Review

Shared cognitive and behavioral impairments in epilepsy and Alzheimer's disease and potential underlying mechanisms

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ARTICLE INFO

ABSTRACT

Seizures in patients with Alzheimer's disease (AD) have been examined by many investigators over the last several decades, and there are diverse opinions about their potential relevance to AD pathophysiology. Some studies suggest that seizures appear to be a fairly uncommon co-morbidity, whereas other studies report a higher incidence of seizures in patients with AD. It was previously thought that seizures play a minor role in AD pathophysiology because of their low frequency, and also because they may only be noticed during late stages of AD, suggesting that seizures are likely to be a consequence of neurodegeneration rather than a contributing factor. However, clinical reports indicate that seizures can occur early in the emergence of AD symptoms, particularly in familial AD. In this case, seizures may be an integral part of the emerging pathophysiology. This view has been supported by evidence of recurrent spontaneous seizures in transgenic mouse models of AD in which familial AD is simulated. Additional data from transgenic animals suggest that there may be a much closer relationship between seizures and AD than previously considered. There is also evidence that seizures facilitate production of amyloid β (Aβ) and can cause impairments in cognition and behavior in both animals and humans. However, whether seizures play a role in the early stages of AD pathogenesis is still debated. Therefore, it is timely to review the similarities and differences between AD and epilepsy, as well as data suggesting that seizures may contribute to cognitive and behavioral dysfunction in AD. Here we focus on AD and temporal lobe epilepsy (TLE), a particular type of epilepsy that involves the temporal lobe, a region that influences behavior and is critical to memory. We also consider potential neurobiological mechanisms that support the view that the causes of seizures in TLE may be related to the causes of cognitive dysfunction in AD. We suggest that similar underlying mechanisms may exist for at least some of the aspects of AD that are also found in TLE.

This article is part of a Special Issue entitled "The Future of Translational Epilepsy Research".

1. Introduction

Disorders or conditions that affect synaptic function are often associated with seizures or are risk factors for epilepsy, including traumatic brain injury, autism, schizophrenia, and Alzheimer's disease (AD). This is not surprising, considering that the brain is made up of over 1 billion neurons, and each neuron can form tens of thousands of synapses. Such a complex structure requires numerous cellular and circuit mechanisms to regulate neuronal network activity and maintain stable function that also can adapt to environmental demand [1]. Although the brain can generally meet this challenge, disorders that impact synaptic function may overcome the capacity to maintain normal function. Changes to synaptic function may result in seizures by numerous mechanisms, creating an imbalance between excitation and inhibition either directly or indirectly, e.g., by inducing maladaptive compensatory responses.

Focusing on synaptic regulation is important in AD, which has been referred to as a "disease of synaptic failure" [2,3]. It also is considered to be central in epilepsy, and therefore, it may not be surprising that seizures have been described in patients with AD [4–7]. The fact that patients with AD have recurrent spontaneous seizures, which defines 'epilepsy,' has also been noted [6,8], but the role of epilepsy in AD pathophysiology has largely been unexplored. Seizures have traditionally been attributed to neuronal loss in the late stages of disease, and may, therefore, be a possible epiphenomenon of little pathophysiological relevance. However, as discussed in this review, recent studies have provided more experimental support for the idea that

there is a greater connection between epilepsy and AD than previously recognized. These experimental studies, particularly those utilizing mouse models of AD, support the idea that seizures may contribute in a critical fashion to the emergence of AD symptoms, i.e., cognitive impairment, in early stages of AD [9]. Notably, epilepsy and AD also have similar psychiatric co-morbidities, suggesting that seizures may influence a wider range of brain function in AD than memory impairment. This article reviews the evidence that cognitive and psychiatric symptoms of AD and TLE are not merely byproducts of widespread temporal lobe pathology in both conditions but may share underlying mechanisms.

2. Seizures in AD

2.1. Seizures in patients with AD

The occurrence of seizures in patients with AD has been thoroughly reviewed recently [4–7]. The incidence of unprovoked seizures is 5–10-fold greater in sporadic AD than in reference populations, and as much as 87-fold greater in patients with "early" disease onset (before 60 yrs of age [5,6,10–12]). In autosomal dominant forms of AD, the relationship between seizures and AD is most remarkable. In these forms of AD, there are either mutations in amyloid precursor protein (APP), the precursor to Aβ, or one of the presenilins (presenilin-1, PS1; presenilin-2, PS2; critical components of the γ-secretase complex that cleaves APP to produce Aβ), or other genetic causes such as duplication of the APP gene. Approximately 50–80% of patients with these forms of AD present with overt (convulsive) seizures [11,13,14]. All of the genetic alterations that cause autosomal dominant AD increase Aβ production or aggregation, which suggests that Aβ accumulation contributes to the seizures. This idea is supported by studies of Down's syndrome, in which there is an extra copy of the APP gene, and in which a high percentage of individuals develop seizures [6,15,16]. Recent studies in mouse models of AD suggest that neurofibrillary tangles and specifically tau, which is a major component of tangles, also contribute to seizures [17,18].

Despite the significant seizure incidence in patients with AD relative to reference populations, episodes of convulsive seizures are relatively infrequent [6]. However, non-convulsive seizures may be underestimated because of their subtle behavioral manifestations, which could easily be missed by someone without an understanding of epilepsy. Retrospective studies and clinical reports have demonstrated that patients with AD do have an increased incidence of non-convulsive seizures [8,19,20]. This idea is also supported by the fact that mouse models of AD also exhibit non-convulsive seizures [21]. Thus, convulsive seizures may be fairly well documented, but non-convulsive seizures are likely to be underestimated [8,20,22]. Non-convulsive seizures are similar in both humans and mice: they can include behavior such as staring with a frozen posture for a few seconds, making them difficult to detect without EEG recordings [23–25]. Two examples of non-convulsive seizures are absence seizures and partial seizures. Absence seizures are associated with a blank expression, even in the middle of a conversation, which makes the person appear to be 'staring off into space'; these 'absences' are accompanied by generalized 3-Hz spike-and-wave discharge [23–25]. Partial seizures may be accompanied by "automatisms," which are perseverative movements such as licking the lips or chewing without food in the mouth. For both absence and partial seizures, the episodes are usually not remembered by the patient. One of the potential reasons for a patient's inability to recall seizures is that seizure activity associated with these non-convulsive behaviors interrupts normal thalamocortical sensory processing (in absence seizures) or memory that is dependent on structures such as the hippocampus (in partial seizures). Although not recognized by the patient, the behaviors associated with these types of non-convulsive seizures are commonly described by caregivers of patients with AD [26].

2.2. Epilepsy and TLE in AD

As mentioned above, patients with AD can exhibit *seizures*. But do these patients have *epilepsy*? The definition of epilepsy only requires that an individual exhibit more than one spontaneous seizure, so in fact, the answer may be yes.

Do individuals with AD have temporal lobe epilepsy (TLE)? Here, the definition of TLE is important. Some researchers consider TLE to depend on a particular pattern of pathology called mesial temporal lobe sclerosis (MTS), which is not clear in AD. When one examines hippocampal pathology in AD and TLE, some similarities are observed, such as sparing of dentate gyrus granule cells when other neurons in the hippocampus are damaged. In addition, there is circuit reorganization and other changes in the dentate gyrus that are similar in some patients with AD and TLE [27]. Therefore, some pathological characteristics are shared between some patients with AD and some patients with TLE.

The type of seizure that characterizes TLE is also important to consider: seizures in TLE are typically simple partial or complex partial. However, this is not always true. For example, generalized tonic-clonic seizures can develop. A variety of seizure types also occur in patients with AD [8]. Therefore, one cannot necessarily infer that all patients with AD who have recurrent seizures have a TLE-like syndrome, but some may have, and in others, some overlap in pathology and seizure type can occur.

2.3. Seizures in transgenic mice used to study AD pathophysiology

One of the difficulties in resolving clinical questions about seizures in AD is practical — lengthy or invasive (and hence more accurate) EEG monitoring is prohibitive. In these cases, animal models can provide an alternative approach to gain more insight. In this regard, mouse models of AD pathophysiology, particularly those that express high levels of Aβ, have provided a great resource. Recent studies in transgenic mouse models of AD with high levels of Aβ suggest that seizures occur much earlier than had been expected relative to the progression of Aβ accumulation and amyloid pathology [21,28]. These new data have suggested a different time course in the disease, where seizures and cognitive impairment occur earlier than the development of amyloid plaques. In addition, the data suggest that seizures could contribute to the progressive decline in cognition and progressive neurodegeneration in AD. Although these hypotheses have to be tested directly in human patients, the studies in mouse models have led to a greater understanding of how seizures might arise and affect cognition in AD.

The mouse models in which seizures have been primarily studied to date are transgenic mice that express human amyloid precursor protein (hAPP) carrying one or more mutations associated with familial forms of AD. Mutant APP is expressed in neurons in a relatively widespread manner in these mice because the promoter used to drive neuronal expression is normally located throughout the brain, such as platelet-derived growth factor (PDGF). In some mouse models, hAPP transgenic mice are crossed with transgenic mice overexpressing mutant human PS1 to simulate another genetic, autosomal dominant form of AD. These mutations increase the production and accumulation of Aβ within the first months of life, which continues as the animals age. Electroencephalographic recordings from these mice often demonstrate spontaneous seizures early in adulthood, and the seizures can occur with and without convulsive behaviors [17,21,28–33]. The seizures are robust electrographic events, even if they are not accompanied by convulsions, with large voltage excursions, lasting tens of seconds or longer [21,28]. The typical rhythmicity of seizures and fast frequencies are also observed. Some spike-wave discharges are found. When multiple electrodes are used, many seizures appear to be generalized. The mouse models of AD that exhibit seizures also exhibit numerous impairments in behavioral tests of cognitive (e.g., spatial memory) and

emotional (e.g., anxiety) functions [21,28,34–36]. A causal relationship between the seizures and the cognitive/behavioral impairments is suggested by the reduction in deficits when seizures are reduced [17,37].

Importantly, spontaneous seizures develop with age and rising Aβ levels and are generally not evident in transgenic mice that do not have high levels of Aβ [17,21]. Thus, epileptiform activity is unlikely to be a nonspecific effect of transgene overexpression. The role of Aβ may be important even before plaques form, presumably due to the actions of oligomeric Aβ species [21]. It is notable that these AD mouse models exhibit little or no neuronal loss [36], indicating that the general assumption that seizures result only at the end stage of AD, after extensive neurodegeneration, is not true, at least in the mouse models. It would be valuable to know whether this occurs also in patients with AD, but systematic long-term quantitative EEG evaluation (with neuropathology) is not available. Epileptiform activity in hAPP mice induces gene expression and circuit reorganization that is potentially neuroprotective, such as upregulation of neuropeptide Y levels in GABAergic neurons and the mossy fiber pathway of the hippocampus [21,38]; upregulation of neuropeptide Y also occurs in epileptic rodents and in the same hippocampal pathways — the mossy fiber pathway and GABAergic neurons called HIPP cells [17,21,38]. Therefore, the "neuroprotection" in hAPP mice does not necessarily (effectively) protect against seizures. It is important to keep in mind, however, that the magnitude of induction of the "neuroprotective" alterations may provide a reliable measure of the severity of underlying seizure activity even if their functional effects are not clear. The reason is that neuropeptide Y expression in mossy fibers appears to occur whenever there are recurrent seizures in rodents [21,27,39–41]. These "neuroprotective" alterations may also be relevant to cognitive deficits, because the magnitude of some of the changes in circuitry in hAPP mice that are considered protective is correlated tightly with hippocampal-dependent memory deficits [34]. The remarkable similarities between the hAPP or hAPP/PS1 mice and rodent models of epilepsy [27] suggest that seizures play a potential role in cognitive deficits and underscore the need to identify the underlying mechanisms.

2.4. Epilepsy in AD mouse models: is it TLE?

Changes in hippocampal circuitry in the same mice are similar to what has been found in animal models of TLE (described further below). Therefore, one might assume that these animal models of AD have TLE or a TLE-like syndrome. However, it is hard to judge from the literature whether this is true or not. Hippocampal discharges and seizures involving temporal lobe areas have been shown in mouse models of AD Ref. [21,28], but this does not prove that a TLE-like syndrome exists. One needs to record from multiple sites in the brain to be sure that the hippocampal discharges/seizures are initiated in that structure, rather than caused by a seizure elsewhere.

There are also a few additional reasons to be cautious about concluding that mouse models of AD have a TLE-like syndrome. First, the rodent models of TLE are commonly criticized for having characteristics unlike human TLE, such as excessive hippocampal degeneration. In addition, there is a diversity of animal models of TLE, not just one, and they are quite different in seizure phenotype and pathology. Therefore, the fact that mouse models of AD and rodent models of TLE share some characteristics is interesting and may lead to important insights, but may not be particularly helpful to address the question of clinical similarity between AD and TLE.

2.5. Insight into the similarities and differences between epilepsy and AD from studying mechanisms of hyperexcitability and seizures in experimental preparations

Several studies in transgenic mouse models of AD suggest that mechanisms underlying the abnormalities in excitability in both epilepsy and AD may be shared. The mechanistic information suggests

that widespread brain damage is not necessarily what AD and TLE have in common and is not what causes seizures — instead, there are specific defects in the molecular mechanisms that regulate excitability that are shared. Seizures may be worse in epilepsy than they are in AD because of slight differences in the molecular defects, even if they are similar defects. For example, a mutation in an ion channel that causes complete loss of function would be likely to cause a more severe disturbance than a mutation in the ion channel that causes partial loss of function.

In AD, it seems likely that a source of increased excitability, particularly in the early stages of the disease, is related to the abnormal metabolism of APP and not to degenerating neurons. In other words, the seizures are due to a "peptidopathy" [42]. Peptide products of APP influence several aspects of neuronal function and increased excitability results. On the other hand, abnormal metabolism of APP in epilepsy is not considered relevant to the underlying mechanisms of seizures.

The peptides that result from APP cleavage influence excitability in AD but may do so in a complex manner. For example, Aβ increases hippocampal glutamatergic synaptic transmission and long-term potentiation (LTP) at levels that are just above normal, but an excess of the same peptide reduces excitability [43,44]. These data suggest that APP metabolites need to be regulated within a tight window or hyperexcitability may result.

In addition to the peptides that result from abnormal metabolism of APP, there are potential abnormalities in excitability that arise from mutations in other proteins. Presenilin-1 is an example. Mutations or deletion of PS1 increases excitability, decrease seizure threshold, and are associated with seizures in patients [45]. Tau also appears to affect excitability and seizure threshold in rodents; reduction of tau reduces seizures [17,38].

Amyloid β-independent mechanisms of abnormal excitability may be shared in AD and epilepsy. For example, in hAPP mice, expression of the voltage-gated sodium channel subunit $Na_v1.1$ is reduced in GABAergic interneurons, and it has been suggested that the consequence is a loss of inhibition [46]. Thus, increased excitability may not be a direct effect of Aβ per se, but an indirect effect of altered $Na_v1.1$ levels. The hAPP mice with deficits in $Na_v1.1$ expression are interesting to consider because the hAPP mice are similar to two syndromes — generalized epilepsy with febrile seizures + (GEFS +) and severe myoclonic epilepsy of infancy (SMEI), two genetic epilepsy syndromes in which $Na_v1.1$ is mutated. The comparison suggests that at least one molecular target in hAPP mice and mouse models of epilepsy can be the same ($Na_v1.1$) and located similarly (GABAergic neurons) but the type of deficit is different: decreased levels in hAPP mice and mutation in the epileptic animals.

Modulation of voltage-gated sodium channel subunits may also contribute to hyperexcitability due to the actions of BACE1, the rate-limiting enzyme that cleaves APP to produce Aβ. Another substrate of BACE1 is the β2 subunit of voltage-gated sodium channels [47,48], which is an accessory subunit that is responsible for proper membrane localization of pore-forming α subunits. Cleavage of the β2 subunit by BACE1 produces a C-terminal fragment that is subsequently cleaved by γ-secretase to release an intracellular domain (ICD). The β2-ICD translocates to the nucleus and triggers the expression of $Na_v1.1$, which gets trafficked to the cell surface in part via binding to β2 [47,48]. However, overexpression of BACE1 in transgenic mice or cell lines results in excessive cleavage of β2 subunits and surplus expression of $Na_v1.1$ that is intracellularly retained, leading to reduced surface levels of $Na_v1.1$, reduced sodium currents, and impairment in action potentials [48]. The $Na_v1.1$ channel is highly expressed in the subtype of GABAergic interneuron that exerts a powerful inhibition on principal cells. Thus, a loss of functional $Na_v1.1$ subunits in these interneurons may contribute to disinhibition of cortical networks [46]. The β2 subunit cleavage and reduced levels of functional $Na_v1.1$ subunits might also occur in neuronal populations that control activity of other brain regions, which could

also lead to disinhibition. Thus, regulation of Na$_v$1.1 expression may have an important effect on network activity. Indeed, mouse models in which β subunits of voltage-gated sodium channels are ablated or mutated exhibit a predisposition to seizures [48–52].

Notably, BACE1 levels are increased in the brains of patients with AD and hAPP mouse models of AD [48,53–60], and the magnitude of the increase is correlated with increased β2 subunit cleavage in the brains of patients with AD [48]. These studies suggest that BACE1-mediated cleavage of the β2 subunit may contribute to AD-related increase in principal cell activity, although this has yet to be determined. Other lines of research suggest that BACE1 has diverse roles in modulating sodium channel function and seizures: for example, ablation of BACE1 can produce opposing changes in sodium channels but still increase the susceptibility to seizures [61–64]. Such studies indicate that a balance of BACE1 activity must be maintained to preserve normal neuronal and network activity.

Such comparisons show that AD and epilepsy indeed may have similarities that are so much alike that they are unlikely to be coincidental. Moreover, the few differences that occur may help explain why there are more seizures in epilepsy than in AD. For example, in the discussion above, the amino acid sequence of Na$_v$1.1 is normal in AD but its levels of surface expression are reduced. In the types of epilepsy where Na$_v$1.1 is involved (GEFS+ and SMEI), there is a mutation in the Na$_v$1.1 sequence which is a potentially more severe defect. The fact that there is a normal amino acid sequence in Na$_v$1.1 in AD, but it is mutated in epilepsy, may lead to less severe seizures in AD than in GEFS+ or SMEI.

3. Cognitive and behavioral impairments in patients with AD and TLE

One of the reasons that the idea of seizures in AD has gained so much interest is that TLE and AD can appear quite similar in their cognitive and behavioral impairments. These impairments are considered "co-morbidities" in TLE and include deficits that span multiple cognitive domains and a wide range of 'emotional' symptoms ranging from mood disorders such as depression to anxiety. Clinically, AD is characterized by a progressive loss of cognitive function, particularly regarding episodic memory, executive function, and language and visuospatial abilities [65,66]. These aspects of cognitive function are also particularly vulnerable in epilepsy, especially TLE [67–69]. The similarity in impairments, and the fact that a wide range of impairments are shared in both TLE and AD, is important to consider because it suggests that seizures may actively contribute to several aspects of AD-related alterations. On the other hand, a 'devil's advocate' might argue that TLE and AD simply create diverse types of pathology in multiple brain regions associated with cognition and behavior, and any disease that does so would have common symptoms. It has also been noted that the types of impairments in AD that involve memory are different than the types of memory deficits in TLE [70]. Below we address the extent to which some impairments in AD and TLE are similar, as well as evidence that the impairments, and potential underlying mechanisms, are distinct.

3.1. Episodic memory

One of the most characteristic features of AD is a profound impairment in episodic memory, a function that relies on a highly functioning hippocampus. Episodic memory is the learning and retention of new information, such as day-to-day activities or the ability to remember a shopping list or current events. Episodic memory in patients with AD is impaired relative to healthy controls, and performance in some verbal tasks of episodic memory can even differentiate patients in very early stages of AD from healthy aged controls with greater than 90% accuracy [71]. Episodic memory is also impaired in patients with AD relative to patients that suffer from other dementing disorders, such as

frontotemporal dementia, Lewy body disease, or Huntington's disease. Although those conditions are also associated with cognitive decline, the exquisite vulnerability of episodic memory is particular to AD [65]. Evidence from several studies demonstrate that patients with AD rapidly forget information and are impaired on both recognition and free recall tasks, suggesting that ineffective consolidation or storage of new information underlies the episodic memory deficits in AD [71]. The occurrence of episodic memory impairments in the early stages of the disease is consistent with neuropathological and imaging studies that demonstrate that the entorhinal cortex and hippocampus are particularly vulnerable in AD [72,73].

Episodic memory is also a signature problem in epilepsy, particularly TLE [68]. Because episodic memory requires the hippocampus, it is not surprising that diseases and disorders that heavily impact the hippocampus and temporal lobe strongly impair episodic memory. The degree of memory impairment in TLE correlates with duration of chronic epilepsy [74], suggesting that recurrent seizures can have cumulative effects on cognitive function. The relationship between duration of epilepsy and severity of impairments in memory and cognitive abilities is stronger in patients with fewer years of formal education, suggesting that higher cognitive functioning can protect against the deleterious effects of seizures on cognitive function [74–76]. It is of interest to note that higher levels of cognitive ability are also associated with lower incidence of AD [77].

3.2. Executive function

Executive function refers to a set of cognitive processes that include planning, working memory, attention, multi-tasking, mental flexibility, and initiation and monitoring of actions. Whereas episodic memory relies on the hippocampus, executive functions are indicative of frontal cortical function. Mild-to-moderately impaired patients with AD exhibit deficits in tasks that require executive function [65]. Impairments in executive functions are also evident in mild cognitive impairment (MCI), in which executive dysfunction in addition to impaired delayed memory recall can predict progression to AD [71]. Executive dysfunction in AD typically manifests first as decreased attention and problem-solving or working memory skills but is also associated with impairments in decision-making [78]. Thus, even though the hippocampus is particularly vulnerable in AD, cortical areas and function are also affected, and are affected even in the early stages of disease.

Although seizures in TLE are often suggested to be caused by hippocampal pathology, there is pathology in the neocortex, primarily in the frontal and temporal cortices, and this pathology appears to be important to the cognitive impairments [68,79]. For example, reduced volumes in specific areas of the prefrontal cortex are related to poor executive function [80]. It has been suggested that impairments in executive function relate to the propagation of temporal lobe seizure activity to neocortical areas [79]. Regardless, the shared deficits in executive function between TLE and AD are striking. For example, a typical task used to assess executive function is the Wisconsin Card Sorting Test (WCST), which tests the ability of subjects to display flexibility despite changing schedules of reinforcement throughout the testing period. Both patients with TLE and patients with AD show prominent deficits in this test, exemplifying shared impairments in executive function [71,79].

3.3. Visuospatial abilities

Visuospatial skills relate to the visual perception of objects and the spatial relationships between them in both two and three dimensions (i.e., putting a jigsaw puzzle together, finding one's way around a familiar environment). Visuospatial abilities are typically assessed with neuropsychological assessments using tests of object/face recognition, mental rotation, complex figure copy or clock drawing, or

tests that require angle discrimination. Although visual acuity is relatively spared in patients with AD, they exhibit deficits in visuospatial function early during the course of the disease, typically after impairments in episodic memory and executive function arise [65,71]. Homozygous carriers of the ApoE4 allele that is associated with AD also exhibit impaired performance in tasks that require visuospatial skills, even prior to the development of clinically symptomatic cognitive impairment [81]. However, the precise mechanisms by which the presence of the ApoE4 allele is associated with poor visuospatial performance at this stage are unclear. Visuospatial deficits may be related to the reduced effectiveness of information processing in the cortical and hippocampal regions thought to underlie visuospatial function [71,82]. Spatial memory is also impaired in patients with AD and is evident in navigational tests that require the patient to navigate a familiar route [83]. Such spatial memory deficits are linked to hippocampal volume and function [83], consistent with the critical role of the hippocampus in encoding spatial information. Because spatial memory is relatively straightforward to assess in transgenic mouse models of AD, this aspect of cognitive function is routinely assessed in them. These transgenic mouse models exhibit age- and disease-related impairments in spatial memory similar to that observed in Alzheimer's patients [36]. Notably, several rodent models of epilepsy, including genetic and pharmacological models, also exhibit robust impairments in spatial memory [69].

Visuospatial abilities are also affected in several types of epilepsy. Patients with transient epileptic amnesia, which is sometimes confused with dementia due to similarities in their presentation, exhibit impairments in visuospatial perception tests [84]. Juvenile myoclonic epilepsy is also associated with impairments in visuospatial function [85]. Hippocampal function can strongly influence performance in tasks requiring visuospatial abilities, as shown in studies of TLE. Although hippocampal sclerosis is not necessary for the impairments, patients with TLE with hippocampal sclerosis score significantly worse in visuospatial tasks than those without hippocampal sclerosis [86]. As mentioned above, spatial memory relies on hippocampal function and is impaired also in patients with TLE, whether or not hippocampal sclerosis is present. Both spatial navigation and spatial memory are impaired in TLE, and the degree of impairment can be modulated by the presence of hippocampal sclerosis [69,87,88].

In summary, at least three major aspects of cognitive function – episodic memory, executive function, and visuospatial abilities – are impaired in both TLE and AD. The fact that deficits in these cognitive domains are apparent in both TLE and AD does not necessarily mean that they must arise from common underlying mechanisms. However, the identification of both similarities and differences between these two diseases is mechanistically informative and provides a better understanding of just how related AD and TLE may be.

3.4. The role of seizures in causing cognitive dysfunction

One potential shared mechanism of cognitive dysfunction in AD and TLE is the seizures themselves. Seizures are a major disruption of brain activity, even if they are focal and occur in one part of the brain, such as the temporal lobe. But what is the evidence that seizures can cause cognitive dysfunction, particularly the types of cognitive dysfunction that are observed in AD and TLE? Moreover, could there be additional shared mechanisms that are not a direct consequence of seizure activity, but are due to the changes in gene expression or circuit remodeling that can arise after seizures?

The evidence that seizures cause cognitive dysfunction is available from both patients with seizures and animals with seizures. In patients, there is a loss of consciousness during many of the seizures in TLE. Most patients do not recall the seizure, which also suggests major impairments in brain function during the seizure and afterwards. However, many patients can appear normal before and after a seizure. Although they may appear normal, the cognitive tests mentioned above show that there are impairments. While the impairments during a seizure and impairments related to the recall of the seizure are directly caused by the seizure itself, altered cognitive function as described in the testing of the patients during interictal periods may be related to other effects of seizures. The potential mechanisms that have received the greatest attention in TLE are those resulting from hippocampal sclerosis. Loss of neurons in the hippocampus and associated gliosis seem to be logical reasons for impairments related to hippocampal function. More recently, the concept has expanded to include neuronal loss and gliosis in other areas that are damaged in TLE (and, notably, in AD) such as the entorhinal cortex [73,89]. In addition, other hypotheses have emerged that include changes in gene expression in surviving neurons and epigenetic effects of seizures that lead to long-lasting alterations in gene expression [90]. Also, seizures are accompanied by synaptic and vascular remodeling, and changes associated with the immune system [91].

Seizures have also been shown to impair cognitive function in animals, mostly by tests for learning and memory, such as the Morris water maze or radial arm maze, placing an emphasis on spatial memory [27,69,92]. These studies have shown that there is impairment in spatial memory in many different animal models of epilepsy, especially those with recurrent spontaneous convulsive seizures. However, the role of recurrent seizures in causing the impairments in spatial memory is unclear. The idea that seizures directly cause impairments is supported by results showing that anticonvulsants improve performance [69]. Another study showed that aberrant interictal spiking impairs behavior [93], suggesting that even brief interictal abnormalities could contribute to cognitive deficits.

Remarkably, many of the proposed mechanisms for defects in spatial memory are supported by human data, where available [27]. For example, there is evidence for circuit remodeling in TLE and AD, and some of the changes in circuitry occur in the hippocampus [27]. Also, some of the molecular alterations described in animals such as impaired $Na_v1.1$ function occur in humans [46,48]. However, it is not clear which potential mechanisms cause cognitive impairment in TLE and AD. One possibility, impaired postnatal neurogenesis, is considered below. However, many potential mechanisms exist, and until the mechanisms are clarified, it remains plausible that a spectrum of changes in both TLE and AD exists, with multiple mechanisms, and can lead to similar cognitive impairments even if mechanisms are not identical.

4. Psychiatric symptoms in patients with AD and TLE or epilepsy

Changes in behavior are common in both epilepsy and in AD [94–96]. Almost all people (over 90%) diagnosed with AD develop neuropsychiatric symptoms at some stage during disease progression [94–96], typically at early stages. Indeed, regression analyses indicate that in patients with AD, there are significant associations between mood disorders [97]. Similarly, depression, anxiety, and other neuropsychiatric symptoms are common in people with epilepsy [94,95,98].

That such changes manifest in both epilepsy and AD does not mean that they necessarily share similar underlying mechanisms, but it is at least consistent with the hypothesis that some mechanisms may be shared between the two diseases. A skeptic might suggest that the common emergence of psychiatric symptoms in both epilepsy and AD may not imply that the diseases are necessarily similar, because cognitive and psychiatric symptoms often manifest together [99]. However, from the perspective of an epileptologist, the similarities are interesting because periodic seizures or epileptiform discharges appear to cause psychiatric symptoms in patients with epilepsy.

The similarities between psychiatric features in AD and epilepsy can be mechanistically informative with regard to the underling neural systems associated with such symptoms. Below, we focus on depression as an example of a common neuropsychiatric characteristic

in patients with AD and TLE where there have been many advances in understanding potential shared mechanisms.

4.1. Depression in AD

Studies from clinical settings show that the prevalence of a major depressive episode in patients with AD is 20–25%, with other depressive syndromes and minor depression occurring in an additional 20–30% of patients [100]. These rates are three to four times higher than those observed in people over the age of 65 without dementia. The frequency of depression can reach close to 90% of patients with AD when including mild dysthymia, a chronic type of depression that is less severe than major depressive disorder [100,101]. Together, such studies suggest that depression is a disease-related feature of AD and that identifying the underlying causes will help both define disease pathophysiology as well as lead the way for treatments for this neuropsychiatric co-morbidity.

There are several risk factors for depression in AD, which include family history of mood disorders, prior personal history, female gender, and younger age of onset [100,102,103]. However, the evolution of depression in AD is not well-characterized and appears to be heterogeneous among patients [104]. Depression is frequently an early symptom of AD [100,105]. Epidemiological studies indicate that depression is common in early to moderate AD but is less prevalent in severe dementia [100]. However, it is not clear whether the decline in prevalence of depression in later stages of AD is related to the difficulty in assessing it. Several factors can complicate the diagnosis of depression in later stages of AD [104]. Symptoms of depression can sometimes be too subtle to detect, particularly because they may overlap with apathy or other neuropsychiatric symptoms, and because older adults with depression tend to report fewer affective symptoms. In addition, depressive symptoms can fluctuate over time, and the expression of depressive symptoms can change with the progression of AD. Finally, patients in the later stages of AD typically also have impairments in communication, such as aphasia, that make it difficult to assess symptoms of depression in the same manner that can be used to assess it in patients in earlier stages of AD.

Although different studies suggest different courses of history for depression in AD, there is clear consensus that depression has negative consequences for patients with AD. Greater disabilities in cognitive function and activities of daily living have been associated with depression in patients with AD [97,104] and appear to contribute to earlier placement in assisted living or nursing facilities [104].

4.2. Depression in epilepsy

Approximately 40–50% of patients with epilepsy have depression symptoms [106,107]. Patients with epilepsy are at high risk for developing major depression relative to the general population, with upwards of 5–20-fold higher incidence of depression in patients with epilepsy [95,108,109]. Individuals with major depressive disorders also have a 4–7-fold increased risk of developing new-onset epilepsy [95,109], indicating a complex interrelationship between epilepsy and depression. Focal epilepsy and complex partial seizures, particularly in TLE, are associated with depression [94,106]. Moreover, high seizure frequency and drug-resistant epilepsy are linked to depression [94].

4.3. Depression in AD and TLE: a comparison of potential mechanisms

4.3.1. Serotonin and norepinephrine

One of the most common hypotheses for depression is dysfunction of the serotonergic system, and this hypothesis is often expanded to include a role for other ascending brainstem projections such as the noradrenergic neurons of the locus coeruleus. Depression in AD has

been suggested to result from loss of serotonergic and/or noradrenergic neurons [100]. Similarly, deficits in serotonergic and noradrenergic transmission are associated with depression in TLE [95]. Therefore, in both depression and AD, an underlying vulnerability of the monoaminergic brainstem ascending pathways appears to be present.

Whether depression gives rise to seizures or seizures that involve hippocampus lead to depression is unclear, and in publications about depression and epilepsy, a bidirectionality is proposed [95]. In AD, there is evidence that there is a loss of monoaminergic tone in the early stages of the disease, suggesting that it may occur before any other symptoms. However, as mentioned above, seizures in AD can occur in the early stages of the disease and as a result, could drive the depression. In TLE, the stage at which monoamines decline and depressive symptoms occur is variable, suggesting that the decline may be involved in the seizures or arise as seizures emerge. Therefore, the data from patients make it difficult to conclude – although an attractive hypothesis – that monoamine deficits cause depression in both AD and TLE, and that hyperexcitability or seizures contribute.

4.3.2. Network excitability

In addition to alterations in ascending brainstem systems, cross-sectional studies demonstrate that hippocampal hyperactivation is also associated with depression [110]. These findings may be related to serotonergic hypofunction because serotonin acts to hyperpolarize some neuronal cell types, such as dentate gyrus granule cells; in addition, serotonin appears to excite GABAergic interneurons [111–114]. When patients with depression were imaged both before and after receiving pharmacological or behavioral treatments, results indicated that a decrease of metabolism in the hippocampal formation was associated with treatment efficacy [110,115]. Thus, depression appears to be associated with a relative state of hyperactivation of the hippocampus, along with other regions of the frontal lobe including subregions of the anterior cingulate gyrus, caudate, thalamus, and amygdala [110,115]. In TLE, hippocampal activity/metabolism alternates between basal hypometabolism and phases of hypermetabolism that occur during seizures and that can invade cortical regions [110,116,117], which could contribute to hippocampal hyperactivity and its associated state, depression.

There is evidence for hippocampal hyperactivation from fMRI studies in asymptomatic subjects with elevated genetic risk for AD, patients with mild cognitive impairment (MCI), and patients with AD [118]. Patients with MCI also display hyperactivation of the hippocampus and the entorhinal cortex [9,118,119]. Cognitively intact individuals with genetic risk factors for AD, such as the ApoE4 allele or mutations in presenilin-1, perform equivalently on various tasks but show significantly greater activation of medial–temporal lobe regions including the hippocampus compared to noncarriers [120], leading to the hypothesis that hippocampal hyperactivation might reflect compensatory mechanisms. However, longitudinal evaluation of patients with MCI showed that the greater the degree of hyperactivation during baseline recordings, the greater the degree of cognitive decline upon follow-up [121]. In a subset of patients with MCI with the highest risk for conversion to AD, normalizing hyperactivity with the antiepileptic drug levetiracetam improved performance on hippocampal-dependent tasks [9]. Patients with AD per se display hypoactivation of medial–temporal lobe areas concordant with atrophy [119]. These studies suggest an inverse U-shaped curve wherein hippocampal hyperactivation in presymptomatic/prodromal stages may be compensatory; however, as disease progresses, continued hyperactivation precipitates cognitive decline and, perhaps, psychiatric symptoms such as depression that are also associated with hippocampal hyperactivity.

It is noteworthy that one feature that is shared by depression, epilepsy, and AD is that deep brain stimulation (DBS) provides some therapeutic benefit for all of these conditions. The shared therapeutic effect could be related to an activation of inhibitory mechanisms that in turn counteract hyperactivity, but it is not known. Stimulation of

the anterior thalamic nucleus provides seizure control, particularly for drug-resistant epilepsy [122]; stimulation of the anterior thalamic nucleus or the anterior cingulate gyrus improves symptoms of depression [110,123]; and recently, it was found that stimulation of the fornix in patients with AD improved cognition over a one-year period, whereas non-stimulated patients typically show noticeable cognitive decline during that timeframe [124]. That similar therapeutic strategies produce benefit for seemingly unrelated conditions provides support for the hypothesis that they share common neurobiological mechanisms.

4.3.3. Postnatal neurogenesis

One of the hypotheses for the basic mechanisms underlying depression is that postnatal neurogenesis in the dentate gyrus is disrupted, because postnatal neurogenesis is critical in stabilizing mood. This idea was proposed after it became clear that postnatal neurogenesis in the dentate gyrus is a robust phenomenon in both rodents and humans [125] and that postnatal neurogenesis is decreased in animal models of depression; furthermore, antidepressants increase postnatal neurogenesis [126,127].

A defect in postnatal neurogenesis may help explain the common observation of depression in AD and TLE because defects in postnatal neurogenesis are present in the animal models of both disorders. In APP mice, it has been shown that the rate of neurogenesis is altered, usually decreased, although increases have been reported [128–130]. In animal models of TLE, it has been shown that there is a chronic reduction in postnatal neurogenesis in the dentate gyrus in models where brain damage is severe [131], although acute seizures increase neurogenesis [132,133].

How can these various studies be reconciled? One possibility is that depression occurs when postnatal neurogenesis is altered in a robust manner, regardless of whether it is up- or down-regulated. Another explanation is based on the finding that acute seizures cause a rise in the rate of postnatal neurogenesis, irrespective of the cause of the seizures [132–135]. Moreover, the new neurons that arise after seizure-induced neurogenesis are often abnormal [136,137]. Therefore, in both AD and TLE, there could be many changes in the rate of neurogenesis, i.e., up- or down-regulation, but a common defect in that new neurons do not appropriately integrate into the existing circuitry. Consistent with this possibility, it has been shown that an imbalance between GABAergic and glutamatergic signaling in the dentate gyrus of APP mice impairs the morphological and functional maturation of newborn neurons [138]. Thus, abnormal new neurons may be a common element of AD and TLE and result in similar depressive phenotypes.

Postnatal neurogenesis may also play a role in cognitive function in AD and TLE because it has been linked to functions of the dentate gyrus related to pattern separation. Pattern separation is the discrimination of patterns of afferent input. The type of pattern separation that is dependent on the dentate gyrus is the type that discriminates minor differences in patterns of input, such as two objects that are identical except for a subtle difference in the shape or position in space. How new neurons support this function is not clear, but several studies now suggest that they are critical [139,140].

In summary, dysregulation of postnatal neurogenesis is a potential common mechanism for depression in both TLE and AD. The defect could be a change in the rate of neurogenesis or the altered state of newborn neurons. However, the end result could be similar: defects in the function of the new neurons. This mechanism may also explain common cognitive impairments in TLE and AD that are related to discrimination of features in the environment that are usually easily detected. In turn, confusion or anxiety may develop, which is a common finding in patients. However, as attractive as postnatal neurogenesis is as a potential mechanism for depression, there are also many other possible mechanisms underlying depression, and depression itself includes many subtypes that are likely to depend on different mechanisms. Therefore, many more studies will be required, both in the clinic and in animal models, before the mechanisms are clear.

5. Conclusions and avenues for future research

Identifying similarities and differences between epilepsy and AD is important because it could help define new targets for drug development in these diseases. Broadening the target pool is greatly needed in epilepsy because the antiepileptic drugs that are currently available often fail to stop seizures or have adverse side effects. In AD, new drugs are also sorely needed, because disease-modifying therapeutics are currently not available, and the numbers of affected individuals are growing rapidly as the aged sector of the population increases. One of the first places to gain clarity about similarities and differences with epilepsy is the clinic, by more comprehensive analyses. Unfortunately the ideal (prospective) studies may take years, even decades, to complete because of the slow progression of AD. The use of animal models can help shed light on the mechanisms of disease pathogenesis because of the relatively short lifespan of rodents, the most commonly used laboratory animals to study AD. However, rodents do not develop seizures or AD without transgenic or other experimental manipulations, unlike humans. When experimental methods are used to induce pathology in rodents that simulate epilepsy or AD, the animals still fail to simulate the complete repertoire of alterations/pathology associated with the human disease. Despite these limitations, however, rodents are excellent models for testing hypotheses about how specific AD- or seizure-related molecules and/or mechanisms contribute to disease pathogenesis [36,141]. Many new advances are being made regarding how seizures may affect network, cognitive, and behavioral processes in AD mouse models, with implications for human AD. The analysis of seizures in AD mouse models has highlighted key processes and possible therapeutic approaches that deserve further analysis with respect to the clinical population. For example, as shown in a recent study, levetiracetam was highly effective in a mouse model of AD, even if other anticonvulsants were not: levetiracetam reduced seizures and improved cognitive function [37]. Similarly, levetiracetam reduced the hyperactivation of the dentate gyrus and ameliorated impairments in dentate function in a patient with a prodromal form of AD [9]. Therefore, studying seizures in mouse models of AD or complementary use of AD mouse models and animal models of epilepsy may provide clues to new therapeutic opportunities in the future.

Acknowledgments

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