# Amyloid-β: a potential link between epilepsy and cognitive decline

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Abstract | People with epilepsy — in particular, late-onset epilepsy of unknown aetiology — have an elevated risk of dementia, and seizures have been detected in the early stages of Alzheimer disease (AD), supporting the concept of an epileptic AD prodrome. However, the relationship between epilepsy and cognitive decline remains controversial, with substantial uncertainties about whether epilepsy drives cognitive decline or vice versa, and whether shared pathways underlie both conditions. Here, we review evidence that amyloid-β (Aβ) forms part of a shared pathway between epilepsy and cognitive decline, particularly in the context of AD. People with epilepsy show an increased burden of Aβ pathology in the brain, and Aβ-mediated epileptogenic alterations have been demonstrated in experimental studies, with evidence suggesting that Aβ pathology might already be pro-epileptogenic at the soluble stage, long before plaque deposition. We discuss the hypothesis that Aβ mediates — or is at least a major determinant of — a continuum spanning epilepsy and cognitive decline. Serial cognitive testing and assessment of Aβ levels might be worthwhile to stratify the risk of developing dementia in people with late-onset epilepsy. If seizures are a clinical harbinger of dementia, people with late-onset epilepsy could be an ideal group in which to implement preventive or therapeutic strategies to slow cognitive decline.

Aβ-facilitated tauopathy
The hypothesis that Alzheimer disease (AD) is the trigger for the accumulation and spread of tau pathology, leading to overt neurodegeneration.

Late-onset epilepsy
Epilepsy that develops in late adult life. Cerebrovascular events, such as ischaemic or haemorrhagic stroke, are the main cause, but late-onset epilepsy might also arise from metabolic, infectious or structural (for example, neoplastic) disorders or dementia.

Aβ plaques
Aggregates of amyloid-β (Aβ) protein, which accumulate to form neuritic plaques during the course of Alzheimer disease (AD).

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With the prospect of an ageing population, the global burden of cognitive decline is expected to increase substantially. According to WHO estimates, >80 million people are likely to have dementia by 2030 (REFS[1,2]). Alzheimer disease (AD) is the most common cause of dementia: according to Global Burden of Disease systematic reports, >50 million people currently live with AD[2,3].

Early diagnosis of dementia is crucial, especially in AD, as novel treatments are being developed to reduce amyloid-β (Aβ) aggregation in the brain[4]. Aβ is derived from the proteolytic cleavage of amyloid precursor protein (APP) by a complex family of enzymes, including α-secretase, β-secretase and γ-secretase. Aβ peptides agglomerate into dense fibrillary plaques, which, together with neurofibrillary tangles consisting of intracellular cytoplasmic deposits of hyperphosphorylated tau protein, are the characteristic histopathological findings in AD. The accumulation of neuritic plaques and neurofibrillary tangles is toxic to neurons, resulting in shrinkage of dendrites, destabilization of synapses and eventually neuronal death. Post-mortem and PET studies have shown that Aβ pathology spreads from basal–frontal and temporal lobes to the hippocampus, the limbic system and finally to the whole neocortex[5,6]. Accumulation of Aβ promotes and potentiates the burden of tau pathology, triggering its spread beyond the temporal lobe[7] and leading to overt neurodegeneration (Aβ-facilitated tauopathy)[6–8].

Aβ accumulation is likely to be an initiating event in AD, as it can develop years before tau accumulation and decades before neurodegeneration and clinical symptoms emerge[6,9]. How Aβ affects neuronal functioning and survival through such an extensive 'latent period' is matter of controversy[10–12]. Recent studies suggest that epileptogenic properties of Aβ could have a major influence on the trajectory of cognitive decline[13,14]. Aβ has been shown to promote network deregulation, leading to hypersynchrony and seizures, which in turn worsen neurodegeneration[15]. Seizures can occur early in the course of AD, when Aβ pathology is building and neurodegeneration has yet to become apparent, and people with late-onset epilepsy have an increased risk of AD[14,16]. In addition, seizures promote deposition of Aβ plaques[17], Aβ pathology is increased in late-onset epilepsy[12,13,18,19] and late-onset epilepsy itself can be prodromal to AD[20,21]. Together, these observations point towards a potential chain of events in which amyloidopathy might promote and act synergistically with seizures, resulting in cognitive decline[12,13,15,18,19].

**Key points**

- Seizures and cognitive decline are interrelated: people with epilepsy have a threefold increased risk of dementia compared with the general population, and the risk is particularly high when the onset of epilepsy is in late adult life.
- Around 25% of people who develop epilepsy in late adulthood have no defined cause for their seizures, leading to the diagnosis of late-onset epilepsy of unknown aetiology (LOEU).
- People with LOEU have been shown to have amyloid pathology in the brain, with amyloid-β (Aβ) deposition increasing their risk of developing cognitive decline over the decades following seizure onset.
- Experimental studies support a role for Aβ in promoting seizures: Aβ is pro-epileptogenic at the oligomer stage, long before plaque deposition, and its accumulation fosters network hyperexcitability.
- Seizures can be a harbinger of dementia, and identification of people at high risk of cognitive decline at epilepsy onset might allow crucial interventions early in Aβ deposition, thereby preventing further neurodegeneration.
- Neuropsychological and biomarker assessment should be used to stratify patients with LOEU at an early stage to enable personalized treatment and potential enrolment in disease-modifying drug trials.

Late-onset epilepsy of unknown aetiology (LOEU). Epilepsy that develops in late adult life in the absence of vascular, metabolic, infectious, structural or neurocognitive causes. Up to 20% of adults who develop epilepsy in late adulthood have an unknown cause; amyloid-β pathology might contribute to epilepsy and cognitive decline in these patients.

Epileptic prodromal AD Retrospective definition denoting patients with an Alzheimer disease (AD) diagnosis preceded by seizures in adulthood.

In this article, we review data on the link between late-onset epilepsy and AD, with specific attention being given to Aβ-mediated mechanisms. We propose that late-onset epilepsy of unknown aetiology (LOEU), epileptic prodromal AD and seizures in AD are all possible clinical correlates of an Aβ-driven continuum. A better understanding of the pathways that lead from late-onset epilepsy to cognitive decline might enable populations at risk of AD to be identified at the beginning of Aβ accumulation, when neurodegeneration is not entrenched and therapeutic interventions might be most beneficial.

## Insights from experimental studies

***Epileptogenic properties of Aβ.*** Aβ plaques were identified as a histopathological hallmark of AD through a combination of neuropathological studies and epidemiological and genetic associations. Decades after Alois Alzheimer's original description of the disease[22], evidence has accumulated to support a role for Aβ in AD pathogenesis[23,24] (BOX 1). The finding that people with Down syndrome, who have trisomy of the *APP* gene on chromosome 21, develop early dementia[25] provided additional insights into the role of the Aβ cascade in AD[24]. Amyloidopathy was subsequently shown to occur early in the course of AD[26], to promote tau-related pathology[8,27] and to constitute a clear risk factor for progression to amnestic mild cognitive impairment (aMCI) or AD, even when detected in cognitively healthy individuals[28]. Beyond contributing to the disease course, structural variations in Aβ fibrils can contribute to the clinical subtype of AD[23].

Aβ has been extensively studied in paradigms of neurodegeneration, but its epileptogenic potential has only recently emerged[29]. Initially, an unexpected increased risk of sudden death was noted in various strains of mice with age-related Aβ accumulation, leading researchers to suspect an underlying terminal seizure[30–32] (TABLE 1). The high early mortality by sudden death seemed to be linked to the synaptic toxicity of Aβ, as inhibition of Aβ accumulation through specific proteases and tyrosine kinases led to a substantial reduction in early death rates[31,32]. Increased mortality was also observed in mice carrying human APP (hAPP) with the Swedish double mutation (APPswe), which, despite no gross Aβ pathology on post mortem evaluation[33], displayed spontaneous epileptiform activity and hyperactive hippocampal networks[34,35]. Standardized video-EEG recordings identified seizures in 65% of APPswe/PS1ΔE9 mice[11] — one of several APP/PS1 transgenic lines, which harbour mutations in both the *APP* and presenilin 1 (*PSEN1*) genes[36]. Suppression of mutant hAPP expression resulted in short-term reduction of epileptic discharges despite having no influence on cerebral levels of insoluble Aβ[37]. The epileptogenic potential of Aβ was also confirmed in other APP/PS1 models[38,39], in which neurons with epileptic discharges colocalized with Aβ plaques[40–42].

Together, these data raise a key question: might the pro-epileptogenic effect of Aβ precede plaque formation and, if so, does this effect contribute to or even cause neuronal loss? Compelling evidence points towards the epileptogenic potential of Aβ at pre-plaque stages[15,42–44]. In APP/PS1 mice, epileptiform activity can be detected during early stages of Aβ pathology, with fibrillary but still soluble fibrils of Aβ promoting hyperactivity of hippocampal neurons[11]. Exposure to Aβ oligomers can produce spontaneous neuronal firing in hippocampal neurons[42,43] and impair long-term potentiation by interacting with NMDA receptors, which are crucial for synaptic function[15,43]. Aβ oligomers have also been shown to be synaptotoxic[43,45–48] and can induce epileptic discharges before plaque deposition[12,49]. The impact of Aβ oligomerization status on neuronal firing is not yet fully understood, however. In vitro studies have produced conflicting findings regarding changes in neuronal firing after exposure to small Aβ oligomers[50–52], and larger Aβ oligomers are thought to induce neural excitatory imbalance[11,12,53] (BOX 2).

In vivo studies have demonstrated that exposure of hippocampal neurons to Aβ oligomers elicits pro-epileptogenic changes[54,55], and a single intracisternal injection of Aβ is sufficient to facilitate seizures and uncouple signalling in Schaffer collaterals[56]. In the Tg2576 mouse, a model with a slow progressive increase in Aβ burden[57], Aβ oligomers affect intrinsic and extrinsic neuronal properties, impair dentate gyrus transmission and lower hippocampal seizure thresholds[12,58]. Such changes occur under the age of 3 months[12,58,59], before plaque deposition, which typically manifests at 10 months of age[60]. Similarly, hippocampal long-term

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potentiation impairment and a decrease in dendritic spine density occur months before plaque deposition and cognitive decline, supporting the plausibility of associations between early epileptogenesis and hippocampal network dysfunction[59,60]. In vivo calcium imaging studies indicate that exposure to Aβ dimers is sufficient to increase firing in hippocampal CA1 neurons[52]. Over time, Aβ pathology might cause more neurons to adopt a hyperactive phenotype, consistent with a crucial role for early Aβ pathology in driving excitatory–inhibitory imbalance[61,62] (BOX 2). As a final component of the cascade, epileptiform activity has been shown to promote Aβ deposition in hippocampal neurons, which have a crucial involvement in AD[15,63].

Taken together, the experimental findings suggest a model in which Aβ induces synaptic impairment and initiates epileptogenesis, leading to seizures, which in turn increase Aβ deposition and facilitate neuronal loss (FIG. 1). Such processes, especially in hippocampal neurons, might act as a trigger for overt epileptic activity and take an active part in subsequent neurodegeneration, creating an Aβ-driven vicious circle[15,64]. Other proteins, including tau, other *APP* metabolites and prion proteins, could further affect the neuronal excitatory–inhibitory balance and promote neurodegeneration[62,65–68] (BOX 3).

The suggestion that early Aβ pathology produces notable changes in neuronal excitability at the preplaque stage[42,52,53,62] seems consistent with clinical reports of epilepsy being prodromal to dementia in some cases (discussed in more detail below)[12,14,16]. Therefore, very early Aβ pathology might represent a 'druggable' target to tackle epileptogenesis and, potentially, neurodegeneration[13,21,69,70] (TABLE 2).

***Limiting Aβ epileptogenic potential.*** Several strategies have been trialled to limit Aβ-induced epileptogenic changes[71,72]. One approach that has been tested is Aβ immunoclearance through passive immunization with a human APP/Aβ antibody, which consistently prevented seizures and limited epileptic discharges in the 3×Tg mouse model of AD[73].

Anti-seizure medications (ASMs) have also been widely explored[55,74] (TABLE 2). In APP/PS1 transgenic mice, chronic treatment with lamotrigine suppressed abnormal cortical epileptic activity, attenuated memory deficits and prevented loss of dendritic spines[75], and carbamazepine consistently reduced spontaneous electrographic epileptic discharges[76]. In the same mouse model, phenytoin reduced epileptiform discharges in up to 80% of mice, although adverse events were reported[76]. The efficacy of phenytoin was not replicated in other studies; for example, this drug had a minimal effect on spike–wave discharges in either APP/PS1 or 3×Tg mice[74]. Exacerbation of seizures and cognitive deficits by phenytoin has also been demonstrated in hAPP[77,78] and APP/PS1ΔE9 mice[76] and might be attributable to reduced or aberrant expression of sodium channels in GABAergic terminals[15,76,78]. Valproate has been shown to successfully limit or suppress epileptiform activity in a dose-dependent fashion in APP/PS1 mice, although these effects did not persist 1 week after drug discontinuation[76,79].

Perhaps the most promising data relate to levetiracetam, which, when tested in APP/PS1 mice, demonstrated considerable suppression of corticohippocampal spikes and electroclinical seizures[38], a finding that was replicated in 3×Tg[74] and hAPP mice[77] (TABLE 2). Such findings might relate to specific actions of levetiracetam on presynaptic terminals and calcium signalling[80,81]. Calcium dyshomeostasis at presynaptic and postsynaptic sites seems to occur very early in AD pathophysiology, recruits other metabolic pathways to maintain synaptic transmission and is accelerated by Aβ oligomers[82–84]. Targeting calcium dyshomeostasis, either with levetiracetam or other medications acting at presynaptic or postsynaptic sites, might, therefore, reduce hyperexcitability and Aβ deposition[84,85].

ASMs could also directly affect the Aβ cascade, including plaque deposition[38,55,74] (TABLE 2). In APP/PS1 mice, topiramate, valproate and levetiracetam reduced Aβ plaque deposition in both the cortex and the hippocampus[86]. Although direct effects on Aβ turnover were not confirmed in a similar experimental setting using APP/PS1 and 3×Tg models[38,55,74], levetiracetam was shown to restore synaptic function[77] and prevent neuronal loss after exposure of hippocampal neurons to Aβ fragments[87]. Such neuronal shielding probably derives from the effects of levetiracetam on excitotoxicity, particularly the prevention of Aβ-induced glutamate release at extrasynaptic sites[88]. Valproate reduced the concentration of Aβ oligomers in a cellular model of Aβ pathology[89], although the consequences of limiting Aβ deposition in a more complex environment are still

Box 1 | **The role of Aβ in cognitive decline**

Proteinopathies have been implicated in cognitive decline since the Aβ cascade hypothesis was first formulated[8,27]. The poor results of Aβ immunoclearance trials led to a reconsideration of this hypothesis in favour of a more comprehensive proteinopathy paradigm, also including tau, to account for neurodegeneration[8,165]. However, issues with trial cohort selection — especially regarding disease stage — and the fact that Aβ plaques in healthy adults might represent prodromal disease stages[10,166–168] limited the interpretation of the role of Aβ.

Aβ deposition occurs in individuals with normal cognition, precedes and promotes tau accumulation, predicts evolution to AD later stages[7,169] and self-perpetuates to increase the risk of cognitive decline[167,170]. Dual proteinopathy (Aβ and tau accumulation) mediates the association of initial Aβ deposition with cognitive status[169], and Aβ has a fundamental role in early high-level tau accumulation[7]. Therefore, although tauopathy might correlate more closely than Aβ pathology with cognitive status, Aβ is still the initial insult[7,8]. Moreover, Aβ seems to be a major contributor to cognitive decline in other neurodegenerative diseases, including α-synucleinopathies. Aβ pathology predicts onset and severity of cognitive impairment in Parkinson disease, where it promotes a protein-aggregating vicious circle involving α-synuclein and tau[171–174]. A synergistic bidirectional link between Aβ and α-synuclein is also apparent in dementia with Lewy bodies (DLB). In DLB, Aβ accumulation occurs early and correlates with cognitive decline, potentially explaining the premature onset of cognitive disturbances in this condition compared with Parkinson disease[173,175–177].

The impact of Aβ pathology also extends to healthy adults. People with subjective memory concerns frequently have Aβ pathology[178,179], raising the possibility that hallmarks of AD are present at prodromal 'subjective-only' stages of memory impairment[179]. Aβ accumulation occurs long before tauopathy in healthy adults[169] and predicts cognitive decline independently of clinical conversion to dementia[168,180,181], leading to proposals to measure blood Aβ levels in these individuals to help stratify the risk of dementia[182]. Therefore, though not the sole driver of cognitive decline, Aβ is a pivotal component in this process and provides leverage for other proteinopathies to develop and converge towards mutual cell death pathways.

Table 1 | **Experimental models supporting Aβ epileptogenic potential**

| Model | Genes or exposure involved | Main findings |
|---|---|---|
| 3×Tg | *APP*, *PSEN1*, *MAPT* | 40% of 3×Tg mice had epileptiform discharges, which correlated with spatial memory impairment[161] |
| | | Cytological alterations caused by synaptic toxicity and abnormal neurogenesis were found in hippocampal neurons and the dentate gyrus[74] |
| APP/TTA | *APP* | Frequent epileptic discharges, which were reduced considerably by genetic suppression of Aβ[37,72] |
| APP23×PS45 | *APP*, *PSEN1* | 21% of neurons, exclusively near Aβ plaques, were hyperactive (spontaneous firing)[40,42] |
| | | Suppression of APP production by γ-secretase inhibitor rescued normal hippocampal firing[42] |
| APP/PS1 | *APP*, *PSEN1* | Early death observed in 15% of mice[33]; fivefold increase in risk of epileptiform discharges compared with wild-type mice[11,38,39] |
| | | Unprovoked seizures detected in up to 65% of mice[11]; seizures appeared with Aβ plaque deposition[41] |
| hAPP | *APP* | Sudden death occurred more frequently and at a younger age than in non-transgenic mice[30] |
| | | Overexpression of Aβ-degrading proteases, such as insulin-degrading enzyme or neprilysin, slowed Aβ plaque formation and reverted premature lethality[31] |
| | | Depletion of FYN tyrosine kinase, which is involved in Aβ toxicity, reduced premature mortality[32] |
| arcAβ | *APP* | Short epileptiform discharges were more frequent than in APPswe and wild-type mice |
| | | Aβ deposition occurred early and was associated with cognitive impairment[48,49] |
| hAPPJ20 | *APP* | Spontaneous non-convulsive seizures and pro-epileptogenic changes were detected in cortical and hippocampal networks, including GABAergic sprouting and synaptic plasticity deficits in the dentate gyrus[34,77,78] |
| Tg2576 | *APP* | Animals showed higher mortality than wild-type mice, along with frequent spontaneous and drug-induced seizures[12,58] |
| | | Decreased dendritic spine density, impaired LTP and behavioural deficits occurred months before Aβ plaque deposition[60]; epileptic discharges appeared at just 5 weeks of age, before memory impairment or Aβ deposition[59] |
| TgDimer | *APP* | Deficits in hippocampal LTP, learning and memory detected before amyloid plaque formation[46] |
| In vitro electrophysiology | Hippocampal slices exposed to Aβ oligomers | Aβ oligomers induced spontaneous firing[11] and direct facilitation of epileptic activity in dentate gyrus and hippocampal neurons[12,42,47,54], and also produced long-lasting pro-epileptogenic changes in hippocampal networks, reduced Schaffer collateral pathway coupling, impaired LTP and reduced dendritic spine density[43,56] |

Aβ, amyloid-β; *APP*, amyloid precursor protein; LTP, long-term potentiation; *MAPT*, microtubule-associated protein tau; *PSEN1*, presenilin 1.

unclear[79,86]. Effects on both early and late stages of the Aβ cascade were reported for lamotrigine, with a reduction of Aβ cleavage by β-secretase and a decrease in the number and size of Aβ plaques[75,90]. Similar findings were reported for carbamazepine, which also improved cognitive impairment in APP/PS1ΔE9 mice[91]. In addition, phenytoin has been shown to provide neuroprotection from the excitotoxic effects of Aβ fibrils[92]. Overall, the limited experimental evidence suggests that ASMs can potentially limit, or at least decelerate, the progression of Aβ pathology. This situation is especially intriguing as the currently available ASMs were strictly designed to prevent seizures rather than to block the processes underlying epilepsy[93].

Some evidence also supports a role for ASMs in limiting the spontaneous epileptiform activity seen in animal Aβ models, with a positive impact on the Aβ cascade[38,55,74]. The synergy across mechanisms might derive from a feedback cycle involving activity-dependent production of Aβ species. Synaptic transmission results in increased APP endocytosis, leading to generation and release of Aβ[94]. The formation of Aβ colocalizes with spontaneous neuronal activity[95] and is locally increased by neuronal firing, a process that might be able to produce an epileptogenic focus[96]. In turn, epileptic activity can induce neuronal injury and neurodegeneration[80,97]. As ASMs can control epileptic activity and might affect Aβ production, these drugs could potentially have an anti-epileptic rather than simply an anti-seizure effect. The available data indicate that further investigation of the use of ASMs in early-stage AD is warranted, although the potential benefits of these

drugs in people with AD who have not had seizures remain unknown.

## Insights from clinical studies

***Risk of seizures in AD.*** Despite possible shared neurodegenerative mechanisms, little attention has been given to the link between cognitive decline and epilepsy, especially in the older population[19,21,98]. Although the relationship seems to be bidirectional, the vast majority of studies have addressed the risk of seizures among patients with AD rather than the risk of cognitive deterioration among people with epilepsy[99]. In the 1980s, anecdotal reports prompted the first observational longitudinal study on the occurrence of epilepsy among people with autopsy-proven AD[100], which suggested a direct relationship between AD duration and the risk of seizures, with the cumulative prevalence of seizures in this population reaching 26%.

Further confirmation of an increased prevalence of seizures among people with AD was provided by subsequent reports. A longitudinal case–control study in patients with AD who were seizure-free at study entry reported generalized tonic–clonic seizures in 23% of participants over a 90-month follow-up period, with prevalence increasing with AD stage[101]. A survey of 75 inpatients with AD found that 21% developed seizures after AD onset[102], and a large case–control study involving inpatients with dementia aged >55 years highlighted the frequent occurrence of seizures (9.1%) compared with age-matched and sex-matched controls[103]. A similar prevalence of epilepsy was reported among patients with mild AD, who were up to eight times more likely to experience epilepsy than the age-matched general population[104]. In addition, a large nationwide study in Taiwan confirmed an increased incidence of seizures among patients with AD, with advanced age and disease stage being identified as risk factors for seizures[105].

Box 2 | **Modulation of neuronal activity by soluble Aβ peptides**

The fact that epileptic phenotypes can be observed before the amyloid-β (Aβ) plaque stage in animal models of amyloidopathy indicates that early Aβ pathology can promote dysfunction at the neuronal and network levels[44,62,118]. Researchers have explored oligomerization status, potential threshold concentrations and impact of pre-existing neuronal activity to elucidate the timing and stability of perturbations induced by soluble Aβ peptides[42,53,62,118].

Large oligomers were found to silence neuronal activity, whereas small oligomers enhanced excitability[50]. These findings were supported by those of studies using in vivo calcium imaging, which showed excitatory effects of Aβ dimers on hippocampal neurons[42,52] and were in agreement with the general hypothesis of presynaptic facilitation even with small increases in Aβ levels[47]. Reduction of soluble Aβ species in the region surrounding the plaque rescued neuronal hyperactivity, adding further support to a link between Aβ oligomer release and neuronal firing[62,183]. However, these findings were challenged by reports that small Aβ oligomers reduce neuronal firing[51,118].

Single epileptic spikes and spike–wave discharges were reported to be similar in three mouse lines with different Aβ loads. These discharges were not affected by β-secretase inhibitors, indicating that additional factors, including other amyloid precursor protein metabolites, can participate in neuronal hyperactivity[68]. These findings, in contrast to previous reports of reversal of neuronal hyperexcitability with secretase inhibition[42,183], highlight the need to further address the complex effects of Aβ pathology, taking into account protein–protein interactions (BOX 3), oligomer threshold concentrations to induce neuronal dysfunction[46,62,118], and fluctuations in neuronal activity over time[61,62].

Although the early studies consistently showed that AD is a risk factor for epilepsy[106,107], they failed to discriminate specific disease courses or discern shared aetiologies. Heterogeneity in EEG assessment, AD diagnostic criteria and study design further limit the interpretation of these results[107]. Nevertheless, the high prevalence of seizures among patients with AD raises pertinent questions. For example, do epileptogenic processes start before, in parallel with or after AD onset? What factors perpetuate epileptogenesis in people with AD? And do AD and epilepsy share common molecular pathways and, if so, can we act on such pathogenic processes?

***Evidence for Aβ involvement.*** A step forward in the understanding of pathogenic processes and their temporal contribution to epilepsy in AD came from studies of patients carrying AD-associated genetic mutations, including those involving the *PSEN1*, *PSEN2* and *APP* genes[108–111]. Seizures occurred in 57% of patients with autosomal dominant early-onset AD who harboured an *APP* duplication[110,111], and *APP* point mutations were associated with an increased risk of both focal and generalized seizures in the early stages of the disease[112,113]. In people with Down syndrome, who show 50% overexpression of *APP* owing to trisomy of chromosome 21, the prevalence of epilepsy reaches 84%, with seizures presenting early in the disease course[25,114]. Similarly, in people with *PSEN* gene mutations[106,108], seizure onset can predate cognitive decline, suggesting a possible connection between early onset of seizures and progressive deterioration in cognitive function[115–117].

The risk of seizures in people carrying AD-associated genetic mutations seems considerably higher than that reported for people with late-onset AD[101]. As both *APP* and *PSEN* mutations converge on the amyloid cascade and increase the burden of Aβ, the data from preclinical settings would seem to translate well into clinical phenotypes. However, a substantial mismatch between experimental and clinical settings needs to be addressed. The experimental studies were mainly based on incomplete models of the disease, even limited to single peptides in some cases, so are unlikely to mimic or replicate the complex environment of the human brain[62,118]. In addition, most of the clinical studies only recorded overt seizures and lack the extensive data collected through EEG monitoring in animal models[62]. Development of a model that faithfully represents AD pathology and allows in-depth monitoring would substantially aid investigation of the contribution of Aβ to both epilepsy and AD.

The finding that Aβ can promote epileptogenesis before plaque formation and neurodegeneration are observed[12,46,73], combined with the occurrence of seizures before cognitive decline, lends weight to the concept of a continuum whereby amyloid drives both epilepsy and cognitive decline. In dementias other than AD, the prevalence of seizures is low, indicating a specific relevance of Aβ to seizures[106]. Studies in individuals with sporadic AD revealed that AD itself is a risk factor for epilepsy, with an average time from onset of cognitive decline to the first epileptic event of 3–4 years[72,99]. However, the associations of early seizures with a dementing process

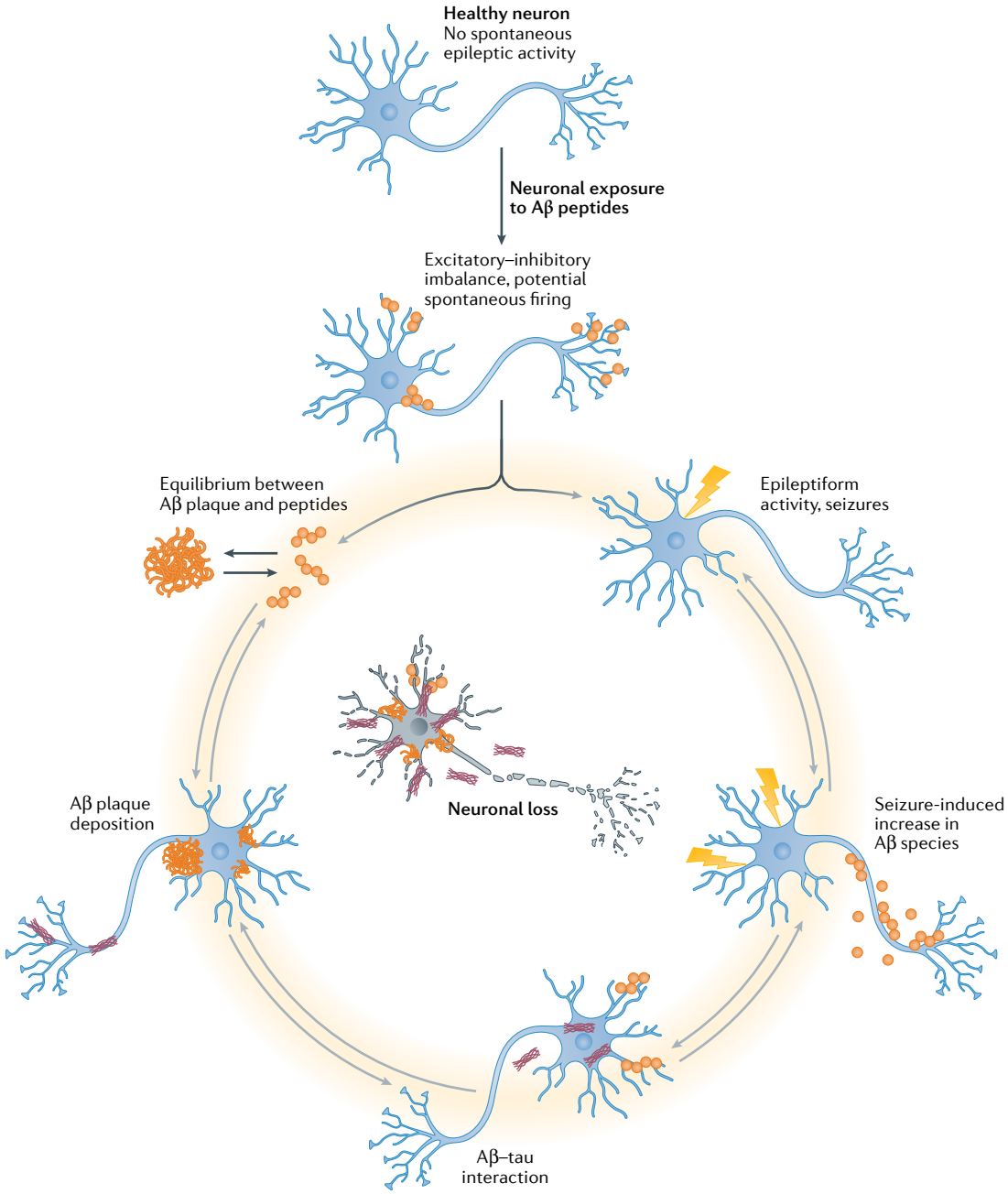


Fig. 1 | **Aβ at the interface of epileptogenesis and neuronal loss.** Amyloid-β (Aβ) might have epileptogenic potential in the early stages of the amyloid cascade. Preclinical studies have demonstrated that Aβ oligomers can induce spontaneous epileptiform discharges as well as clinically overt seizures. The epileptogenic potential of oligomers might depend on oligomerization status, as well as threshold concentrations and interaction with other proteins[52,62] (BOXES 2,3). Production of Aβ species is activity-dependent and consistently increases with neuronal firing[96]. Moreover, epileptiform activity fosters plaque deposition. Aβ plaque deposition alters neuronal signalling, maintains a dynamic environment in equilibrium with oligomers and promotes epileptiform activity, creating a vicious circle. The contribution of each single item to the vicious circle has yet to be fully understood, given that experimental models do not satisfactorily replicate mild Alzheimer disease stages. Dissection of each individual mechanism might aid the development of multitarget strategies.

have largely been ignored. For example, in the 1984 NINDS–ADRDA AD criteria, an AD diagnosis was considered 'unlikely' in patients in whom seizures occurred early in the disease course[119]. In recent years, attention has progressively shifted towards prodromal AD stages, suggesting a need for further research into seizures that present before AD diagnosis.

***Seizures in prodromal AD.*** An early population-based study in people with early-onset (<65 years of age) sporadic AD, found that 7% of patients had experienced seizures prior to a diagnosis of AD[120]. In a prospective single-centre study, 6.8% of patients with AD had a history of a seizure disorder at the time of AD diagnosis, with half of these individuals reporting onset of seizures

approximating to the onset of cognitive decline[121]. Seizures were more frequently observed among patients with younger age at AD onset[104,122], suggesting that epilepsy and cognitive decline are interdependent. However, the temporal relationship between epilepsy and AD remained uncertain[21,121,123].

In 2013, a retrospective observational study applying systematic EEG screening to patients with AD or aMCI, a probable harbinger of AD, highlighted that seizures were already apparent at the aMCI stage[124]. Epilepsy was also associated with earlier onset of AD, suggesting detrimental effects on cognition, and with a more severe disease course[124]. Several studies have shown that seizures can precede the onset of cognitive decline by variable amounts of time[20,125–127] (TABLE 3), leading some to hypothesize that seizures could represent the first clinical symptom of AD (epileptic variant AD).

Beyond overt clinical seizures, subclinical epileptiform activity has been reported in people with AD. During prolonged EEG monitoring, subclinical epileptic activity, occurring mostly during sleep and preferentially involving the temporal lobe regions, was found in more than one third of individuals with AD[128]. Subclinical epileptiform activity has also been detected at aMCI stages and was associated with earlier onset of cognitive impairment[124] and accelerated cognitive decline[128]. In a small case series, an increased prevalence of subclinical epileptiform activity was reported among patients with AD who had already been diagnosed with epilepsy[129]. These findings are concordant with those from experimental models, in which interictal spikes can be identified during sleep at early disease stages[38,59].

Box 3 | **Aβ interactions with tau and prion protein**

Although amyloid-β (Aβ) and tau pathologies can develop in different timeframes in Alzheimer disease (AD), experimental data support synergistic effects on the excitatory–inhibitory balance[35,67]. Tau is a highly soluble protein that is necessary for microtubule function. In AD, tau undergoes hyperphosphorylation and aggregation into neurofibrillary tangles[27,67,184], and tau accumulation correlates with cognitive impairment and neurodegeneration[10,27,67]. In temporal lobe epilepsy, tau seems to be more involved than Aβ pathology in the processes leading to epilepsy, neurodegeneration and cognitive decline[98,185–187].

Similar to Aβ, tau alters neuronal function at pre-deposition stages. Reducing levels of endogenous tau has been shown to prevent behavioural disturbances and protect against Aβ-induced excitotoxicity in animal models[65,188], potentially by normalizing glutamate transmission and limiting the effects of Aβ–FYN interaction[32,188]. Genetic reduction of tau partially protected against Aβ-dependent neural excitability in animal models of Aβ pathology[34]. Therefore, tau might participate in Aβ-induced neuronal hyperexcitability, although its effects at higher Aβ concentrations are still unclear[62,189]. At a structural level, tau is necessary for Aβ-induced axonal transportation[190] and, in synergy with Aβ, promotes dendritic spine loss in AD models[191].

Aβ also interacts with prion protein (PrP), which contains a high-affinity binding site for Aβ oligomers even at nanomolar concentrations[192]. PrP–Aβ oligomer complexes alter FYN tyrosine kinase function and deregulate glutamate receptors, thereby inducing neuronal dysfunction[193,194]. Synaptic dysfunction can be prevented by the administration of anti-PrP antibodies, suggesting a crucial interaction of Aβ with non-pathological PrP[192]. Overall, proteinopathies are likely to develop and act within an interactive environment, which might help explain the negative results from trials of drugs targeting a single axis. It is unlikely that a single peptide can induce neuronal dysfunction in isolation[8,67,118]. Notably, levetiracetam has been shown to counteract tau-dependent as well as Aβ-dependent neural network dysfunction[77,88,184] and, therefore, remains a drug of considerable interest in clinical trials.

The discovery that seizures can occur early in the disease course of AD leads us to consider whether people with epilepsy are at increased risk of AD. Does Aβ drive epilepsy as well as cognitive decline, and can we identify individuals with epilepsy who are at high risk of developing dementia? Also, can we modify the trajectory of cognitive decline, possibly with ASMs[19,130]? These important questions require a clear step change from a retrospective focus to prospective evaluation of cognition in patients with epilepsy.

## Shifting paradigms: epilepsy as a risk factor for AD

Perhaps surprisingly, cognitive decline among people with epilepsy has received less attention than seizure occurrence among people with AD. Nevertheless, the increased risk of dementia among people with epilepsy has been recognized since the early 1990s, with several case–control studies supporting the hypothesis[131–137]. In 1991, a collaborative reanalysis of case–control studies, including all papers reporting age at onset of epilepsy and dementia, demonstrated a 1.6% increase in relative risk of dementia in patients with epilepsy[131]. The relative risk of dementia doubled when epilepsy presented within 10 years before AD onset compared with epilepsy dating back more than 10 years[131], which hints towards an association between late-onset epilepsy and the risk of AD[21,130].

In a nationwide Dutch registry from 1980 to 1989, adults with epilepsy aged >50 years were found to have a 1.5% increase in relative risk of AD compared with age-matched and sex-matched controls[132]. In an electronic record-based study conducted in Taiwan, people with late-onset epilepsy had a threefold increase in the risk of developing dementia[138], a finding that was replicated by a retrospective investigation using data from the Atherosclerosis Risk in Communities (ARIC) cohort study[139]. Cross-sectional studies have demonstrated that epilepsy is associated with global cognitive changes and impaired cognitive performance[140–142] (TABLE 4). In a small case–control study, cognitive deficits in adults with epilepsy were more severe than in adults with MCI, and ASM polytherapy was associated with worse scores on neuropsychological testing[141]. However, the results of these studies were limited by heterogeneity in design, diagnostic criteria and work-up. The role of several factors that could potentially influence both epilepsy and cognitive decline, such as occult cerebrovascular disease, remained undisclosed. These aspects are particularly relevant in patients with late-onset epilepsy, in whom stroke, small vessel disease, tumours, infections and systemic disorders account for >75% of aetiologies[12,143–145]. Given the consistent impact of such factors — especially stroke and small-vessel disease — on cognition, the fraction of cognitive decline attributable to epilepsy alone is difficult to calculate accurately.

In ~25% of people with late-onset epilepsy, despite extensive diagnostic work-up, no specific cause can be identified, leading to a diagnosis of LOEU[18]. People with LOEU have no evidence of cerebrovascular disease, infection or systemic or structural disorders that could cause epilepsy. Therefore, the LOEU population is a relatively homogeneous cohort in which to

Table 2 | **Experimental studies on modulation of epileptiform activity in models of Aβ pathology**

| Medication | Animal model | Experimental model | Epileptic activity/ seizure model | Dosage of anti-seizure medication | Anti-seizure and cognitive effects | Anti-amyloid effect |
|---|---|---|---|---|---|---|
| Anti-human APP/Aβ antibody | 3×Tg mice[73] | Electrophysiology on hippocampal slices | Audiogenic seizures; ictal-like EDs | Passive immunization with a single intraperitoneal injection (40 or 18.4 µl)[73] | Reduced audiogenic seizure susceptibility and reduced epileptic discharges in hippocampal CA3 region | Decreased intraneuronal Aβ expression |
| Brivaracetam | APP/PS1 or 3×Tg mice[74] | EEGcr | Spontaneous SWDs[74] | Single intraperitoneal injection (10 mg/kg) or chronic treatment (daily intraperitoneal injection 8.5 mg/kg for 28 days) | SWDs reduced by 41%; chronic treatment fully reversed memory impairment | Chronic treatment did not affect Aβ levels, Aβ plaque burden or synapse density |
| Carbamazepine | APP/PS1 mice[76] | EEGcr | Spontaneous seizures and EDs (high-amplitude spikes, SWDs and slow waves) | 10 or 40 mg/kg intraperitoneal injection three times a day | 10 mg/kg reduced ED frequency by >50% in 56% of mice; 40 mg/kg reduced ED frequency by >50% in 50% of mice | In other studies, the drug promoted neuronal survival in hippocampal cultures exposed to $Aβ_{25–35}$ fibrils[92] and reduced Aβ plaque burden[91] |
| Ethosuximide | APP/PS1 mice[38] | EEGcr | Spontaneous EDs (cortical spikes, corticohippocampal spikes, giant spikes and SWDs) | 200 mg/kg intraperitoneal injection 30 min before recording | Reduced corticohippocampal spikes; mixed effects on giant spikes, no effect on SWDs | No data |
| | APP/PS1 or 3×Tg mice[74] | EEGcr | Spontaneous SWDs | Single intraperitoneal injection (200 mg/kg) or chronic treatment (30 mg/ml in drinking water for 45 days) | Loading dose reduced SWDs by 93% in APP/PS1 mice and 83% in 3×Tg mice; chronic treatment reduced SWDs by 78% (no effect on memory) | No effect on Aβ levels or Aβ plaque burden |
| Lamotrigine | APP/PS1 mice[75] | Electrophysiology on hippocampal slices, EEGcr | Spontaneous EDs (epileptic spikes and small spikes) | 30 mg/kg daily for 2 months from the age of 3 months | Reduced epileptic spikes, no effect on small spikes; prevention of dendritic spine loss, attenuation of deficits in synaptic plasticity and learning and memory | Reduced Aβ cleavage[90]; reduced numbers and size of Aβ plaques and increased BDNF and NGF expression[75] |
| Levetiracetam | hAPP mice[77] | EEGcr | Spontaneous EDs | Acute treatment with single 5, 50 or 200 mg/kg intraperitoneal injection or chronic treatment with 75 or 150 mg/kg daily intraperitoneal injection | Epileptic discharge suppression; chronic treatment reversed behavioural abnormalities and memory impairment | No effect on Aβ deposition, but normalized levels of synaptic proteins (calbindin and neuropeptide Y) |
| | APP/PS1 or 3×Tg mice[74] | EEGcr | Spontaneous SWDs | Single intraperitoneal injection (20 mg/kg) | Loading dose reduced SWDs by 45% in APP/PS1 mice and by 61% in 3×Tg mice | In other studies, the drug reduced Aβ plaque burden in vivo in APP/PS1 mice[86] and prevented neuronal loss caused by exposure of hippocampal cultures to $Aβ_{25–35}$ fragments[87] |
| | APP/PS1 mice[38] | EEGcr | Spontaneous EDs (cortical spikes, corticohippocampal spikes, giant spikes and SWDs) | 75 mg/kg intraperitoneal injection 30 min before recording | Suppression of fast spindle-associated spikes, no effect on SWDs | |
| Phenytoin | hAPP mice[78] | EEGcr | Spontaneous EDs | Single intraperitoneal injection (100 mg/kg) or chronic treatment with 25, 50, 70 or 85 mg/kg daily via drinking water | Phenytoin triggered epileptiform activity and worsened memory impairment | Survival in hippocampal neurons exposed to $Aβ_{25–35}$ fibrils promoted by drug exposure (100 nM to 1 µM), associated with reduction in calcium transients[92] |
| | APP/PS1 mice[76] | EEGcr | Spontaneous seizures and EDs (high-amplitude spikes, SWDs and slow waves) | 10 or 40 mg/kg Intraperitoneal injection three times daily | 10 mg/kg reduced EDs below 50% in 37.5% of mice; 40 mg/kg reduced EDs below 50% in 80% of mice but exacerbated in 20% of mice | |
| | APP/PS1 or 3×Tg mice[74] | EEGcr | Spontaneous SWDs | 20 mg/kg intraperitoneal injection | No decrease in SWDs compared with untreated mice | |

Table 2 (cont.) | **Experimental studies on modulation of epileptiform activity in models of Aβ pathology**

| Medication | Animal model | Experimental model | Epileptic activity/ seizure model | Dosage of anti-seizure medication | Anti-seizure and cognitive effects | Anti-amyloid effect |
|---|---|---|---|---|---|---|
| Valproate | APP/PS1 mice[79] | EEGcr | Spontaneous seizures and EDs | 30 or 300 mg/kg intraperitoneal injection[79] | Reduced EDs for ≥1 week after treatment discontinuation but not in the longer term; uncertain effect on seizure reduction | No effect on Aβ plaques; increased long-term acetylation of histone H3 at promoters of *BDNF*, *CDK5* and *NR2A* genes |
| | APP/PS1 mice[76] | EEGcr | Spontaneous seizures and EDs (high-amplitude spikes, SWDs and slow waves) | 260 or 400 mg/kg intraperitoneal injection twice daily | Both doses reduced EDs below 50% versus baseline in ≥75% of mice, although the higher dose was less tolerable than the lower dose | Other studies showed reductions in Aβ oligomers[89] and Aβ deposition[86] and increased survival of neurons exposed to $Aβ_{25–35}$ fibrils[92] |

Aβ, amyloid-β; APP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; *CDK5*, cyclin-dependent-like kinase 5; ED, epileptiform discharge; EEGcr, EEG continuous recording; NGF, nerve growth factor; *NR2A*, subunit of NMDA receptor; SWD, spike–wave discharge.

explore cognition, given the lack of major confounding factors[18,146].

***Cognition in late-onset epilepsy.*** Few detailed reports are available on cognitive performance in people with late-onset epilepsy. An observational study detected impairments in executive function in 58% of individuals with late-onset epilepsy at the time of diagnosis and before treatment initiation[147]. In an exploratory study, patients with LOEU had lower scores on the Mini-Mental State Examination than age-matched and sex-matched healthy controls[12].

Extensive neuropsychological testing in a wider cohort from a cross-sectional study showed that 59% of patients with LOEU had MCI at the time of epilepsy diagnosis, with a particularly high prevalence of multi-domain MCI compared with age-matched and sex-matched non-epileptic patients with MCI[16]. Therefore, the presence of epilepsy might modify the domain-specific features of MCI. Resting-state quantitative EEG analysis indicated that patients with LOEU had a reduction in alpha source connectivity similar to that documented in people with AD, even at the MCI stage[16,148]. Moreover, cerebrospinal fluid (CSF) analysis showed that the presence of cognitive impairment was associated with an increased prevalence of Aβ pathology in patients with LOEU[16]. The key findings of this work were that more than 50% of people with LOEU had subtle cognitive impairment before initiating ASMs, and that cognitive deficits were associated with abnormalities in cortical connectivity and CSF biomarkers that were also found in people with AD, raising the question of whether people with LOEU are at an increased risk of developing AD.

Quantitative EEG analysis
Analysis of cortical connectivity and neuronal synchronization of rhythmic oscillations at various frequencies. Abnormalities in cortical connectivity can be used to detect patients with mild cognitive impairment and predict evolution to Alzheimer disease (AD).

***Risk of AD and Aβ pathology in patients with LOEU.*** Several longitudinal studies have investigated the risk of AD in people with LOEU[18,146,149]. In a retrospective study, patients with LOEU had a 10% cumulative hazard rate for dementia in the 5 years following epilepsy diagnosis[149]. These findings were replicated in an electronic medical record-based retrospective study that compared adults with LOEU with age-matched and sex-matched controls from a single community hospital database[146]. Using neuropsychological test scores, extensive diagnostics and the International League Against Epilepsy classification, the authors found that up to 61% of adults with LOEU developed dementia in the 7 years following epilepsy diagnosis. Similarly, in a retrospective multicentre cohort study involving 292,262 veterans from the US Veterans Health Administration medical centres, individuals with LOEU had a twofold increased risk of receiving a dementia diagnosis during a 3.5-year follow-up period[14].

A population-based study using amyloid ligand PET showed that adults with childhood-onset epilepsy had an increased Aβ load in late middle age compared with age-matched controls, suggesting that epilepsy creates a predisposition to Aβ pathology[150]. In the same cohort, childhood-onset epilepsy was associated with an increased prevalence of cognitive impairment[151].

Additional evidence for a link between LOEU and dementia emerged from a small multicentre study, which compared cognitive trajectories in 40 adults with LOEU who did not have dementia at baseline and 43 age-matched and sex-matched healthy individuals[18]. In this prospective study, LOEU was consistently associated with an increased risk of AD over a 3-year follow-up period. Notably, among the patients with LOEU, Aβ pathology was common at the time of diagnosis, before ASM initiation. Almost 40% of people with LOEU had pathological CSF Aβ levels, and those with Aβ pathology were three times more likely to develop AD during follow-up than those with normal Aβ levels. Therefore, the clinical data lend weight to the concept that Aβ pathology participates in the transition from LOEU to AD (FIG. 2).

***Can anti-seizure medications improve cognition in AD?*** Seizures can occur early in the course of AD and seem to accelerate cognitive decline; therefore, ASMs might be expected to have a positive impact on the cognitive trajectory by modulating hippocampal networks or Aβ deposition (TABLE 2).

Several studies have investigated the relationship between ASM use and cognition. In a population-based prospective cohort study in Canadian individuals

Table 3 | **Observational studies on epilepsy in patients with cognitive impairment**

| Ref. | Diagnosis (sample size) | Design | Mean age (years) | | Main findings |
|---|---|---|---|---|---|
| | | | At first seizure | At cognitive impairment | |
| Cretin et al. (2016)[20] | MCI due to AD (13) | Retrospective case series | 63 | 66 | Pharmacosensitive temporal lobe epilepsy syndrome preceded MCI by up to 7 years |
| | | | | | Aβ pathology found in 70% of cases |
| DiFrancesco et al. (2017)[126] | AD (23) | Retrospective observational study | 68 | 71 | Seizures preceded cognitive decline by 4.6 years on average |
| | | | | | Epilepsy was 17 times more likely in people with AD than in the general population |
| Nardi Cesarini et al. (2020)[16] | LOEU (27) | Prospective case–control study | 69 | 71 | 59% of patients with LOEU had MCI, mostly with multidomain impairment |
| | | | | | Aβ pathology was frequently found on cerebrospinal fluid analysis |
| Rao et al. (2009)[123] | MCI (10), AD (9), vascular dementia (6) or DLB (5) | Retrospective chart review | 62 | 71 | 3.6% of patients in AD registry had epilepsy |
| | | | | | Focal unaware seizures were well controlled with anti-seizure medications |
| Sarkis et al. (2016)[127] | Probable or possible AD (64), mixed dementia (4), DLB (4), frontotemporal dementia (3), vascular dementia (1) or primary progressive aphasia (1) | Retrospective chart review | 74 | 68 | Seizures could precede cognitive symptoms by up to 4 years, but could also manifest up to 7 years later than cognitive symptoms |
| Sarkis et al. (2017)[125] | MCI due to AD (3) | Retrospective case series | 68 | 69 | Epileptic auras could precede cognitive symptoms in AD |
| Vossel et al. (2013)[124] | Amnestic MCI (12) or AD (35) | Retrospective observational study | 67 | 65 | Patients with amnestic MCI and epilepsy showed cognitive decline 6.8 years earlier on average than those without epilepsy |
| | | | | | Subclinical epileptiform activity was associated with faster decline in cognitive function |
| Vossel et al. (2016)[128] | Mild AD (33) | Prospective case–control study | 58 | 62 | Subclinical epileptiform activity was associated with rapid cognitive decline |

Aβ, amyloid-β; AD, Alzheimer disease; DLB, dementia with Lewy bodies; LOEU, late-onset epilepsy of unknown aetiology; MCI, mild cognitive impairment.

aged ≥65 years, the use of phenytoin — but not other ASMs — was associated with a significantly increased risk of developing dementia[152]. In a placebo-controlled randomized controlled trial involving 313 people with mild-to-moderate AD, valproate provided no substantial benefit with regard to absolute hippocampal volume loss or cognitive performance[153,154]. However, the potential of this drug to restore the hippocampal network might not have been apparent owing to the disease stage studied. If early intervention is assumed to be most beneficial, patients with mild-to-moderate AD up to 8 years into the disease course, as were included in this study, might have insufficient network reserve to restore. Preliminary results from the Valproic Acid in Subjects with Intact Cognition – Proof of Concept Study (VPA) (NCT01729598) indicated a link between

Table 4 | **Studies exploring cognitive performance in adults with epilepsy**

| Ref. | Study design and sample size | Mean age (years) | | ASM status | Cognitive assessment battery | Main findings |
|---|---|---|---|---|---|---|
| | | At study baseline | At epilepsy onset | | | |
| Costa et al. (2016)[12] | Cross-sectional: 35 people with late-onset epilepsy and 43 healthy controls | 68.0 ± 7.0 | 68.0 ± 7.0 | Naive | MMSE at diagnosis | Patients with LOEU had worse mean MMSE scores than controls<br>Cerebrospinal fluid biomarker analysis revealed amyloid pathology in LOEU |
| Costa et al. (2019)[18] | Prospective longitudinal: 40 people with late-onset epilepsy and 43 healthy controls | 70.0 ± 6.4 | 70.0 ± 6.4 | Naive | MMSE, Rey AVLT, TMT and CDR at diagnosis and after 3.5 years | Compared with controls, patients with LOEU had similar profile but higher risk of conversion to Alzheimer disease dementia over 3.5-year follow-up<br>37.5% of people with LOEU had amyloid pathology |
| Griffith et al. (2006)[141] | Cross-sectional: 26 people with epilepsy, 25 healthy controls and 26 people with MCI | 64.7 ± 3.8 | Not provided (minimum age 0) | Treated (15 monotherapy, 11 polytherapy) | Mattis DRS, Logical Memory tests (WMS-II immediate and delayed recall subtests) and word fluency 30 years after starting ASM | Patients with epilepsy had worse cognitive profile than controls, and those receiving ASM polytherapy had worse neuropsychological test scores than untreated patients with MCI |
| Griffith et al. (2007)[162] | Prospective longitudinal: 17 people with late-onset epilepsy and 17 healthy controls | 67.7 ± 4.2 | 37 ± 21.8 | Treated (9 monotherapy, 8 polytherapy) | Mattis DRS, Logical Memory tests (WMS-II immediate and delayed recall subtests), word fluency and Executive Interview Test (EXIT-25) 27 years after starting ASM | Patients with epilepsy had worse cognitive profiles than controls and showed worsening of executive function over time |
| Liguori et al. (2019)[155] | Prospective longitudinal: 58 people with late-onset epilepsy, no control group | 64.7 ± 9.5 | 64.7 ± 9.5 | Naive at baseline, 45 monotherapy and 13 polytherapy at follow-up | MMSE, Rey AVLT, ROCF and phonological and semantic verbal fluency tests at diagnosis and after 1 year | Patients with LOEU showed deterioration of cognitive performance at follow-up, with no significant difference between ASM polytherapy and monotherapy<br>Use of oxcarbazepine (versus other ASMs) was associated with an increase in MMSE score at follow-up |
| Martin et al. (2005)[142] | Cross-sectional: 25 people with epilepsy and 27 healthy controls | 64.6 ± 3.9 | 35 ± 18.8 | Treated (14 monotherapy, 11 polytherapy) | Mattis DRS, Logical Memory tests and word fluency 27 years after starting ASM | Patients with epilepsy showed impairment on all tests<br>ASM polytherapy was associated with greater impairment than monotherapy |
| Miller et al. (2016)[163] | Cross-sectional: 38 people with epilepsy and 29 healthy controls | 65.2 ± 7.9 | 40.1 ± 25.2 | Treated (19 monotherapy, 21 polytherapy) | Mattis DRS, MMSE, Hopkins Verbal Learning Test, Verbal Paired Associates, Brief Visuospatial Memory Test, TMT A and B, Digit Symbol Coding, Controlled Word Association, Boston Naming Test, Animal Fluency, ROCF and Judgment Of Line Orientation 25 years after starting ASM | Patients with epilepsy showed impairment on most domains<br>Anxiety and ASM polytherapy were associated with worse performance on some cognitive domains |
| Nardi Cesarini et al. (2020)[16] | Cross-sectional: 46 people with late-onset epilepsy, 21 people with non-epileptic MCI and 11 healthy controls | 67.5 ± 6.8 | 67.5 ± 6.8 | Naive | MMSE, Rey AVLT, TMT A and B, Frontal Assessment Battery, verbal fluency test, verbal semantic category, RCPM, Mental Deterioration Battery, Clock Drawing Test and CDR at diagnosis | 58.7% of patients with LOEU had MCI at epilepsy onset<br>People with LOEU plus MCI had amyloid pathology, and were more frequently diagnosed with multidomain MCI than non-epileptic patients with MCI |
| Piazzini et al. (2006)[140] | Cross-sectional: 40 people with epilepsy and 40 healthy controls | 67.0 ± 5.9 | 47 ± 16.5 | Treated (8 monotherapy, 32 polytherapy) | RCPM, TMT, Attentional Matrices, Story Test, ROCF, Digit Span, verbal fluency test and Token Test 20 years after starting ASM | Patients with epilepsy had worse cognitive performance than controls<br>Individuals receiving ASM polytherapy had worse performance than those receiving monotherapy |
| Witt et al. (2014)[147] | Cross-sectional: 257 people with late-onset epilepsy, no control group | 71.5 ± 7.2 | 71.5 ± 7.2 | Naive | Epitrack (executive function and subjective rating of cognition) at diagnosis | Impairment in executive function was observed in 59% of ASM-naive patients with late-onset epilepsy |

ASM, anti-seizure medication; AVLT, Rey Auditory Verbal Learning Test; CDR, Clinical Dementia Rating; DRS, Dementia Rating Scale; LOEU: late-onset epilepsy of unknown aetiology; MCI: mild cognitive impairment; MMSE: Mini-Mental State Examination; RCPM, Raven's Coloured Progressive Matrices; ROCF, Rey–Osterrieth Complex Figure test; TMT, Trail Making Test; WMS-II, Wechsler Memory Scale second edition.

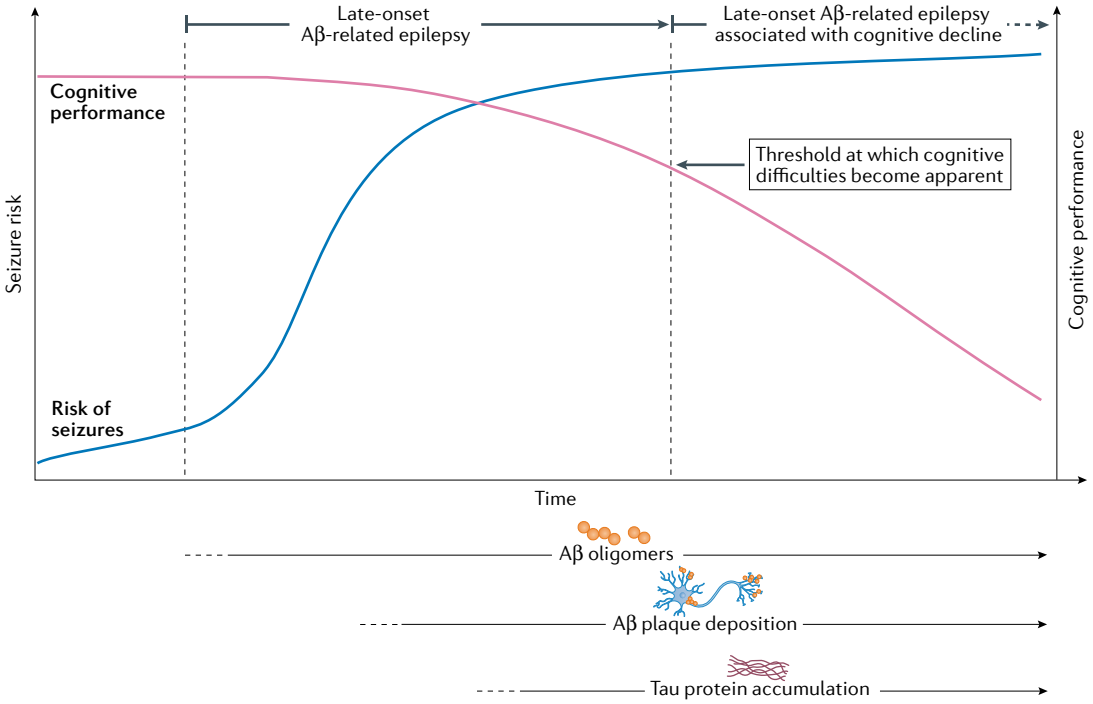


Fig. 2 | **Aβ accumulation, late-onset epilepsy and cognitive decline.** Amyloid-β (Aβ) pathology might contribute to both epilepsy and cognitive decline. The figure shows the progressive increase in burden of Aβ and tau pathology over time, which should, however, be considered in light of the limitations on oligomer detection in humans[164]. Early Aβ pathology can trigger pro-epileptogenic changes that translate into clinical seizures in adults long before overt cognitive decline is reached. This finding lends weight to the concept of a specific subtype of late-onset epilepsy of otherwise unknown aetiology, potentially related to early Aβ pathology. Aβ might promote epileptogenesis in the short term and the progressive increase in Aβ burden might interconnect with tau accumulation to promote neurodegeneration. People with late-onset Aβ-related epilepsy might benefit from early intervention to limit network hyperexcitability and Aβ pathology. Therefore, it is reasonable to advocate in-depth cognitive and biomarker assessment in people with late-onset epilepsy of unknown aetiology, as subjective cognitive impairment or mild cognitive impairment can already be present at the time of epilepsy diagnosis[16,19].

valproate use and improved cognitive performance and reduced Aβ pathology in cognitively healthy individuals. In a small ($n = 58$) multicentre observational study addressing cognitive decline over 12 months in people with LOEU, levetiracetam and valproate were associated with improved verbal fluency, although global cognitive performance declined[155] (BOX 4). Similar effects for valproate and levetiracetam were reported in adults with structural epilepsy[156], and both ASMs seemed to protect against dementia in a large self-controlled study based on insurance data[157].

In a prospective, randomized, three-arm parallel-group trial, people with AD and seizures ($n = 95$) were randomly assigned to levetiracetam, phenobarbital or lamotrigine, with a 4-week dose adjustment plus a 12-month dose evaluation period[158]. Cognitive trajectories were tracked through neuropsychological testing at 6 and 12 months, and each ASM group was compared with controls matched for age, sex and AD stage. Compared with patients receiving phenobarbital or lamotrigine, whose performance worsened over time, patients receiving levetiracetam showed a slight improvement on cognitive tests, especially with regard to memory and verbal fluency[158]. In a series of functional MRI studies, treatment with low-dose levetiracetam normalized hyperactivity in the dentate gyrus and hippocampal CA3 regions and improved performance in memory tasks in people with aMCI[69,159]. The fact that positive effects were found in patients without epilepsy allows us to cautiously suggest a possible benefit of levetiracetam during prodromal AD stages, irrespective of comorbidity with epilepsy[69]. Randomized trials, including An Investigation of Levetiracetam in Alzheimer's Disease (ILiAD) (NCT03489044) and Levetiracetam for Alzheimer's Disease-Associated Network Hyperexcitability (LEV-AD) (NCT02002819), are investigating people without epilepsy in the early stages of AD to explore whether ASMs can prevent or slow cognitive decline.

## An integrated view

Evidence from preclinical and clinical settings suggest that Aβ pathology, epilepsy and neurodegeneration are closely intertwined[19,21]. Improved understanding of these pathways is essential at both the clinical and experimental levels. Definition of an epileptic prodromal form of AD would offer new therapeutic opportunities, and clinical studies in this area need to be prospective, given the difficulties of retrospective evaluation of possible seizures in people with a diagnosis of AD. Studies that prospectively and comprehensively evaluate LOEU with thorough cognitive and biomarker assessments could have a

Box 4 | **ASM choice in older individuals**

Anti-seizure medication (ASM) selection is challenging in late-onset epilepsy. Older individuals have fewer options than younger patients, and adverse effects are more likely, especially in cognitive and behavioural domains[19,195–197]. In terms of efficacy, levetiracetam and lamotrigine outperform phenytoin for seizure control in patients with Alzheimer disease and epileptiform activity[124,198]. A systematic review published in 2018, updating previous versions[199], suggested that levetiracetam is more effective than lamotrigine (and other ASMs) in late-onset epilepsy, although lamotrigine has the best tolerability profile[200]. Therefore, levetiracetam or lamotrigine might be preferred over older ASMs.

Potential adverse effects and comorbidities should be carefully considered when prescribing ASMs to older individuals. Levetiracetam can have adverse effects on mood and behaviour[195], whereas the broad spectrum agent valproate has mostly beneficial effects on mood but can cause weight gain, tremor and hyperammonaemic encephalopathy[201,202]. An association of ASM polytherapy with cognitive impairment has also been reported[19,140], and although the data are inconclusive, evidence suggests that efforts should be directed towards the use of a single ASM whenever possible. However, a decline in cognitive performance should not be ascribed to ASMs alone. Observational studies have demonstrated that ASMs do not independently drive cognitive impairment[196,203], and a substantial decline in cognitive performance is observed in all patients with late-onset epilepsy of unknown aetiology, regardless of the ASM prescribed[155,196]. Therefore, standardized evaluation of ASM adverse effects[204,205] and serial neuropsychological testing are advised to enable tailoring of treatment to patients and identification of variations in the cognitive trajectory.

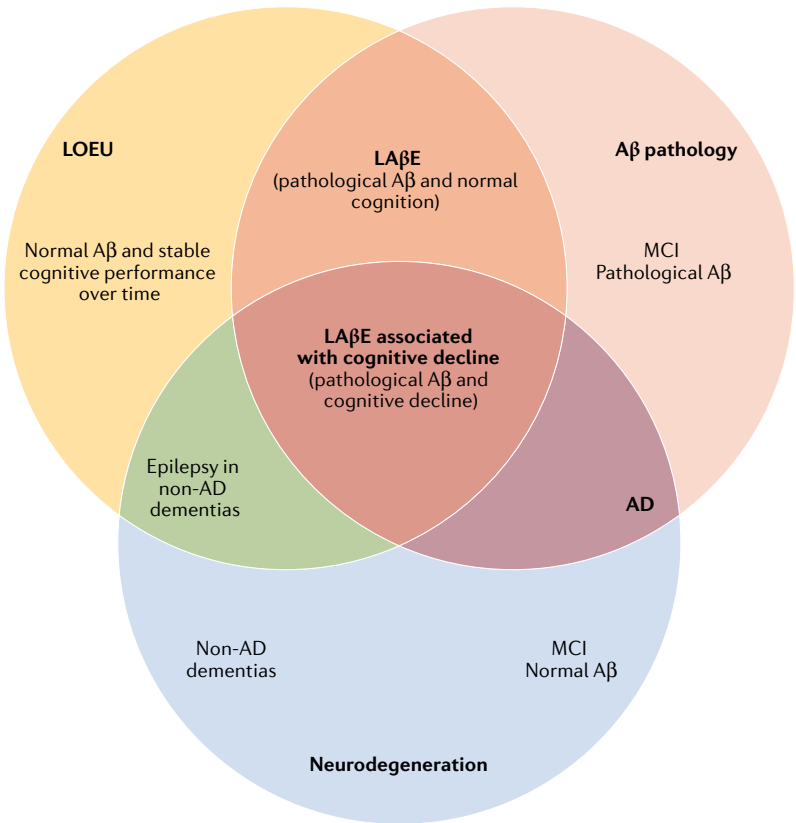


Fig. 3 | **Aβ pathology, LOEU and neurodegeneration.** Amyloid-β (Aβ) might represent a crucial interface between late-onset epilepsy of unknown aetiology (LOEU) and neurodegeneration. Half of patients with LOEU have mild cognitive impairment (MCI) at the time of diagnosis, and a consistent proportion demonstrate biomarkers consistent with Aβ pathology. Evidence supports the epileptogenic potential of Aβ, which might represent the epileptogenic substrate in patients with LOEU with otherwise unclear aetiology. Patients with late-onset Aβ-related epilepsy (LAβE) might have or transition to cognitive decline or Alzheimer disease (AD).

substantial impact on patient management. If Aβ is shown to promote epileptogenesis and mediate the transition to cognitive impairment, early measurement of Aβ levels will be essential. In addition, LOEU might need to be reclassified to reflect the role of Aβ as a potential driver of both processes (FIG. 3). Efforts should be directed towards accurate stratification of the risk of dementia among people with LOEU, for whom accumulation of Aβ seems to be a predisposing factor to the cognitive decline observed in later life. These arguments underpin the concept that epilepsy is a symptom of broader neuronal network dysfunction rather than a disease per se[19].

On the basis of evidence from clinical studies, we propose a possible classification of late-onset epilepsy where the aetiology is not known: first, patients with normal Aβ levels and normal cognitive status (LOEU); second, patients with pathological Aβ levels and normal cognition (late-onset Aβ-related epilepsy (LAβE)); and third, patients with pathological Aβ levels and worsening cognition (late-onset Aβ-related epilepsy associated with cognitive impairment (LAβE+)). Patients in the first of these categories might have a marginal risk of cognitive impairment and patients in the third category have an extreme risk of AD. Advanced neuroimaging (including amyloid PET), refined CSF biomarker assessments and quantitative EEG analysis represent potential tools to accurately stratify patients according to their predicted cognitive trajectory. This integrated view might allow clinicians to identify patients at high risk of cognitive decline at a stage where neurodegeneration is still minimal, enabling interventions targeting the Aβ cascade to be implemented at a time when they are likely to offer the most benefit. Among other agents, ASMs could be monitored for their impact on cognition (both positive and negative), so as to identify the best treatment options in this particular population[19,26]. Results from longitudinal observational studies, such as Predictive Value of Biomarkers of the Alzheimer's Disease (AD) in Elderly Patients with New-onset Epilepsy (BIOMALEPSIE) (NCT02861846), are awaited to further refine our understanding of LOEU.

## Conclusions and future directions

The relationship between epilepsy and cognitive decline is still controversial, with uncertainties regarding which of the two comes first, as well as the mechanisms possibly underlying both processes[21]. In this Review, we specifically evaluate the potential of Aβ as a driver of both epilepsy and AD.

Aβ-mediated epileptogenesis has been extensively demonstrated in experimental settings. Epileptic discharges and seizures can occur during prodromal stages of AD, can be triggered by Aβ oligomers, and increase progressively with Aβ deposition, supporting the hypothesis that Aβ-related epileptogenesis sets the stage for subsequent neurodegeneration[15,43,160]. These findings seem to translate into clinical experience, with seizures occurring frequently in patients with prodromal AD[20,26] and people with late-onset epilepsy being at high risk of dementia[14,18,146]. Around 50% of patients with late-onset epilepsy are diagnosed with MCI at the time of seizure onset and before ASM initiation[16,141], and a consistent proportion have Aβ pathology, which carries a high

risk of dementia[18,151]. Therefore, it seems reasonable to suggest that Aβ might mediate a continuum spanning epilepsy and cognitive decline.

Taken together, the current findings suggest a clear need for thorough evaluation of people with late-onset epilepsy, including cognitive testing and biomarker assessment at the time of diagnosis. Although seizures are often well controlled with ASM monotherapy, late-onset epilepsy is not a benign disease. As is often the case in people with epilepsy, the comorbidities and associated conditions require the most attention. Our efforts should, therefore, be directed towards an appropriate aetiological classification and accurate stratification of the risk of cognitive decline. This approach will enable the identification of people who are eligible for therapeutic interventions at early prodromal stages before Aβ triggers neurodegeneration — a time-critical window during which disease-modifying treatment is likely to be most beneficial.

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1. The Lancet Neurology. Response to the growing dementia burden must be faster. *Lancet Neurol.* **17**, 651 (2018).
2. Nichols, E. et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* **18**, 88–106 (2019).
3. Lozano, R. et al. Measuring universal health coverage based on an index of effective coverage of health services in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* **396**, 1250–1284 (2020).
4. Schneider, L. Alzheimer's disease and other dementias: update on research. *Lancet Neurol.* **16**, 4–5 (2017).
5. Braak, H. & Braak, E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol. Aging* **18**, 351–357 (1997).
6. Masters, C. L. et al. Alzheimer's disease. *Nat. Rev. Dis. Primers* **1**, 15056 (2015).
7. Jack, C. R. et al. The bivariate distribution of amyloid-β and tau: relationship with established neurocognitive clinical syndromes. *Brain* **142**, 3230–3242 (2019).
8. Polanco, J. C. et al. Amyloid-β and tau complexity — towards improved biomarkers and targeted therapies. *Nat. Rev. Neurol.* **14**, 22–40 (2018).
9. Jack, C. R. et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol.* **12**, 207–216 (2013).
10. Bloom, G. S. Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurol.* **71**, 505–508 (2014).
11. Minkeviciene, R. et al. Amyloid-induced neuronal hyperexcitability triggers progressive epilepsy. *J. Neurosci.* **29**, 3453–3462 (2009).
12. Costa, C. et al. Epilepsy, amyloid-β, and D1 dopamine receptors: a possible pathogenetic link? *Neurobiol. Aging* **48**, 161–171 (2016).
13. Costa, C., Romoli, M. & Calabresi, P. Late onset epilepsy and Alzheimer's disease: exploring the dual pathogenic role of amyloid-β. *Brain* **53**, 467–472 (2018).
14. Keret, O., Hoang, T. D., Xia, F., Rosen, H. J. & Yaffe, K. Association of late-onset unprovoked seizures of unknown etiology with the risk of developing dementia in older veterans. *JAMA Neurol.* **77**, 710–715 (2020).
15. Palop, J. J. & Mucke, L. Network abnormalities and interneuron dysfunction in Alzheimer disease. *Nat. Rev. Neurosci.* **17**, 777–792 (2016).
16. 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.* **11**, 199 (2020).
17. Ovsepian, S. V. & O'Leary, V. B. Neuronal activity and amyloid plaque pathology: an update. *J. Alzheimers Dis.* **49**, 13–19 (2015).
18. Costa, C. et al. Alzheimer's disease and late-onset epilepsy of unknown origin: two faces of beta amyloid pathology. *Neurobiol. Aging* **73**, 61–67 (2019).
19. Sen, A., Jette, N., Husain, M. & Sander, J. W. Epilepsy in older people. *Lancet* **395**, 735–748 (2020).
20. Cretin, B. et al. Epileptic prodromal Alzheimer's disease, a retrospective study of 13 new cases: expanding the spectrum of Alzheimer's disease to an epileptic variant? *J. Alzheimers Dis.* **52**, 1125–1133 (2016).
21. Sen, A., Capelli, V. & Husain, M. Cognition and dementia in older patients with epilepsy. *Brain* **141**, 1592–1608 (2018).
22. Stelzmann, R. A., Schnitzlein, H. N. & Murtagh, F. R. An English translation of Alzheimer's 1907 paper "Über eine eigenartige Erkrankung der Hirnrinde". *Clin. Anat.* **8**, 429–431 (1995).
23. Qiang, W., Yau, W.-M., Lu, J.-X., Collinge, J. & Tycko, R. Structural variation in amyloid-β fibrils from Alzheimer's disease clinical subtypes. *Nature* **541**, 217–221 (2017).
24. Hardy, J. & Higgins, G. Alzheimer's disease: the amyloid cascade hypothesis. *Science* **256**, 184–185 (1992).
25. Menéndez, M. Down syndrome, Alzheimer's disease and seizures. *Brain Dev.* **27**, 246–252 (2005).
26. Vossel, K. A., Tartaglia, M. C., Nygaard, H. B., Zeman, A. Z. & Miller, B. L. Epileptic activity in Alzheimer's disease: causes and clinical relevance. *Lancet Neurol.* **16**, 311–322 (2017).
27. van der Kant, R., Goldstein, L. S. B. & Ossenkoppele, R. Amyloid-β-independent regulators of tau pathology in Alzheimer disease. *Nat. Rev. Neurosci.* **21**, 21–35 (2020).
28. Roberts, R. O. et al. Prevalence and outcomes of amyloid positivity among persons without dementia in a longitudinal, population-based setting. *JAMA Neurol.* **75**, 970–979 (2018).
29. Palop, J. J. & Mucke, L. Amyloid-β-induced neuronal dysfunction in Alzheimer's disease: from synapses toward neural networks. *Nat. Neurosci.* **13**, 812–818 (2010).
30. Hsiao, K. K. et al. Age-related CNS disorder and early death in transgenic FVB/N mice overexpressing Alzheimer amyloid precursor proteins. *Neuron* **15**, 1203–1218 (1995).
31. Leissring, M. A. et al. Enhanced proteolysis of β-amyloid in APP transgenic mice prevents plaque formation, secondary pathology, and premature death. *Neuron* **40**, 1087–1093 (2003).
32. Chin, J. et al. Fyn kinase modulates synaptotoxicity, but not aberrant sprouting, in human amyloid precursor protein transgenic mice. *J. Neurosci.* **24**, 4692–4697 (2004).
33. Jankowsky, J. L. et al. Mutant presenilins specifically elevate the levels of the 42 residue β-amyloid peptide in vivo: evidence for augmentation of a 42-specific γ secretase. *Hum. Mol. Genet.* **13**, 159–170 (2004).
34. Palop, J. J. et al. Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. *Neuron* **55**, 697–711 (2007).
35. Palop, J. J. & Mucke, L. Epilepsy and cognitive impairments in Alzheimer disease. *Arch. Neurol.* **66**, 435–440 (2009).
36. Jankowsky, J. L. & Zheng, H. Practical considerations for choosing a mouse model of Alzheimer's disease. *Mol. Neurodegener.* **12**, 89 (2017).
37. Born, H. A. et al. Genetic suppression of transgenic APP rescues hypersynchronous network activity in a mouse model of Alzheimer's disease. *J. Neurosci.* **34**, 3826–3840 (2014).
38. Gureviciene, I. et al. Characterization of epileptic spiking associated with brain amyloidosis in APP/PS1 mice. *Front. Neurol.* **10**, 1151 (2019).
39. Jin, N., Lipponen, A., Koivisto, H., Gurevicius, K. & Tanila, H. Increased cortical beta power and spike-wave discharges in middle-aged APP/PS1 mice. *Neurobiol. Aging* **71**, 127–141 (2018).
40. Busche, M. A. et al. Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. *Science* **321**, 1686–1689 (2008).
41. Reyes-Marin, K. E. & Nuñez, A. Seizure susceptibility in the APP/PS1 mouse model of Alzheimer's disease and relationship with amyloid β plaques. *Brain Res.* **1677**, 93–100 (2017).
42. Busche, M. A. et al. Critical role of soluble amyloid-β for early hippocampal hyperactivity in a mouse model of Alzheimer's disease. *Proc. Natl Acad. Sci. USA* **109**, 8740–8745 (2012).
43. Shankar, G. M. et al. Amyloid-β protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat. Med.* **14**, 837–842 (2008).
44. Tomiyama, T. et al. A mouse model of amyloid β oligomers: their contribution to synaptic alteration, abnormal tau phosphorylation, glial activation, and neuronal loss in vivo. *J. Neurosci.* **30**, 4845–4856 (2010).
45. Smith, L. M. & Strittmatter, S. M. Binding sites for amyloid-β oligomers and synaptic toxicity. *Cold Spring Harb. Perspect. Med.* **7**, a024075 (2017).
46. Müller-Schiffmann, A. et al. Amyloid-β dimers in the absence of plaque pathology impair learning and synaptic plasticity. *Brain* **139**, 509–525 (2016).
47. Abramov, E. et al. Amyloid-β as a positive endogenous regulator of release probability at hippocampal synapses. *Nat. Neurosci.* **12**, 1567–1576 (2009).
48. Knobloch, M., Konietzko, U., Krebs, D. C. & Nitsch, R. M. Intracellular Aβ and cognitive deficits precede β-amyloid deposition in transgenic arcAβ mice. *Neurobiol. Aging* **28**, 1297–1306 (2007).
49. Ziyatdinova, S. et al. Increased epileptiform EEG activity and decreased seizure threshold in Arctic APP transgenic mouse model of Alzheimer's disease. *Curr. Alzheimer Res.* **13**, 817–830 (2016).
50. Orbán, G. et al. Different electrophysiological actions of 24- and 72-hour aggregated amyloid-beta oligomers on hippocampal field population spike in both anesthetized and awake rats. *Brain Res.* **1354**, 227–235 (2010).
51. Gavello, D. et al. Early alterations of hippocampal neuronal firing induced by Abeta42. *Cereb. Cortex* **28**, 433–446 (2018).
52. Zott, B. et al. A vicious cycle of β amyloid-dependent neuronal hyperactivation. *Science* **365**, 559–565 (2019).
53. Zott, B., Busche, M. A., Sperling, R. A. & Konnerth, A. What happens with the circuit in Alzheimer's disease in mice and humans? *Annu. Rev. Neurosci.* **41**, 277–297 (2018).
54. Cuevas, M. E. et al. Soluble Aβ1-40 peptide increases excitatory neurotransmission and induces epileptiform activity in hippocampal neurons. *J. Alzheimers Dis.* **23**, 673–687 (2011).
55. Lei, M. et al. Soluble Aβ oligomers impair hippocampal LTP by disrupting glutamatergic/GABAergic balance. *Neurobiol. Dis.* **85**, 111–121 (2016).
56. Alcantara-Gonzalez, D., Villasana-Salazar, B. & Peña-Ortega, F. Single amyloid-beta injection exacerbates 4-aminopyridine-induced seizures and changes synaptic coupling in the hippocampus. *Hippocampus* **29**, 1150–1164 (2019).
57. D'Amelio, M. et al. Caspase-3 triggers early synaptic dysfunction in a mouse model of Alzheimer's disease. *Nat. Neurosci.* **14**, 69–79 (2011).
58. Westmark, C. J., Westmark, P. R., Beard, A. M., Hildebrandt, S. M. & Malter, J. S. Seizure susceptibility and mortality in mice that over-express amyloid precursor protein. *Int. J. Clin. Exp. Pathol.* **1**, 157–168 (2008).
59. Kam, K., Duffy, Á. M., Moretto, J., LaFrancois, J. J. & Scharfman, H. E. Interictal spikes during sleep are an early defect in the Tg2576 mouse model

of β-amyloid neuropathology. *Sci. Rep.* **6**, 20119 (2016).
60. Jacobsen, J. S. et al. Early-onset behavioral and synaptic deficits in a mouse model of Alzheimer's disease. *Proc. Natl Acad. Sci. USA* **103**, 5161–5166 (2006).
61. Korzhova, V., Marinković, P., Goltstein, P. M., Herms, J. & Liebscher, S. Long-term dynamics of aberrant neuronal activity in Alzheimer's disease. Preprint at *bioRxiv* https://doi.org/10.1101/801902 (2019).
62. Harris, S. S., Wolf, F., De Strooper, B. & Busche, M. A. Tipping the scales: peptide-dependent dysregulation of neural circuit dynamics in Alzheimer's disease. *Neuron* **107**, 417–435 (2020).
63. Kamenetz, F. et al. APP processing and synaptic function. *Neuron* **37**, 925–937 (2003).
64. Sima, X., Xu, J., Li, J., Zhong, W. & You, C. Expression of β-amyloid precursor protein in refractory epilepsy. *Mol. Med. Rep.* **9**, 1242–1248 (2014).
65. Roberson, E. D. et al. Reducing endogenous tau ameliorates amyloid β-induced deficits in an Alzheimer's disease mouse model. *Science* **316**, 750–754 (2007).
66. Busche, M. A. et al. Tau impairs neural circuits, dominating amyloid-β effects, in Alzheimer models in vivo. *Nat. Neurosci.* **22**, 57–64 (2019).
67. Busche, M. A. & Hyman, B. T. Synergy between amyloid-β and tau in Alzheimer's disease. *Nat. Neurosci.* **23**, 1183–1193 (2020).
68. Johnson, E. C. B. et al. Behavioral and neural network abnormalities in human APP transgenic mice resemble those of App knock-in mice and are modulated by familial Alzheimer's disease mutations but not by inhibition of BACE1. *Mol. Neurodegener.* **15**, 53 (2020).
69. Bakker, A. et al. Reduction of hippocampal hyperactivity improves cognition in amnestic mild cognitive impairment. *Neuron* **74**, 467–474 (2012).
70. Sarkis, R. A., Willment, K. C., Pennell, P. B. & Marshall, G. Late-onset unexplained epilepsy: what are we missing? *Epilepsy Behav.* **99**, 106478 (2019).
71. Garg, N., Joshi, R. & Medhi, B. Cracking novel shared targets between epilepsy and Alzheimer's disease: need of the hour. *Rev. Neurosci.* **29**, 425–442 (2018).
72. Born, H. A. Seizures in Alzheimer's disease. *Neuroscience* **286**, 251–263 (2015).
73. Kazim, S. F. et al. Early-onset network hyperexcitability in presymptomatic Alzheimer's disease transgenic mice is suppressed by passive immunization with anti-human APP/Aβ antibody and by mGluR5 blockade. *Front. Aging Neurosci.* **9**, 71 (2017).
74. Nygaard, H. B. et al. Brivaracetam, but not ethosuximide, reverses memory impairments in an Alzheimer's disease mouse model. *Alzheimers Res. Ther.* **7**, 25 (2015).
75. Zhang, M. Y. et al. Lamotrigine attenuates deficits in synaptic plasticity and accumulation of amyloid plaques in APP/PS1 transgenic mice. *Neurobiol. Aging* **35**, 2713–2725 (2014).
76. Ziyatdinova, S. et al. Spontaneous epileptiform discharges in a mouse model of Alzheimer's disease are suppressed by antiepileptic drugs that block sodium channels. *Epilepsy Res.* **94**, 75–85 (2011).
77. 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. USA* **109**, E2895–E2903 (2012).
78. Verret, L. et al. Inhibitory interneuron deficit links altered network activity and cognitive dysfunction in alzheimer model. *Cell* **149**, 708–721 (2012).
79. Ziyatdinova, S., Viswanathan, J., Hiltunen, M., Tanila, H. & Pitkänen, A. Reduction of epileptiform activity by valproic acid in a mouse model of Alzheimer's disease is not long-lasting after treatment discontinuation. *Epilepsy Res.* **112**, 43–55 (2015).
80. Toniolo, S., Sen, A. & Husain, M. Modulation of brain hyperexcitability: potential new therapeutic approaches in Alzheimer's disease. *Int. J. Mol. Sci.* **21**, 1–37 (2020).
81. Romoli, M. et al. Synaptic vesicle protein 2A tumoral expression predicts levetiracetam adverse events. *J. Neurol.* **266**, 2273–2276 (2019).
82. Chakroborty, S., Kim, J., Schneider, C., West, A. R. & Stutzmann, G. E. Nitric oxide signaling is recruited as a compensatory mechanism for sustaining synaptic plasticity in Alzheimer's disease mice. *J. Neurosci.* **35**, 6893–6902 (2015).
83. Demuro, A., Parker, I. & Stutzmann, G. E. Calcium signaling and amyloid toxicity in Alzheimer disease. *J. Biol. Chem.* **285**, 12463–12468 (2010).
84. Bezprozvanny, I. & Mattson, M. P. Neuronal calcium mishandling and the pathogenesis of Alzheimer's disease. *Trends Neurosci.* **31**, 454–463 (2008).
85. Leal, S. L., Landau, S. M., Bell, R. K. & Jagust, W. J. Hippocampal activation is associated with longitudinal amyloid accumulation and cognitive decline. *eLife* **6**, e22978 (2017).
86. Shi, J. Q. et al. Antiepileptics topiramate and levetiracetam alleviate behavioral deficits and reduce neuropathology in APPswe/PS1dE9 transgenic mice. *CNS Neurosci. Ther.* **19**, 871–881 (2013).
87. Sendrowski, K., Sobaniec, W., Stasiak-Barmuta, A., Sobaniec, P. & Popko, J. Study of the protective effects of nootropic agents against neuronal damage induced by amyloid-beta (fragment 25-35) in cultured hippocampal neurons. *Pharmacol. Rep.* **67**, 326–331 (2015).
88. Sanz-Blasco, S., Piña-Crespo, J. C., Zhang, X., McKercher, S. R. & Lipton, S. A. Levetiracetam inhibits oligomeric Aβ-induced glutamate release from human astrocytes. *Neuroreport* **27**, 705–709 (2016).
89. Williams, R. S. B. & Bate, C. Valproic acid and its congener propylisopropylacetic acid reduced the amount of soluble amyloid-β oligomers released from 7PA2 cells. *Neuropharmacology* **128**, 54–62 (2018).
90. Wu, H. et al. Lamotrigine reduces β-site AβPP-cleaving enzyme 1 protein levels through induction of autophagy. *J. Alzheimers Dis.* **46**, 863–876 (2015).
91. Li, L. et al. Autophagy enhancer carbamazepine alleviates memory deficits and cerebral amyloid-β pathology in a mouse model of Alzheimer's disease. *Curr. Alzheimer Res.* **10**, 433–441 (2013).
92. Mark, R. J., Ashford, J. W., Goodman, Y. & Mattson, M. P. Anticonvulsants attenuate amyloid β-peptide neurotoxicity, $Ca^{2+}$ deregulation and cytoskeletal pathology. *Neurobiol. Aging* **16**, 187–198 (1995).
93. French, J. A. & Perucca, E. Time to start calling things by their own names? The case for antiseizure medicines. *Epilepsy Curr.* **20**, 69–72 (2020).
94. Cirrito, J. R. et al. Endocytosis is required for synaptic activity-dependent release of amyloid-β in vivo. *Neuron* **58**, 42–51 (2008).
95. Bero, A. W. et al. Neuronal activity regulates the regional vulnerability to amyloid-β deposition. *Nat. Neurosci.* **14**, 750–756 (2011).
96. Yamamoto, K. et al. Chronic optogenetic activation augments aβ pathology in a mouse model of Alzheimer disease. *Cell Rep.* **11**, 859–865 (2015).
97. Naegele, J. R. Neuroprotective strategies to avert seizure-induced neurodegeneration in epilepsy. *Epilepsia* **48**, 107–117 (2007).
98. Sen, A. & Romoli, M. Pathological brain ageing in epilepsy and dementia: two sides of the same coin? *Brain* **144**, 9–11 (2021).
99. Mendez, M. F. & Lim, G. T. H. Seizures in elderly patients with dementia: epidemiology and management. *Drugs Aging* **20**, 791–803 (2003).
100. Hauser, W. A., Morris, M. L., Heston, L. L. & Anderson, V. E. Seizures and myoclonus in patients with Alzheimer's disease. *Neurology* **36**, 1226–1226 (1986).
101. Romanelli, M. F., Morris, J. C., Ashkin, K. & Coben, L. A. Advanced Alzheimer's disease is a risk factor for late-onset seizures. *Arch. Neurol.* **47**, 847–850 (1990).
102. Volicer, L., Smith, S. & Volicer, B. J. Effect of seizures on progression of dementia of the Alzheimer type. *Dementia* **6**, 258–263 (1995).
103. McAreavey, M. J., Ballinger, B. R. & Fenton, G. W. Epileptic seizures in elderly patients with dementia. *Epilepsia* **33**, 657–660 (1992).
104. Amatniek, J. C. et al. Incidence and predictors of seizures in patients with Alzheimer's disease. *Epilepsia* **47**, 867–872 (2006).
105. Cheng, C.-H. et al. Incidence and risk of seizures in Alzheimer's disease: a nationwide population-based cohort study. *Epilepsy Res.* **115**, 63–66 (2015).
106. Larner, A. J. Epileptic seizures in AD patients. *Neuromolecular Med.* **12**, 71–77 (2010).
107. Subota, A. et al. The association between dementia and epilepsy: a systematic review and meta-analysis. *Epilepsia* **58**, 962–972 (2017).
108. Cortini, F., Cantoni, C. & Villa, C. Epileptic seizures in autosomal dominant forms of Alzheimer's disease. *Seizure* **61**, 4–7 (2018).
109. Larner, A. J. & Doran, M. Clinical phenotypic heterogeneity of Alzheimer's disease associated with mutations of the presenilin-1 gene. *J. Neurol.* **253**, 139–158 (2006).
110. Zarea, A. et al. Seizures in dominantly inherited Alzheimer disease. *Neurology* **87**, 912–919 (2016).
111. Cabrejo, L. et al. Phenotype associated with APP duplication in five families. *Brain* **129**, 2966–2976 (2006).
112. Edwards-Lee, T. et al. An African American family with early-onset Alzheimer disease and an APP (T714I) mutation. *Neurology* **64**, 377–379 (2005).
113. Lindquist, S. G. et al. Atypical early-onset Alzheimer's disease caused by the Iranian APP mutation. *J. Neurol. Sci.* **268**, 124–130 (2008).
114. Lott, I. T. et al. Down syndrome and dementia: seizures and cognitive decline. *J. Alzheimers Dis.* **29**, 177–185 (2012).
115. Ryan, N. S. et al. Clinical phenotype and genetic associations in autosomal dominant familial Alzheimer's disease: a case series. *Lancet Neurol.* **15**, 1326–1335 (2016).
116. Jayadev, S. et al. Alzheimer's disease phenotypes and genotypes associated with mutations in presenilin 2. *Brain* **133**, 1143–1154 (2010).
117. Liu, J. et al. Diagnostic approach of early-onset dementia with negative family history: implications from two cases of early-onset Alzheimer's disease with de novo PSEN1 mutation. *J. Alzheimers Dis.* **68**, 551–558 (2019).
118. Mucke, L. & Selkoe, D. J. Neurotoxicity of Amyloid β-protein: synaptic and network dysfunction. *Cold Spring Harb. Perspect. Med.* **2**, a006338 (2012).
119. 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* **34**, 939–939 (1984).
120. Samson, W. N., van Duijn, C. M., Hop, W. C. J. & Hofman, A. Clinical features and mortality in patients with early-onset Alzheimer's disease. *Eur. Neurol.* **36**, 103–106 (1996).
121. Lozsadi, D. A. & Larner, A. J. Prevalence and causes of seizures at the time of diagnosis of probable Alzheimer's disease. *Dement. Geriatr. Cogn. Disord.* **22**, 121–124 (2006).
122. Scarmeas, N. et al. Seizures in Alzheimer disease: who, when, and how common? *Arch. Neurol.* **66**, 992–997 (2009).
123. Rao, S. C., Dove, G., Cascino, G. D. & Petersen, R. C. Recurrent seizures in patients with dementia: frequency, seizure types, and treatment outcome. *Epilepsy Behav.* **14**, 118–120 (2009).
124. Vossel, K. A. et al. Seizures and epileptiform activity in the early stages of Alzheimer disease. *JAMA Neurol.* **70**, 1158–1166 (2013).
125. Sarkis, R. A., Willment, K. C., Gale, S. A. & Dworetzky, B. A. Recurrent epileptic auras as a presenting symptom of Alzheimer's disease. *Front. Neurol.* **8**, 360 (2017).
126. Difrancesco, J. C. et al. Adult-onset epilepsy in presymptomatic Alzheimer's disease: a retrospective study. *J. Alzheimers Dis.* **60**, 1267–1274 (2017).
127. Sarkis, R. A., Dickerson, B. C., Cole, A. J. & Chemali, Z. N. Clinical and neurophysiologic characteristics of unprovoked seizures in patients diagnosed with dementia. *J. Neuropsychiatry Clin. Neurosci.* **28**, 56–61 (2016).
128. Vossel, K. A. et al. Incidence and impact of subclinical epileptiform activity in Alzheimer's disease. *Ann. Neurol.* **80**, 858–870 (2016).
129. Horváth, A., Szcs, A., Barcs, G. & Kamondi, A. Sleep EEG detects epileptiform activity in Alzheimer's disease with high sensitivity. *J. Alzheimers Dis.* **56**, 1175–1183 (2017).
130. Sen, A. & Husain, M. Reply: Late onset epilepsy and Alzheimer's disease: exploring the dual pathogenic role of amyloid-β. *Brain* **141**, e61–e61 (2018).
131. Breteler, M. M. et al. Medical history and the risk of Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *Int. J. Epidemiol.* **20** (Suppl. 2), S36–S42 (1991).
132. Breteler, M. M. B., De Groot, R. R. M., Van Romunde, L. K. J. & Hofman, A. Risk of dementia in patients with Parkinson's disease, epilepsy, and severe head trauma: a register-based follow-up study. *Am. J. Epidemiol.* **142**, 1300–1305 (1995).

133. French, L. R. et al. A case-control study of dementia of the Alzheimer type. *Am. J. Epidemiol.* **121**, 414–421 (1985).
134. Broe, G. A. et al. A case-control study of Alzheimer's disease in Australia. *Neurology* **40**, 1698–1698 (1990).
135. Shalat, S. L., Seltzer, B., Pidcock, C. & Baker, E. L. Risk factors for Alzheimer's disease: a case-control study. *Neurology* **37**, 1630–1633 (1987).
136. Hofman, A. et al. History of dementia and Parkinson's disease in 1st-degree relatives of patients with Alzheimer's disease. *Neurology* **39**, 1589–1592 (1989).
137. Kokmen, E. et al. Clinical risk factors for Alzheimer's disease: a population-based case-control study. *Neurology* **41**, 1393–1397 (1991).
138. Tsai, Z.-R. et al. Late-onset epilepsy and subsequent increased risk of dementia. *Aging* **13**, 3573–3587 (2021).
139. Johnson, E. L. et al. Dementia in late-onset epilepsy: the Atherosclerosis Risk in Communities study. *Neurology* **95**, e3248–e3256 (2020).
140. Piazzini, A., Canevini, M. P., Turner, K., Chifari, R. & Canger, R. Elderly people and epilepsy: cognitive function. *Epilepsia* **47**, 82–84 (2006).
141. Griffith, H. R., Martin, R. C., Bambara, J. K., Marson, D. C. & Faught, E. Older adults with epilepsy demonstrate cognitive impairments compared with patients with amnestic mild cognitive impairment. *Epilepsy Behav.* **8**, 161–168 (2006).
142. Martin, R. C. et al. Cognitive functioning in community dwelling older adults with chronic partial epilepsy. *Epilepsia* **46**, 298–303 (2005).
143. Acharya, J. & Acharya, V. Epilepsy in the elderly: special considerations and challenges. *Ann. Indian Acad. Neurol.* **17**, S18–S26 (2014).
144. Johnson, E. L. et al. Association between midlife risk factors and late-onset epilepsy: results from the Atherosclerosis Risk in Communities study. *JAMA Neurol.* **75**, 1375–1382 (2018).
145. Johnson, E. L. et al. Association between white matter hyperintensities, cortical volumes, and late-onset epilepsy. *Neurology* **92**, E988–E995 (2019).
146. Kawakami, O. et al. Incidence of dementia in patients with adult-onset epilepsy of unknown causes. *J. Neurol. Sci.* **395**, 71–76 (2018).
147. Witt, J. A. et al. Cognitive-behavioral screening in elderly patients with new-onset epilepsy before treatment. *Acta Neurol. Scand.* **130**, 172–177 (2014).
148. Babiloni, C. et al. Cortical sources of resting state EEG rhythms are sensitive to the progression of early stage Alzheimer's disease. *J. Alzheimers Dis.* **34**, 1015–1035 (2013).
149. Kawakami, O. et al. Is adult onset epilepsy of unknown cause a predictor of Alzheimer disease? [abstract]. *J. Neurol. Sci.* **381** (Suppl.), 545 (2017).
150. Joutsa, J. et al. Association between childhood-onset epilepsy and amyloid burden 5 decades later. *JAMA Neurol.* **74**, 583–590 (2017).
151. Joutsa, J. et al. Brain glucose metabolism and its relation to amyloid load in middle-aged adults with childhood-onset epilepsy. *Epilepsy Res.* **137**, 69–72 (2017).
152. Carter, M. D., Weaver, D. F., Joudrey, H. R., Carter, A. O. & Rockwood, K. Epilepsy and antiepileptic drug use in elderly people as risk factors for dementia. *J. Neurol. Sci.* **252**, 169–172 (2007).
153. Tariot, P. N. et al. Chronic divalproex sodium to attenuate agitation and clinical progression of Alzheimer disease. *Arch. Gen. Psychiatry* **68**, 853–861 (2011).
154. Fleisher, A. S., Truran, D., Langbaum, J. B. S., Weiner, M. W. & Schneider, L. S. Chronic divalproex sodium use and brain atrophy in Alzheimer disease. *Neurology* **77**, 1263–1272 (2011).
155. Liguori, C. et al. Cognitive performances in patients affected by late-onset epilepsy with unknown etiology: a 12-month follow-up study. *Epilepsy Behav.* **101**, 106592 (2019).
156. De Groot, M. et al. Levetiracetam improves verbal memory in high-grade glioma patients. *Neuro Oncol.* **15**, 216–223 (2013).
157. Kern, D. M., Cepeda, M. S., Lovestone, S. & Seabrook, G. R. Aiding the discovery of new treatments for dementia by uncovering unknown benefits of existing medications. *Alzheimers Dement.* **5**, 862–870 (2019).
158. Cumbo, E. & Ligori, L. D. Levetiracetam, lamotrigine, and phenobarbital in patients with epileptic seizures and Alzheimer's disease. *Epilepsy Behav.* **17**, 461–466 (2010).
159. Bakker, A., Albert, M. S., Krauss, G., Speck, C. L. & Gallagher, M. Response of the medial temporal lobe network in amnestic mild cognitive impairment to therapeutic intervention assessed by fMRI and memory task performance. *Neuroimage Clin.* **7**, 688–698 (2015).
160. Tambasco, N., Romoli, M. & Calabresi, P. Selective basal ganglia vulnerability to energy deprivation: experimental and clinical evidences. *Prog. Neurobiol.* **169**, 55–75 (2018).
161. Hamilton, L. K. et al. Widespread deficits in adult neurogenesis precede plaque and tangle formation in the 3xTg mouse model of Alzheimer's disease. *Eur. J. Neurosci.* **32**, 905–920 (2010).
162. Griffith, H. R. et al. Cognitive functioning over 3 years in community dwelling older adults with chronic partial epilepsy. *Epilepsy Res.* **74**, 91–96 (2007).
163. Miller, L. A. et al. Cognitive impairment in older adults with epilepsy: characterization and risk factor analysis. *Epilepsy Behav.* **56**, 113–117 (2016).
164. Kasai, T. et al. Aβ levels in the jugular vein and high molecular weight Aβ oligomer levels in CSF can be used as biomarkers to indicate the anti-amyloid effect of IVIg for Alzheimer's disease. *PLoS ONE* **12**, e0174630 (2017).
165. Lewczuk, P. et al. Validation of the Erlangen Score algorithm for the prediction of the development of dementia due to Alzheimer's disease in pre-dementia subjects. *J. Alzheimers Dis.* **48**, 433–441 (2015).
166. Selkoe, D. J. Alzheimer disease and aducanumab: adjusting our approach. *Nat. Rev. Neurol.* **15**, 365–366 (2019).
167. Insel, P. S. et al. Accelerating rates of cognitive decline and imaging markers associated with β-amyloid pathology. *Neurology* **86**, 1887–1896 (2016).
168. Harrington, K. D. et al. Amyloid β-associated cognitive decline in the absence of clinical disease progression and systemic illness. *Alzheimers Dement.* **8**, 156–164 (2017).
169. Hanseeuw, B. J. et al. Association of amyloid and tau with cognition in preclinical Alzheimer disease: a longitudinal study. *JAMA Neurol.* **76**, 915–924 (2019).
170. Insel, P. S., Hansson, O., Mackin, R. S., Weiner, M. & Mattsson, N. Amyloid pathology in the progression to mild cognitive impairment. *Neurobiol. Aging* **64**, 76–84 (2018).
171. Lim, E. W. et al. Amyloid-β and Parkinson's disease. *J. Neurol.* **266**, 2605–2619 (2019).
172. Siderowf, A. et al. CSF amyloid β 1-42 predicts cognitive decline in Parkinson disease. *Neurology* **75**, 1055–1061 (2010).
173. Parnetti, L. et al. Cerebrospinal fluid biomarkers in Parkinson's disease with dementia and dementia with Lewy bodies. *Biol. Psychiatry* **64**, 850–855 (2008).
174. Blennow, K., Biscetti, L., Eusebi, P. & Parnetti, L. Cerebrospinal fluid biomarkers in Alzheimer's and Parkinson's diseases — from pathophysiology to clinical practice. *Mov. Disord.* **31**, 836–847 (2016).
175. Edison, P. et al. Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [$^{11}$C]PIB positron emission tomography. *J. Neurol. Neurosurg. Psychiatry* **79**, 1331–1338 (2008).
176. Calabresi, P., Picconi, B., Parnetti, L. & Di Filippo, M. A convergent model for cognitive dysfunctions in Parkinson's disease: the critical dopamine-acetylcholine synaptic balance. *Lancet Neurol.* **5**, 974–983 (2006).
177. Nedelska, Z. et al. Association of longitudinal β-amyloid accumulation determined by positron emission tomography with clinical and cognitive decline in adults with probable Lewy body dementia. *JAMA Netw. Open* **2**, e1916439 (2019).
178. Zwan, M. D. et al. Subjective memory complaints in APOE ε4 carriers are associated with high amyloid-β burden. *J. Alzheimers Dis.* **49**, 1115–1122 (2015).
179. Perrotin, A., Mormino, E. P., Madison, C. M., Hayenga, A. O. & Jagusr, W. J. Subjective cognition and amyloid deposition imaging: a Pittsburgh Compound B positron emission tomography study in normal elderly individuals. *Arch. Neurol.* **69**, 223–229 (2012).
180. Rodrigue, K. M. et al. β-Amyloid burden in healthy aging: regional distribution and cognitive consequences. *Neurology* **78**, 387–395 (2012).
181. Svenningsson, A. L. et al. β-Amyloid pathology and hippocampal atrophy are independently associated with memory function in cognitively healthy elderly. *Sci. Rep.* **9**, 11180 (2019).
182. van Oijen, M., Hofman, A., Soares, H. D., Koudstaal, P. J. & Breteler, M. M. Plasma Aβ1-40 and Aβ1-42 and the risk of dementia: a prospective case-cohort study. *Lancet Neurol.* **5**, 655–660 (2006).
183. Keskin, A. D. et al. BACE inhibition-dependent repair of Alzheimer's pathophysiology. *Proc. Natl Acad. Sci. USA* **114**, 8631–8636 (2017).
184. Das, M. et al. Neuronal levels and sequence of tau modulate the power of brain rhythms. *Neurobiol. Dis.* **117**, 181–188 (2018).
185. Gourmaud, S. et al. Alzheimer-like amyloid and tau alterations associated with cognitive deficit in temporal lobe epilepsy. *Brain* **143**, 191–209 (2020).
186. Tai, X. Y. et al. Hyperphosphorylated tau in patients with refractory epilepsy correlates with cognitive decline: a study of temporal lobe resections. *Brain* **139**, 2441–2455 (2016).
187. Kaestner, E. et al. Atrophy and cognitive profiles in older adults with temporal lobe epilepsy are similar to mild cognitive impairment. *Brain* **144**, 236–250 (2021).
188. Roberson, E. D. et al. Amyloid-/Fyn-induced synaptic, network, and cognitive impairments depend on tau levels in multiple mouse models of Alzheimer's disease. *J. Neurosci.* **31**, 700–711 (2011).
189. Angulo, S. L. et al. Tau and amyloid-related pathologies in the entorhinal cortex have divergent effects in the hippocampal circuit. *Neurobiol. Dis.* **108**, 261–276 (2017).
190. Vossel, K. A. et al. Tau reduction prevents Aβ-induced axonal transport deficits by blocking activation of GSK3β. *J. Cell Biol.* **209**, 419–433 (2015).
191. Chabrier, M. A., Cheng, D., Castello, N. A., Green, K. N. & LaFerla, F. M. Synergistic effects of amyloid-beta and wild-type human tau on dendritic spine loss in a floxed double transgenic model of Alzheimer's disease. *Neurobiol. Dis.* **64**, 107–117 (2014).
192. Laurén, J., Gimbel, D. A., Nygaard, H. B., Gilbert, J. W. & Strittmatter, S. M. Cellular prion protein mediates impairment of synaptic plasticity by amyloid-β oligomers. *Nature* **457**, 1128–1132 (2009).
193. Um, J. W. et al. Metabotropic glutamate receptor 5 is a coreceptor for Alzheimer aβ oligomer bound to cellular prion protein. *Neuron* **79**, 887–902 (2013).
194. Um, J. W. et al. Alzheimer amyloid-β oligomer bound to postsynaptic prion protein activates Fyn to impair neurons. *Nat. Neurosci.* **15**, 1227–1235 (2012).
195. Romoli, M., Perucca, E. & Sen, A. Pyridoxine supplementation for levetiracetam-related neuropsychiatric adverse events: a systematic review. *Epilepsy Behav.* **103**, 106861 (2020).
196. Foster, E. et al. Antiepileptic drugs are not independently associated with cognitive dysfunction. *Neurology* **94**, e1051–e1061 (2020).
197. Romoli, M. et al. Antiepileptic drugs in migraine and epilepsy: who is at increased risk of adverse events? *Cephalalgia* **38**, 274–282 (2018).
198. Belcastro, V. et al. Levetiracetam monotherapy in Alzheimer patients with late-onset seizures: a prospective observational study. *Eur. J. Neurol.* **14**, 1176–1178 (2007).
199. Liu, J., Wang, L. N., Wu, L. Y. & Wang, Y. P. Treatment of epilepsy for people with Alzheimer's disease. *Cochrane Database Syst. Rev.* **12**, CD011922 (2018).
200. Lezaic, N. et al. The medical treatment of epilepsy in the elderly: a systematic review and meta-analysis. *Epilepsia* **60**, 1325–1340 (2019).
201. Romoli, M. et al. Valproic acid and epilepsy: from molecular mechanisms to clinical evidences. *Curr. Neuropharmacol.* **17**, 926–946 (2019).
202. Perucca, E. Pharmacological and therapeutic properties of valproate: a summary after 35 years of clinical experience. *CNS Drugs* **16**, 695–714 (2002).
203. Read, C. L. et al. Cognitive effects of anticonvulsant monotherapy in elderly patients: a placebo-controlled study. *Seizure* **7**, 159–162 (1998).
204. Romoli, M. et al. Liverpool Adverse Events Profile: Italian validation and predictive value for dropout from antiepileptic treatment in people with epilepsy. *Epilepsy Behav.* **81**, 111–114 (2018).
205. Panelli, R. J. et al. The Liverpool Adverse Events Profile: relation to AED use and mood. *Epilepsia* **48**, 456–463 (2007).



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**Review criteria**
We selected references by searching PubMed, EMBASE and Cochrane CENTRAL for articles published in English before 1 February 2021, the main search string being "Alzheimer disease" or "cognitive decline", and "late onset epilepsy". Assorted combinations of the following terms were used to retrieve all papers: "epilepsy", "late onset epilepsy", "seizures", "epileptiform activity", "network hyperexcitability", "epileptogenesis", "epileptogenic", "antiepileptic drugs", "antiseizure medications", "anticonvulsants", "dementia", "amyloid", "amyloid precursor protein" or "APP", "presenilin" or "PSEN". We reviewed reference lists within original research and review articles for additional references through backward citation search. We finalized the reference list on the basis of originality and relevance to the scope of this Review. We focused on scientific literature in the English language published from 1990 onwards, but also included older publications of high value, merit or originality.