to human A $\beta$ , making it less prone to aggregation into plaques as compared to human A $\beta$  [321]. Therefore, many transgenic mouse models for AD overexpress genes causing familial AD in human AD patients. This initially led to the development of transgenic mice expressing human mutant APP, which progressively exhibit the pathological hallmarks of AD, such as A $\beta$  deposits, synaptic loss, and gliosis [322]. Transgenic animal models are now available that replicate other aspects of AD, including abnormal A $\beta$  and tau expression, neurodegeneration, and/or neurobehavioral deficits, such as the 3xTg-AD mice [323, 324]. The 5xFAD mouse model co-expresses five mutations in genes that cause familial AD, including three mutations in APP and two mutations in PSEN1, under control of the forebrain neuronal *Thy-1* promoter [325, 326]. This mouse model for AD exhibits A $\beta$  deposition, astro- and microgliosis starting from the age of two months [325, 326], epileptiform spikes were reported at the age of 4 months [327] and cognitive dysfunction at 4 to 5 months of age [325]. Similar

to patients, 5xFAD female mice are more cognitively affected [328]. Moreover, female 5xFAD mice have more amyloid neuropathology than males [325, 326]. At the age of 9 months, 5xFAD mice exhibit spatial learning impairment [329]. In order to test spatial learning and cognitive flexibility in mice, a multiple-choice learning paradigm in a home-cage setting can be used [330, 331]. This setup shows impaired spatial learning [330] and impaired cognitive flexibility at 3 months of age [331] in APP/PS1 mice. Spontaneous seizures are detected in multiple AD mouse models using intracranial electrodes [151, 152, 155, 157, 158].



**Figure 2. Phenotypes of widely utilized AD mouse models (Figure adapted and reprinted from [319], source: Alzforum.org).**

## **6. Scope and outline of the thesis**

Epilepsy and Alzheimer's disease (AD) are complex neurological disorders that share a significant, bidirectional clinical link, particularly concerning epileptiform activity and cognitive impairments, for which no cure currently exists. These conditions exhibit overlapping neuropathological features to a certain extent, including neuroinflammation, homeostatic imbalances, and structural brain alterations. Comprehensive understanding of the neurobiological mechanisms underlying epileptiform activity-induced cognitive dysfunction is crucial for developing and improving therapeutic strategies. Therefore, the aim of this thesis is to unravel mechanisms of dysregulated processes in the epileptogenic brain and utilize this knowledge to identify new treatment strategies.

In **chapter 2**, we explored changes at the BBB (endothelial cells), neurons and glial cells in epilepsy and AD by examining the endothelial, neuronal and glial expression of LRP1. This investigation utilized resected hippocampi from drug-resistant TLE patients and the electrically induced post-SE rat model to study epileptogenesis. Additionally, we assessed its expression levels in hippocampi from autopsy AD patients. Furthermore, we studied soluble A $\beta$  and amyloid plaque deposition in human and experimental epilepsy.

**Chapter 3** aimed to further investigate the effects of inducible knockout of brain endothelial LRP1 on epileptogenesis in transgenic mice using the 5xFAD model of AD. We also studied the expression of markers from glial cells that are important for the neuroinflammatory response, as well as soluble A $\beta$  and amyloid plaque deposition in these mice.

In **chapter 4**, we examined the potential effects of inducible knockout of brain endothelial LRP1 on cognition in transgenic mice, again using the 5xFAD model. Additionally, we investigated the expression of hippocampal proteins related to neuroplasticity and cognition in these mice.

Finally, **chapter 5** aims to summarize and discuss in depth the main findings of this thesis in relation to epileptiform activity-induced cognitive dysfunction from a broader perspective and to suggest various novel therapeutic strategies for epilepsy and AD.

## References

1. Ngugi, A.K., et al., *Estimation of the burden of active and life-time epilepsy: a meta-analytic approach*. *Epilepsia*, 2010. **51**(5): p. 883-90.
2. Fisher, R.S., et al., *Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)*. *Epilepsia*, 2005. **46**(4): p. 470-2.
3. Fisher, R.S., et al., *ILAE official report: a practical clinical definition of epilepsy*. *Epilepsia*, 2014. **55**(4): p. 475-82.
4. Sen, A., et al., *Epilepsy in older people*. *Lancet*, 2020. **395**(10225): p. 735-748.
5. Cloyd, J., et al., *Epidemiological and medical aspects of epilepsy in the elderly*. *Epilepsy Res*, 2006. **68 Suppl 1**: p. S39-48.
6. de la Court, A., et al., *Prevalence of epilepsy in the elderly: the Rotterdam Study*. *Epilepsia*, 1996. **37**(2): p. 141-7.
7. Olafsson, E., et al., *Incidence of unprovoked seizures and epilepsy in Iceland and assessment of the epilepsy syndrome classification: a prospective study*. *Lancet Neurol*, 2005. **4**(10): p. 627-34.
8. Forsgren, L., et al., *Incidence and clinical characterization of unprovoked seizures in adults: a prospective population-based study*. *Epilepsia*, 1996. **37**(3): p. 224-9.
9. Baker, G.A., et al., *The stigma of epilepsy: a European perspective*. *Epilepsia*, 2000. **41**(1): p. 98-104.
10. Kwon, C.S., et al., *Systematic review of frequency of felt and enacted stigma in epilepsy and determining factors and attitudes toward persons living with epilepsy-Report from the International League Against Epilepsy Task Force on Stigma in Epilepsy*. *Epilepsia*, 2022. **63**(3): p. 573-597.
11. de Boer, H.M., M. Mula, and J.W. Sander, *The global burden and stigma of epilepsy*. *Epilepsy Behav*, 2008. **12**(4): p. 540-6.
12. Kanner, A.M., *Management of psychiatric and neurological comorbidities in epilepsy*. *Nat Rev Neurol*, 2016. **12**(2): p. 106-16.
13. Pitkanen, A., et al., *Epileptogenesis*. *Cold Spring Harb Perspect Med*, 2015. **5**(10).
14. Scheffer, I.E., et al., *ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology*. *Epilepsia*, 2017. **58**(4): p. 512-521.
15. de Lanerolle, N.C., et al., *Hippocampal interneuron loss and plasticity in human temporal lobe epilepsy*. *Brain Res*, 1989. **495**(2): p. 387-95.
16. van Vliet, E.A., et al., *Progression of temporal lobe epilepsy in the rat is associated with immunocytochemical changes in inhibitory interneurons in specific regions of the hippocampal formation*. *Exp Neurol*, 2004. **187**(2): p. 367-79.
17. Aronica, E., et al., *Epileptogenesis in tuberous sclerosis complex-related developmental and epileptic encephalopathy*. *Brain*, 2023. **146**(7): p. 2694-2710.
18. Escartin, C., et al., *Reactive astrocyte nomenclature, definitions, and future directions*. *Nat Neurosci*, 2021. **24**(3): p. 312-325.
19. Verhoog, Q.P., et al., *Astrocytes as Guardians of Neuronal Excitability: Mechanisms Underlying Epileptogenesis*. *Front Neurol*, 2020. **11**: p. 591690.

20. Koizumi, T., et al., *Vessel-Associated Immune Cells in Cerebrovascular Diseases: From Perivascular Macrophages to Vessel-Associated Microglia*. *Front Neurosci*, 2019. **13**: p. 1291.
21. Paolicelli, R.C., et al., *Microglia states and nomenclature: A field at its crossroads*. *Neuron*, 2022. **110**(21): p. 3458-3483.
22. Vezzani, A., et al., *The role of inflammation in epilepsy*. *Nat Rev Neurol*, 2011. **7**(1): p. 31-40.
23. Kan, A.A., et al., *Protein expression profiling of inflammatory mediators in human temporal lobe epilepsy reveals co-activation of multiple chemokines and cytokines*. *J Neuroinflammation*, 2012. **9**: p. 207.
24. Vezzani, A., et al., *Astrocytes in the initiation and progression of epilepsy*. *Nat Rev Neurol*, 2022. **18**(12): p. 707-722.
25. Tsai, S.J., *Effects of interleukin-1beta polymorphisms on brain function and behavior in healthy and psychiatric disease conditions*. *Cytokine Growth Factor Rev*, 2017. **37**: p. 89-97.
26. Viviani, B., et al., *Interleukin-1beta enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases*. *J Neurosci*, 2003. **23**(25): p. 8692-700.
27. Takahashi, D.K., J.R. Vargas, and K.S. Wilcox, *Increased coupling and altered glutamate transport currents in astrocytes following kainic-acid-induced status epilepticus*. *Neurobiol Dis*, 2010. **40**(3): p. 573-85.
28. van Vliet, E.A., et al., *Inhibition of mammalian target of rapamycin reduces epileptogenesis and blood-brain barrier leakage but not microglia activation*. *Epilepsia*, 2012. **53**(7): p. 1254-63.
29. Crespel, A., et al., *Inflammatory reactions in human medial temporal lobe epilepsy with hippocampal sclerosis*. *Brain Res*, 2002. **952**(2): p. 159-69.
30. Ravizza, T., et al., *Innate and adaptive immunity during epileptogenesis and spontaneous seizures: evidence from experimental models and human temporal lobe epilepsy*. *Neurobiol Dis*, 2008. **29**(1): p. 142-60.
31. Dobson, H., et al., *Elevated plasma neurofilament light and glial fibrillary acidic protein in epilepsy versus nonepileptic seizures and nonepileptic disorders*. *Epilepsia*, 2024.
32. Robel, S., et al., *Reactive astrogliosis causes the development of spontaneous seizures*. *J Neurosci*, 2015. **35**(8): p. 3330-45.
33. Abraham, J., et al., *Minocycline attenuates microglia activation and blocks the long-term epileptogenic effects of early-life seizures*. *Neurobiol Dis*, 2012. **46**(2): p. 425-30.
34. Zhao, X., et al., *Noninflammatory Changes of Microglia Are Sufficient to Cause Epilepsy*. *Cell Rep*, 2018. **22**(8): p. 2080-2093.
35. Xanthos, D.N. and J. Sandkuhler, *Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity*. *Nat Rev Neurosci*, 2014. **15**(1): p. 43-53.
36. Daneman, R., *The blood-brain barrier in health and disease*. *Ann Neurol*, 2012. **72**(5): p. 648-72.
37. Sweeney, M.D., et al., *Blood-Brain Barrier: From Physiology to Disease and Back*. *Physiol Rev*, 2019. **99**(1): p. 21-78.
38. Sorokin, L., *The impact of the extracellular matrix on inflammation*. *Nat Rev Immunol*, 2010. **10**(10): p. 712-23.

39. Attwell, D., et al., *Glial and neuronal control of brain blood flow*. Nature, 2010. **468**(7321): p. 232-43.
40. Armulik, A., et al., *Pericytes regulate the blood-brain barrier*. Nature, 2010. **468**(7323): p. 557-61.
41. Winkler, E.A., R.D. Bell, and B.V. Zlokovic, *Central nervous system pericytes in health and disease*. Nat Neurosci, 2011. **14**(11): p. 1398-1405.
42. Rustenhoven, J., et al., *Brain Pericytes As Mediators of Neuroinflammation*. Trends Pharmacol Sci, 2017. **38**(3): p. 291-304.
43. van Vliet, E.A. and N. Marchi, *Neurovascular unit dysfunction as a mechanism of seizures and epilepsy during aging*. Epilepsia, 2022. **63**(6): p. 1297-1313.
44. Profaci, C.P., et al., *The blood-brain barrier in health and disease: Important unanswered questions*. J Exp Med, 2020. **217**(4).
45. Meijer, W.C. and J.A. Gorter, *Role of blood-brain barrier dysfunction in the development of poststroke epilepsy*. Epilepsia, 2024.
46. van Vliet, E.A., et al., *Blood-brain barrier leakage may lead to progression of temporal lobe epilepsy*. Brain, 2007. **130**(Pt 2): p. 521-34.
47. Gorter, J.A., E. Aronica, and E.A. van Vliet, *The Roof is Leaking and a Storm is Raging: Repairing the Blood-Brain Barrier in the Fight Against Epilepsy*. Epilepsy Curr, 2019. **19**(3): p. 177-181.
48. van Vliet, E.A., E. Aronica, and J.A. Gorter, *Blood-brain barrier dysfunction, seizures and epilepsy*. Semin Cell Dev Biol, 2015. **38**: p. 26-34.
49. Loscher, W. and A. Friedman, *Structural, Molecular, and Functional Alterations of the Blood-Brain Barrier during Epileptogenesis and Epilepsy: A Cause, Consequence, or Both?* Int J Mol Sci, 2020. **21**(2).
50. Klement, W., et al., *A pericyte-glia scarring develops at the leaky capillaries in the hippocampus during seizure activity*. Epilepsia, 2019. **60**(7): p. 1399-1411.
51. Garbelli, R., et al., *PDGFRbeta(+) cells in human and experimental neuro-vascular dysplasia and seizures*. Neuroscience, 2015. **306**: p. 18-27.
52. Klement, W., et al., *Seizure progression and inflammatory mediators promote pericytosis and pericyte-microglia clustering at the cerebrovasculature*. Neurobiol Dis, 2018. **113**: p. 70-81.
53. Bar-Klein, G., et al., *Losartan prevents acquired epilepsy via TGF-beta signaling suppression*. Ann Neurol, 2014. **75**(6): p. 864-75.
54. Ivens, S., et al., *TGF-beta receptor-mediated albumin uptake into astrocytes is involved in neocortical epileptogenesis*. Brain, 2007. **130**(Pt 2): p. 535-47.
55. Tanaka, A., et al., *Clinical characteristics and treatment responses in new-onset epilepsy in the elderly*. Seizure, 2013. **22**(9): p. 772-5.
56. Blumcke, I., et al., *Histopathological Findings in Brain Tissue Obtained during Epilepsy Surgery*. N Engl J Med, 2017. **377**(17): p. 1648-1656.
57. Aronica, E., et al., *Characterization of pathology, in Models of Seizures and Epilepsy*. 2017, Elsevier. p. 139-160.
58. Blumcke, I., et al., *International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task Force report from the ILAE Commission on Diagnostic Methods*. Epilepsia, 2013. **54**(7): p. 1315-29.

59. Mathern, G.W., et al., *The clinical-pathogenic mechanisms of hippocampal neuron loss and surgical outcomes in temporal lobe epilepsy*. Brain, 1995. **118 ( Pt 1)**: p. 105-18.
60. Blumcke, I., et al., *Towards a clinico-pathological classification of granule cell dispersion in human mesial temporal lobe epilepsies*. Acta Neuropathol, 2009. **117(5)**: p. 535-44.
61. Kwan, P., et al., *Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies*. Epilepsia, 2010. **51(6)**: p. 1069-77.
62. Tellez-Zenteno, J.F., et al., *A validation of the new definition of drug-resistant epilepsy by the International League Against Epilepsy*. Epilepsia, 2014. **55(6)**: p. 829-34.
63. Tallis, R., et al., *Epilepsy in elderly people: management issues*. Epileptic Disord, 2002. **4 Suppl 2**: p. S33-9.
64. Rao, S.C., et al., *Recurrent seizures in patients with dementia: frequency, seizure types, and treatment outcome*. Epilepsy Behav, 2009. **14(1)**: p. 118-20.
65. Wiebe, S., et al., *A randomized, controlled trial of surgery for temporal-lobe epilepsy*. N Engl J Med, 2001. **345(5)**: p. 311-8.
66. de Tisi, J., et al., *The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study*. Lancet, 2011. **378(9800)**: p. 1388-95.
67. Bell, B., et al., *The neurobiology of cognitive disorders in temporal lobe epilepsy*. Nat Rev Neurol, 2011. **7(3)**: p. 154-64.
68. Englot, D.J., et al., *Rates and Predictors of Seizure Freedom With Vagus Nerve Stimulation for Intractable Epilepsy*. Neurosurgery, 2016. **79(3)**: p. 345-53.
69. Fan, J.J., et al., *Research progress of vagus nerve stimulation in the treatment of epilepsy*. CNS Neurosci Ther, 2019. **25(11)**: p. 1222-1228.
70. Rho, J.M., *How does the ketogenic diet induce anti-seizure effects?* Neurosci Lett, 2017. **637**: p. 4-10.
71. Lima, P.A., L.P. Sampaio, and N.R. Damasceno, *Neurobiochemical mechanisms of a ketogenic diet in refractory epilepsy*. Clinics (Sao Paulo), 2014. **69(10)**: p. 699-705.
72. Liu, H., et al., *Ketogenic diet for treatment of intractable epilepsy in adults: A meta-analysis of observational studies*. Epilepsia Open, 2018. **3(1)**: p. 9-17.
73. Kang, H.C., et al., *Early- and late-onset complications of the ketogenic diet for intractable epilepsy*. Epilepsia, 2004. **45(9)**: p. 1116-23.
74. Assis, T.R., et al., *Etiological prevalence of epilepsy and epileptic seizures in hospitalized elderly in a Brazilian tertiary center - Salvador - Brazil*. Arq Neuropsiquiatr, 2015. **73(2)**: p. 83-9.
75. Cvetkovska, E., et al., *Prevalence of various risk factors associated with new-onset epilepsy after the age of 50: a retrospective population-based study*. Epileptic Disord, 2022. **24(1)**: p. 95-101.
76. Hesdorffer, D.C., et al., *Dementia and adult-onset unprovoked seizures*. Neurology, 1996. **46(3)**: p. 727-30.
77. DeLorenzo, R.J., et al., *A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia*. Neurology, 1996. **46(4)**: p. 1029-35.
78. Knake, S., et al., *Incidence of status epilepticus in adults in Germany: a prospective, population-based study*. Epilepsia, 2001. **42(6)**: p. 714-8.

79. Trinka, E., et al., *A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus*. *Epilepsia*, 2015. **56**(10): p. 1515-23.
80. Trinka, E., J. Hofler, and A. Zerbs, *Causes of status epilepticus*. *Epilepsia*, 2012. **53 Suppl 4**: p. 127-38.
81. Hermann, B.P., et al., *Cognitive prognosis in chronic temporal lobe epilepsy*. *Ann Neurol*, 2006. **60**(1): p. 80-7.
82. Hermann, B., et al., *Cognitive phenotypes in temporal lobe epilepsy*. *J Int Neuropsychol Soc*, 2007. **13**(1): p. 12-20.
83. Witt, J.A., et al., *Cognitive-behavioral screening in elderly patients with new-onset epilepsy before treatment*. *Acta Neurol Scand*, 2014. **130**(3): p. 172-7.
84. Helmstaedter, C. and C.E. Elger, *Chronic temporal lobe epilepsy: a neurodevelopmental or progressively dementing disease?* *Brain*, 2009. **132**(Pt 10): p. 2822-30.
85. Hermann, B.P., et al., *Vascular, inflammatory, and metabolic factors associated with cognition in aging persons with chronic epilepsy*. *Epilepsia*, 2017. **58**(11): p. e152-e156.
86. Fernandes, M., et al., *Cognitive functioning, cerebrospinal fluid Alzheimer's disease biomarkers and cerebral glucose metabolism in late-onset epilepsy of unknown aetiology: A prospective study*. *Eur J Neurosci*, 2022. **56**(9): p. 5384-5396.
87. McKhann, G., et al., *Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease*. *Neurology*, 1984. **34**(7): p. 939-44.
88. ALZHEIMER'S ASSOCIATION REPORT 2023 *Alzheimer's disease facts and figures*. *Alzheimers Dement*, 2023. **19**(4): p. 1598-1695.
89. Jellinger, K.A., *Recent update on the heterogeneity of the Alzheimer's disease spectrum*. *J Neural Transm (Vienna)*, 2022. **129**(1): p. 1-24.
90. Crimins, J.L., et al., *The intersection of amyloid beta and tau in glutamatergic synaptic dysfunction and collapse in Alzheimer's disease*. *Ageing Res Rev*, 2013. **12**(3): p. 757-63.
91. Seshadri, S., et al., *Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study*. *Neurology*, 1997. **49**(6): p. 1498-504.
92. Evans, D.A., et al., *Prevalence of Alzheimer's disease in a community population of older persons. Higher than previously reported*. *JAMA*, 1989. **262**(18): p. 2551-6.
93. Silva, M.V.F., et al., *Alzheimer's disease: risk factors and potentially protective measures*. *J Biomed Sci*, 2019. **26**(1): p. 33.
94. Dorszewska, J., et al., *Molecular Basis of Familial and Sporadic Alzheimer's Disease*. *Curr Alzheimer Res*, 2016. **13**(9): p. 952-63.
95. Albert, M.S., et al., *The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease*. *Alzheimers Dement*, 2011. **7**(3): p. 270-9.
96. Self, W.K. and D.M. Holtzman, *Emerging diagnostics and therapeutics for Alzheimer disease*. *Nat Med*, 2023. **29**(9): p. 2187-2199.
97. Budd Haeberlein, S., et al., *Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease*. *J Prev Alzheimers Dis*, 2022. **9**(2): p. 197-210.
98. van Dyck, C.H., et al., *Lecanemab in Early Alzheimer's Disease*. *N Engl J Med*, 2023. **388**(1): p. 9-21.

99. Cummings, J., et al., *Alzheimer's disease drug development pipeline: 2022*. *Alzheimers Dement (N Y)*, 2022. **8**(1): p. e12295.
100. Schnier, C., et al., *A nationwide, retrospective, data-linkage, cohort study of epilepsy and incident dementia*. *Neurology*, 2020. **95**(12): p. e1686-e1693.
101. Johnson, E.L., et al., *Dementia in late-onset epilepsy: The Atherosclerosis Risk in Communities study*. *Neurology*, 2020. **95**(24): p. e3248-e3256.
102. Stefanidou, M., et al., *Bi-directional association between epilepsy and dementia: The Framingham Heart Study*. *Neurology*, 2020. **95**(24): p. e3241-e3247.
103. Tang, T., R. Zhang, and X. Pan, *Meta-analysis of the risk of dementia in elderly patients with late-onset epilepsy*. *Clin Neurol Neurosurg*, 2022. **223**: p. 107499.
104. Huang, L., et al., *Late-onset epilepsy and the risk of dementia: a systematic review and meta-analysis*. *Aging Clin Exp Res*, 2022. **34**(8): p. 1771-1779.
105. Keret, O., et al., *Association of Late-Onset Unprovoked Seizures of Unknown Etiology With the Risk of Developing Dementia in Older Veterans*. *JAMA Neurol*, 2020. **77**(6): p. 710-715.
106. Kawakami, O., et al., *Incidence of dementia in patients with adult-onset epilepsy of unknown causes*. *J Neurol Sci*, 2018. **395**: p. 71-76.
107. Costa, C., et al., *Cognitive Decline Risk Stratification in People with Late-Onset Epilepsy of Unknown Etiology: An Electroencephalographic Connectivity and Graph Theory Pilot Study*. *J Alzheimers Dis*, 2022. **88**(3): p. 893-901.
108. Ophir, K., et al., *Ten year cumulative incidence of dementia after late onset epilepsy of unknown etiology*. *J Clin Neurosci*, 2021. **86**: p. 247-251.
109. Dun, C., et al., *Bi-directional associations of epilepsy with dementia and Alzheimer's disease: a systematic review and meta-analysis of longitudinal studies*. *Age Ageing*, 2022. **51**(3).
110. Costa, C., et al., *Alzheimer's disease and late-onset epilepsy of unknown origin: two faces of beta amyloid pathology*. *Neurobiol Aging*, 2019. **73**: p. 61-67.
111. Reyes, A., et al., *Diagnosing cognitive disorders in older adults with epilepsy*. *Epilepsia*, 2021. **62**(2): p. 460-471.
112. Nardi Cesarini, E., et al., *Late-Onset Epilepsy With Unknown Etiology: A Pilot Study on Neuropsychological Profile, Cerebrospinal Fluid Biomarkers, and Quantitative EEG Characteristics*. *Front Neurol*, 2020. **11**: p. 199.
113. Johnson, E.L., et al., *Association Between Midlife Risk Factors and Late-Onset Epilepsy: Results From the Atherosclerosis Risk in Communities Study*. *JAMA Neurol*, 2018. **75**(11): p. 1375-1382.
114. Mendez, M. and G. Lim, *Seizures in elderly patients with dementia: epidemiology and management*. *Drugs Aging*, 2003. **20**(11): p. 791-803.
115. Voglein, J., et al., *Seizures in Alzheimer's disease are highly recurrent and associated with a poor disease course*. *J Neurol*, 2020. **267**(10): p. 2941-2948.
116. Nicastro, N., F. Assal, and M. Seeck, *From here to epilepsy: the risk of seizure in patients with Alzheimer's disease*. *Epileptic Disord*, 2016. **18**(1): p. 1-12.
117. Zhao, B., et al., *Risk of seizures and subclinical epileptiform activity in patients with dementia: A systematic review and meta-analysis*. *Ageing Res Rev*, 2021. **72**: p. 101478.
118. Romoli, M., et al., *Amyloid-beta: a potential link between epilepsy and cognitive decline*. *Nat Rev Neurol*, 2021. **17**(8): p. 469-485.

119. Zarea, A., et al., *Seizures in dominantly inherited Alzheimer disease*. *Neurology*, 2016. **87**(9): p. 912-9.
120. Voglein, J., et al., *Seizures as an early symptom of autosomal dominant Alzheimer's disease*. *Neurobiol Aging*, 2019. **76**: p. 18-23.
121. Zelano, J., F. Brigo, and S. Garcia-Patek, *Increased risk of epilepsy in patients registered in the Swedish Dementia Registry*. *Eur J Neurol*, 2020. **27**(1): p. 129-135.
122. Wang, X., et al., *Predictors of New-Onset Epilepsy in People With Younger-Onset Neurocognitive Disorders*. *Front Aging Neurosci*, 2021. **13**: p. 637260.
123. Amatniek, J.C., et al., *Incidence and predictors of seizures in patients with Alzheimer's disease*. *Epilepsia*, 2006. **47**(5): p. 867-72.
124. Voglein, J., et al., *Seizure prevalence in neurodegenerative diseases—a study of autopsy proven cases*. *Eur J Neurol*, 2022. **29**(1): p. 12-18.
125. Rauramaa, T., et al., *Epilepsy in neuropathologically verified Alzheimer's disease*. *Seizure*, 2018. **58**: p. 9-12.
126. Tabuas-Pereira, M., et al., *Increased CSF tau is associated with a higher risk of seizures in patients with Alzheimer's disease*. *Epilepsy Behav*, 2019. **98**(Pt A): p. 207-209.
127. Arnaldi, D., et al., *Epilepsy in Neurodegenerative Dementias: A Clinical, Epidemiological, and EEG Study*. *J Alzheimers Dis*, 2020. **74**(3): p. 865-874.
128. Blank, L.J., et al., *Neurodegenerative disease is associated with increased incidence of epilepsy: a population based study of older adults*. *Age Ageing*, 2021. **50**(1): p. 205-212.
129. Lyou, H.J., et al., *Association of Alzheimer's Disease with the Risk of Developing Epilepsy: a 10-Year Nationwide Cohort Study*. *Dement Neurocogn Disord*, 2018. **17**(4): p. 156-162.
130. Vossel, K.A., et al., *Seizures and epileptiform activity in the early stages of Alzheimer disease*. *JAMA Neurol*, 2013. **70**(9): p. 1158-66.
131. Baker, J., et al., *The prevalence and clinical features of epileptic seizures in a memory clinic population*. *Seizure*, 2019. **71**: p. 83-92.
132. Horvath, A., et al., *Prevalence, Semiology, and Risk Factors of Epilepsy in Alzheimer's Disease: An Ambulatory EEG Study*. *J Alzheimers Dis*, 2018. **63**(3): p. 1045-1054.
133. Beagle, A.J., et al., *Relative Incidence of Seizures and Myoclonus in Alzheimer's Disease, Dementia with Lewy Bodies, and Frontotemporal Dementia*. *J Alzheimers Dis*, 2017. **60**(1): p. 211-223.
134. Lam, A.D., et al., *Silent hippocampal seizures and spikes identified by foramen ovale electrodes in Alzheimer's disease*. *Nat Med*, 2017. **23**(6): p. 678-680.
135. Irizarry, M.C., et al., *Incidence of new-onset seizures in mild to moderate Alzheimer disease*. *Arch Neurol*, 2012. **69**(3): p. 368-72.
136. Barbour, A.J., et al., *Seizures exacerbate excitatory: inhibitory imbalance in Alzheimer's disease and 5XFAD mice*. *Brain*, 2024.
137. Baker, J., et al., *A Longitudinal Study of Epileptic Seizures in Alzheimer's Disease*. *Front Neurol*, 2019. **10**: p. 1266.
138. DiFrancesco, J.C., et al., *Adult-Onset Epilepsy in Presymptomatic Alzheimer's Disease: A Retrospective Study*. *J Alzheimers Dis*, 2017. **60**(4): p. 1267-1274.
139. Staley, K.J. and F.E. Dudek, *Interictal spikes and epileptogenesis*. *Epilepsy Curr*, 2006. **6**(6): p. 199-202.

140. Lin, Y.Y., et al., *Magnetoencephalographic yield of interictal spikes in temporal lobe epilepsy. Comparison with scalp EEG recordings.* Neuroimage, 2003. **19**(3): p. 1115-26.
141. Yeh, W.C., et al., *Association between Subclinical Epileptiform Discharge and the Severity of Cognitive Decline in Alzheimer's Disease: A Longitudinal Cohort Study.* J Alzheimers Dis, 2022. **90**(1): p. 305-312.
142. Lam, A.D., et al., *Association of epileptiform abnormalities and seizures in Alzheimer disease.* Neurology, 2020. **95**(16): p. e2259-e2270.
143. Vossel, K.A., et al., *Incidence and impact of subclinical epileptiform activity in Alzheimer's disease.* Ann Neurol, 2016. **80**(6): p. 858-870.
144. Musaeus, C.S., et al., *Detection of subclinical epileptiform discharges in Alzheimer's disease using long-term outpatient EEG monitoring.* Neurobiol Dis, 2023. **183**: p. 106149.
145. Horvath, A.A., et al., *Subclinical epileptiform activity accelerates the progression of Alzheimer's disease: A long-term EEG study.* Clin Neurophysiol, 2021. **132**(8): p. 1982-1989.
146. Brunetti, V., et al., *Subclinical epileptiform activity during sleep in Alzheimer's disease and mild cognitive impairment.* Clin Neurophysiol, 2020. **131**(5): p. 1011-1018.
147. Horvath, A., et al., *Sleep EEG Detects Epileptiform Activity in Alzheimer's Disease with High Sensitivity.* J Alzheimers Dis, 2017. **56**(3): p. 1175-1183.
148. Horak, P.C., et al., *Interictal epileptiform discharges impair word recall in multiple brain areas.* Epilepsia, 2017. **58**(3): p. 373-380.
149. Kleen, J.K., et al., *Hippocampal interictal epileptiform activity disrupts cognition in humans.* Neurology, 2013. **81**(1): p. 18-24.
150. Kleen, J.K., et al., *Hippocampal interictal spikes disrupt cognition in rats.* Ann Neurol, 2010. **67**(2): p. 250-7.
151. Kam, K., et al., *Interictal spikes during sleep are an early defect in the Tg2576 mouse model of beta-amyloid neuropathology.* Sci Rep, 2016. **6**: p. 20119.
152. Gureviciene, I., et al., *Characterization of Epileptic Spiking Associated With Brain Amyloidosis in APP/PS1 Mice.* Front Neuro, 2019. **10**: p. 1151.
153. Lisgaras, C.P. and H.E. Scharfman, *Interictal spikes in Alzheimer's disease: Preclinical evidence for dominance of the dentate gyrus and cholinergic control by the medial septum.* Neurobiol Dis, 2023. **187**: p. 106294.
154. Bezzina, C., et al., *Early onset of hypersynchronous network activity and expression of a marker of chronic seizures in the Tg2576 mouse model of Alzheimer's disease.* PLoS One, 2015. **10**(3): p. e0119910.
155. Fu, C.H., et al., *Early Seizure Activity Accelerates Depletion of Hippocampal Neural Stem Cells and Impairs Spatial Discrimination in an Alzheimer's Disease Model.* Cell Rep, 2019. **27**(13): p. 3741-3751 e4.
156. Verret, L., et al., *Inhibitory interneuron deficit links altered network activity and cognitive dysfunction in Alzheimer model.* Cell, 2012. **149**(3): p. 708-21.
157. Minkeviciene, R., et al., *Amyloid beta-induced neuronal hyperexcitability triggers progressive epilepsy.* J Neurosci, 2009. **29**(11): p. 3453-62.
158. Palop, J.J., et al., *Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease.* Neuron, 2007. **55**(5): p. 697-711.
159. Bakker, A., et al., *Reduction of hippocampal hyperactivity improves cognition in amnesic mild cognitive impairment.* Neuron, 2012. **74**(3): p. 467-74.

160. Vossel, K., et al., *Effect of Levetiracetam on Cognition in Patients With Alzheimer Disease With and Without Epileptiform Activity: A Randomized Clinical Trial*. JAMA Neurol, 2021. **78**(11): p. 1345-1354.
161. Sanchez, P.E., et al., *Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model*. Proc Natl Acad Sci U S A, 2012. **109**(42): p. E2895-903.
162. Sen, A., V. Capelli, and M. Husain, *Cognition and dementia in older patients with epilepsy*. Brain, 2018. **141**(6): p. 1592-1608.
163. Kamondi, A., et al., *Epilepsy and epileptiform activity in late-onset Alzheimer disease: clinical and pathophysiological advances, gaps and conundrums*. Nat Rev Neurol, 2024. **20**(3): p. 162-182.
164. Chin, J. and H.E. Scharfman, *Shared cognitive and behavioral impairments in epilepsy and Alzheimer's disease and potential underlying mechanisms*. Epilepsy Behav, 2013. **26**(3): p. 343-51.
165. Noebels, J., *A perfect storm: Converging paths of epilepsy and Alzheimer's dementia intersect in the hippocampal formation*. Epilepsia, 2011. **52 Suppl 1**(Suppl 1): p. 39-46.
166. Mehta, A., et al., *Excitotoxicity: bridge to various triggers in neurodegenerative disorders*. Eur J Pharmacol, 2013. **698**(1-3): p. 6-18.
167. Rao, Y.L., et al., *Hippocampus and its involvement in Alzheimer's disease: a review*. 3 Biotech, 2022. **12**(2): p. 55.
168. Leitner, D., et al., *Similar brain proteomic signatures in Alzheimer's disease and epilepsy*. Acta Neuropathol, 2024. **147**(1): p. 27.
169. Herholz, K., *Cerebral glucose metabolism in preclinical and prodromal Alzheimer's disease*. Expert Rev Neurother, 2010. **10**(11): p. 1667-73.
170. DiFrancesco, J.C., et al., *Temporal lobe dysfunction in late-onset epilepsy of unknown origin*. Epilepsy Behav, 2021. **117**: p. 107839.
171. Selkoe, D.J. and J. Hardy, *The amyloid hypothesis of Alzheimer's disease at 25 years*. EMBO Mol Med, 2016. **8**(6): p. 595-608.
172. Villemagne, V.L., et al., *Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study*. Lancet Neurol, 2013. **12**(4): p. 357-67.
173. Murphy, M.P. and H. LeVine, 3rd, *Alzheimer's disease and the amyloid-beta peptide*. J Alzheimers Dis, 2010. **19**(1): p. 311-23.
174. Vassar, R., et al., *Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE*. Science, 1999. **286**(5440): p. 735-41.
175. De Strooper, B., et al., *A presenilin-1-dependent gamma-secretase-like protease mediates release of Notch intracellular domain*. Nature, 1999. **398**(6727): p. 518-22.
176. Jarrett, J.T., E.P. Berger, and P.T. Lansbury, Jr., *The carboxy terminus of the beta amyloid protein is critical for the seeding of amyloid formation: implications for the pathogenesis of Alzheimer's disease*. Biochemistry, 1993. **32**(18): p. 4693-7.
177. Morris, A.W., et al., *The Cerebrovascular Basement Membrane: Role in the Clearance of beta-amyloid and Cerebral Amyloid Angiopathy*. Front Aging Neurosci, 2014. **6**: p. 251.
178. Garcia-Osta, A. and C.M. Alberini, *Amyloid beta mediates memory formation*. Learn Mem, 2009. **16**(4): p. 267-72.

179. Kent, S.A., T.L. Spires-Jones, and C.S. Durrant, *The physiological roles of tau and Abeta: implications for Alzheimer's disease pathology and therapeutics*. Acta Neuropathol, 2020. **140**(4): p. 417-447.
180. Yang, A., et al., *Attenuation of beta-Amyloid Toxicity In Vitro and In Vivo by Accelerated Aggregation*. Neurosci Bull, 2017. **33**(4): p. 405-412.
181. Aizenstein, H.J., et al., *Frequent amyloid deposition without significant cognitive impairment among the elderly*. Arch Neurol, 2008. **65**(11): p. 1509-17.
182. Teller, J.K., et al., *Presence of soluble amyloid beta-peptide precedes amyloid plaque formation in Down's syndrome*. Nat Med, 1996. **2**(1): p. 93-5.
183. Lue, L.F., et al., *Soluble amyloid beta peptide concentration as a predictor of synaptic change in Alzheimer's disease*. Am J Pathol, 1999. **155**(3): p. 853-62.
184. McLean, C.A., et al., *Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease*. Ann Neurol, 1999. **46**(6): p. 860-6.
185. Shankar, G.M., et al., *Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory*. Nat Med, 2008. **14**(8): p. 837-42.
186. Strozyk, D., et al., *CSF Abeta 42 levels correlate with amyloid-neuropathology in a population-based autopsy study*. Neurology, 2003. **60**(4): p. 652-6.
187. Zetterberg, H. and K. Blennow, *Moving fluid biomarkers for Alzheimer's disease from research tools to routine clinical diagnostics*. Mol Neurodegener, 2021. **16**(1): p. 10.
188. Banote, R.K., et al., *CSF biomarkers in patients with epilepsy in Alzheimer's disease: a nation-wide study*. Brain Commun, 2022. **4**(4): p. fcac210.
189. Fonseca, E., et al., *Amyloid deposition in adults with drug-resistant temporal lobe epilepsy*. Epilepsia, 2024.
190. Mackenzie, I.R. and L.A. Miller, *Senile plaques in temporal lobe epilepsy*. Acta Neuropathol, 1994. **87**(5): p. 504-10.
191. Joutsa, J., et al., *Association Between Childhood-Onset Epilepsy and Amyloid Burden 5 Decades Later*. JAMA Neurol, 2017. **74**(5): p. 583-590.
192. Gourmaud, S., et al., *Alzheimer-like amyloid and tau alterations associated with cognitive deficit in temporal lobe epilepsy*. Brain, 2020. **143**(1): p. 191-209.
193. Aroor, A., et al., *Assessment of tau phosphorylation and beta-amyloid pathology in human drug-resistant epilepsy*. Epilepsia Open, 2023. **8**(2): p. 609-622.
194. Thom, M., et al., *Neurofibrillary tangle pathology and Braak staging in chronic epilepsy in relation to traumatic brain injury and hippocampal sclerosis: a post-mortem study*. Brain, 2011. **134**(Pt 10): p. 2969-81.
195. Silva, J.C., et al., *Low prevalence of amyloid and tau pathology in drug-resistant temporal lobe epilepsy*. Epilepsia, 2021. **62**(12): p. 3058-3067.
196. Tai, X.Y., et al., *Hyperphosphorylated tau in patients with refractory epilepsy correlates with cognitive decline: a study of temporal lobe resections*. Brain, 2016. **139**(Pt 9): p. 2441-55.
197. Sima, X., et al., *Expression of beta-amyloid precursor protein in refractory epilepsy*. Mol Med Rep, 2014. **9**(4): p. 1242-8.
198. Sheng, J.G., et al., *Increased neuronal beta-amyloid precursor protein expression in human temporal lobe epilepsy: association with interleukin-1 alpha immunoreactivity*. J Neurochem, 1994. **63**(5): p. 1872-9.
199. Canet, G., et al., *Seizure activity triggers tau hyperphosphorylation and amyloidogenic pathways*. Epilepsia, 2022. **63**(4): p. 919-935.

200. Kodam, A., et al., *A role for astrocyte-derived amyloid beta peptides in the degeneration of neurons in an animal model of temporal lobe epilepsy*. Brain Pathol, 2019. **29**(1): p. 28-44.
201. Yan, X.X., et al., *Chronic temporal lobe epilepsy is associated with enhanced Alzheimer-like neuropathology in 3xTg-AD mice*. PLoS One, 2012. **7**(11): p. e48782.
202. Gourmaud, S., et al., *The role of mTORC1 activation in seizure-induced exacerbation of Alzheimer's disease*. Brain, 2022. **145**(1): p. 324-339.
203. Ge, X., et al., *Increased Microglial Exosomal miR-124-3p Alleviates Neurodegeneration and Improves Cognitive Outcome after rmTBI*. Mol Ther, 2020. **28**(2): p. 503-522.
204. Busche, M.A., et al., *Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease*. Science, 2008. **321**(5896): p. 1686-9.
205. Jolas, T., et al., *Long-term potentiation is increased in the CA1 area of the hippocampus of APP(swe/ind) CRND8 mice*. Neurobiol Dis, 2002. **11**(3): p. 394-409.
206. Vande Vyver, M., et al., *Higher susceptibility to 6 Hz corneal kindling and lower responsiveness to antiseizure drugs in mouse models of Alzheimer's disease*. Epilepsia, 2022. **63**(10): p. 2703-2715.
207. Del Pozo, A., et al., *Chronic evoked seizures in young pre-symptomatic APP/PS1 mice induce serotonin changes and accelerate onset of Alzheimer's disease-related neuropathology*. Prog Neurobiol, 2024. **235**: p. 102591.
208. Del Vecchio, R.A., et al., *Increased seizure threshold and severity in young transgenic CRND8 mice*. Neurosci Lett, 2004. **367**(2): p. 164-7.
209. Gschwind, T., et al., *Contribution of early Alzheimer's disease-related pathophysiology to the development of acquired epilepsy*. Eur J Neurosci, 2018. **47**(12): p. 1534-1562.
210. Busche, M.A., et al., *Critical role of soluble amyloid-beta for early hippocampal hyperactivity in a mouse model of Alzheimer's disease*. Proc Natl Acad Sci U S A, 2012. **109**(22): p. 8740-5.
211. Lei, M., et al., *Soluble Abeta oligomers impair hippocampal LTP by disrupting glutamatergic/GABAergic balance*. Neurobiol Dis, 2016. **85**: p. 111-121.
212. Yamamoto, K., et al., *Chronic optogenetic activation augments abeta pathology in a mouse model of Alzheimer disease*. Cell Rep, 2015. **11**(6): p. 859-865.
213. Talantova, M., et al., *Abeta induces astrocytic glutamate release, extrasynaptic NMDA receptor activation, and synaptic loss*. Proc Natl Acad Sci U S A, 2013. **110**(27): p. E2518-27.
214. Hascup, K.N. and E.R. Hascup, *Soluble Amyloid-beta42 Stimulates Glutamate Release through Activation of the alpha7 Nicotinic Acetylcholine Receptor*. J Alzheimers Dis, 2016. **53**(1): p. 337-47.
215. Zott, B., et al., *A vicious cycle of beta amyloid-dependent neuronal hyperactivation*. Science, 2019. **365**(6453): p. 559-565.
216. Um, J.W., et al., *Alzheimer amyloid-beta oligomer bound to postsynaptic prion protein activates Fyn to impair neurons*. Nat Neurosci, 2012. **15**(9): p. 1227-35.
217. Ciccone, R., et al., *Amyloid beta-Induced Upregulation of Na(v)1.6 Underlies Neuronal Hyperactivity in Tg2576 Alzheimer's Disease Mouse Model*. Sci Rep, 2019. **9**(1): p. 13592.
218. Alfaro-Ruiz, R., et al., *The Expression and Localisation of G-Protein-Coupled Inwardly Rectifying Potassium (GIRK) Channels Is Differentially Altered in the Hippocampus of Two Mouse Models of Alzheimer's Disease*. Int J Mol Sci, 2021. **22**(20).

219. Murgas, P., B. Godoy, and R. von Bernhardi, *Abeta potentiates inflammatory activation of glial cells induced by scavenger receptor ligands and inflammatory mediators in culture*. *Neurotox Res*, 2012. **22**(1): p. 69-78.
220. Brier, M.R., et al., *Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease*. *Sci Transl Med*, 2016. **8**(338): p. 338ra66.
221. Goedert, M., B. Ghetti, and M.G. Spillantini, *Frontotemporal dementia: implications for understanding Alzheimer disease*. *Cold Spring Harb Perspect Med*, 2012. **2**(2): p. a006254.
222. Lewis, J., et al., *Enhanced neurofibrillary degeneration in transgenic mice expressing mutant tau and APP*. *Science*, 2001. **293**(5534): p. 1487-91.
223. Jin, M., et al., *Soluble amyloid beta-protein dimers isolated from Alzheimer cortex directly induce Tau hyperphosphorylation and neuritic degeneration*. *Proc Natl Acad Sci U S A*, 2011. **108**(14): p. 5819-24.
224. Blennow, K., et al., *Cerebrospinal fluid and plasma biomarkers in Alzheimer disease*. *Nat Rev Neurol*, 2010. **6**(3): p. 131-44.
225. Sen, A., et al., *Pathological tau tangles localize to focal cortical dysplasia in older patients*. *Epilepsia*, 2007. **48**(8): p. 1447-54.
226. Crespo-Biel, N., et al., *Kainate induces AKT, ERK and cdk5/GSK3beta pathway deregulation, phosphorylates tau protein in mouse hippocampus*. *Neurochem Int*, 2007. **50**(2): p. 435-42.
227. Prada Jardim, A., et al., *Characterising subtypes of hippocampal sclerosis and reorganization: correlation with pre and postoperative memory deficit*. *Brain Pathol*, 2018. **28**(2): p. 143-154.
228. Toscano, E.C.B., et al., *Hyperphosphorylated Tau in Mesial Temporal Lobe Epilepsy: a Neuropathological and Cognitive Study*. *Mol Neurobiol*, 2023. **60**(4): p. 2174-2185.
229. Puvenna, V., et al., *Is phosphorylated tau unique to chronic traumatic encephalopathy? Phosphorylated tau in epileptic brain and chronic traumatic encephalopathy*. *Brain Res*, 2016. **1630**: p. 225-40.
230. Smith, K.M., et al., *Tau deposition in young adults with drug-resistant focal epilepsy*. *Epilepsia*, 2019. **60**(12): p. 2398-2403.
231. Jones, A.L., et al., *Chronic traumatic encephalopathy in an epilepsy surgery cohort: Clinical and pathologic findings*. *Neurology*, 2018. **90**(6): p. e474-e478.
232. Garcia-Cabrero, A.M., et al., *Hyperexcitability and epileptic seizures in a model of frontotemporal dementia*. *Neurobiol Dis*, 2013. **58**: p. 200-8.
233. Gomez-Murcia, V., et al., *Hyperexcitability and seizures in the THY-Tau22 mouse model of tauopathy*. *Neurobiol Aging*, 2020. **94**: p. 265-270.
234. Przybyla, M., et al., *Onset of hippocampal network aberration and memory deficits in P301S tau mice are associated with an early gene signature*. *Brain*, 2020. **143**(6): p. 1889-1904.
235. Roberson, E.D., et al., *Reducing endogenous tau ameliorates amyloid beta-induced deficits in an Alzheimer's disease mouse model*. *Science*, 2007. **316**(5825): p. 750-4.
236. Wu, J.W., et al., *Neuronal activity enhances tau propagation and tau pathology in vivo*. *Nat Neurosci*, 2016. **19**(8): p. 1085-92.
237. Bohannon, D.G., et al., *Functionally distinct pericyte subsets differently regulate amyloid-beta deposition in patients with Alzheimer's disease*. *Brain Pathol*, 2024: p. e13282.

238. Rogeberg, M., et al., *Identification of peptide products from enzymatic degradation of amyloid beta*. *Biochimie*, 2014. **105**: p. 216-20.
239. Vekrellis, K., et al., *Neurons regulate extracellular levels of amyloid beta-protein via proteolysis by insulin-degrading enzyme*. *J Neurosci*, 2000. **20**(5): p. 1657-65.
240. Qiu, W.Q., et al., *Insulin-degrading enzyme regulates extracellular levels of amyloid beta-protein by degradation*. *J Biol Chem*, 1998. **273**(49): p. 32730-8.
241. Tarasoff-Conway, J.M., et al., *Clearance systems in the brain-implications for Alzheimer disease*. *Nat Rev Neurol*, 2015. **11**(8): p. 457-70.
242. Ullah, R. and E.J. Lee, *Advances in Amyloid-beta Clearance in the Brain and Periphery: Implications for Neurodegenerative Diseases*. *Exp Neurobiol*, 2023. **32**(4): p. 216-246.
243. Iwata, N., et al., *Identification of the major Aβ<sub>1-42</sub>-degrading catabolic pathway in brain parenchyma: suppression leads to biochemical and pathological deposition*. *Nat Med*, 2000. **6**(2): p. 143-50.
244. Wyss-Coray, T., et al., *Adult mouse astrocytes degrade amyloid-beta in vitro and in situ*. *Nat Med*, 2003. **9**(4): p. 453-7.
245. Wyss-Coray, T., et al., *TGF-β<sub>1</sub> promotes microglial amyloid-beta clearance and reduces plaque burden in transgenic mice*. *Nat Med*, 2001. **7**(5): p. 612-8.
246. Zuroff, L., et al., *Clearance of cerebral Aβ<sub>1-42</sub> in Alzheimer's disease: reassessing the role of microglia and monocytes*. *Cell Mol Life Sci*, 2017. **74**(12): p. 2167-2201.
247. Roberts, K.F., et al., *Amyloid-beta efflux from the central nervous system into the plasma*. *Ann Neurol*, 2014. **76**(6): p. 837-44.
248. Candela, P., et al., *Apical-to-basolateral transport of amyloid-beta peptides through blood-brain barrier cells is mediated by the receptor for advanced glycation end-products and is restricted by P-glycoprotein*. *J Alzheimers Dis*, 2010. **22**(3): p. 849-59.
249. Zlokovic, B.V., *Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders*. *Nat Rev Neurosci*, 2011. **12**(12): p. 723-38.
250. Mawuenyega, K.G., et al., *Decreased clearance of CNS beta-amyloid in Alzheimer's disease*. *Science*, 2010. **330**(6012): p. 1774.
251. Cockerill, I., et al., *Blood-Brain Barrier Integrity and Clearance of Amyloid-beta from the BBB*. *Adv Exp Med Biol*, 2018. **1097**: p. 261-278.
252. Bres, E.E. and A. Faissner, *Low Density Receptor-Related Protein 1 Interactions With the Extracellular Matrix: More Than Meets the Eye*. *Front Cell Dev Biol*, 2019. **7**: p. 31.
253. Herz, J. and H.H. Bock, *Lipoprotein receptors in the nervous system*. *Annu Rev Biochem*, 2002. **71**: p. 405-34.
254. Li, Y., et al., *Differential functions of members of the low density lipoprotein receptor family suggested by their distinct endocytosis rates*. *J Biol Chem*, 2001. **276**(21): p. 18000-6.
255. Lillis, A.P., et al., *LDL receptor-related protein 1: unique tissue-specific functions revealed by selective gene knockout studies*. *Physiol Rev*, 2008. **88**(3): p. 887-918.
256. Rohlmann, A., et al., *Inducible inactivation of hepatic LRP gene by cre-mediated recombination confirms role of LRP in clearance of chylomicron remnants*. *J Clin Invest*, 1998. **101**(3): p. 689-95.
257. Herz, J., D.E. Clouthier, and R.E. Hammer, *LDL receptor-related protein internalizes and degrades uPA-PAI-1 complexes and is essential for embryo implantation*. *Cell*, 1992. **71**(3): p. 411-21.

258. Herz, J., D. Couthier, and R.E. Hammer, *Correction: LDL receptor-related protein internalizes and degrades uPA-PAI-1 complexes and is essential for embryo implantation*. *Cell*, 1993. **73**(3): p. 428.
259. Nakajima, C., et al., *The lipoprotein receptor LRP1 modulates sphingosine-1-phosphate signaling and is essential for vascular development*. *Development*, 2014. **141**(23): p. 4513-25.
260. Liu, Q., et al., *Amyloid precursor protein regulates brain apolipoprotein E and cholesterol metabolism through lipoprotein receptor LRP1*. *Neuron*, 2007. **56**(1): p. 66-78.
261. Liu, Q., et al., *Neuronal LRP1 knockout in adult mice leads to impaired brain lipid metabolism and progressive, age-dependent synapse loss and neurodegeneration*. *J Neurosci*, 2010. **30**(50): p. 17068-78.
262. Zhao, Z., et al., *Central role for PICALM in amyloid-beta blood-brain barrier transcytosis and clearance*. *Nat Neurosci*, 2015. **18**(7): p. 978-87.
263. Storck, S.E., et al., *Endothelial LRP1 transports amyloid-beta(1-42) across the blood-brain barrier*. *J Clin Invest*, 2016. **126**(1): p. 123-36.
264. Winkler, E.A., et al., *GLUT1 reductions exacerbate Alzheimer's disease vasculo-neuronal dysfunction and degeneration*. *Nat Neurosci*, 2015. **18**(4): p. 521-530.
265. Shibata, M., et al., *Clearance of Alzheimer's amyloid-ss(1-40) peptide from brain by LDL receptor-related protein-1 at the blood-brain barrier*. *J Clin Invest*, 2000. **106**(12): p. 1489-99.
266. Deane, R., et al., *LRP/amyloid beta-peptide interaction mediates differential brain efflux of Abeta isoforms*. *Neuron*, 2004. **43**(3): p. 333-44.
267. Zhu, D., et al., *Magnesium Reduces Blood-Brain Barrier Permeability and Regulates Amyloid-beta Transcytosis*. *Mol Neurobiol*, 2018. **55**(9): p. 7118-7131.
268. Yamada, K., et al., *The low density lipoprotein receptor-related protein 1 mediates uptake of amyloid beta peptides in an in vitro model of the blood-brain barrier cells*. *J Biol Chem*, 2008. **283**(50): p. 34554-62.
269. Bell, R.D., et al., *Transport pathways for clearance of human Alzheimer's amyloid beta-peptide and apolipoproteins E and J in the mouse central nervous system*. *J Cereb Blood Flow Metab*, 2007. **27**(5): p. 909-18.
270. Storck, S.E., et al., *The concerted amyloid-beta clearance of LRP1 and ABCB1/P-gp across the blood-brain barrier is linked by PICALM*. *Brain Behav Immun*, 2018. **73**: p. 21-33.
271. Cirrito, J.R., et al., *P-glycoprotein deficiency at the blood-brain barrier increases amyloid-beta deposition in an Alzheimer disease mouse model*. *J Clin Invest*, 2005. **115**(11): p. 3285-90.
272. Hartz, A.M., D.S. Miller, and B. Bauer, *Restoring blood-brain barrier P-glycoprotein reduces brain amyloid-beta in a mouse model of Alzheimer's disease*. *Mol Pharmacol*, 2010. **77**(5): p. 715-23.
273. Kanekiyo, T., et al., *LRP1 in brain vascular smooth muscle cells mediates local clearance of Alzheimer's amyloid-beta*. *J Neurosci*, 2012. **32**(46): p. 16458-65.
274. Ma, Q., et al., *Blood-brain barrier-associated pericytes internalize and clear aggregated amyloid-beta42 by LRP1-dependent apolipoprotein E isoform-specific mechanism*. *Mol Neurodegener*, 2018. **13**(1): p. 57.
275. Kang, D.E., et al., *Modulation of amyloid beta-protein clearance and Alzheimer's disease susceptibility by the LDL receptor-related protein pathway*. *J Clin Invest*, 2000. **106**(9): p. 1159-66.

276. Grimmer, T., et al., *LRP-1 polymorphism is associated with global and regional amyloid load in Alzheimer's Disease in humans in-vivo*. *Neuroimage Clin*, 2014. **4**: p. 411-6.
277. Storck, S.E. and C.U. Pietrzik, *Endothelial LRP1 - A Potential Target for the Treatment of Alzheimer's Disease : Theme: Drug Discovery, Development and Delivery in Alzheimer's Disease Guest Editor: Davide Brambilla*. *Pharm Res*, 2017. **34**(12): p. 2637-2651.
278. Quinn, K.A., et al., *Soluble low density lipoprotein receptor-related protein (LRP) circulates in human plasma*. *J Biol Chem*, 1997. **272**(38): p. 23946-51.
279. Sagare, A., et al., *Clearance of amyloid-beta by circulating lipoprotein receptors*. *Nat Med*, 2007. **13**(9): p. 1029-31.
280. Boucher, P. and J. Herz, *Signaling through LRP1: Protection from atherosclerosis and beyond*. *Biochem Pharmacol*, 2011. **81**(1): p. 1-5.
281. Mantuano, E., et al., *LDL receptor-related protein-1 regulates NFkappaB and microRNA-155 in macrophages to control the inflammatory response*. *Proc Natl Acad Sci U S A*, 2016. **113**(5): p. 1369-74.
282. Gaultier, A., et al., *A shed form of LDL receptor-related protein-1 regulates peripheral nerve injury and neuropathic pain in rodents*. *J Clin Invest*, 2008. **118**(1): p. 161-72.
283. Bell, R.D., et al., *Apolipoprotein E controls cerebrovascular integrity via cyclophilin A*. *Nature*, 2012. **485**(7399): p. 512-6.
284. Bres, E.E., et al., *Lipoprotein receptor loss in forebrain radial glia results in neurological deficits and severe seizures*. *Glia*, 2020. **68**(12): p. 2517-2549.
285. He, Y., et al., *Silencing of LRP1 Exacerbates Inflammatory Response Via TLR4/NF-kappaB/MAPKs Signaling Pathways in APP/PS1 Transgenic Mice*. *Mol Neurobiol*, 2020. **57**(9): p. 3727-3743.
286. Yang, L., et al., *LRP1 modulates the microglial immune response via regulation of JNK and NF-kappaB signaling pathways*. *J Neuroinflammation*, 2016. **13**(1): p. 304.
287. Donahue, J.E., et al., *RAGE, LRP-1, and amyloid-beta protein in Alzheimer's disease*. *Acta Neuropathol*, 2006. **112**(4): p. 405-15.
288. Osgood, D., et al., *Aging alters mRNA expression of amyloid transporter genes at the blood-brain barrier*. *Neurobiol Aging*, 2017. **57**: p. 178-185.
289. Silverberg, G.D., et al., *Amyloid efflux transporter expression at the blood-brain barrier declines in normal aging*. *J Neuropathol Exp Neurol*, 2010. **69**(10): p. 1034-43.
290. Halliday, M.R., et al., *Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease*. *J Cereb Blood Flow Metab*, 2016. **36**(1): p. 216-27.
291. Bartolini, E., et al., *Glycaemic Imbalances in Seizures and Epilepsy of Paediatric Age: A Literature Review*. *J Clin Med*, 2023. **12**(7).
292. Yan, F.L., Y. Zheng, and F.D. Zhao, *Effects of ginkgo biloba extract EGb761 on expression of RAGE and LRP-1 in cerebral microvascular endothelial cells under chronic hypoxia and hypoglycemia*. *Acta Neuropathol*, 2008. **116**(5): p. 529-35.
293. Bell, R.D., et al., *SRF and myocardin regulate LRP-mediated amyloid-beta clearance in brain vascular cells*. *Nat Cell Biol*, 2009. **11**(2): p. 143-53.
294. Farrell, J.S., et al., *Postictal behavioural impairments are due to a severe prolonged hypoperfusion/hypoxia event that is COX-2 dependent*. *Elife*, 2016. **5**.

295. Owen, J.B., et al., *Oxidative modification to LDL receptor-related protein 1 in hippocampus from subjects with Alzheimer disease: implications for Abeta accumulation in AD brain*. *Free Radic Biol Med*, 2010. **49**(11): p. 1798-803.
296. Pauletti, A., et al., *Targeting oxidative stress improves disease outcomes in a rat model of acquired epilepsy*. *Brain*, 2019. **142**(7): p. e39.
297. Rumia, J., et al., *Oxidative stress markers in the neocortex of drug-resistant epilepsy patients submitted to epilepsy surgery*. *Epilepsy Res*, 2013. **107**(1-2): p. 75-81.
298. Ionescu-Tucker, A. and C.W. Cotman, *Emerging roles of oxidative stress in brain aging and Alzheimer's disease*. *Neurobiol Aging*, 2021. **107**: p. 86-95.
299. Storck, S.E., M. Kurtyka, and C.U. Pietrzik, *Brain endothelial LRP1 maintains blood-brain barrier integrity*. *Fluids Barriers CNS*, 2021. **18**(1): p. 27.
300. Jaeger, L.B., et al., *Testing the neurovascular hypothesis of Alzheimer's disease: LRP-1 antisense reduces blood-brain barrier clearance, increases brain levels of amyloid-beta protein, and impairs cognition*. *J Alzheimers Dis*, 2009. **17**(3): p. 553-70.
301. Lee, J., et al., *ANKS1A regulates LDL receptor-related protein 1 (LRP1)-mediated cerebrovascular clearance in brain endothelial cells*. *Nat Commun*, 2023. **14**(1): p. 8463.
302. Kanekiyo, T., et al., *Neuronal clearance of amyloid-beta by endocytic receptor LRP1*. *J Neurosci*, 2013. **33**(49): p. 19276-83.
303. Van Gool, B., et al., *LRP1 Has a Predominant Role in Production over Clearance of Abeta in a Mouse Model of Alzheimer's Disease*. *Mol Neurobiol*, 2019. **56**(10): p. 7234-7245.
304. Rauch, J.N., et al., *LRP1 is a master regulator of tau uptake and spread*. *Nature*, 2020. **580**(7803): p. 381-385.
305. Liu, C.C., et al., *Astrocytic LRP1 Mediates Brain Abeta Clearance and Impacts Amyloid Deposition*. *J Neurosci*, 2017. **37**(15): p. 4023-4031.
306. Keck, M., et al., *Proteomic profiling of epileptogenesis in a rat model: Focus on cell stress, extracellular matrix and angiogenesis*. *Neurobiol Dis*, 2018. **112**: p. 119-135.
307. van Vliet, E.A. and J.A. Gorter, *Electrical stimulation seizure models*, in *Models of seizures and epilepsy*. 2017, Elsevier. p. 474-488.
308. Vezzani, A., et al., *Infections, inflammation and epilepsy*. *Acta Neuropathol*, 2016. **131**(2): p. 211-234.
309. Shimada, T. and K. Yamagata, *Pentylentetrazole-Induced Kindling Mouse Model*. *J Vis Exp*, 2018(136).
310. Levesque, M., M. Avoli, and C. Bernard, *Animal models of temporal lobe epilepsy following systemic chemoconvulsant administration*. *J Neurosci Methods*, 2016. **260**: p. 45-52.
311. Gorter, J.A., et al., *Progression of spontaneous seizures after status epilepticus is associated with mossy fibre sprouting and extensive bilateral loss of hilar parvalbumin and somatostatin-immunoreactive neurons*. *Eur J Neurosci*, 2001. **13**(4): p. 657-69.
312. Gorter, J.A., et al., *Differential and long-lasting alterations of high-voltage activated calcium currents in CA1 and dentate granule neurons after status epilepticus*. *Eur J Neurosci*, 2002. **16**(4): p. 701-12.
313. Gorter, J.A. and E.A. van Vliet, *Post-status epilepticus models: electrical stimulation*, in *Models of seizures and epilepsy*. 2017, Elsevier. p. 637-650.
314. Gorter, J.A., E.A. van Vliet, and E. Aronica, *Status epilepticus, blood-brain barrier disruption, inflammation, and epileptogenesis*. *Epilepsy Behav*, 2015. **49**: p. 13-6.

315. Pearson, J.N., K.M. Schulz, and M. Patel, *Specific alterations in the performance of learning and memory tasks in models of chemoconvulsant-induced status epilepticus*. *Epilepsy Res*, 2014. **108**(6): p. 1032-40.
316. Kotloski, R., et al., *Repeated brief seizures induce progressive hippocampal neuron loss and memory deficits*. *Prog Brain Res*, 2002. **135**: p. 95-110.
317. Lopes da Silva, F.H., J.A. Gorter, and W.J. Wadman, *Kindling of the hippocampus induces spatial memory deficits in the rat*. *Neurosci Lett*, 1986. **63**(2): p. 115-20.
318. Sanchez-Varo, R., et al., *Transgenic Mouse Models of Alzheimer's Disease: An Integrative Analysis*. *Int J Mol Sci*, 2022. **23**(10).
319. Bharadwaj, P., *Animal Models of Alzheimer's Disease*. *Neurodegeneration and Alzheimer's Disease: The Role of Diabetes, Genetics, Hormones, and Lifestyle*, 2019: p. 291-310.
320. Zhong, M.Z., et al., *Updates on mouse models of Alzheimer's disease*. *Mol Neurodegener*, 2024. **19**(1): p. 23.
321. Xu, G., et al., *Murine Abeta over-production produces diffuse and compact Alzheimer-type amyloid deposits*. *Acta Neuropathol Commun*, 2015. **3**: p. 72.
322. Games, D., et al., *Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein*. *Nature*, 1995. **373**(6514): p. 523-7.
323. Oddo, S., et al., *Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction*. *Neuron*, 2003. **39**(3): p. 409-21.
324. Billings, L.M., et al., *Intraneuronal Abeta causes the onset of early Alzheimer's disease-related cognitive deficits in transgenic mice*. *Neuron*, 2005. **45**(5): p. 675-88.
325. Oakley, H., et al., *Intraneuronal beta-amyloid aggregates, neurodegeneration, and neuron loss in transgenic mice with five familial Alzheimer's disease mutations: potential factors in amyloid plaque formation*. *J Neurosci*, 2006. **26**(40): p. 10129-40.
326. Forner, S., et al., *Systematic phenotyping and characterization of the 5xFAD mouse model of Alzheimer's disease*. *Sci Data*, 2021. **8**(1): p. 270.
327. Abe, Y., et al., *Behavioral and electrophysiological evidence for a neuroprotective role of aquaporin-4 in the 5xFAD transgenic mice model*. *Acta Neuropathol Commun*, 2020. **8**(1): p. 67.
328. Sil, A., et al., *Sex Differences in Behavior and Molecular Pathology in the 5XFAD Model*. *J Alzheimers Dis*, 2022. **85**(2): p. 755-778.
329. Wang, X., et al., *Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression*. *Cell Res*, 2019. **29**(10): p. 787-803.
330. Rummelink, E., et al., *Measuring discrimination- and reversal learning in mouse models within 4 days and without prior food deprivation*. *Learn Mem*, 2016. **23**(11): p. 660-667.
331. Brosens, N., et al., *Early Life Stress Enhances Cognitive Decline and Alters Synapse Function and Interneuron Numbers in Young Male APP/PS1 Mice*. *J Alzheimers Dis*, 2023. **96**(3): p. 1097-1113.