REVIEW **OPEN ACCESS**

Epilepsy and Alzheimer Disease

Epidemiologic, Clinical, Molecular, and Neuropathologic Convergences and Divergences

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Abstract

Purpose of Review

Alzheimer disease (AD) and epilepsy are major causes of neurologic disability and are reciprocally related: epileptiform discharges, subclinical seizures, and epilepsy are more prevalent in patients with AD compared with controls; progressive cognitive impairment commonly afflicts epilepsy patients; and late-onset epilepsy patients have higher rates of new-onset dementia.

Recent Findings

Epidemiologic studies support shared risk factors (e.g., genetic variants, vascular disease, sleep disorders, microbiome) with notable divergences. AD and epilepsy have some overlapping anatomic (e.g., hippocampus, entorhinal, and association cortex), clinical (e.g., memory, attentional, and executive) impairments, and neuropathologic (e.g., amyloid, tau, neurofibrillary tangles) features. Shared clinical and translational challenges include underlying mechanisms (e.g., genetic variants, neuroinflammation, metabolic and mitochondrial dysfunction, excitatory/inhibitory imbalance, microbiome, and sociodemographic factors) and identifying valid and reliable biomarkers (e.g., total tau and phosphorylated tau (p-tau), amyloid deposition, Aβ42/Aβ40 ratio) to assess disease progression, predict outcomes, and assess potentially disease-modifying interventions.

Summary

Identifying convergences and divergences between epilepsy and AD may inform our understanding. The clinical, neurophysiologic, neuropathologic, and molecular pathologic changes in AD and epilepsy may reveal pathophysiologic insights and therapeutic opportunities.

Epidemiology and Risk Factors

The incidences of Alzheimer disease (AD) and epilepsy rise after 65 years, with the sharpest rise after 75 years.[1,2] The number of US adults who will develop AD and related dementias (ADRD) will increase from ∼514,000 in 2020 to ∼1,000,000 in 2060.[1] Globally, there are ∼416 million people with prodromal, preclinical, or clinical AD; >20% of people were 50 years or older.[3] By contrast, ∼1.5% of people older than 65 years have epilepsy.[2]

Epilepsy and AD are reciprocally related. Epilepsy can cause progressive cognitive impairment[4]; epilepsy patients who are 65 years or older (elderly) have increased rates of memory, executive, language, attention, and dementia[4,]. Among the elderly, cardiovascular disease is the most common cause of new-onset epilepsy (49%), followed by dementia (12%; AD–7%, other dementias–5%).[4] Among patients with AD, the frequency of at least 1 unprovoked seizures range from 1.5% to 31.3%,[5] with most studies finding rates of 10%–22%.[6] Higher

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rates have been observed in early-onset AD,[5] African Americans,[7] advanced stages of AD, and with focal epileptiform discharges.[7] AD patients with epilepsy are less frequent than those with seizures, among those with AD onset before 65 years, epilepsy occurs in up to 40% of populations studied across their lifespan of AD together with prolonged EEG including non-REM sleep.[8] Epilepsy in patients with AD predicts a more severe course and more rapid cognitive decline.[9]

Epilepsy and AD share genetic risk factors. A polymorphism of the *apolipoprotein E* $APOE^{\varepsilon 4}$ allele is the major genetic risk factor for sporadic AD, leading to accumulation of amyloid-beta (Aβ) plaques.[7] *APOE* is a multifunctional gene that influences not only lipid metabolism and cardiovascular health but also plays a critical role in brain health and potentially immune responses. *APOE* isoforms differentially regulate synaptic plasticity and repair. Compared with the common $APOE^{\varepsilon 3}$, the $APOE^{\varepsilon 4}$ is associated with a dose-dependent (2 > 1 > no $APOE^{\varepsilon 4}$ alleles higher risk) risk for AD and earlier AD onset.[10] The less common $APOE^{\varepsilon 2}$ protects against AD.[10] Temporal lobe epilepsy (TLE) patients with long epilepsy durations and an $APOE^{\varepsilon 4}$ allele had the poorest verbal and nonverbal memory,[11] supporting shared vulnerabilities for cognitive impairment in AD and TLE patients. $APOE^{\varepsilon 4}$ is a dose-dependent risk factor for late-onset epilepsy (LOE; >60 years).[12] A mendelian randomization study linked AD and amyloid pathology with generalized epilepsy and focal epilepsy with hippocampal sclerosis.[13]

The Framingham Heart Study (FHS) supports that epilepsy, dementia, and stroke are comorbid disorders. FHS participants with lower executive function and attention measures, and a greater white matter hyperintensity volumes had an increased risk of developing epilepsy (see below).[14] For elderly FHS subjects, new onset of epilepsy was 1.8-fold more frequent in those with vs without dementia. New onset of dementia was 2.0-fold greater in epilepsy patients. Among post high school educated individuals, those with epilepsy had a 4.7-fold greater risk of developing dementia.[15] Hypertension increased late-onset epilepsy risk 2.0–2.5-fold; risk persisted after controlling for strokes. Hypertension may increase new-onset epilepsy risk in older adults independent of stroke through microvascular disease or hypertension-related disorders (e.g., metabolic syndrome and diabetes) that are independent risk factors for dementia. However, in the FHS, vascular risk factors (e.g., diabetes, hyperlipidemia, smoking) did not predict the risk of new-onset epilepsy. Elderly subjects have higher rates of microvascular and vascular disease, antiseizure medication (ASM) use, and sleep disorders. Stroke and dementia can cause epilepsy, and ASMs can contribute to cognitive impairments.[16]

Patients with AD have reduced sleep efficiency, slow-wave sleep (SWS), and REM sleep duration.[17,18] Decreased SWS and REM sleep are significantly correlated with lower Mini Mental Status Exam scores, indicating links between sleep disruption and cognitive decline.[17] Non-REM sleep and reduced REM sleep promote hyperexcitability.[19] Sleep spindle[20] reduction, particularly in fast spindles, is linked to worse cognitive performance. Sleep disturbances may both result from and contribute to AD progression, reflecting a bidirectional relationship.[21] Neuroinflammation may mediate the relationship between poor sleep and increased AD risk by promoting amyloid-β accumulation[22]

Epilepsy, AD, vascular disease, ASMs, sleep and mood disorders, and other factors (e.g., genetics, neuroinflammation, microbiome, nutritional toxicities [e.g., advanced glycation end-products], sarcopenia and frailty, chronic stress, loneliness) share complex relations.[23,24] Diagnostic challenges make it difficult to determine the frequency of undiagnosed or subclinical epilepsy in healthy elderly and AD populations (see below).[4,16]

Clinical Features of Epilepsy and Epileptiform Activity in AD

Epilepsy and epileptiform activity are common comorbidities of AD. Epilepsy develops in up to a third of patients with AD[8] but often goes undiagnosed unless the patient's family recognizes focal aware or unaware seizures or the patient undergoes a prolonged EEG that records sleep.

Clinical seizures in patients with AD are usually (~65%) focal, often presenting with impaired awareness, while progression of focal to bilateral tonic-clonic seizures is infrequent, usually seen only as neurodegeneration advances.[4,8,13,16] Seizures primarily originate from temporal and frontal regions, often left-sided. Left-sided predominance in epileptiform discharges occurs across the age spectrum but is most prominent in older individuals, especially older than 80 years[25] The biological basis for this asymmetry remains unknown. Routine electroencephalograms (EEGs; 20–30 minutes) in AD patients with epilepsy rarely detect interictal epileptiform discharges (IEDs). IEDs are paroxysmal, background-disrupting ms spikes (20–70 ms) and sharp waves (70–200 ms), usually but not always, followed by a slow wave which are observed in patients with a history of seizures. However, in patients with AD, prolonged (e.g., >8 hours) EEGs including sleep are far more likely to detect electroclinical and electrographic nonmotor seizures as well as IEDs.[26] IEDs are most prevalent over the left temporal region during early non-REM sleep, and IED frequency correlates with seizure frequency.[27] In early AD, the EEG is often normal, but focal slowing often develops as the disease progresses. Temporal intermittent rhythmic delta activity supports a potential temporal lobe seizure focus. Seizure incidence increases with dementia severity, and seizure frequency is associated with accelerated cognitive deterioration.[9] Compared with AD patients without epilepsy, those with epilepsy have earlier onset and longer dementia durations and greater visuo-spatial impairments.[28]

The AD pathologic proteins, Aβ and pTau, may induce neuronal hyperexcitability or hypoexcitability,[26] as early hyperexcitability evolving into hypoexcitability as the disease progresses, although effects on seizure threshold can vary based on relative impact on inhibitory vs excitatory neural networks. In AD, pathologic proteins can accumulate 15–20 years before mild cognitive impairment (MCI) symptoms develop[29]; hyperexcitability may develop during this early phase. Higher PET amyloid and tau burdens occur in the hemisphere where seizures originate, linking seizure foci with amyloid and tau deposition (Figure 1).[30]

It remains uncertain how many patients without cognitive symptoms who meet fluid biomarker-based diagnostic criteria of AD have pathologic brain hyperexcitability. Subclinical epileptiform activity (SEA) is a proxy for hyperexcitability. SEAs are IEDs that may be undetectable on scalp EEG. In 2 patients with AD, prominent epileptiform activity including “silent seizures” were detected with foramen ovale electrodes, while the scalp EEG showed no alterations.[31] SEA are often lower in amplitude than classical IEDs and may lack an after going slow wave. SEAs have a more subtle morphology than most IEDs and are definitionally limited to people without a history of seizures, while IEDs occur in patients with epilepsy (i.e., interictal implies a finding between seizures). SEAs occur in 10%–25% of cognitively healthy older adults,[32] in whom amyloid/tau status is unknown, but may include subjects with stage 1 AD (normal cognition/positive amyloid or tau PET or CSF). Neuronal hyperexcitability (i.e., increased excitability:inhibitory (E:I) balance) can manifest as SEAs, IEDs, and seizures; all become more frequent as AD progresses.

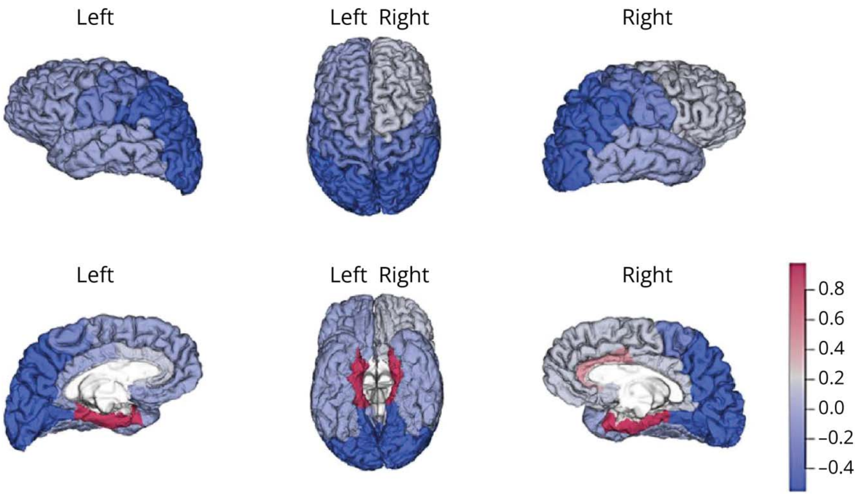
Elderly patients with late onset epilepsy of unknown origin (LOEU) have a ~2.5-fold higher risk of MCI or dementia compared with elderly controls.[33] At first LOEU seizure (i.e., >60–65 years), patients may have clinical stage 1 (no cognitive symptoms) or 2 (subjective cognitive decline) revised AD stages,[34] when patients are cognitively intact on standard tests but biomarkers indicate early disease (i.e., pathologic amyloid or tau PET or pathologic CSF/blood amyloid and tau concentrations).

SEA occur in 30%–50% of AD patients with prolonged EEG recordings including stage 2 non-REM sleep (Figure 2).[35] Like IEDs, SEAs occur most frequently over the left temporal region. As AD progresses, SEA frequency increases.[36] Among amyloid/tau fluid biomarker positive AD patients with stage 1 (no cognitive decline) and stage 2–4 (MCI to mild dementia), SEA occurred in 31% vs 8% in biomarker negative controls with normal cognition.[35] SEA occurred in 50% of patients with severe cognitive symptoms, 27% of MCI patients, and 25% of biomarker positive cognitively intact patients (Preclinical AD).

Among elderly epilepsy patients, ASM, especially polytherapy, is a risk factor for cognitive impairment,[16] as well as lower educational level, higher seizure frequency, generalized tonic-clonic seizures (GTCS), and longer epilepsy duration.[37] Lamotrigine (LTG) and levetiracetam (LEV) are better tolerated than older ASMs (e.g., phenytoin, valproic acid), although we lack prospective ASMs studies in elderly epilepsy subjects.

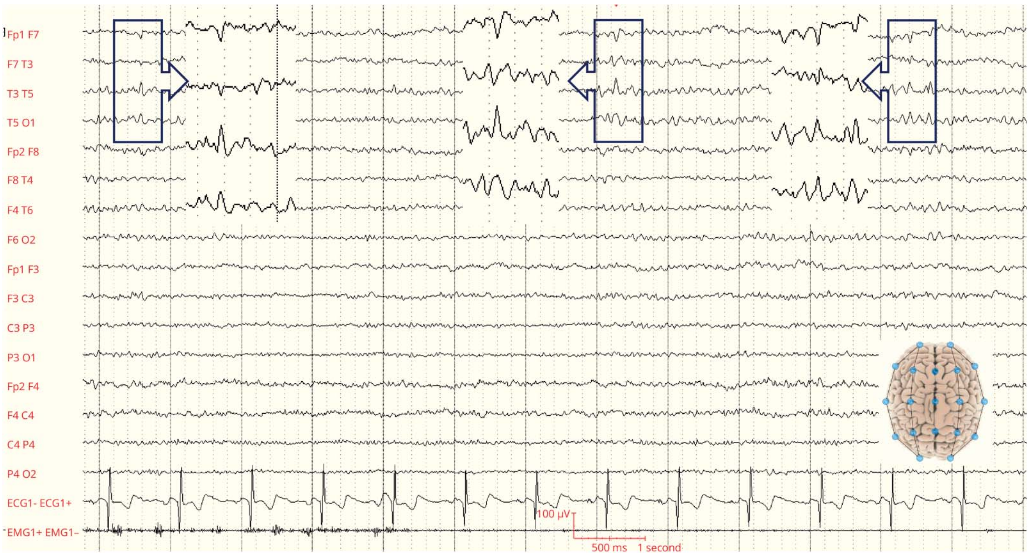
ASM therapy is recommended for patients with AD with clinical seizures to reduce seizure effects (e.g., trauma, postictal confusion) and potentially slow cognitive decline associated with pathologic hyperexcitability.[38] ASM selection should consider side effects and medication interactions. LEV, brivaracetam (BRV), LTG, and lacosamide (LCM) are often preferred in patients with AD[38] and should be initiated shortly after the first seizure since recurrence occurs in ~70% of patients with AD within a year after without ASMs.[39]

Figure 1 Amyloid PET Studies in Temporal Lobe Epilepsy (TLE)



18F-flutemetamol uptake ratio (FUR; z-score) distribution in left and right hemisphere cortical surface templates in adults with medication-resistant TLE. Higher FURs in the mesial temporal regions (red). With permission from Fonesca E, et al. *Epilepsia* 2024; 65:3664–3675.

Figure 2 Subclinical Epileptiform Activity (SEA) in Alzheimer Disease



Left temporal small spikes (SEA), in the left temporal region drowsiness in a 66-year-old woman with mild Alzheimer disease but no seizures and not on antiseizure medication.

Do ASMs increase or decrease AD risk? A study of >90,000 people found that ASMs significantly increased incident dementia (odds ratio [OR] 1.28) and AD [OR 1.15]) risk. ASM with cognitive side effects (e.g., barbiturates, benzodiazepines, phenytoin, zonisamide) had a higher risk than those without cognitive side effects (e.g., LEV, LTG, LCM, oxcarbazepine) (OR 1.59 v. 1.19). By contrast, another study found that cognitive deterioration in MCI-AD patients with epilepsy receiving ASM therapy was similar to MCI-AD patients without epilepsy,[40] suggesting ASMs slow deterioration in early AD. Compared with placebo, ASMs in AD patients with SEA improved executive functions and spatial learning.[41] Although seizures, IEDs, and SEA are modifiable factors of AD progression, we lack systematic, well-powered prospective studies on risks and benefits of ASMs in AD. Older ASMs have more drug interactions and greater adverse effects in elderly patients. Comparing phenobarbital to LTG or LEV monotherapy in AD patients with epilepsy,[42] seizure control was similar for all ASMs, but cognition improved in the LEV group but worsened for LTG or phenobarbital groups.

LEV and BRV act on the synaptic vesicle 2 (SV2) protein family (SV2A, SV2B, SV2C), which play a crucial role in neurotransmission. Decreased hippocampal SV2A is associated with increased Aβ and pathologic p-tau levels. LEV reduces glutamate release and may reduce epileptiform activity and AD-related pathology in animal models,[43,44] as well as normalizing hippocampal hyperexcitability and increasing hippocampal blood flow, suggesting possible neuroprotective effects. In AD animal models, LEV improves memory,[45] benefits that may arise from seizure control, direct effects on brain function, or both. BRV, a more selective SV2A ligand, has stronger cognition-enhancing and anti-epileptogenic effects in AD mouse models.[46]

LEV and brivaracetam (BRV) have few drug interactions and act on the SV2A transmembrane protein which is involved in neurotransmission and Aβ and pTau homeostasis,[47] suggesting that they may be first-line ASM therapy for patients with AD, often effective in low doses.[38,41] LEV has higher rates of irritability, agitation, depression, and psychosis than BRV with similar efficacy, suggesting that BRV may be a potential first-line therapy, but we lack randomized controlled trials on all 4 of the ASMs with low cognitive risks (i.e., LCM, LTG, LEV, and BRV). In AD, SEA, and IEDs, seizures may accelerate of cognitive decline, as IEDs can induce cognitive dysfunction in epilepsy patients without AD (e.g., developmental and epileptic encephalopathies). Reducing neuroexcitability and spike activity may improve cognitive outcomes. However, most ASMs reduce seizure but not necessarily IED or SEA activity. Further studies are needed.

Neuroimaging

MRI is an essential diagnostic tool for AD and epilepsy. PET scans help diagnose AD and localize seizure foci in presurgical evaluations. In AD, structural MRI reveals brain atrophy, initially in the medial temporal lobe (MTL); hippocampal volumes reduced ∼25% and entorhinal cortex volumes reduced ∼40%.[48] As AD progresses, atrophy affects all MTL gray matter, the fusiform gyrus, and temporal pole, followed by amygdala, cingulate gyrus, thalamus, and association cortices. Atrophy in (1) MTL correlates with memory impairment, (2) limbic regions with behavioral disorders, and (3) association cortex with higher cognitive impairments. Greater MTL atrophy distinguishes AD from dementias due to Parkinson disease and Lewy body disease. WMHs in AD are maximal in frontal regions and correlate with axonal loss and demyelination; however, they are more prominent in vascular dementia than in AD. Fluorodeoxyglucose (FDG)-PET scans initially show reduced glucose metabolism in MTL as well as parietotemporal association, posterior cingulate, and medial parietal (precuneus) cortices. As AD progresses, hypometabolism spreads to frontal cortices, striatum, and primary sensorimotor areas. Relatively preserved metabolism in the posterior cingulate suggests possible Lewy body dementia. Amyloid and tau PET scans are abnormal in early AD.

MRI findings in epilepsy reflect etiology, seizure focus localization and lateralization, and epilepsy duration. TLE is associated with hippocampal atrophy and mesial temporal sclerosis with PET MTL hypometabolism. Among patients with late-onset nonlesional epilepsy, FDG-PET hypometabolism is associated with cognitive decline in 74% of cases, while normal metabolism predicted no neurodegeneration or neuroinflammation in 88% of cases.[49] Functional MRI, which can help identify sensory motor and language areas during presurgical epilepsy evaluations, is not used clinically in AD. There are sparse data on MRI and FDG-PET studies in patients with both AD and EPI; these features suggest that overlap with epilepsy and patients with AD, but small sample sizes limit power; more studies are needed. Diffusion tensor imaging, arterial spin labelling, and magnetic resonance spectroscopy are primary research tools in AD and epilepsy.

Biomarkers in Epilepsy and AD

AD diagnosis once depended on autopsy, but amyloid and tau PET and CSF biomarkers biologically define AD: the amyloid, tau, and neurodegeneration (ATN) framework assesses AD neuropathology and has a ≥20-year preclinical period (Table).[34] The updated ATN framework incorporates plasma biomarkers, including inflammatory/immune processes (I), vascular pathology (V), and α-synuclein (S) in an "ATNIVS" staging.[50] AD is associated with other neuropathologies influencing symptom types and severities.

Epilepsy and excitatory:inhibitory imbalance contribute to AD pathogenesis. Epilepsy can develop in early and preclinical ("epileptic variant of AD") or advanced AD stages.[54] Reduced CSF Aβ42/Aβ40 ratio and elevated total tau (t-tau) and phosphorylated tau (p-tau) establish preclinical AD; follow-up studies show progression from normal to MCI and dementia.[54] In AD, CSF biomarkers are more abnormal in epilepsy cases, suggesting greater Aβ-related and tau-related pathology.[53] From ~300 AD patients without stroke or head trauma, CSF neurofilament light (NfL), glial fibrillary acidic protein (GFAP), t-tau, p-tau$_{181}$, and Aβ42 were assessed. The 851 AD subjects with epilepsy (AD-EPI) had higher t-tau and p-tau$_{181}$ levels and lower Aβ42 levels than the AD patients without epilepsy (AD-NO-EPI), consistent with more severe AD-related neuropathology.[53] Lower Aβ42 CSF levels were found in 37.5% of an epilepsy cohort, with greater dementia during follow-up.[55] A prospective study of 52 elderly (older than 50 years) TLE patients compared their imaging and CSF biomarkers to: (1) MCI cases with abnormal CSF markers for AD (MCI-AD), (2) MCI cases with normal CSF AD biomarkers (MCI-noAD), and (3) age-matched controls. The LO-TLE group had normal Aβ and ptau$_{181}$ levels, significantly different from the MCI-AD group. Four LO-TLE subjects had abnormal low CSF Aβ42 and 3 had elevated p-tau$_{181.}$[51] This inconsistent association of CSF biomarkers and epilepsy may reflect seizures in the LO-TLE group as an early harbinger of dementia, before CSF biomarker changes.[56] More sensitive biomarkers (e.g., CSF p-tau$_{217}$) may support an association.[56] Plasma Aβ42/Aβ40 ratio and late-onset epilepsy were studied longitudinally in 15,792 US 45–65 years old followed for 35 years. The Aβ42/Aβ40 ratio was measured between 50–71 years and 67–90 years[52] Decreased plasma Aβ42/Aβ40 ratio was associated with increased risk of subsequent epilepsy. For every 50% reduction Aβ42/Aβ40, epilepsy increased 2-fold.[52] Prospective studies with more sensitive biomarkers of epilepsy (e.g., prolonged EEGs) and AD (e.g., plasma and CSF Aβ42/Aβ40, NfL, GFAP, t-tau, p-tau$_{181}$, p-tau$_{217}$) are needed.[56]

Molecular Mechanisms in AD and Epilepsy

Epileptiform activity and cognitive deficits are linked with tau, mTOR signaling, amyloid precursor protein functions, and other mechanisms (Figure 3). Tau pathology occurs in early AD and is associated with specific phosphorylation sites (e.g., ptau^{217}), *APOE*$^{\varepsilon 4}$, and less well-characterized regions such as the brainstem.[57] Pathologic p-tau is increased in the hippocampus of AD, dual diagnosed (AD-EPI), and some epilepsy patients; levels correlate with cognitive dysfunction.[58] Early pretangle tau pathology occurs in the brainstem locus coeruleus and dorsal raphe nucleus, regions that modulate sleep, arousal, and selective attention, which project to limbic and cortical regions affected in AD and epilepsy. CSF tau and amyloid levels follow a sleep-wake cycle, and sleep is affected by, and contributes to, AD and epilepsy. Studies on tau pathology in epilepsy and AD-EPI groups are limited to specific tau phosphorylation sites and brain regions.[58] In AD animal models, tau reduction decreased excitotoxicity-induced neuronal dysfunction and in epilepsy, improved behavior, and reduced mortality and seizure frequency.[59] In epilepsy and AD, many altered proteins interact with tau or are regulated by tau expression; with increased hippocampal p-tau$_{217}$ and p-tau$_{231}$ in some epilepsy cases.[58]

The mTOR pathway, implicated in epileptogenesis and cognitive deficits, is involved in tau phosphorylation as well as Aβ generation and clearance.[31] In AD-EPI cases, tau (p212/

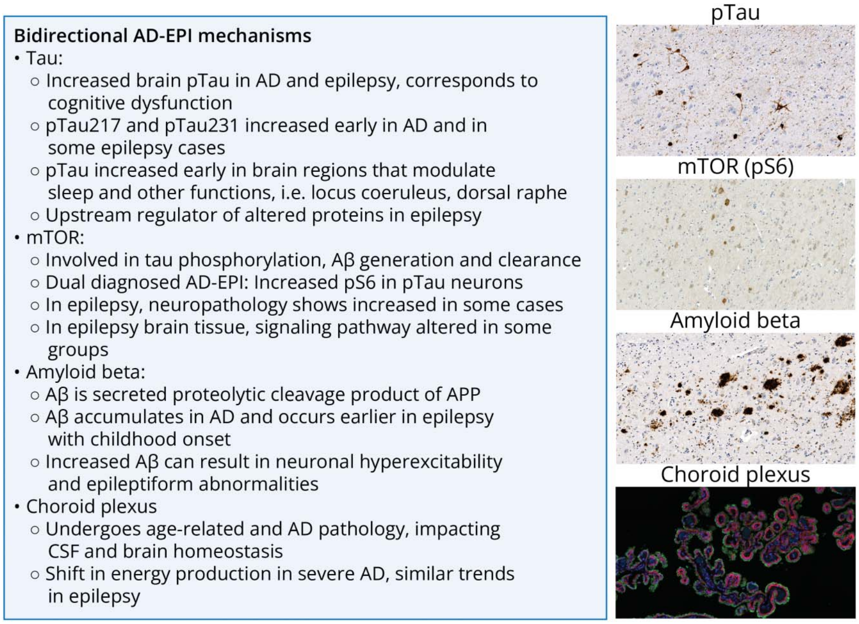
Table 1 Alzheimer Disease/Epilepsy Biofluid Biomarkers

		Amyloid beta	Tau	NFL	GFAP
AD	CSF	↓ Aβ42/Aβ40 ratio[50]	↑ Total tau, pTau-181, pTau-217, pTau-231[50]	↑ NFL[50]	↑ GFAP[50]
	Plasma	Same trends as CSF but not limited use variable and nonspecific[50,e6]	Same trends as CSF, limited use variable and nonspecific[50,e6] ↑ pTau-217 and pTau-231[50,e6]	↑ NFL[50,e6]	↑ GFAP[50,e6]
EPI	CSF	LOEU, ↓ Aβ42 in 37.5% and 17.5% develop dementia[e7] LOEU, ↓ Aβ42 in 16.4%[e8] In LO-TLE, Aβ42/Aβ40 ratio and Aβ42 similar as MCI-noAD ↑ MCI-AD[51]	LOEU: Total tau elevated but not pTau-181 (n = 40) vs controls (n = 43)[e7] In LOEU, ↑ total tau 14.5% and ↑ pTau-181 in 12.7%[e8] In LO-TLE, total tau and pTau-181 similar as MCI-noAD lower than in MCI-AD[51]	N/A	N/A
	Plasma	↓ Aβ42/Aβ40 ratio with ↑ risk of LOE (ARIC)[52]	Total tau similar in epilepsy vs other disorders[e9]	↑ NFL some epilepsies[e9,e10]	↑ GFAP some epilesies[e9,e10]
AD-EPI	CSF	↓ Aβ42 in AD-EPI vs AD[38] ↓ Aβ42 LOEU-MCI vs LOEU-CN, similar in LOEU-MCI and NE-MCI[e11]	↑ Total tau a and pTau-181 in AD-EPI (n = 320) vs AD, (n = 302)[53] Total tau and pTau-181 similar LOEU-MCI and LOEU-CN or LOEU-MCI and NE-MCI[e11]	Similar in AD-EPI vs AD[53]	Similar in AD-EPI vs AD
	Plasma	N/A	N/A	N/A	N/A

Abbreviations: ↓ = decreased; ↑ = increased; AD = Alzheimer disease; ARIC = atherosclerosis risk in communities study; EPI = epilepsy; LOE = late-onset epilepsy; N/A = not applicable; p-tau = phosphorylated tau; LOEU = late-onset epilepsy of unknown origin; LO-TLE = late-onset temporal lobe epilepsy; MCI = mild cognitive impairment; NE-MCI normal elderly with mild cognitive impairment; TLE = temporal lobe epilepsy.
N/A = not available.

214) pathology is increased in temporal cortex vs controls and AD cases without seizures. The same AD-EPI cases had increased mTOR signaling (pS6 p235/236) in cells with p-tau pathology compared with AD cases without seizures.[31] In epilepsy patients, including those with focal cortical dysplasia type II or tuberous sclerosis, mTOR signaling is increased in some neurons on histologic and proteomic studies.[58] It remains uncertain if mTOR signaling is increased in neurons with other tau pathology (e.g., p-tau$_{217}$) in AD-EPI cases and how increased mTOR signaling relates to tau pathology in epilepsy.

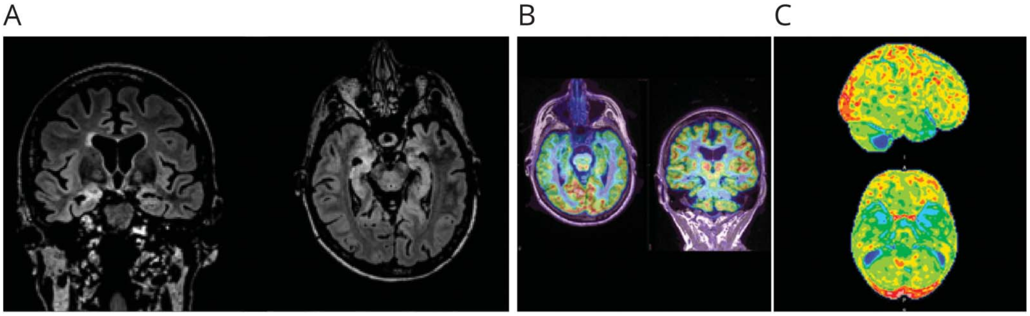
Figure 3 Bidirectional Alzheimer Disease—Epilepsy Mechanisms



Bidirectional AD-EPI mechanisms

- Tau:
  - Increased brain pTau in AD and epilepsy, corresponds to cognitive dysfunction
  - pTau217 and pTau231 increased early in AD and in some epilepsy cases
  - pTau increased early in brain regions that modulate sleep and other functions, i.e. locus coeruleus, dorsal raphe
  - Upstream regulator of altered proteins in epilepsy
- mTOR:
  - Involved in tau phosphorylation, Aβ generation and clearance
  - Dual diagnosed AD-EPI: Increased pS6 in pTau neurons
  - In epilepsy, neuropathology shows increased in some cases
  - In epilepsy brain tissue, signaling pathway altered in some groups
- Amyloid beta:
  - Aβ is secreted proteolytic cleavage product of APP
  - Aβ accumulates in AD and occurs earlier in epilepsy with childhood onset
  - Increased Aβ can result in neuronal hyperexcitability and epileptiform abnormalities
- Choroid plexus
  - Undergoes age-related and AD pathology, impacting CSF and brain homeostasis
  - Shift in energy production in severe AD, similar trends in epilepsy

Figure 4 MRI and PET Scans in Temporal Lobe Epilepsy (TLE)



A 75-year-old woman with well-controlled right TLE and memory complaints. (A) MRI Flair left mesial temporal sclerosis. Left: Axial. Right: Coronal. (B) FDG-PET mild left mesial temporal hypometabolism. Left: Axial. Right: Coronal. (C) FDG-PET mild left mesial temporal hypometabolism. Top: Lateral, right hemisphere. Bottom: Inferior surface.

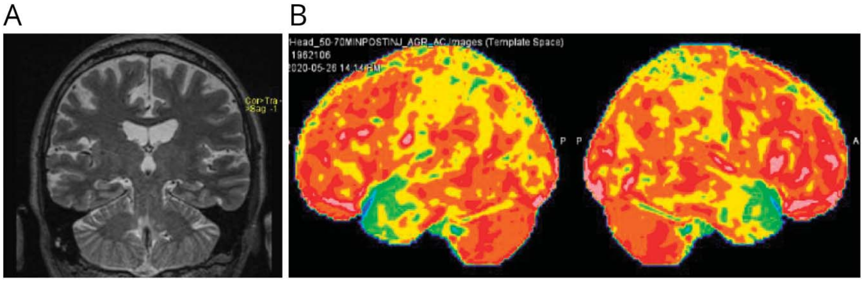
Increased amyloid can cause neuronal hyperexcitability and epileptiform abnormalities.[60] Neuropathologic studies reveal amyloid pathology in AD and AD-EPI cases. Amyloid pathology occurs in some epilepsy patients.[e1] Increased amyloid on PET imaging occurs in middle aged subjects with childhood-onset epilepsy compared with controls.[e2] Animal and cell models show that soluble and fibrillar amyloid affects many pathways, which can increase action potential firing and hyperexcitability, lower levels of potassium voltage gated channels, impair calcium homeostasis, and alter glutamatergic signaling.[60]

Brain proteomics can create unbiased comprehensive datasets to identify molecular mechanisms, novel biomarkers, and therapeutic targets. Transcriptomic approaches are complementary but do not always parallel protein levels and may have limited therapeutic translation. In AD, protein changes occur in multiple regions and affect neuronal and glial proteins in studies on amyloid plaques, tau pathology, and cerebral amyloid angiopathy.[e3] Proteomics studies in epilepsy are limited for brain regions but absent in AD-EPI. Similar to brain tissue proteomics, there are more studies in AD CSF and plasma, but limited studies in epilepsy[e4]; we found no proteomic studies in AD-EPI cases. We need prospective studies of AD, epilepsy, and AD-EPI cases assessing plasma and CSF biomarkers, PET imaging, EEG, and phenotypic features, with complementary proteomics and transcriptomics across brain regions and cell types to identify novel biomarkers and therapeutic targets.

Diagnostic Challenges

The reciprocal epilepsy-AD relationship makes the diagnosis both disorders challenging.[16,e5] Thus, if an elderly individual with epilepsy has self-identified or family-identified cognitive complaints, this could result from the etiology (e.g., stroke or trauma), recurrent GTCS or focal seizures, abundant IEDs, ASMs, comorbid sleep or psychiatric disorders, or a coincidental neurocognitive disorder (Figures 4 and 5). Diagnosing seizures and epilepsy in elderly subjects is challenging and more difficult with a neurocognitive disorder such as MCI or dementia. Seizures in the elderly tend to be shorter with fewer objective motor features than younger subjects. Seizures are usually focal, nonconvulsive and with subjective phenomena, impaired awareness or confusion, which may be misattributed to aging or mistaken for metabolic disorders, medication side effects (especially with polypharmacy), cognitive impairment, sundowning, or psychiatric disorders.[10] Postictal states and seizures may be prolonged and lead to misdiagnosis.

Figure 5 Neuroimaging and EEG in a 62-Year-Old Man With 4-Year Progressive Memory Impairment Without Seizures



EEG left temporal slowing and sharp waves. CSF positive for phospho-tau$_{177}$ (CSF autoimmune encephalitis panel and Lyme titer negative). (A) Coronal T2 MRI: left > right hippocampal atrophy. (B) PET Scan (Lateral view) left > right temporal and parietal hypometabolism.

Scalp EEG is a widely available tool to identify seizures and IEDs. Short (e.g., 30 minutes) EEGs during wakefulness are unlikely to record IEDs in AD patients. Longer duration (≥8 hours) EEGs, including sleep, are far more likely to detect IEDs, SEA, or nonconvulsive seizures in AD or pre-AD patients (Figure 4B). Quantitative EEG may identify network alterations leading to pathologic hyperexcitability in AD. Although IEDs, SEA, and seizures can negatively affect AD patients, we lack EEG diagnostic guidelines. Although some biomarker recommendation for diagnosing neurocognitive diseases only include EEG in initial investigations for patients with seizures, we recommend prolonged EEG recordings with sleep in MCI or mild dementia patients to identify a potentially treatable pathophysiology.

Conclusions

Epilepsy and AD are reciprocally related, lying within a concatenation of disorders affecting cognition, behavior, sleep, and vascular and somatic systems, as well as genetic and environmental factors. These interwoven relationships defy current understanding. To advance diagnostic and therapeutic strategies, we need more studies on the natural history of normal aging and move from one-dimensional studies (e.g., incidence of epileptiform discharges or epilepsy in AD patients) to simultaneously examining multiple risk factors and outcomes using validated prospective, serial measures that integrate genetic, epigenetic, sociodemographic, medical, neurologic, microbiome, and psychiatric evaluations with assessments of physical and mental resilience, sleep hygiene, diet, stress, and social support. Clinical trials should assess ASM therapies defined by medication and dose to potentially slow cognitive decline in AD-EPI patients or AD patients with IEDs or SEAs. Future studies should assess the potential efficacy and toxicity of ASMs in AD patients across the spectrum of increased E:I balance (e.g., without SEAs, with SEAs, with seizures no IEDs, seizures and IEDs—and those with SEAs, IEDs, and seizures can be subdivided based on abundance of epileptiform activity and seizures). To better assess the presence and implications of increased E:I balance in AD, we need to better define the diagnostic criteria of excess (and deficient) E:I on patients' EEGs and more accurately classify in AD subgroups with excess E:I, since this subgroup may be most likely to benefit from ASMs. We should seek to prevent epilepsy and limit adverse effects of pathologic network hyperexcitability in AD patients while limiting adverse effects of ASMs.

Finally, we must beware of "selection bias and positive data spin." The emerging field of AD and epilepsy has generated great interest, facilitating publications in a high impact journals and grant funding when results support the AD-epilepsy connection and potential efficacy of ASMs. Studies that are underpowered, subject to selection bias, and lack correction for multiple comparisons can produce highly positive results of uncertain relevance. For example, 2 AD patients with IEDs on scalp EEG showed prominent findings including "silent seizures" with foramen ovale electrodes;[e12] consistent with studies in non-AD patients with IEDs or epilepsy since the 1980s. Similarly, the study of low-dose levetiracetam in 28 subjects failed to find significant results for any primary or secondary outcome, despite a lack of correction for multiple analyses; 2 subgroup analyses among multiple exploratory measures led to publication.[42] The literature on AD and epilepsy is vulnerable to potential selection bias in patients and outcome measures, interpretation of ambivalent findings (e.g., EEG waveforms), statistical analysis, viewpoint, and failure to publish negative findings. All can be potently but subtly biased by academic rewards.

Author Contributions

O. Devinsky: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. D.F. Leitner: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. A. Kamondi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. T. Wisniewski: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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