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Commonalities in epileptogenic processes from different acute brain insults. Does it translate?

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Supporting Information

Additional Supporting Information may be found in the online version of this article

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Abstract

The most common forms of acquired epilepsies arise following acute brain insults such as traumatic brain injury, stroke, or CNS infections. Treatment is effective for only 60-70% of patients and remains symptomatic despite decades of effort to develop epilepsy prevention therapies. Recent preclinical efforts are focused on likely primary drivers of epileptogenesis, namely inflammation, neuron loss, plasticity and circuit reorganization. This review suggests a path to identify neuronal and molecular targets for clinical testing of specific hypotheses about epileptogenesis and its prevention or modification. Acquired human epilepsies with different etiologies share some features with animal models. We identify these commonalities and discuss their relevance to development of successful epilepsy prevention or disease modification strategies. Risk factors for developing epilepsy that appear common to multiple acute injury etiologies include intracranial bleeding, disruption of the blood-brain barrier, more severe injury and early seizures within a week of injury. In diverse human epilepsies and animal models, seizures appear to propagate within a limbic or thalamocortical/cortico-cortical network. Common histopathology features of epilepsy of diverse and mostly focal origin are microglial activation and astrogliosis, heterotopic neurons in the white matter, loss of neurons, and the presence of inflammatory cellular infiltrates. Astrocytes exhibit smaller K^+ conductances and lose gap junction coupling in many animal models as well as in sclerotic hippocampi from temporal lobe epilepsy patients. There is increasing evidence that epilepsy can be prevented or aborted in preclinical animal models of acquired epilepsy by interfering with processes that appear common to multiple acute injury etiologies, e.g., in post-status epilepticus models of focal epilepsy by transient treatment with a trkB/PLCγ1 inhibitor, isoflurane or HMGB1 antibodies and by topical administration of adenosine, in the cortical fluid percussion injury model by focal cooling, and in the albumin post-traumatic epilepsy model by losartan. Preclinical studies further highlight the

roles of mTOR1 pathways, JAK-STAT3, IL-1R/TLR4 signaling and other inflammatory pathways in the genesis or modulation of epilepsy after brain injury. The wealth of commonalities, diversity of molecular targets identified preclinically, and likely multidimensional nature of epileptogenesis argue for a combinatorial strategy in prevention therapy. Going forward, the identification of impending epilepsy biomarkers to allow better patient selection, together with better alignment with multi-site preclinical trials in animal models, should guide the clinical testing of new hypotheses for epileptogenesis and its prevention.

Keywords

Epileptogenesis; acquired epilepsy; antiepileptogenesis; traumatic brain injury; stroke; status epilepticus; CNS infections

Introduction and clinical context

Approximately 20-60% of all epilepsy is caused by acute CNS insults[1]. In the U.S., traumatic brain injury (TBI) causes approximately 6% of all epilepsies, cerebrovascular accident (CVA) 11%, infections 4%, and new onset cryptogenic status epilepticus (SE) <1%[2].

The ability to prevent epilepsy after brain injury or reduce its severity is one of the great unmet needs in neurology[3]. A latent period of days to years often exists between the acute insult and the onset of clinically obvious epilepsy[4] (Fig. 1). This post-injury interval offers an opportunity to intervene with treatment to prevent or delay epilepsy. No preventive treatment exists, yet few preventive studies have been conducted during the last 25 years despite the availability of a variety of drugs marketed for non-epilepsy indications that may have antiepileptogenic or disease-modifying effects in animal models.[3,5,6,7] One reason for this is that -in the absence of prospective invasive EEG data- the incidence of epilepsy after acute epileptogenic insults appears relatively low (e.g., 20-50% after moderate to severe TBI), and the clinical diagnosis of spontaneous (“late”) seizures can take years, making clinical trials logistically challenging. Furthermore, there is uncertainty about whether the results of animal studies can be extrapolated to humans. The most commonly used animal models of epileptogenesis are post-SE models of temporal lobe epilepsy (TLE) and kindling models. The validity of applying results from these models to human epilepsy developing after TBI, CVA or infections has not been established.

In some implementations of fluid percussion injury (FPI; a model of TBI) with invasive-EEG monitoring, only 20-50% of the animals appear to develop epilepsy and their epileptic seizures are infrequent.[8,9] However, optimization of the FPI model to maximize incidence and speed of epileptogenesis, and EEG montage to detect focal perilesional neocortical seizures, has resulted in a post-traumatic epilepsy (PTE) model that produces rapid epileptogenesis (>90% incidence of spontaneous seizures within 1 month of brain injury) and frequent seizures, including focal neocortical seizures that do not spread to the hippocampus, and this model has been successfully deployed in anti-epileptogenesis studies.[10,11]

Clinical evidence points to common elements among the acute brain injuries that lead to human epilepsy (Fig. 1), which may provide insights into common mechanisms of epileptogenesis. (Box 1 and Supplementary Text 1). Although only a small proportion of patients with TBI, CVA and infections develop epilepsy, certain subgroups of patients have a higher risk. Risk factors (Table 1) may provide insights into common mechanisms of epileptogenesis. The highest risk factors for epilepsy after acute injury include extravasation of blood due to breach of blood vessels (TBI with intracranial hemorrhage, CVA due to cerebral hemorrhage or ischemic CVA with hemorrhagic conversion), severe injury, disruption of blood-brain barrier (BBB) with cerebral edema (encephalitis, febrile SE), early seizures occurring within one week after injury, and involvement of frontal or temporal lobes (Table 1). All but locus of injury are associated with an inflammatory response; other converging mechanisms by which these risk factors may promote epilepsy are discussed in Supplementary Text 1. The focal epilepsies resulting from such brain insults, e.g., TLE with hippocampal alterations or neocortical epilepsy, which can also involve hippocampal abnormalities, are often similar and reinforce the notion of commonalities in epileptogenic processes.

The purpose of this review is to examine the evidence for possible commonalities in epileptogenic processes among different causes of acute injury in humans, and among different animal models of acquired epileptogenesis. We attempt to answer the question whether evidence from diverse animal models can be applied across the different common causes of human epilepsy after acute injury, and be utilized in translational studies of epilepsy prevention.

Clinical evidence for commonalities in focal epilepsies resulting from different acute injuries in adults and children is described in more detail in Supplementary Text 1.

Acute brain injury EEG findings and how they relate to later epilepsy

The similarities in acute EEG findings in a variety of acute brain injuries are much more striking than the differences. Nonconvulsive seizures are seen in 13-25% overall, and are increasingly seen with more cortical involvement, more intraparenchymal blood, acute clinical seizures, and the presence of coma.[12,13] Similarly, spreading depolarizations (a form of peri-injury spreading depression seen on intracranial EEG) are common in a variety of acute brain injuries, including subarachnoid hemorrhage, TBI, spontaneous intraparenchymal hemorrhage, and malignant ischemic stroke.[14] Acute nonconvulsive seizures, periodic discharges and spreading depolarizations have been independently correlated with adverse physiological effects and worse neurological outcomes in numerous studies.[15]

Only a few investigations have looked at the later development of epilepsy based on acute EEG findings, but they seem to have predictive value as well. For example, a study of children undergoing continuous EEG monitoring in the pediatric ICU showed that 47% of those with acute symptomatic electrographic SE went on to develop epilepsy, versus 11% in those without this EEG finding.[16] Electrographic SE had an odds ratio of 13.3 for development of epilepsy; it was also associated with worse functional outcome and quality

of life. In a study of >100 survivors who had lateralized periodic discharges (LPDs) or nonconvulsive seizures (NCSzs), new development of epilepsy was seen in 17% of those with LPDs only, 38% with NCSzs only, and 48% with both LPDs and NCSzs.[17] Thus, patients with these acute EEG findings may be an appropriate cohort for epilepsy-prevention trials.

In critically ill patients, invasive EEG reveals seizures and PDs in a higher percentage of patients than can be seen on scalp EEG, some of which appear to be causing metabolic distress.[18,19] Whether these findings will predict later epilepsy, or whether detection of acute high-frequency oscillations (HFOs) with this type of recording will be as predictive as they are in animal models[20], remains to be determined.

Thus, there appear to be commonalities in the acute EEG findings and in their prognostic significance, regardless of the specific type of acute brain injury. However, there has been minimal work on whether serial scalp EEGs can detect those patients that are in the process of developing epilepsy, or whether the specific type of acute brain injury matters once a given pattern is seen.

Genetic aspects in patients

There is little doubt that genetic factors have a role in the likelihood of developing epilepsy after acquired acute brain insults. The study of the genetic basis of familial epilepsies with Mendelian inheritance and the epileptic encephalopathies has clearly established the role of genes expressing ion channels, components of synaptic machinery, and other cellular determinants of network excitability.[21,22] Some of these same genetic variants (e.g., DEPDC5, LGI1, PCDH19, SCN1A, GRIN2A, KCNQ2, GABRG2, and others) are weakly associated with common forms of non-acquired epilepsy where a genetic basis is suspected given there is no identifiable insult or lesion.[23] Thus, as suggested decades ago[24], it is highly likely that variants in these and other genes in normal humans influence the likelihood of developing epilepsy after acute brain injury. This concept is supported by the observation that the genetic background of rodents can be a major determinant in the development of chronic, recurrent seizures following a variety of brain insults[25]. The observation that coexpression of two different genes with epilepsy-causing mutations can mask the severity of epilepsy caused by each acting individually[26] likely contributes to the variable penetrance of epilepsy risk genes. However, it is not yet known whether any of the mechanisms of network dysfunction associated with the myriad of genetic epilepsies overlap with the underlying molecular basis of the acquired epilepsies.

Few clinical or epidemiological studies of epilepsy following brain injury have investigated the role of genetics. Jennett reported that a family history of epilepsy was more common in young patients with posttraumatic epilepsy[27], but other studies showed no association in patients of any age.[28,29,30] Ottman et al. found no increased family history of epilepsy in patients who developed chronic seizures after stroke or meningitis/encephalitis. In the most definitive study of TBI to date, Christensen and colleagues[31] followed more than 1.6 million Danish children and adults for up to 30 years after TBI, and found that patients with a family history of epilepsy had a notably higher risk of epilepsy after mild (Relative Risk 5.75) and

severe (10.1) TBI. In epilepsy developing after SE, twin studies have suggested a clear genetic influence in both febrile and afebrile SE[32,33], but no large-scale studies in the general population have been completed to date.

With regard to the identification of *specific* genetic variants associated with the development of epilepsy following brain injury in humans, most findings come from studies of TBI. A recent review by Bennett et al.[34] summarizes the results of 31 separate studies describing polymorphisms in 24 genes, including genes involved in the inflammatory response (e.g. pro- and anti-inflammatory cytokines such as tumor necrosis factor(TNF)-α and interleukin(IL)-6), neuronal plasticity (e.g. brain-derived neurotrophic factor, BDNF), and cognitive function (e.g. catechol-O-methyl transferase). Some of these genes are of particular interest given the roles of inflammatory factors and growth factors in epileptogenesis.[35,36] Other reports have implicated glutamic acid decarboxylase[37], glutamate transport genes[38], and the adenosine A1 receptor[39]. Only two studies have reported genetic associations with PSE; one identified a polymorphism in a TNF receptor, CD4[40], and the other in mitochondrial aldehyde dehydrogenase 2[41]. Much more work is required to verify these findings as well as their biological relevance.

Common neuropathology findings in focal human epilepsies

The neuropathology in 9,523 patients with focal epilepsy and epilepsy surgery in 36 European centers was recently reviewed (European Epilepsy Brain Bank; for details see Blümcke et al.[42]). 36 histopathology diagnoses were described, classified into seven categories. Hippocampal sclerosis, brain tumors, and malformations of cortical development (MCD) were most common, accounting for 78.8% of the series. 72% of lesions were located in the temporal lobe, compared to 13% in frontal and 9% in multiple lobes.

The following structural commonalities were identified:

1. Reactive astrogliosis is always visible in epilepsy surgery specimens.[43] In the neocortex of patients with epilepsy, astrocytes are typically activated at the BBB or blood-CSF-barrier (Fig. 2A). In subcortical white matter, fibrillary (or spider) gliosis can be seen. It is difficult to microscopically identify single astrocytes in this condition as they are covered and hidden by a dense meshwork of spider-like ramifying processes (Fig. 2B). This pattern is the likely cause for neuroimaging changes in white matter of patients with TLE.[44] Astrocytes may play a significant role in epileptogenesis (see separate section below).
2. Excess of heterotopic neurons in white matter can be seen in many epilepsy-surgery specimens, such as hippocampal sclerosis or MCD (Fig. 3). This is referred to as “mild malformation of cortical development” when detected only as microscopic abnormality[45,46] Heterotopic neurons are rare in other brain diseases, but consistently reported in epilepsy.[45,48,49] No pathomechanistic hypotheses have been developed yet from this observation.
3. White matter angiopathy is also common[50], seemingly unrelated to a specific disease category, but associated with early seizure onset and long-seizure duration.

4. Inflammatory cellular infiltrates are frequently found. Lymphocytic infiltration can be provoked during peri-surgical manipulation of brain tissue. Intracranial neurophysiology techniques applied during pre-surgical evaluation can also induce a mixed lymphocytic-microglial signature.

A common feature of these histopathology findings is anatomical localization in the white matter which, in epilepsy, is an under-studied anatomical compartment. The epileptogenic lesion is connected via axonal projections to its target regions, together referred to as the *seizure network*. In focal epilepsy, synchronized activation within the seizure network produces the clinical semiology. As yet, we have neither basic nor clinical evidence for seizures arising directly from white matter.

In addition to these histopathology findings, epigenetic alterations may be involved in epileptogenesis.[51] Electrical membrane activity transmits directly into the cell nucleus, thereby driving and adjusting a neuron's response, including molecular memories that underlie long-lasting response to the environment, i.e. the molecular memory of a neuron.[52] Epigenetic histone code modification and long-lasting DNA methylation are a hallmark of molecular memory.[53] Increased DNA methylation patterns occur in various animal models of epilepsy and in drug-resistant human epileptic brain tissue.[51, 54-57] It can be hypothesized that sustained epileptic activity alters the molecular memory of a neuron, promoting the development of a chronic epileptic state, which can be termed "epileptogenic memory".

Commonalities in routes of seizure propagation from different epileptic foci

Commonalities in the pathways of seizure propagation are likely a function of the underlying network architecture - with circuits permissive to re-entrant activity being particularly vulnerable to ictogenesis.[58] In some models of epilepsy (e.g., amygdala kindling, intra-hippocampal kainate injection) primary injury is localized, whereas in others (e.g., SE) injury is diffuse, yet generally, the seizure phenotype is the same.[59] Injuries after TBI, hypoxia/ischemia, or infection may likewise be focal or diffuse, and similarly engage two primary networks when propagating beyond the initial focus: (1) the limbic seizure network seen in TLE, and (2) a thalamocortical network similar to that seen in absence epilepsies, characterized by bilateral spike-and-wave discharges (SWDs) and behavioral arrest. Simply put, because the routes of seizure propagation are constrained by anatomy[60], so are the electrographic and behavioral responses to epileptogenic insults (Fig. 4).

In most SE models, subcortical and temporal cortical damage is thought to drive seizure generating network(s).[61] In many of the TBI and stroke induced epilepsy models, however, the seizure onset zone is likely located in the cortico-thalamo-cortical network, although comprehensive studies remain to be done.[62-66] The hippocampus, amygdala, piriform and entorhinal cortices are low-threshold entry points into the limbic seizure circuit.[67,68] Conceptually, nodes of this network can be thought of as drivers (e.g., cortical regions, hippocampus, amygdala) and distributors (e.g., midline thalamus) that relay ictal activity from the driver focus to a broader network (Fig. 4A). The thalamocortical network has been best examined with absence seizures: corticothalamic drivers recruit intrathalamic distributors which in turn recruit thalamocortical drivers (Fig. 4B).

While the nonconvulsive focal seizures reported in acquired models typically have a higher frequency than that of genetic absence bilateral seizures, they might engage this same circuits.[64, 69, 70] In both of these circuits, primary components may be modulated by inputs that, while not central to ictogenesis, can influence patterns of excitation and/or gate seizure activity.

Perilesional focal seizures or pathological high frequency oscillations (HFOs) at the site of injury often predominate in the early post-injury phase and precede the development of limbic or thalamocortical spreading seizures.[20,71,72] While HFOs are behaviorally silent (i.e., purely electrographic), non-spreading perilesional focal seizures induce behavioral arrest when occurring in the frontal neocortex[63], but appear behaviorally silent when occurring in the parietal or occipital neocortex[72,73]. The emergence of seizure activity beyond the injury site may be thought of as secondary epileptogenesis.

Seizure activity evoked by direct activation of cortical drivers gains rapid access to the limbic seizure network by virtue of cortico-cortical projections, cortico-thalamic projections and projections from cortex to subcortical drivers.[74-77] Similarly, subcortical foci recruit cortical seizure involvement through direct projections and through distributors.[78,79] Cortical foci may likewise recruit the thalamocortical circuit.[80] In many models for example, focal suppression of activity in the thalamus is potently anticonvulsant[64, 79, 81, 82] and the same is true in patients with drug resistant types of focal epilepsy[83].

Direct injury to cortical drivers after TBI - frontal, parietal, or occipital-directed FPI- all trigger pathology in hippocampus, and are associated with both limbic seizures and thalamocortical-like seizures that present -just like in humans- different clinical correlates depending on the ictal sites.[70, 71,73] Suppression of ventrobasal neuron activity after cortical infarct inhibits seizures both in the cortex and thalamus[64], suggesting that just as in some evoked models (e.g., cortical penicillin), activity in the thalamus is necessary to maintain cortical seizures.[80]

Direct injury to sub-cortical drivers (e.g. hippocampus after TBI) is unsurprisingly associated with primary seizure onset zones in the hippocampus. However, seizure onset has also been reported in other nodes of the network, including cortical drivers such as piriform cortex.[84] This pattern is similar in rats and humans, where even within a single subject, seizures may initiate at different foci.[85-87] Direct injury to cortical drivers after TBI is particularly informative - frontal, parietal, or occipital-directed FPI *all* trigger pathology in hippocampus, and are *all* associated with both limbic seizures and thalamocortical-like seizures.[71,73] Primary injury to the hippocampus after focal herpes encephalitis[88-90] or Theiler's murine viral encephalitis[91-93] is likewise associated with hippocampal seizures[94]. Secondary injury to subcortical drivers is also seen after TBI, controlled cortical impact (CCI), and photothrombotic CVA lesions. These changes in hippocampus along with primary cortical injury may underlie the decreased resting state BOLD[95] and the decreased cortical and hippocampal glucose utilization reported after FPI[96].

In addition to the temporal lobe seizure phenotype seen in some models, several models of acquired epilepsy display non-convulsive focal seizures. Brief focal seizures, with

accompanying behavioral arrest have been reported after FPI, ballistic injury, and ischemic injury in rats.[64, 97-100] These are associated with injury to cortical drivers[62, 63,70] and alterations in gene expression and physiology in intrathalamic distributors and drivers.[101] The relevance of these discharges to acquired epilepsies in humans is debated.[72,102,103]

Cases in which seizures originate from sites distal to the injury are perhaps the most interesting and suggest that insults can exert epileptogenic effects by engaging a constrained set of networks. While a great deal is known regarding these networks in evoked seizures and classic models, little network mapping has been conducted following TBI, hypoxia/ischemia, or infection. Even fewer studies have directly manipulated the primary seizure circuitry in these models[64], and *no* studies have manipulated modulators (e.g., basal ganglia, cerebellum) after these insults, although they gate a wide variety of seizures in other models.[104-107] These areas of future exploration may prove essential to determining the degree of network overlap among these models and other models of acute or acquired epilepsy, and may likewise guide network level interventions for acquired epilepsies.

Commonalities in circuit reorganization after acquired brain injuries

Acquired (but also inherited) brain injuries result in complex network reorganizations. To paraphrase Eccles, Ito and Szentágothai's classic book, one can see "Epilepsy as a neuronal plasticity machine". In fact, it is difficult to pinpoint a network parameter that is *not* changed in epilepsy. Moreover, other than those with epileptic encephalopathies, seizures are usually rare events even in people with severe epilepsy (a person with daily seizures will still spend 99.9% of the time not having clinical seizures), pointing to the existence of compensatory mechanisms, which, most of the time, prevent clinical seizures from occurring. Electrophysiological changes in epileptogenesis and ictogenesis are therefore difficult to interpret, as they could constitute compensatory mechanisms, reflecting a different organization of neuronal circuits to carry the same tasks.[108]

The most obvious reorganizations commonly found in patients and animal SE models of epilepsy are cell loss, particularly of GABAergic interneurons[109-111] reactive synaptogenesis and axonal sprouting, in particular from glutamatergic neurons[112-115], and the molecular reorganization of glutamate and GABA receptor subunits.[116-118] Many of these features are also found in TBI models, such as the sprouting of excitatory axons, the increase in excitatory drive and decrease in inhibitory drive.[119,120] However, some changes, for example, GABA subunit changes during epileptogenesis, may be insult-specific.[121] Whether these modifications are similar in animal models and patients is difficult to address. In humans, the lack of proper control tissue (peritumoral non-epileptogenic tissue is usually used as control) prevents an appropriate comparison. Despite this caveat, commonalities are clearly apparent. Do these changes cause similar network consequences?

In rodent models and humans, a loss of interneurons results in decreased GABAergic synaptic (phasic) inputs.[122,123] However, phasic inhibition is decreased in the dendrites but increased in the soma in pyramidal cells[123], despite a reduction in GABA quantal release.[124] GABA also exerts tonic inhibition of neurons via activation of extrasynaptic receptors. In animal post-SE epilepsy, TBI and stroke models and in human epilepsy, there is a

preservation (or indeed an increase) in tonic inhibition, despite the decrease in phasic inhibition.[125-128] The computational consequences of the shift of GABAergic inhibition from dendritic to somatic results in inhibitory drive being more capable of synchronising principal cells, and the shift of inhibition from phasic to tonic results in an increase in the gain of neurons, whilst preserving their baseline.[123,129] The predicted net result is an increase in synchronisation and excitability during periods of increased network activity. Large scale realistic computer models now exist to test this prediction directly.[130]

The inhibitory action of GABA depends upon the reversal potential of Cl^- currents (E_{Cl}). A minority of neurons in human slices show altered E_{Cl} making GABA depolarizing[131,132], a result reproduced in rodent models but only before animals developed spontaneous seizures[133]. Interictal activity appears to depend upon depolarizing GABA *in vitro*.[131,132] In experimental models *in vivo*, interictal activity originates from interneuron firing.[134] Interneurons may play opposing roles during the progression and spread of seizure activity, and these roles may be determined both by the synchronising effects of somatic inhibition and the propensity for inhibition to become depolarising during excessive activity.[135,136] Glutamatergic drive is also increased in epileptogenic tissue from humans[137] and rodents[115], with an increased contribution of NMDA receptors, which contribute to the bursting response.[138-140]

Finally, acquired channelopathies, which could change the excitability and integrative properties of cells, have been described in experimental models.[141,142] Interestingly, genetic overexpression of Kv1.1 K^+ channels can be disease modifying in experimental models.[143] These issues remain to be investigated in human tissue.

Commonalities in electrophysiological alterations extend to seizures themselves. Seizure dynamics appear to follow general rules across species (from flies to humans) and brain regions[144], but whether electrophysiological commonalities can “explain” epilepsy is not known, as, for most, no causal link has been established. There are many different biophysical paths to seizures in any given neuronal circuit[144], and it is likely that, in most cases, the electrophysiological changes that occur just reflect lowered threshold for seizure genesis and/or facilitated seizure propagation.[145]

Common hippocampal and parahippocampal circuits and structural lesions

Many animal models of epileptogenesis involve structural etiologies, *e.g.*, TBI, stroke, and cortical dysplasia.[146] A variety of seemingly unrelated insults, including head trauma, prolonged febrile seizures, vascular abnormalities and encephalitis, can cause similar hippocampal pathology[43,147-149] and the same seizure disorder, i.e. acquired mesial TLE with hippocampal sclerosis.[150,151] The hippocampal and temporal cortical damage after experimental SE resembles that found in resected tissue of patients with refractory TLE of different etiologies, including loss of dentate hilar and hippocampal pyramidal cells, layer III damage in the entorhinal cortex, gliosis, and mossy fiber sprouting.[152-154] Notably, dentate hilar neuron loss (endfolium sclerosis) was reported to be the single common pathology in epilepsy patients with any detectable hippocampal pathology.[147]

TBI models induced with CCI or lateral FPI result in loss of hilar cells, mossy fiber sprouting, gliosis and neurogenesis, whereas granule and pyramidal cell damage is less severe than in SE models.[155] Hippocampal inhibitory neurons appear particularly vulnerable to lateral FPI.[156] In correspondence with animal models, a subpopulation of patients with TBI shows progressive hippocampal volume loss and white matter atrophy in MRI.[157,158] Taken together, hippocampal atrophy is often seen in acquired epilepsy patients and experimental models. However no study has compared hippocampal pathology between experimental models or humans with or without post-SE, post-TBI or post-stroke epilepsy, which is critical to pinpoint epileptogenesis-specific pathologies.[8]

In some rodent models, prolonged dentate granule cell discharge selectively destroys vulnerable hippocampal neurons that control granule cell inhibition[109,159], thus weakening the normal gating function of the dentate gyrus.[161-165] Mild to moderate fluid percussion injury can also cause selective hilar neuron loss and granule cell hyperexcitability.[166] Why do dissimilar insults sometimes produce similar pathology and the same neurological condition?

A central role has been proposed for excitatory dentate hilar mossy cells in establishing granule cell inhibition via activation of inhibitory neurons[159,160], and for mossy cell loss in granule cell disinhibition[109,152,165]. Optogenetic activation or silencing of dentate granule cells promoted or suppressed seizures in a unilateral hippocampal kainate mouse model, respectively[106], in support of the dentate gate hypothesis. Similar studies capable of selectively exciting or silencing residual mossy cells are needed to refute or confirm the “dormant basket cell” hypothesis.[152,167] Regardless of the network mechanism underlying injury-related granule cell hyperexcitability, the selective loss of entorhinal cortex Layer III neurons[168] and dentate hilar neurons[159] may be a common pathology produced by different insults.

An alternate perspective holds that epileptogenesis requires prolonged molecular and/or structural changes triggered by acute brain injury, because epilepsy develops only after a seizure-free period that can last for decades.[169] In this scenario, during the period from insult to clinical epilepsy the epileptogenic mechanism gradually elaborates.[66,170,172] Hippocampal transcriptomics and miRNA changes in SE and TBI models and in human TLE have been studied in an effort to identify critical pathways (Fig. 5 and Supplementary Tables 1 and 2). Very few similarities have been identified in hippocampal transcriptomics and miRNA networks among the various structural models, even when data from the same etiology (e.g., SE models) are compared, or between the experimental data and the sparse data available from human epileptic hippocampus. However, comparison of these findings has been difficult because of variability in cell types, tissue sampling, timing of tissue sampling during the course of epileptogenic process, analysis platforms, brain regions, methods for inducing injury, age and species of animals, and unknown epilepsy phenotype of animals sampled at early time points. Dingledine et al. overcame some of the methodological difficulties.[172] They performed a well-powered transcriptomics analysis of laser-dissected dentate granule cells in three different SE models, each model generated in two laboratories, used the same analysis platform, and found only 4.5% concordance of differentially expressed genes among the models.

The same hippocampal network that can serve as a primary seizure source when the hippocampal formation is injured may play a secondary role when seizure activity from extratemporal foci spreads to, and recruits, the hippocampal formation.[173] Several brain regions innervate and influence the hippocampal formation, including non-temporal neocortex, thalamus, amygdala, and septum[174], and it is likely that both the damaged and undamaged hippocampus can generate the same clinical signs regardless of where seizures start. Seizures that originate from temporal neocortical- and even extra-temporal neocortical foci may propagate to the hippocampal formation in both humans[175,176] and rodents[71].

In sum, qualitative similarities in hippocampal pathology are evident among the SE, TBI, and stroke models as well as between experimental and human TLE triggered by these etiologies. These deserve further analysis in the context of search for biomarkers (Box 2, Supplementary Table 3 and Text 2) and treatment targets of epileptogenesis.

Dysfunctional astrocytes and microglia: commonalities in epileptogenic processes

A common pathological hallmark in the sequence of events converting a normal brain into an epileptic brain after an acquired insult is microglial activation and subsequent astrogliosis, which results from inflammatory processes.[177-180] Astrocytes regulate and amplify immune-mediated mechanisms implicated in epileptogenesis.[177,181-186] Evidence from experimental epileptogenesis studies and from studies of established human epilepsy shows that astrocytes undergo functional changes including dysregulation of astroglial K_{ir} and gap junction channels, which together alter glio-neuronal communication and, by impairing uptake and redistribution of extracellular K^+ accumulated during neuronal activity, can contribute to or cause seizures.[178,185-189] Downregulation of astrocytic K_{ir} channels appears to be a common response to brain injury and has been observed after TBI[190], CVA[191], BBB damage[192], entorhinal cortex lesions[193], and freeze-lesion induced cortical dysplasia[194,195], and in association with experimentally induced posttraumatic epilepsy.[70] Similarly, patch clamp analysis in neurosurgical specimens from TLE patients reveals reduction in astroglial K^+ currents in sclerotic vs. non-sclerotic hippocampi.[196] Reduced glial K^+ conductances and loss of astrocyte gap junction coupling compromise the clearance of extracellular K^+ and impair K^+ homeostasis. Loss of coupling is mediated by pro-inflammatory cytokines and precedes alterations in neurons and K^+ clearance, suggesting a causal role of dysfunctional K^+ buffering by astrocytes in the etiology of different epilepsies.[185,186] Reduced astrocyte coupling was also reported after acute CVA *in situ*.[197] Whether glial coupling is affected after TBI is unknown. One study observed enhanced phosphorylation of Cx43 protein in astrocytes after experimental TBI[198] but functional coupling was not assessed.

Albumin extravasation into the brain following focal injury causes inflammation and activation of a TGF-β pathway in astrocytes, which impairs K^+ homeostasis and leads to epilepsy. Importantly, treatment with losartan, a clinically used angiotensin II type I receptor inhibitor, prevented epilepsy in most mice.[199] In addition to its known action as an

angiotensin II type I receptor inhibitor, losartan exhibits effects on inflammatory pathways and potassium channels[200] that might contribute to its antiepileptogenesis effect.

Astrocytes control the availability of the brain's endogenous anticonvulsant, adenosine, through expression of ADK.[201] As a molecular link between energy homeostasis and metabolic demand, ADK expression undergoes acute downregulation followed by chronic overexpression, triggered by ischemia or TBI, and chemically or electrically induced SE.[57, 202-207] Overexpression of ADK is linked to astrogliosis and has been reported in human TLE surgical specimens with hippocampal sclerosis and in tumor-associated epilepsy.[205,208-210] Increased ADK lowers tissue levels of adenosine, thereby increasing neuronal excitability and precipitating seizures.[203,206,211] In addition, increased ADK promotes DNA methylation as an epigenetic contributor to epileptogenesis.[55,57] Overexpression of ADK has been associated with progression and worsening of epilepsy.[205] Conversely, therapeutic adenosine augmentation[212,213] suppresses not only seizures but also prevents development and progression of epilepsy in systemic kainate and pilocarpine models[57,214].

In conclusion, dysfunction of glial K_{ir} channels and gap junctions, and subsequent disruption of K^+ and adenosine homeostasis are common responses of the brain to TBI, CVA, SE, BBB damage, cortical lesion and dysplasia, and may contribute to or initiate epileptogenesis. Aquaporin 4, expressed exclusively in astrocytes, is translocated from perivascular astrocytic end-feet to the parenchyma in cortical tissue resected during epilepsy surgery.[215] A role for aquaporin 4 in the disruption of water balance during epileptogenesis is worth following up.[216-218]

Inflammatory processes after acquired brain injuries

Brain inflammation, or neuroinflammation[219], is common after TBI, CNS infections, CVA and SE in humans and animals. Common to all these different acute injuries is the generation of an immune/inflammatory response in CNS-specific cells and cellular components of the BBB. A key common brain response is the rapid activation of microglia[220], which promptly release an array of frontline inflammatory molecules including damage-associated molecular patterns (e.g. HMGB1, ATP, S100β), cytokines (IL-1β, TNF-α, IL-6), various chemokines[221] and related effector pathways including COX-2/PGE2 and complement factors.[36] This shared tissue injury response might be triggered to activate homeostatic programs. However, if the ensuing inflammatory cascade persists, it leads to CNS dysfunction and neuropathology.[220] Non-immune cells like astrocytes and neurons, together with the BBB, play an important role in the immune responses to injuries.[36,179,222] As various inflammatory molecules contribute to the mechanisms of acute and chronic seizures by altering synaptic transmission and neuronal excitability[223] (Fig. 6), it is conceivable that neuroinflammation contributes to the development of various forms of acquired epilepsies.[36,175,224-226] Inflammatory mediators commonly present in human brain and related animal models after acute epileptogenic injuries are shown in Supplementary Table 4. Type and severity of injury determine the relative contribution of innate immunity and circulating leukocytes to increased inflammatory molecules, acute or secondary brain damage[227-229], and neuronal network excitability. While HMGB1 and IL-1β contribute to hyperexcitability and epilepsy

progression after SE in rodents[230-232], IL-6 has a pivotal role in epileptogenesis induced by murine viral encephalitis[233]. While antiinflammatory drugs dampen epileptogenesis in animal models of SE or viral encephalitis[231-235], there is no information whether inflammation is involved in epileptogenesis after stroke or TBI[236,237], except for focal cooling preventing both cortical IL-1 induction and epilepsy after TBI in rats[62]. There is, however, strong evidence that inflammation plays either a pathologic or beneficial role following TBI or stroke depending on the post-injury phase[238,239]. While TNF-α or CX3CR1 knock-out mice showed reduced functional deficits compared to wild-type mice acutely post-TBI, their functional recovery over time was impaired and cortical damage was increased[240-242]. Similarly, TNF-α was involved in both secondary brain damage and regenerative recovery after experimental stroke.[243-245] The pathologic involvement of inflammation is supported by evidence that excessive brain levels of IL-1β, IL-6, TNF-α (exceeding several times their serum changes) or HMGB1[232,246,247] contribute to experimental acute and chronic seizures and SE-induced epileptogenesis[36,179,226]. Importantly, HMGB1 antibodies have been shown to prevent epileptogenesis in the mouse intrahippocampal kainate model.[248] Studies of neuroinflammatory changes in postmortem human brain after CVA/stroke, TBI, infections and SE are limited, although they are essential to validate the potential pathophysiological role of injury-induced inflammation in epileptogenesis. Encephalitis-induced epilepsy caused by neurotropic viruses[226] is associated with activation of Toll-like receptors, which drives neuronal damage but may also promote tissue repair.[249] The precise relationship between viruses, inflammation and seizure development requires further studies in animals and humans.

We need to better understand the difference between pathologic vs. repair and recovery responses, and evaluate more thoroughly potential commonalities across brain injuries, in order to design drugs with broad therapeutic potential. The term “inflammation” covers many pathways some of which are beneficial after injury[238,239], such that targeted intervention at the right time could succeed when global suppression has failed.

Signaling pathway commonalities

Four pathways activated after several types of cerebral insults that are associated with epileptogenesis or epilepsy progression are Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT), mammalian Target of Rapamycin Complex (mTORC), BDNF/tyrosine receptor kinase B/phospholipase Cγ1 (BDNF/trkB/PLCγ1), and IL-1R1/TLR4 pathways (Fig. 7). These signaling pathways mediate cellular physiological mechanisms that are critical for memory formation, long-term depression (LTD) and long-term potentiation (LTP).

The JAK/STAT pathway (Fig. 7A) is activated after many types of epileptogenic injuries in experimental models, including TBI, SE and stroke.[250-255] It regulates expression of genes critical for multiple essential functions including cell proliferation, differentiation, neurogenesis, learning and memory. JAK/STAT mediates decreases in α1 subunit-containing $GABA_A$ receptors in hippocampus that occur after experimental SE and TBI[250,252] and may contribute to the increased hyperexcitability observed in the hippocampus of injured animals and to subsequent development of epilepsy. Inhibition of STAT3 phosphorylation after SE-

induced brain injury reduces the severity of subsequent epilepsy in the rat pilocarpine model[256], suggesting that JAK-STAT activation after SE may contribute to epileptogenesis. In the CCI model of PTE in mice, the JAK/STAT pathway is differentially activated depending on the severity of brain injury, and correlates with the presence and severity of subsequent cognitive co-morbidities.[257] Interestingly, transient inhibition of the JAK/STAT pathway immediately after CCI improved long-term vestibular motor recovery after injury but did not significantly affect memory performance.[257]

In rodent models, epileptogenic brain injuries including SE and TBI trigger an immediate and long-lasting increase in the phosphorylation of the S6 ribosomal protein in the hippocampus, which is a downstream marker of an excessively activated mTORC1 pathway (Fig. 7A).[258-260] Similarly, structural or dysplastic lesions associated with infantile spasms in rodents or humans also demonstrate overactivation of the mTORC1 pathway in the epileptogenic area.[261] Treatment with mTORC1 inhibitors is anti-seizure[262-264] and in some models of acquired epilepsy, particularly tuberous sclerosis, antiepileptogenic.[259,265-267] Excessive activation of the mTORC1 pathway in acquired models of epilepsy is also associated with cognitive and behavioral deficits, which may be reversed following treatment with the mTORC inhibitor rapamycin.[258,266] Taken together, these findings suggest that JAK-STAT and mTORC1 signaling pathway activation following a variety of brain injuries may contribute to development of acquired epilepsy and co-morbid hippocampal-dependent spatial learning and memory deficits.

The interaction of BDNF with receptor trkB is involved in fundamental cellular processes including neuronal proliferation, differentiation and survival as well as neurotransmitter release and synaptic plasticity. Abnormal BDNF-mediated activation of TrkB has been reported in various neurological and psychiatric disorders.[268] Altered TrkB signaling (Fig. 7B) underlies epileptogenesis in both the kindling model[35] and after SE, as demonstrated by the ability of TrkB inhibitors targeting the PLCγ1 signaling pathway that were administered during the latent period to prevent the development of acquired epilepsy in some animals.[100,269] The IL-1R1/TLR4 pathway (Fig. 7A), activated by IL-1β and HMGB1, contributes not only to acute and chronic seizure recurrence[270] and kindling[271] but also to disease progression post-SE in rodents.[231, 232,247]

The pharmacology of animal models of acquired epilepsy

The rat amygdala kindling model (AKM) of TLE has been extensively studied[6,272,273], although kindled rats do not exhibit SRS, and therefore lack a defining feature of human TLE[274]. Nonetheless, drugs effective in human TLE are effective against seizures in fully kindled rats.[275] The efficacy of various anti-seizure drugs (ASDs) in suppressing seizures in fully kindled rats is remarkably similar to their efficacy in reducing the frequency of SRS in post-SE TLE models(Table 2).[276] About 20% of kindled rats are resistant to high doses of ASDs such as phenytoin. Similarly, ASD-resistant rats can be selected from post-SE models of TLE.[275] The pharmacology of SRS developing in models of TBI, stroke or viral encephalitis is largely unknown, with some exceptions.[277-279] In models of TBI and encephalitis, valproate reduced seizure burden while carbamazepine was ineffective, indicating pharmacologic commonalities.[277,279]

Drug treatment during amygdala kindling acquisition has been used to detect disease-modifying efficacy by administering drug before each amygdala stimulation. Retardation of kindling development may indicate a true antiepileptogenic action or simply suppression of the effects of the stimulation. For most ASDs the latter is true, whereas for some drugs, including valproate, levetiracetam, and brivaracetam, effects on kindling acquisition (e.g., reduced seizure duration) persist long after drug wash-out, suggesting enduring disease modification.[6,280-282] The disease-modifying effects of such drugs have been confirmed in post-SE models of TLE[6], suggesting that there are shared mechanisms of epileptogenesis in the kindling and SE models.

A variety of experimental and clinically approved drugs has been evaluated for antiepileptogenic effects in post-SE models of TLE.[6, 275, 282, 283] Among clinically used ASDs, disease-modifying effects (e.g., neuroprotection, prevention of behavioral comorbidities, reduced frequency, duration or severity of SRS) were only detected after treatment with valproate, levetiracetam, brivaracetam or topiramate, although none of these drugs prevented epilepsy.[6, 282] While SE models involve significant neuronal loss, neuroprotection alone may be disease-modifying but not antiepileptogenic.[6] Some studies found that antiinflammatory drugs such as celecoxib or immunosupressive drugs such as rapamycin exert antiepileptogenic activity in post-SE models, but these effects appear to be very sensitive to the antiinflammatory drugs used and the timing of drug administration.[6, 261, 282, 284] Interestingly, bumetanide, which inhibits the Na-K-2Cl importer NKCC1[285] and thus increases the hyperpolarizing action of GABA, was not antiepileptogenic in the lithium-pilocarpine SE model in adult rats[286] although it was reported to have antiepileptogenic actions in a model of complex febrile seizures in rats[287] and in a mouse model of genetic epilepsy[288]. By contrast, in SE models a trkB signaling inhibitor[100,269], the multitargeted drug isoflurane, which exhibits antiinflammatory, antioxidative, antiapoptotic, and neuroprotective effects[289], and HMGB1 antibodies[248] can be antiepileptogenic, providing crucial proof-of-principle that antiepileptogenesis is possible. In addition, inhibition of the IL-1R1/TLR4 pathway, and the associated ROS production, has been shown to mediate disease modifying effects in different post-SE models.[231,232,247]

Only a few studies used TBI models to evaluate possible PTE prevention by drug treatment during the latent period.[9] When PTE was induced by rostral parasagittal FPI in rats, 5 weeks of mild focal cooling of the perilesional neocortex almost completely prevented the development of epilepsy[62], whereas he investigational drug carisbamate exerted no antiepileptogenic efficacy[278], indicating that the model is capable of detecting antiepileptogenic activity. As noted, losartan prevented epileptogenesis in a PTE model, albeit in high doses.[199]

Other studies report antiepileptogenic efficacy of statins in different models[290], and of minocycline in an encephalomyelitis virus infection model[291]. The preclinical effects of statins were translated to a clinical study. Guo et al.[259] reported that acute statin use reduces the risk of poststroke early-onset seizures, and may also prevent the progression of initial poststroke seizures to chronic epilepsy, findings that, if reproducible, would be the first proof-of-concept of antiepileptogenesis in humans.[292] Antiepileptogenic effects of statins are also suggested by two other clinical studies.[293, 294] In addition to effects on serum

cholesterol levels, statins exhibit immunomodulatory, antiinflammatory, and anti-excitotoxic properties[290], which could explain the antiepileptogenic effects that have been observed both experimentally and clinically.

Consequences for translation and development of antiepileptogenic therapies

There are three key questions. First, which of the commonalities described in neuropathology, EEG parameters, and molecular and inflammatory pathways are causes rather than consequences of acquired epilepsy? Second, are these commonalities able to clearly distinguish the patients who develop epilepsy from those who have a similar brain insult, but do not develop epilepsy? Third, to what extent do potential causal or susceptibility genes impact the propensity for developing acquired epilepsy? Biomarkers of impending epilepsy are needed to design feasible clinical trials to address these questions. Nonetheless, the richness of commonalities described in this review supports the potential benefit of combinatorial drug treatment, as already demonstrated in preclinical antiepileptogenesis studies.[295] Furthermore, these commonalities also appear to emphasize the promise of systems and network approaches towards identification of master regulators controlling epileptogenesis that may provide drug targets for future antiepileptogenic therapies.[296-298]

The first step in clinical development of antiepileptogenic therapies would be assessment of their safety and tolerability in healthy volunteers, a standard approach for Phase I studies. It will be advantageous to demonstrate target engagement in the brain before moving into later stages, in order to reduce the risk of development failure.[299,300] A newly developed synaptic density marker appears promising to measure neurodegeneration and neuronal network changes during epileptogenesis.[301] Other indirect target engagement measures could include quantitative EEG or MEG techniques[302] or assessment of specific molecular biomarkers in plasma that are clearly linked with drug activity in the brain. Development of such clinical biomarkers (Box 2) should be performed in parallel with the preclinical drug development of antiepileptogenic drug candidates.

Antiepileptogenesis studies should be performed in homogenous patient cohorts sharing similar clinical features such as, for example, severity of injury, accumulation of intracranial blood and incidence of early seizures, because these appear to be common and most likely predictors of focal epilepsy development (Table 3). Other important stratification factors should include the commonality in early EEG parameters (e.g. HFOs) and similarities in the involvement of the epileptogenic limbic structures (e.g. MRI). Furthermore, whenever possible, stratification based on molecular biomarkers should be applied (Box 2). Subjects sharing involvement of similar mechanisms such as dysregulation of the JAK-STAT, mTOR, or BDNF/trkB pathways and neuroinflammation are preferred for antiepileptogenesis trials. The importance and availability of relevant disease-specific and drug response biomarkers is critical for success in clinical development. A recent analysis of outcome of more than 1000 clinical development programs, performed between 2006 and 2015, showed that clinical development success leading to regulatory approval is three times higher when biomarkers

permit patient stratification.[303] Finally, specific causal or susceptibility genes, if properly validated in enabling studies, should be the ultimate stratification factors since their value was already demonstrated in trials targeting disease modification in other neurodegenerative diseases.[304]

Depending on the clinical development strategy, proof-of-concept studies should accumulate evidence that the onset of epilepsy is delayed after brain injury (ideally prevention of epilepsy) or that core clinical features of an ongoing epilepsy are substantially altered (disease modification). The standard ASD add-on trial design and seizure outcome may be used, the difference being that the follow-up period may need to be much longer in prevention trials to demonstrate a therapeutic effect after withdrawal of the antiepileptogenic agent.[3,283, 305]

Clinical development of drug combinations is associated with a number of significant challenges, therefore the Food and Drug Administration (FDA) issued practical guidelines to facilitate this process.[306,307] It is certainly more straightforward to develop a combination treatment that consists of already approved medications, than for two or more investigational drugs used in combination. However, regardless of the approval status of the drug constituents, the New Drug Application (NDA) submitted to the FDA should contain appropriate data to establish the overall safety and effectiveness for the new dosing regimen or indication as proposed in the combination product. Even in the case of already approved drugs such data may not be easily obtainable or compatible with the proposed drug combination, new indication or treatment regimen.

The biggest challenge in development of combinatorial drug treatments is the need to demonstrate that each constituent contributes to the efficacy. This typically involves the necessity to include single drug arms in the trial, which considerably increases the complexity of the design, overall study duration and costs. It is even more challenging if the optimal doses of each drug are not yet defined, which may require additional dose-finding studies for each drug alone or in combination. Finally, even before embarking on clinical trials additional preclinical data may be needed, e.g., safety/toxicology, pharmacokinetics (drug-drug interactions), target/biomarker interactions, etc.

Lastly, there may be legal, intellectual property and freedom-to-operate limitations, particularly for approved drugs used in combination. This may further complicate the development and commercialization of the new combinatorial product.

Conclusions and future directions

The data reviewed indicate that there are a number of commonalities among the three main acute CNS injuries that lead to epilepsy in humans – TBI, CVA and infection. At the clinical level, the presence of intracranial blood, breakdown of the BBB, severe injury, early clinical seizures and EEG seizures, and periodic discharges on early EEG increase the risk for epilepsy in all three. Common anatomical modifications include astrocytosis, white matter abnormalities impacting seizure network and propagation, and neuronal heterotopia. Common elements in animal models include involvement of anatomically constrained

networks that relay and distribute seizures remotely from the initial locus of injury, which can explain the common phenomenon of secondary epileptogenic involvement of the temporal lobe, activation of astrocytes with impairment of extracellular K^+ buffering and of adenosine homeostasis, selective death of inhibitory interneurons and disinhibition/overinhibition of primary excitatory cells, and activation of the JAK/STAT and mTORC1 pathways. On the other hand transcriptomics have as yet shown few shared gene expression changes across (or within) models, and the role of neuroinflammation and BDNF/Trk signaling in epileptogensis has been demonstrated in SE and kindling models but has not yet been evaluated in animal PTE and PSE. Whether the causes of epilepsy share common mechanisms and features with the causes of the most common comorbidities (anxiety, depression) is an important question to pursue.

Review of the data suggests several conclusions:

1. The three common causes of epilepsy after acute injury, TBI, CVA and infection, share enough risk factors, electrophysiology, and pathology features to possibly consider them, in epileptogenesis, as one broad category (with individual variations). This has major implication for preventive therapeutic development. To validate or disprove this hypothesis, we should target comparison of epileptogenic processes as well as potential biomarker discovery and therapeutic intervention in both clinical and animal studies comparatively across the three types of injury - particularly for TBI and CVA where clinical intervention is logistically most feasible. If the hypothesis proves correct, this would allow a broader approach to development of biomarkers of epileptogenesis and of preventive treatments.
2. It is still unclear whether data obtained from the logistically easier models of SE and kindling are applicable to the human conditions of TBI, CVA and infection because relevant data do not exist. This calls for a concerted effort to systematically evaluate the SE and kindling model findings in the PTE, PSE and infection models. Answering this question will determine whether biomarker and therapeutic intervention studies, which can more easily be done in SE and kindling models, have relevance for human preventive treatment discovery. If they do, this would facilitate translation from animal to clinical studies.
3. Finally, this review identifies a plethora of potential biomarkers, as well as preclinical evidence for several preventive therapeutic strategies that can be followed in human studies. Clinical preventive studies may be significantly strengthened if the preclinical studies were systematically evaluated across the different animal models. Perhaps epileptogenic features, biomarkers and positive treatments common to all the animal models may have the greatest chance of clinical success, and lead, at long last, to a breakthrough in the preventive and/or disease modifying treatment for epilepsy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1

Is the etiology of acquired epilepsy a major prognostic factor for response to treatment?

Observations on the basis of individual case series support the hypothesis that

- children with acquired vs. congenital etiology of seizures have higher seizure frequency and a less favorable outlook for terminal seizure remission,
- diffuse brain damage is more likely to result in pharmacoresistance than other substrates for focal epilepsy,
- posttraumatic and post-infectious epilepsy are commonly severe and refractory to treatment,
- epilepsy develops sooner and with higher incidence in children following SE or non-febrile cause than for febrile SE, and
- drug response is surprisingly similar for epilepsy after stroke, vascular malformation, and tumor.

For further details see Supplementary Table 5 and Supplementary Text 1.

Box 2

Biomarkers of epileptogenesis after different acquired acute brain insults

A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions. Categories of biomarkers include:

- susceptibility/risk biomarkers (e.g., epilepsy susceptibility genes or polymorphisms),
- diagnostic biomarkers (e.g., molecular, electrophysiological, or MRI biomarkers),
- prognostic biomarkers (e.g., molecular and occurrence of pHFOs and rHFOSs).

For further details see Supplementary Table 3 and Supplementary Text 2.

Key points

- Epileptogenesis after common acute brain insults shares enough features to consider it as one broad category
- We identify clinical and preclinical commonalities in epileptogenic processes and their relevance to successful epilepsy prevention strategies
- Status epilepticus (SE) model findings should be corroborated in trauma and stroke models to see whether in future SE data can be used to support human studies
- Preclinical evidence for several recently-identified preventive therapeutic strategies can be followed in human studies

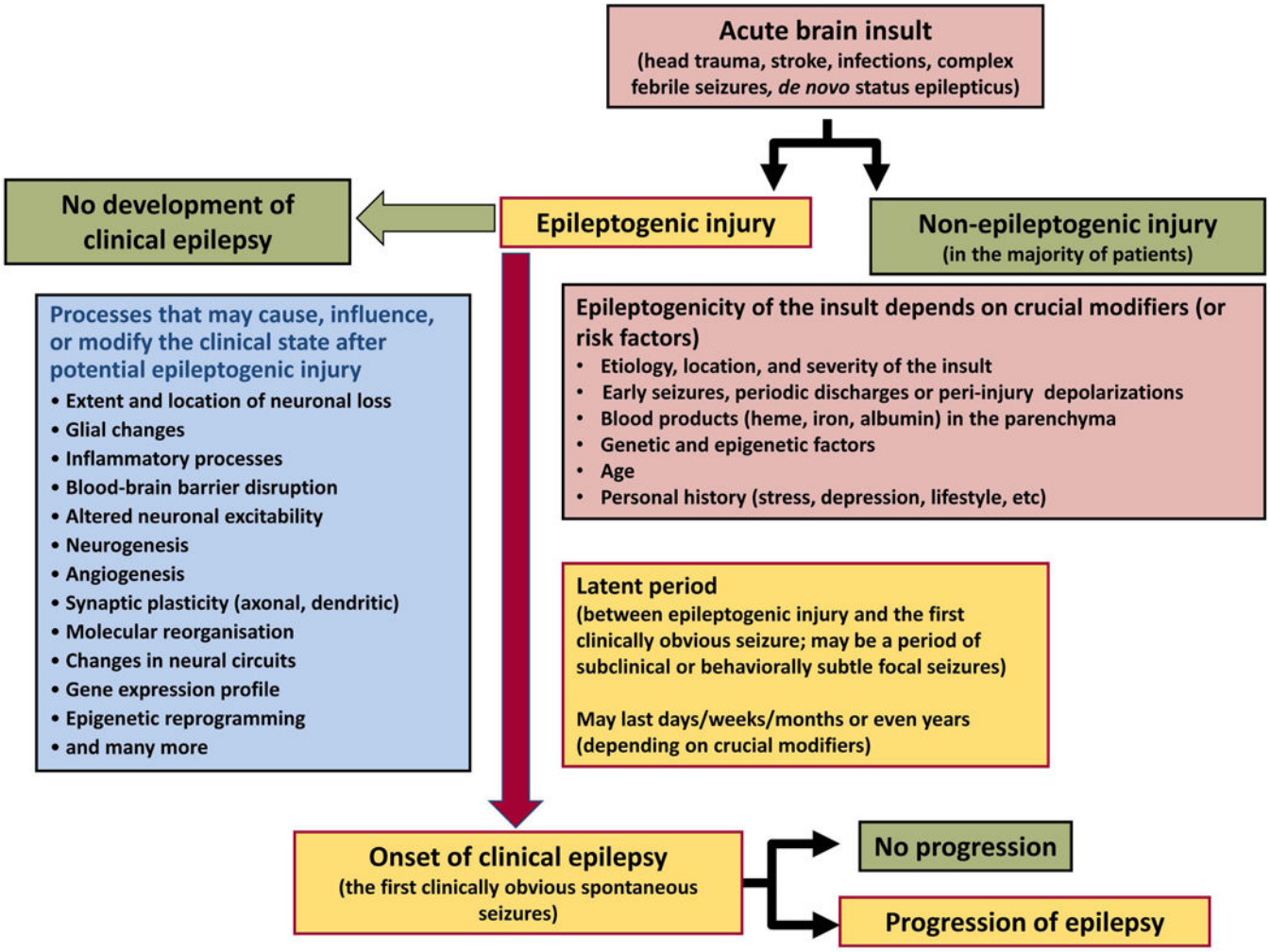

Fig. 1. Epileptogenic processes and risk factors involved in development of epilepsy after acute brain insults: a conceptual view

Possibly depending on crucial modifiers or risk factors, the same brain injury can be epileptogenic or not. In the majority of patients, brain insults do not cause epilepsy as discussed in the text. Furthermore, as illustrated in the figure, not all epileptogenic processes, once initiated, result in epilepsy, i.e. complete their course to clinically obvious disease. The term epileptogenesis includes processes that render the brain susceptible to spontaneous recurrent seizures and processes that intensify seizures and make them more refractory to therapy (progression). During epileptogenesis, multiple brain alterations occur, including altered excitability of neurons and/or neuronal circuits, activation of microglia, astrocyte dysfunction, alterations in expression and function of receptors and ion channels (in part recapitulating ontogenesis), loss of neurons, neurogenesis, axonal and dendritic sprouting, gliosis, inflammatory processes, and more. It is important to note that some of these alterations may be related to post-injury repair or recovery and not suited as targets to halt the epileptogenic process. The figure has been modified from previous versions.[3,15,276]

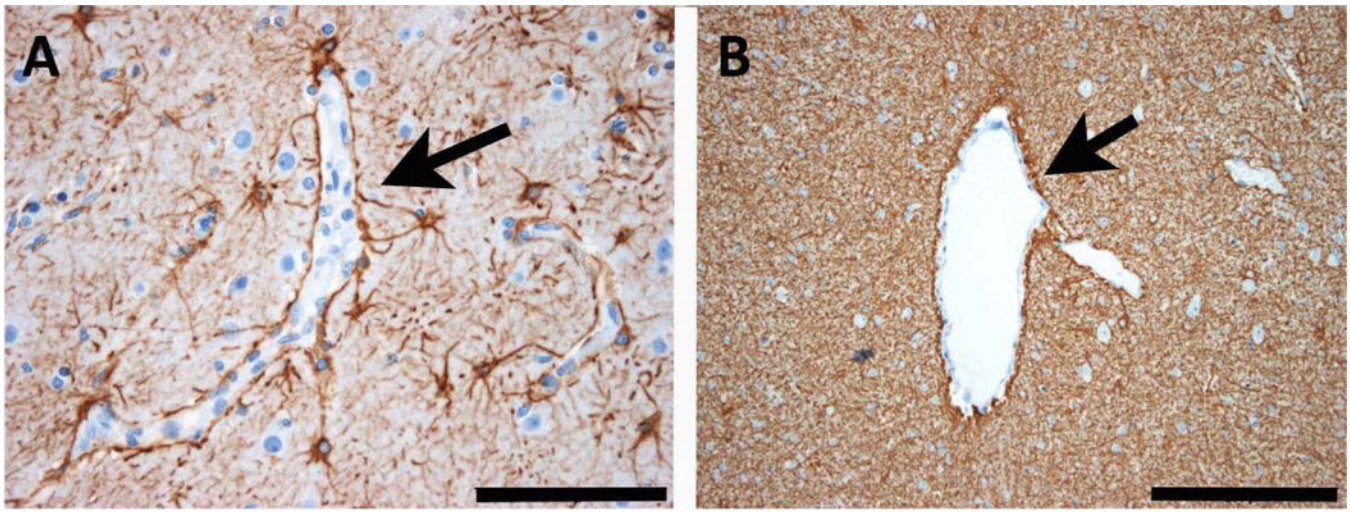

Fig. 2. Common patterns of astrogliosis in epileptic human brain tissue

A: Reactive astrogliosis in the neocortex of human epilepsy surgery brain specimens is commonly seen along cortical capillaries (arrow). ***B:*** In white matter, there is another common pattern of astrogliosis built by a dense glial fibrillary meshwork. The arrow points towards an enlarged venous vessel. Scale bar in A = 100 μm, in B = 200 μm. GFAP immunohistochemistry (brownish color) with bluish hematoxylin counterstaining.

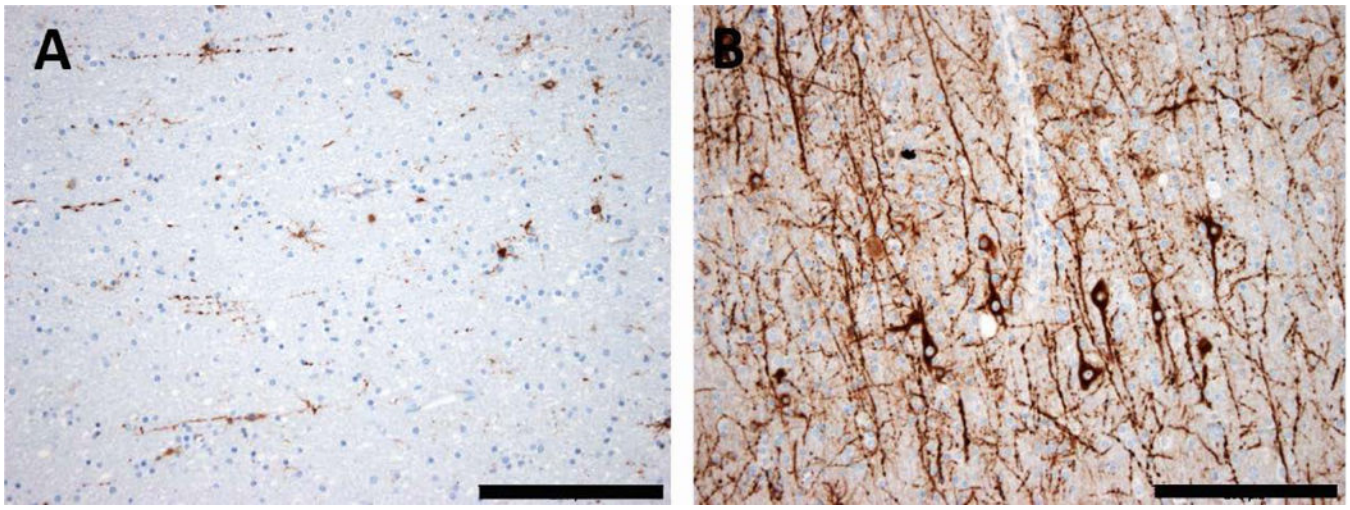

Fig. 3. Common patterns of heterotopic neurons in the white matter of epileptic human brain tissue

A: The white matter of human temporal lobe usually contains only single heterotopic neurons. ***B:*** In many epilepsy specimens of human temporal lobe, there is a vast excess of heterotopic neurons with ramifying neuronal processes in white matter. Scale bar in A and B = 200 μm. MAP2 immunohistochemistry (brownish color) with bluish hematoxylin counterstaining.

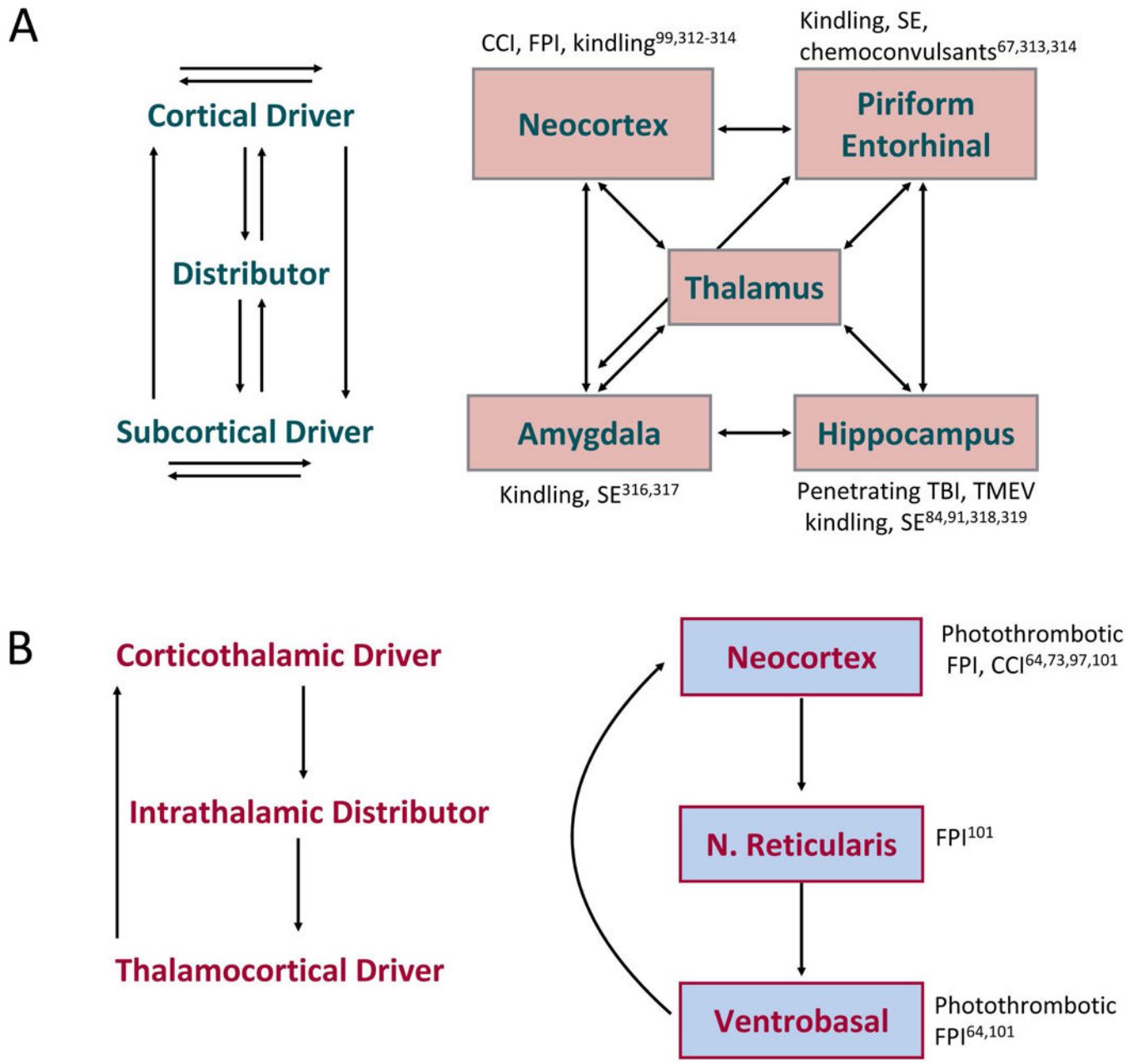

Fig. 4. Schematic illustrating components of the limbic (A) and thalamocortical (B) seizure circuits

Areas impacted by particular epileptogenic insults (both classic and newer models of acquired epilepsy) are noted near particular network nodes. Arrows indicate interconnections between the nodes. Due to the distributed nature of these circuits, many sites may trigger, lead, or participate in seizure activity.[308,309]

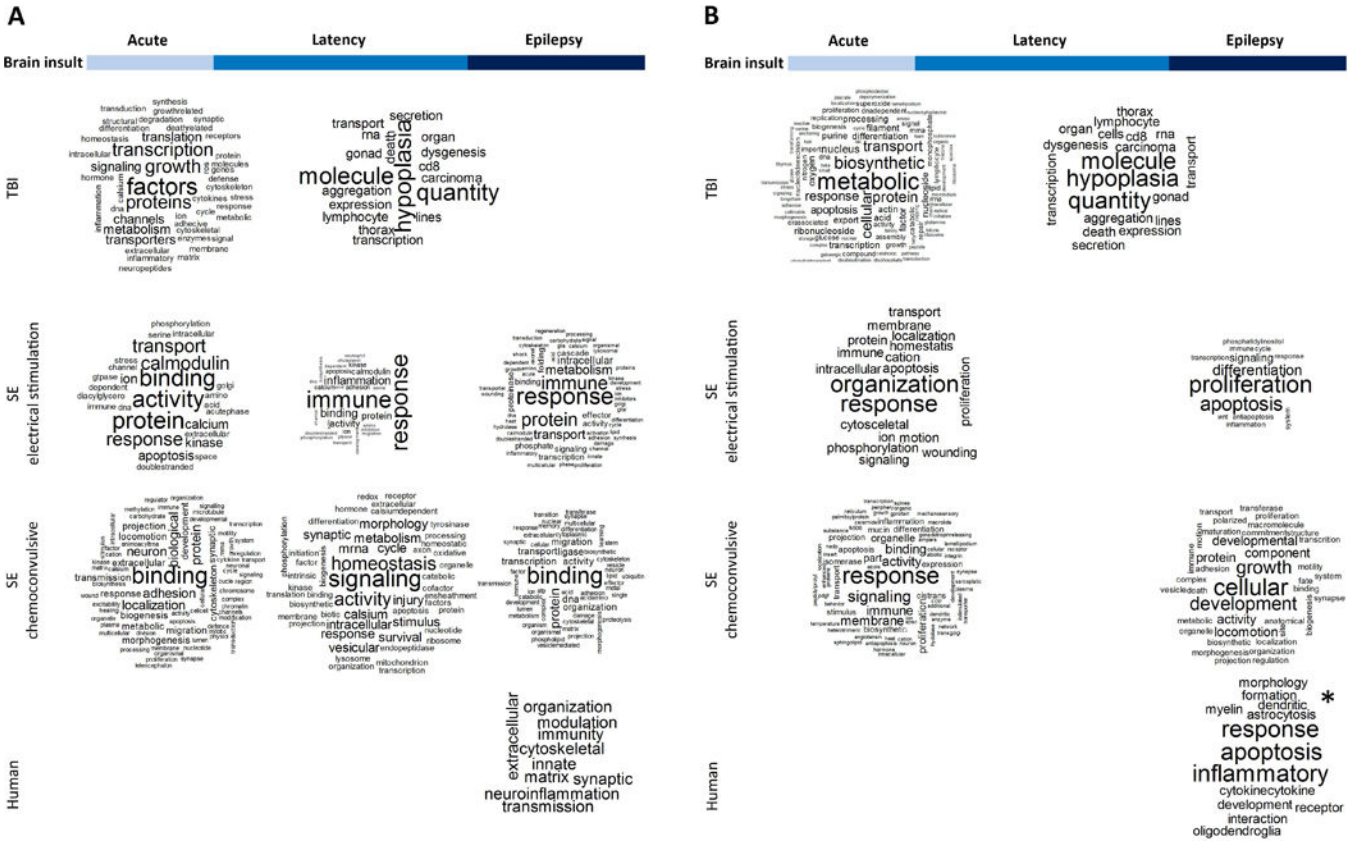

Fig. 5. Word clouds summarizing altered biological processes in the hippocampus in experimental models of structural epilepsies and in human drug-refractory temporal lobe epilepsy (TLE)

The analysis included **(A)** genome-wide (GW) changes in gene expression and **(B)** predicted targets of regulated miRNAs. Studies included in the analysis are listed in Supplementary Tables 2 and 3. Biological functions/processes were collected from the gene ontology (GO) or pathway analyses performed in each study. The data was organized to align with different phases of epileptogenic process (acute post-injury time point, latency phase, and epilepsy phase). Word clouds were generated using Wordcloud for R Package. For the sake of clarity, the words: 'regulation', 'cell', 'cells', 'process' and stop words ('English') were removed from the figures. All other words presented in original articles were included (minimum frequency=1). Larger the word font size in the cloud, more often the word appeared *e.g.* in the DAVID or IPA® analyses. Note that there were differences in the original analyses, for example, in the terminology used to name different classes of biological functions and use of cut-off p-values (*e.g.*, analyses performed by DAVID or IPA®). Also, the word cloud generated from the human data in panel B is not unbiased (asterisk) as it was extracted from the text (no pathway or GO analysis was presented by authors). Major differences between models were observed, especially when predicted miRNA-target regulated processes were compared **(B)**. SE models appeared more similar with each other than with TBI.

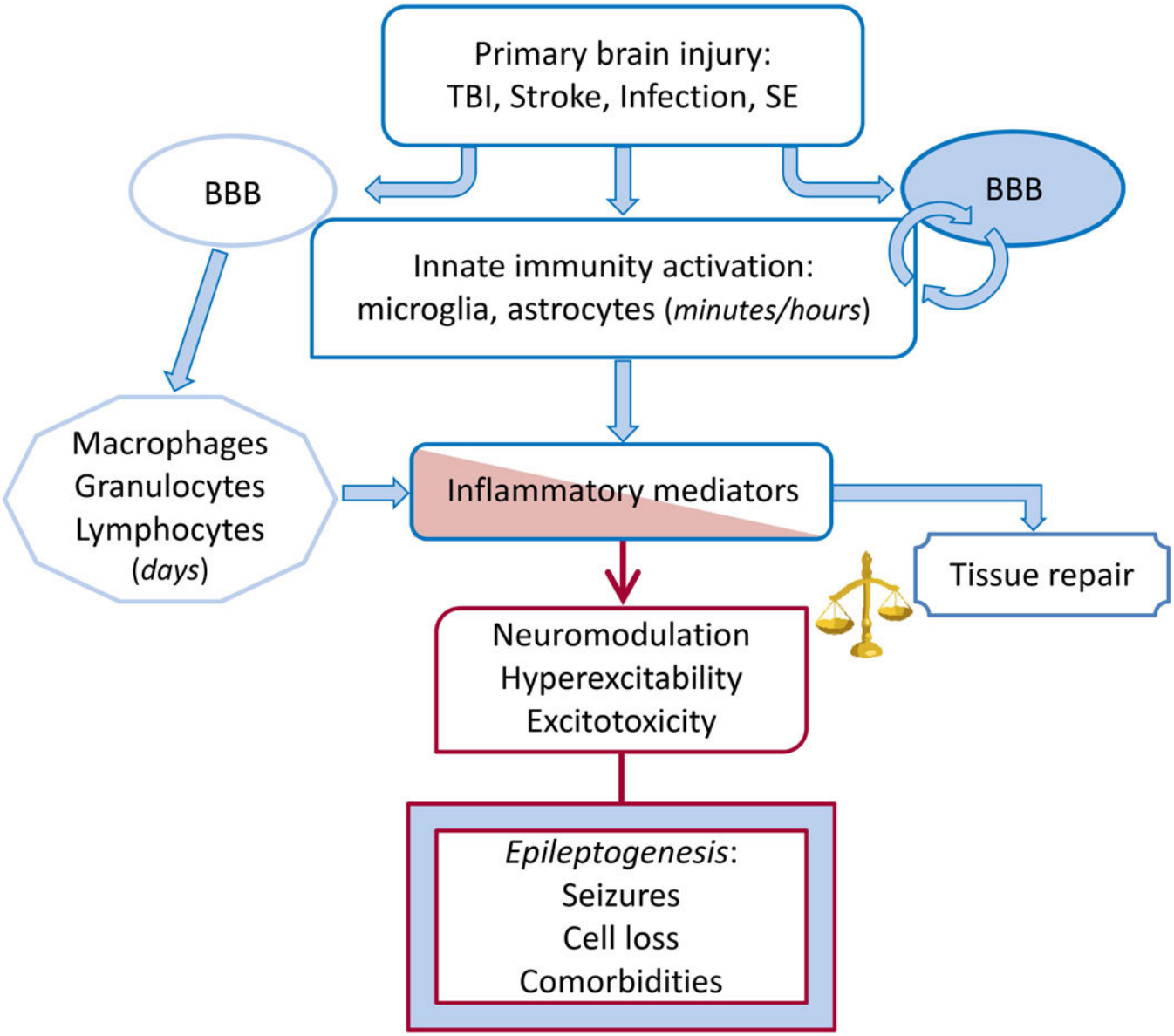

Fig. 6. Pathophysiological immune/inflammatory sequelae triggered by various acute brain injuries

Rapid activation of brain resident innate immunity cells at the site of injury and BBB functional and structural alterations result in the generation of the inflammatory cascade in seizure-prone brain areas. Leukocytes may contribute to perpetuate the inflammatory cascade following interactions with the brain vasculature. The time-locked sequence of these events likely depends on the type of injury. Inflammatory mediators can promote brain damage and dysfunction or contribute to tissue repair depending on their levels and persistence. If the inflammatory *milieu* exceeds the homeostatic threshold it may lead to hyperexcitability, decrease seizure threshold and promote neuropathology thereby contributing to disease progression. These pathologic events depend on the ability of inflammatory molecules such as cytokines, DAMPs and prostaglandins to alter expression and function of gap junctions, voltage-gated or receptor-coupled ion channels thus

contributing to acquired channelopathies, to modify GABA and glutamate release and re-uptake[176,177,185] and to alter BBB permeability. BBB dysfunction results in albumin extravasation which compromises homeostatic astrocytic functions and induces excitatory synaptogenesis by activating the TGF-β/ALK5 signaling.[310,311,320]

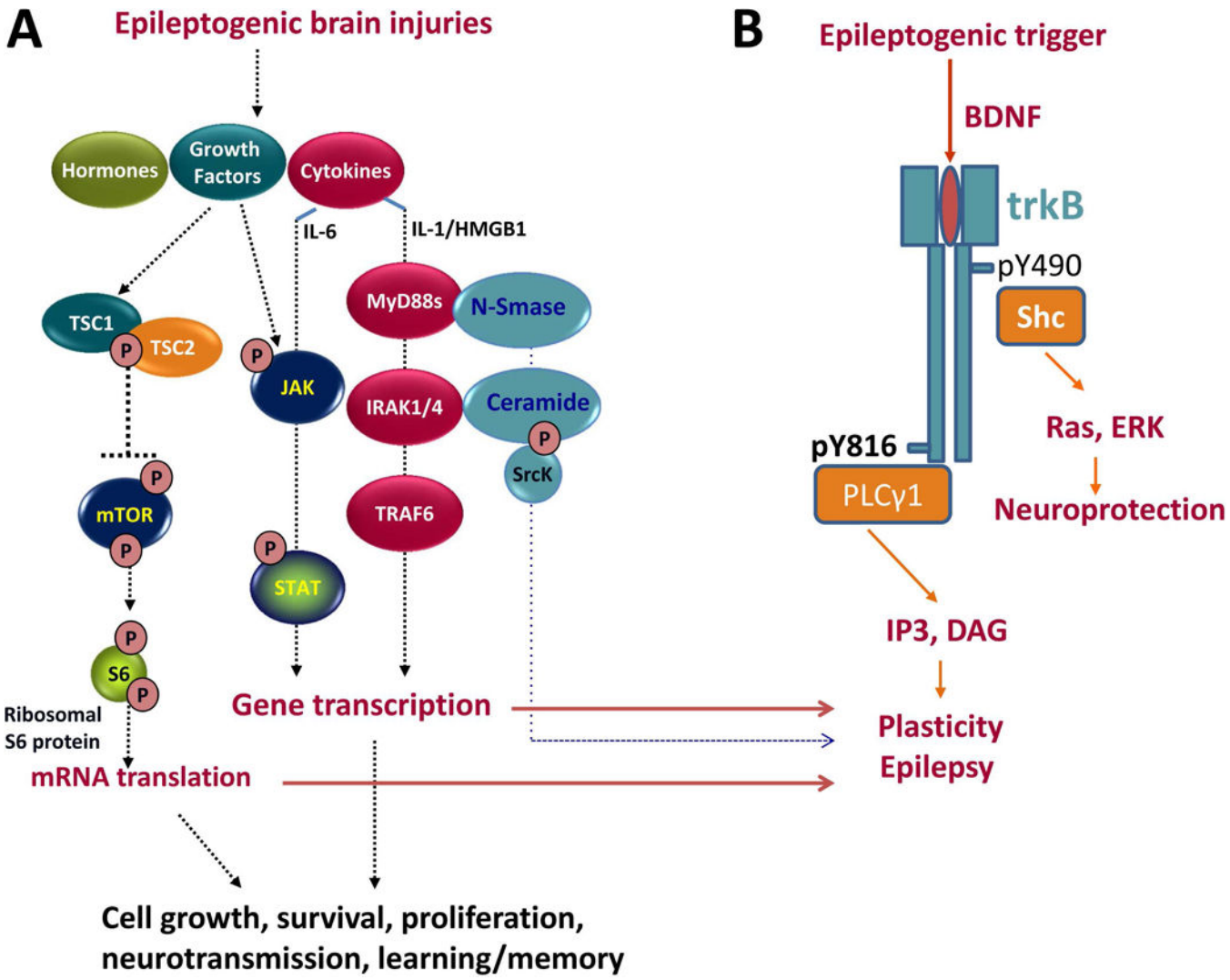

Fig. 7. Signaling pathway commonalities

Epileptogenic brain injuries, including TBI, stroke, and SE, increase levels of growth factors, cytokines and hormones that activate the (A) JAK/STAT, IL-1R1/TLR4 and mTORC1 signaling and (B) BDNF/trkB/PLCγ signaling pathways resulting in altered expression of genes and proteins involved in cell growth, cell survival, cell proliferation, neurotransmission, learning and memory, potentially contributing to epileptogenesis and cognitive co-morbidities.

Table 1
Clinical risk factors for developing epilepsy after TBI, CVA and infection

Data are from Englander et al.[321], Annegers et al.[322], Graham et al.[323], Annegers et al.[324], and Haapaniemi et al.[325]

	Risk Factor		% Epilepsy Risk
PTE	Early post-traumatic seizures		26
	Glasgow coma scale (GCS)	3-8	17
	Glasgow coma scale	9-12	24
	Glasgow coma scale	13-15	8
	Mid-line shift 1-5 mm		15-18
	Mid-Line shift > 5 mm		26
	Contusion, Cortical	multiple	25
	Contusion, Cortical	single	8
	Contusion, Subcortical	single	16
	Contusion, Subcortical	multiple	33
	Contusions, Frontal	unilateral	20
		bilateral	26
	Contusion, Temporal	unilateral	16
		bilateral	31
	Contusion, Parietal	unilateral	19
		bilateral	66
	Subdural hematoma (SDH)		15
	SDH requiring surgery		28-44
	SDH + contusions		35
	Surgery, single		14
	Multiple		37
	Fragment penetration,	bone	0
		metal	25
		bone & metal	63
	Depressed skull fracture		27
CVA	Total Anterior Circulation		29
	Early seizures (after ICH)		27
	Intracranial haemorrhage (ICH)		18
	Cortical location		19-25
	Partial anterior circulation		13
	Age < 65 years		16
	GCS < 8		28
	9-12		25
	13-15		11

	Risk Factor		% Epilepsy Risk
	Barthel Index severe		13
	mild		8
	Subarachnoid hemorrhage		22
Infection	Bacterial meningitis,	with early seizure	13
		without early seizure	2
	Viral encephalitis,	with early seizure	22
		without early seizure	10

Table 2

Efficacy of clinically approved antiseizure drugs to block different types of seizures in acute seizure models (MES, PTZ), the amygdala kindling model, post-SE models of TLE, and patients with focal epilepsy

Data from post-SE models are from rats in which SE was induced by either systemic pilocarpine or kainate, or electrical stimulation of the basolateral amygdala, or from mice in which SE was induced by intrahippocampal administration of kainate. Data are from Löscher.[275, 276] Note that the kindling model correctly predicts efficacy of drugs against focal seizures, whereas the MES test is less predictive in this regard; with some exception, doses of antiseizure drugs to suppress kindled seizures are higher than those effective in the MES test. Furthermore, note the correspondence between drug effects on induced amygdala kindled seizures and spontaneously recurrent seizures in post-SE models. NE, not effective.

Drug	Antiseizure effect in rodents (rats or mice) on				Antiseizure effect on spontaneous focal seizures in patients with epilepy
	MES (generalized tonic seizures)	PTZ (generalized clonic seizures)	Amygdala kindled focal and/or secondarily generalized tonic-clonic seizures	Spontaneous focal and/or secondarily generalized seizures in post-SE models	
Benzodiazepines	+	+	+ (but tolerance)	+	+ (but tolerance)
Brivaracetam	+	+	+		+
Carbamazepine	+	NE	+[3]	+	+
Eslicarbazepine acetate	+	NE	+		+
Ethosuximide	NE	+	NE	NE	NE
Felbamate	+	+	+[3]		+
Gabapentin	+	+	+[3]		+
Lacosamide	+	NE	+[1]		+
Lamotrigine	+	NE	+[3]	+[2]	+
Levetiracetam	NE	NE	+	+[2]	+
Oxcarbazepine	+	NE	+		+
Perampanel	+	+	+		+
Phenobarbital	+	+	+[3]	+[2]	+
Phenytoin	+	NE	+[3]	+[2]	+
Pregabalin	+	+	+[1]	+	+
Primidone	+	+	+		+
Retigabine (ezogabine)	+	+	+		+

Drug	Antiseizure effect in rodents (rats or mice) on				Antiseizure effect on spontaneous focal seizures in patients with epilepy
	MES (generalized tonic seizures)	PTZ (generalized clonic seizures)	Amygdala kindled focal and/or secondarily generalized tonic-clonic seizures	Spontaneous focal and/or secondarily generalized seizures in post-SE models	
Tiagabine	NE	+	+	+	+
Topiramate	+	NE	+[3]	+	+
Valproate	+	+	+[3]	+	+
Vigabatrin	NE	±	+[3]	+	+
Zonisamide	+	NE	+		+

[1] In hippocampal kindled rats;

[2] Responders and nonresponders in post-SE models[275];

[3] Responders and nonresponders in fully amygdala kindled rats[275]

Table 3

Summary of commonalities in epileptogenic processes from different acquired acute brain insults.

	Commonalities resulting from acquired acute brain insults	**Comments**
Partial epilepsies resulting from acquired acute brain insults in adults	• Either temporal lobe or neocortical epilepsy • Intracranial blood • Early post-injury seizures • Severity of injury • Blood-brain barrier disruption	
Partial epilepsies resulting from acquired acute brain insults in children	• Early post-injury seizures • Intracranial blood • Severity of injury • Trauma, stroke, autoimmune, neoplastic etiologies	Febrile status and MTS relationship
Post-insult acute EEG alterations (clinical)	• Nonconvulsive seizures • Periodic discharges • Spreading depolarizations	Invasive EEG findings in critically ill patients show that an even higher percentage of patients have nonconvulsive seizures and periodic discharges than can be seen on scalp EEG (regardless of the specific type of acute brain injury).
Genetic aspects (clinical)	• Preliminary studies in humans, combined with what has been shown in animal models, implicate genes involved in the inflammatory response and neuronal plasticity.	There have essentially been no comparative studies to date.
Pathologies (clinical)	• Common histopathology patterns besides a main structural lesion in epileptic brain tissue encounter astrogliosis and heterotopic neurons in white matter	Difference to non-epileptic lesions with gliosis uncertain; No appropriate animal models for heterotopic neurons
Routes of seizure propagation	• Early seizures at site of injury • Secondary epileptogenesis engages temporal lobe and thalamocortical networks	• Frequency of TLE-like or absence-like phenotypes differ across models; • Little network mapping has been performed after TBI, stroke or viral encephalitis
Circuit reorganization	• Shift of inhibition from phasic towards tonic. • Depolarizing action of GABAergic inhibition, especially during excessive activity • Increased glutamatergic drive • Increased intrinsic neuronal excitability • Canonical rules for seizure generation, independent of species or insult	• Differences in specifics, e.g., shifts in $GABA_A$ receptor subunit expression differ between etiologies. • Many changes are compensatory – trying to stabilize the network. • The lack of adequate control tissue from humans makes it difficult to know what electrophysiological signatures are pathological in human tissue
Role of hippocampus and parahippocampal circuits and structural lesions	• Variable extent but similar pattern of hippocampal formation pathology (neuron loss in entorhinal cortex Layer III,	

	Commonalities resulting from acquired acute brain insults	Comments
	hippocampus, and dentate gyrus), synaptic reorganization, reactive gliosis	
Dysfunctional astrocytes and microglia	• Microglial and astroglial activation • Dysfunctional K^+-buffering • Adenosine deficiency	Downregulation of Kir4.1 conductance and block of Cx43- mediated gap junction coupling compromise K^+ homeostasis
Inflammatory processes	• Generation of an innate immune/ inflammatory response • Rapid activation of microglia • Release of an array of frontline inflammatory molecules from brain resident cells • BBB dysfunction associated with inflammatory changes	Type of acute injury determines cellular sources of inflammatory mediators and pathophysiological role of immune mediators; Scarse information on: • role in post-stroke, post-TBI or post-encephalitis epileptogenesis • acute and subacute neuroinflammatory changes in postmortem human brain • potential commonalities across brain injuries
Signaling pathways	• Pathway activation after multiple forms of acute brain injury (TBI, SE, stroke) • Severity of injury correlates with degree of activation • Pathway inhibition modifies outcomes related to spontaneous seizures and learning/memory	Pathway inhibition is antiepileptic in some models and antiepileptogenic in others
Biomarkers	• HFOs localize and may be prognostic	
Treatment response in patients	• Preliminary observations support the hypothesis that • drug response is surprisingly similar for different types of acquired epilepsy seen in stroke sequelae, vascular malformation, and tumors • diffuse brain damage is more likely to result in pharmacoresistance than other substrates for focal epilepsy	Limitations of the current evidence on drug response in the early days of acquired epilepsy are manifold.
Animal models of acquired epilepsy	• Hippocampal pathology	
Pharmacology of animal models of acquired epilepsy	• Similar pharmacology of evoked kindled seizures and spontaneous recurrent seizures in post-SE models of TLE • Occurrence of drug resistant animals in both kindling and post-SE models of TLE	Only few data on the pharmacology of models of TBI, stroke, or viral encephalitis (see text).