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Potential causes of cognitive alterations in temporal lobe epilepsy

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Abstract

Spatial and non-spatial memories are key processes whereby we process our environment on a daily basis, coding space, time and items to form unique memories. Both types of memory involve distributed and complex temporal lobe (TL) networks. In this review, we will discuss potential causes of spatial and non-spatial memory deficits, taking the example of temporal lobe epilepsy (TLE), a widespread neurological disorder characterized by cognitive comorbidities, in both animal models and TLE patients. We will start by briefly introducing TLE, then highlight by which underlying mechanisms TLE impairs TL-dependent cognitive functions.

**Keywords:** cognition; learning and memory; neurological disease; cognitive deficits; excitatory-inhibitory balance.
**Abbreviations**

AED: Anti-epileptic drugs  
AMPA: Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid  
CA: *Cornu ammonis*  
BOLD: Blood-oxygen-level-dependent  
E-I: (balance) Excitation-Inhibition  
EC: Entorhinal cortex  
GABA: Gamma-aminobutyric acid  
HPC: Hippocampus  
IA: Interictal activity  
INs: Interneurons  
IPSP: Inhibitory postsynaptic potential  
LTD: Long-term depression  
LTP: Long-term potentiation  
NMDA: N-methyl-D-aspartate  
SE: Status Epilepticus  
SRS: Spontaneous and recurrent seizures  
SZ1: First spontaneous seizure  
TL: Temporal lobe  
TLE: Temporal lobe epilepsy
Introduction

The way we process our environment reveals a lot about the functioning of our brain and the way we encode and recall relevant information to learn how the world works, mostly through spatial and non-spatial memory processes. These processes span the way we can locate ourselves in a given environment based on surroundings cues and landmarks, recognize our surroundings, i.e., people, objects and scenes [1], perceive emotions [2], and integrate information to drive our choices and actions based on bottom-up (e.g., novel afferent stimuli) and top-down (e.g., past experiences, expectations) signals. To complete these processes, structural and functional connectivity between distributed temporal lobe (TL) networks underlying cognitive processes is key, as well as the mechanisms necessary to successfully give rise to those mnemonic processes. However, when structural connectivity is disrupted, as it has been largely reported during temporal lobe epilepsy (TLE)[3,4], functional connectivity in memory processing is altered too [4–20], especially spatial memory [21,22]. For a detailed review of recent TLE cognitive deficits in animal models and TLE patients, see [23].

In the current review, we will discuss potential causes of TL-dependent cognitive deficits reported during TLE, a prominent neurological disease in the global population despite being still poorly understood [24]. We will see how these potential causes are intimately related to one another, therefore influence each other. This adds to the complexity of studying and understanding brain disease and in particular TLE comorbidities. We will start by briefly introducing TLE.

A. Temporal lobe epilepsy

TLE is a neurological disease characterized by the frequent occurrence of two types of abnormal activities: (i) spontaneous and recurrent seizures (SRSs) which incapacitate quite a lot TLE patients and
(ii) interictal activity (IA), occurring between SRSs as well as during epileptogenesis in animal models (Fig. 1). In TLE, SRSs can either be focal, i.e., occurring only in TL brain areas, or generalized to the whole brain [25–27]. TLE is also characterized by the frequent impairment of cognitive processes, e.g., learning and memory processes, occurring between the patients’ epileptic seizures and defined as one type of TLE “comorbidities” [28,29]. Interestingly, in TLE animal models, cognitive deficits are already present before the first spontaneous seizure occurs [30]. A significant number of variables have been proposed to be at the origin of these cognitive comorbidities: (i) epilepsy per se, (ii) its underlying abnormal structural TL connectivity, (iii) IA, (iv) SRSs, (vi) the nature, severity and timing of the initial precipitating injury, (v) epileptogenesis, and (vi) anti-epileptic drugs (AEDs). We will start by describing the potential association between epilepsy per se and the impairment of cognitive functions in TLE.

B. Potential causes of TL cognitive alterations in TLE

1. Epilepsy per se (SE and SRSs)

The effect of the initial status epilepticus (SE) on cognition may be related to the type and the etiology of epilepsy [27], to the severity of the SE, and to the age of the patient [31]. Regarding SRS, a question is whether cognitive alterations appear before or after the first occurrence of epileptic seizures? Answering this question would inform whether SRSs have an initial impact on the structural and/or the functional connectivity abnormalities underlying cognitive functions impairment or whether SRSs simply worsen the latter once they already occurred. At the structural level, SRSs have a direct impact on network connectivity, worsening initial post-SE morphological alterations and network reorganizations. At the functional level, SRSs can impair excitatory and inhibitory synaptic conductances, rate and temporal coding of information as well as firing pattern of single-cell activity [32–35] (for review see [29]) which can all convey an aberrant message to downstream targets, thus impair effective processing of information in general cognitive processes. In the pilocarpine rat model, spatial memory deficits
nevertheless appeared since the early stage of epileptogenesis (4 days post-SE), i.e., quite prematurely and ahead of the first spontaneous seizure [10] (SZ1), which means that at this stage, SRSs cannot be the source of TLE comorbidities. This implies that SRSs may instead worsen already present connectivity abnormalities. However, as the spatial deficits we found were persisting in TLE animals without further modification during epileptogenesis [10], even after SRS have occurred, network modifications caused by SRSs at later stages may be more relevant to the process of epileptogenesis and the formation of stable epileptogenic networks than to the worsening of already existing cognitive deficits, at least regarding hippocampus-dependent spatial memory alterations in the model we used. Unfortunately, as this question - whether cognitive alterations appear before or after SRSs occurrence - cannot be addressed in TLE patients, predictive biomarkers of TLE must be identified in order to evaluate cognitive processes in at-risk patients and study their potential underlying mechanisms.

To conclude, SRSs may not have a direct impact on TLE cognitive deficits which appear as primary symptoms of the disease, neither later on, worsening network abnormalities without impacting directly on underlying mnemonic functions as the network may already be impaired enough to promote the occurrence of SRSs and give rise to stable cognitive deficits. SRSs could however seriously impact on the excitatory-inhibitory balance [36], central mechanism in CNS function and cognition.

2. A deficit of the excitatory-inhibitory balance

Indeed, another potential cause of cognitive comorbidities in TLE is a deficit of the excitatory-inhibitory (E-I) balance [37]. E-I balance between functional networks is key in cognitive processes (for a review see [38]). However, focal ictogenesis (SRSs) has been reported by several studies to occur when inhibitory interneurons (INs) synchronization is weakened (but see [39]). A deficit in the E-I balance therefore arises during periods preceding the onset of epileptic seizures (namely, pre-ictal periods) before potentiating again along the seizure itself [40]. This decrease in IN synchronization has
been hypothesized to actually increase during interictal periods [40]. As GABAergic IN activity could be generated by aberrant reorganization of IN networks, for example in focal cortical dysplasia [41], it may lead to network synchronization and consequently, to focal epileptic seizure [42]. Synchrony reduction may thus be causally associated with the occurrence of SRSs (seizure proneness) by increasing self-sustaining activity within the epileptic focus (seizure onset zone). However, recent evidence points toward a potential “excitatory” (or “disinhibitory”) role of GABAergic neurons in epileptic circuit (for reviews see [43,44]), where GABAergic interneurons could either synchronize network activity and lead to SRSs or inhibit other GABAergic cells and prevent excitatory cells from being inhibited, hence a network becoming hyperexcitable and prone to develop SRSs. A recent study elegantly showed a deficit in the E-I balance, in both humans and monkeys, during epileptic seizures [36]. The authors observed a temporal decorrelation between excitatory and inhibitory neuronal ensembles, thus concluded that the E-I balance feature of normal brain states was disrupted in epileptic conditions as a hallmark feature of altered brain networks. We suggest that E-I imbalance may be responsible for the cognitive deficits described in TLE. To support this view, we showed that a decrease of GABAergic and glutamatergic drives preceding SZ1 was sufficient to explain IA dynamics along epileptogenesis [45], confirming previous findings in vitro [46]. In this context of imbalanced E-I dynamics, a precipitating factor leading to SRSs has been suggested to be the loss of pyramidal cell-to-INs synaptic contacts [45]. The altered structural connectivity, in particular the neuronal loss, following the initial insult may indeed lead to aberrant E-I connections and network reorganization, at the origin of a breakdown of the E-I balance, altered E-I transmission, and impaired rhythmic activities, all of them constituting key factors in the generation of cognitive alterations during epileptogenesis.

3. Epileptogenesis, or the intrinsic reorganization due to epilepsy

Epileptogenesis, the process leading to epilepsy (Fig. 1), has been tested by several means on memory processes. A bilateral decrease of the cerebral BOLD signal within the mesial TL, more
pronounced on the ipsilateral side at the onset of seizures, has been related to the duration of epilepsy, the latter being negatively correlated with verbal and visual memory [47]. This study suggests that TLE may affect memory processes in a progressive way, relative to epilepsy duration (probably to the evolution of its underlying network reorganization, reinforcing each other) as the longer TLE lasts, the more reduced bilateral brain activation translated in BOLD activity of the implicated networks is, which then proportionally and progressively impacts on memory functioning [47]. TLE may thus be a dynamic process whose epileptogenicity may evolve with the duration of epilepsy (Fig. 1) [48]. Indeed, TLE associated with HPC sclerosis has been reported to progress over time (for review see [49]), namely, its abnormalities, e.g., IA and SRSs, and associated comorbidities develop (worsen) over time (but see section B1). The main hypothesis is that the occurrence of seizures is the main factor of this progression, according to seizure types, duration, and frequency (e.g., partial or generalized SRSs, brief or prolonged SRSs). Recently, neuroimaging studies shed light into the progressive feature of TLE without understanding yet what underlies such progression [49]. Brain inflammation and SRSs are the major highlights in progressive TLE but multivariate analysis as well as combined studies with neuroimaging should hopefully demystify TLE progression. We suggest that the underlying impaired structural connectivity and network reorganization associated with epileptogenesis may deteriorate even more with the evolution of SRSs (severity, frequency) as TLE progresses [50], thus highly contribute to reinforce epileptogenesis, build up stable epileptogenic networks underlying persistent TLE cognitive comorbidities and/or worsen transient cognitive impairments via transient aberrant processes. The latter could emerge through the occurrence of paroxystic activities, namely SRSs, IA and post-ictal activity.

4. Paroxystic activity

In addition to TLE anatomo-functional modifications, paroxystic activity by itself also impairs cognition. IA, SRSs and post-ictal activities in TLE patients have deleterious effects on cognitive processes [51,52] which could worsen with time, i.e., with the duration of epilepsy (cf. section B3)
Seizures and IA can induce numerous transient or long-term cognitive and behavioral deficits, both in animal models and TLE patients ([32–35,52,54], for review see [55] and [23]). As we already discussed the effect of SRSs on cognitive processes in section 1, we will next describe the effect of IA and post-ictal activities on mnemonic functions, starting with IA.

4.1. Interictal activity

In TLE patients, IA has been described to have no direct impact on cognitive processes [56], with only a mild effect during “mechanistic” cognitive processes, as during attention or mental speed tasks [57]. In developing brains, IA may locally trigger mechanisms at play to process information [58,59], thus have an immediate impact on underlying functions dependent on these coordinated local mechanisms, even in a resistant network state or lower activity propagation mode. In general, IA has been associated with transient cognitive impairments [52,60] (for review see [61] associated with IA laterality), in comparison to chronic cognitive deficits which we suggest may rely on a network already reorganized enough to not be affected by IA occurrence per se during cognitive processing. Indeed, while some studies showed no transient cognitive impairments in patients with IA during the task [62], one hypothesis is that IA effect on cognition may build up and, therefore, only acts on the less stable cognitive functions. IA has therefore been largely described as being deleterious, with its frequency more associated with cognitive deficits than with SRS (for review see [61]). We nevertheless found no direct correlation between IA frequency recorded in the CA1 region of the HPC and the persistent spatial memory deficits observed in our model along epileptogenesis [10]. Alternatively, IA in extra-HPC or extra-CA1 regions may have an impact on network dynamics, or similarly, during critical task periods not investigated in our study [63]. Some authors found memory retrieval impairment caused by IA spikes in epileptic rats but no memory encoding deficits [54], which has also been described in humans [52].
IA during sleep has also been described to correlate with the impairment of mnemonic functions [64]. A recent study showed that IA, time-coordinated with sleep spindles in the prefrontal cortex of TLE rats during non-REM sleep states, correlates with memory consolidation impairment [65]. In addition, IA has been shown to induce on one hand less ripples during non-REM sleep but on the other hand the aberrant occurrence of spindles (10-12 Hz) during REM sleep and awake states [65], usually characterized by theta frequencies. These results in rats have been supported by a similar scenario in four TLE patients with the analogy of temporo-frontal regions. In this case, it seems that IA triggered aberrant physiological mechanisms that probably emerge from abnormal connections, a lack of E-I resources recruited by IA, or both. Similarly, a recent study has yielded the presence of pathological high frequency oscillations (pHFOs) associated with IA in the HPC and occurring mostly during periods of spatial exploration, normally characterized by theta oscillations in healthy conditions [66]. Those pathological oscillations have higher frequency than physiological ripple-like events (around 100 Hz) which occur during non-theta brain states (i.e., periods of rest and slow wave sleep). The occurrence of pHFOs during theta brain states could therefore be responsible of cognitive deficits as pHFOs may recruit resources needed by theta oscillations to process and transmit information necessary to complete cognitive functions. Ewell and colleagues (2019) described immediate effects of pHFOs on network dynamics, as a transient reduction of hippocampal theta power and of spatial precision of place cells activated by the pHFOs, which may influence theta coupling and normal cognitive processing.

Regarding the link between IA dynamics and the emergence of TLE networks which may underlie cognitive impairments, two IA types defining two IA burst types were identified [45]. However, no correlation has been made between their dynamics, which parallel the transition from a seizure-free to a seizure-prone state, with a clear switch in IA dynamics just before SZ1, and the impairment of cognitive functions [45,67]. As we found no direct correlation between IA in general and spatial memory deficits [10] (cf. above), a hypothesis is that IA indirectly acts on mnemonic functions via the impairment of theta rhythm (personal communication, [68]). For a broader spectrum of IA
impact on cognitive functions, we refer the reader to the following comprehensive reviews [55,69], particularly addressing how IA mimics dynamic remodeling of neuronal networks excitability which leads to SRSs and epilepsy.

Finally, while we found consistent memory deficits during the early stages and throughout epileptogenesis [10], an evolution of the anatomo-functional reorganization during the same period was observed [46,70]. If we consider that both IA and network remodeling have an impact on cognition, these data support our hypothesis whereby IA may impair the network when network connectivity is only partially remodeled or even have a protective effect to compensate nascent brain alterations [45,71]; afterwards, IA may lose this effect with network reorganization taking over, thus becoming the essence of stable epileptogenic networks with persistent cognitive dysfunctions dependent on the integrity of network properties [72] and functional dynamics between TL structures [73]. However, network remodeling is to be considered with caution, as we do not know whether such alterations are a consequence of TLE itself (due to SE then to SRSs) or a homeostasis process implemented by the brain to counterbalance early and nascent brain alterations [74]. We therefore suggest that IA may be related to cognitive dysfunctions in an indirect way, impairing existing rhythmic activities, generating aberrant rhythmic dynamics during brain states in which these dynamics would never occur in healthy conditions, and/or by affecting underlying TL network reorganizations. IA would do so according to a dual role depending on its timing of occurrence, namely, a compensatory role before SZ1 and an epileptogenic one after SZ1 (see [23]).

### 4.2. Post-ictal activity (post-ictal state)

Another mechanism underlying TLE cognitive deficits is post-ictal activity [75]. During this state, the patient's brain recovers from the epileptic seizure. Its duration varies according to the duration and severity of the seizure. It is characterized by an altered state of consciousness which translates into
disorienting symptoms, followed by transient amnesia and memory deficits during the recovery, or emergence, process [75]. Current hypotheses explaining this post-ictal state are neurotransmitter (e.g., GABA and glutamate) depletion, modification of receptor (e.g., AMPA and NMDA) expression, active inhibitory mechanisms (e.g., IPSPs, afterhyperpolarisation) and changes in cerebral blood flow (brain perfusion, glucose uptake), all key mechanisms in synaptic plasticity, oscillatory mechanisms, dynamic coordination and transmission of information, essential for the normal processing of cognitive functions. Post-ictal activity may thus influence cognitive functions in TLE by transiently impairing E-I dynamics of distributed TL networks after SRS occur. We propose that post-ictal activity reinforces existing epileptogenic networks, with a more pronounced impact on transient cognitive impairments.

5. Structural network alterations and reorganizations

The various morphological alterations underlying TLE (e.g., the neuronal loss, axonal sprouting and impaired neurogenesis) certainly all contribute to TLE comorbidities (for review, see [69]). Memory and language deficits have been reported to be related to morphological alterations within the HPC and the PRC [76].

Memory is indeed a process which is dependent on the integrity of the network connectivity since the performances are restored when the network connectivity is restored too [77]. As network connectivity is severely altered during TLE [3, 4, 78–82] (for review see [83]), the abnormal structural connectivity may therefore have a deleterious impact on the functional connectivity of large-scale TL brain networks underlying cognition [14, 84–89], probably at the origin of aberrant dynamic coordination between those networks, for example during the encoding and retrieval of episodic memory [11, 12, 83] (Fig. 2). The dendritic sprouting and the synaptogenesis indeed play an important role in the replay of information, learning and memory. Neurogenesis process in the dentate gyrus may also be involved [77]. Likewise, correlations between structural changes of subcortical areas beyond the
HPC (as thalamus, basal ganglia and cerebellum) and cognitive impairments in TLE patients have been found [90,91]. HPC neuronal loss may imbalance EC-HPC coupling networks [92], among other TL brain networks involved in cognitive functions (cf. [23]), thus probably impairing the dynamic gating and routing of information within such networks, as well as the temporal coordination between them, at the origin of cognitive deficits.

The circuitry reorganization, especially regarding connections between neurons and between TL structures, may indeed impact on rhythmic activities underlying cognition. Glutamatergic and GABAergic transmission are centrally involved in oscillations [93–95], and an alteration in one of these transmissions will affect underlying rhythmic activities. Excitatory pyramidal cells and inhibitory GABAergic INs indeed interconnect to give rise to oscillatory cycles, in particular theta (4-12 Hz) and gamma (30-80 Hz) rhythms, key players in memory processes [96,97]. Oscillations are emergent properties of brain networks, especially of TL brain networks associated with memory. E-I networks shaping brain rhythms confer windows of opportunity during which relevant afferent inputs can be potentiated, transmitted and further encoded, key elements in gating incoming information within distributed and complex TL brain networks and depending on oscillatory frequency [98,99]. Through this temporal structure provided by brain oscillations, the latter can synchronize or coordinate afferent information (distributed activity patterns) which can be transmitted to downstream targets within local or remote neuronal networks [100,101]. Theta and gamma rhythms have been intensively involved in memory encoding and retrieval processes via the temporal coordination of activity through their cycles [102–107]. Feature binding to bind different features of an episode (space, time, item, emotion) is hypothesized to occur through theta and gamma cycles to form unique episodes and be able to recall them, the essence of memory (for a recent review see [23]). Thus, an alteration of E-I transmissions underlying rhythmic activities will impact on cognitive processes and the way we process our environment, extract knowledge from past experiences and drive our choices and actions.
A deregulation of the temporoammonic pathway is also crucial in the genesis or the propagation of HPC ictal activity [71]. Despite these alterations, there are still spared interneurons, so less inhibition doesn’t necessarily mean fewer or less functional interneurons. However, the loss of some pyramidal cells induces a loss of excitatory afferences activating these INs, hence a decrease of inhibition (known as the “dormant basket cells” hypothesis [108]). This E-I imbalance may be sufficient to induce pathological activity and facilitate its propagation [70] (cf. section B2). For example, GABAergic inhibitory networks are not only critical to prevent SRS from occurring (but see [39,43,44]) but also key in synaptic integration, oscillatory activity patterns and information transfer [94,109], therefore an impairment of GABAergic transmission system would have a deleterious impact on TL-dependent mnemonic functions. The structural and functional damages of GABA inhibition have been well documented in animal models [110,111]. However, the way these modifications lead to epileptic conditions remains elusive, as some epileptiform activities have been suggested to be promoted by the synchronization of GABAergic mechanisms (for reviews see [112] and [44]).

Lastly, as dentate gyrus mossy cells are gaining interest in the field of HPC-dependent mnemonic processes [113], especially with the use of optogenetics which can specifically silence mossy cells and this way reproduce spatial memory deficits in non-epileptic animals, an alteration of this cell type activity could be considered playing a central role in TLE cognitive comorbidities.

To conclude, this section sheds light on how initial structural network abnormalities may negatively impact on the functional connectivity of large-scale TL networks underlying TLE comorbidities through abnormal E-I connections, impaired E-I transmissions and aberrant synchronization. All these changes will severely affect rhythmic activities, dynamic temporal coordination, and therefore the way information is processed and transmitted to downstream targets, at the origin of cognitive alterations. Indeed, several studies reported altered network dynamics affecting

6. Impairment of synaptic plasticity

Another potential cause of TLE cognitive deficits is a defect in synaptic plasticity, a consequence of altered network dynamics. Synaptic plasticity indeed plays a critical role in general memory processes [117]. While short-term plasticity (from milliseconds to minutes) requires synaptic vesicles depletion and calcium signaling mechanism, long-term plasticity (LTP/LTD) recruits the activation of NMDA and AMPA receptors, various protein kinases and gene expression. Seizure activity induces a saturation of the LTP mechanisms by consuming and decreasing HPC plasticity available for information processing, thus interferes with the processes of encoding and memory consolidation [118]. Indeed, one hypothesis is that LTP mechanisms are recruited to potentiate relevant afferent inputs arriving at the excitatory phase of the theta cycle, while LTD mechanisms are at play to erase irrelevant inputs [119,120]. Reorganization of synaptic activity due to neuronal loss as well as remodeled synaptic strength between excitatory and/or inhibitory synapses may alter E-I (glutamatergic and GABAergic) transmissions, therefore affect the way relevant and irrelevant information from the outer world gets effectively discriminated, encoded and transmitted, central mechanisms in general cognitive processes.

7. Antiepileptic drugs

Lastly, and to add even more complexity to the exhaustive list of potential causes of TLE comorbidities (Fig. 2), AEDs taken by the patients to decrease and/or suppress their seizures frequency have a strong impact on cognitive processes [55], thus should be considered in the evaluation of the patients’ cognitive performances. Indeed, TLE patients have memory and language deficits relative to the AEDs they were administered [121], and this relation is dose-dependent [122]. These drugs’ effects
on behavior and cognition are generally moderate but could also play a critical role in children [123], besides being dependent on the hemisphere implicated in TLE. Due to an exhaustive list of potential side effects, AEDs can provide a significant negative impact on TLE cognitive comorbidities while AEDs may help patients overcome SRSs, which means that SRSs and cognitive comorbidities may share distinct underlying mechanisms.

Conclusion

In conclusion, taking the example of TLE, this review illustrates the intermixed relationship between the structural connectivity among distributed and complex TL brain networks, the oscillatory and cognitive processes and highlights the critical importance of the balance between E-I networks in mnemonic functions. So far, it remains extremely difficult to solve the *chicken and egg problem* [124] and to know which trigger is the initial source of TLE comorbidities. In this review, we discussed several causes of cognitive deficits and hypothesize that impaired structural TL connectivity, as a consequence of the initial insult, implies aberrant connections and network reorganization which impair functional connectivity, imbalance E-I transmissions (impaired E-I balance) and alter activities emerging from these remodeled E-I brain networks. Such activities are oscillatory patterns underlying information processing, synaptic plasticity, dynamic temporal coordination and cognitive functions. In addition to this scenario, SRSs, AEDs and TLE duration worsen this already complex and pathological brain landscape, with IA playing a dual role: while it may compensate nascent brain alterations until SZ1, afterwards it may reinforce network reorganization and TLE comorbidities.

E-I brain networks could be effectively controlled by brief and reversible modifications of the synaptic gain, active dendritic conductances that can introduce non-linearities in input summation, and intrinsic neuronal properties. Shunting inhibition, modulatory signals – e.g., top-down influences that can gate all these brain computations - as well as neuromodulators that can quickly and briefly modify
transmission channels through changes in time and length constants could also modulate E-I networks. Since transmission of information occurs mostly through sparse coding and low activity of short duration and small amplitude, synchronous sparse codes seem a reliable process. This process implies flexible, low-dimensional, brief and energy-efficient information coding. It allows the system to quickly respond to changing input patterns, key in mnemonic functions and cognitive processes in general, allowing us to efficiently process our environment, take actions and make decisions accordingly.

However, when this balance between E-I networks is altered, these mnemonic functions become impaired, leading to comorbidities in neurological diseases like TLE, as we described in this review. This example highlighted the diversity and the complexity whereby distinct and intertwined variables which can be the cause or the consequence of a neurological disease affecting TL brain networks can impair the E-I balance between them. For this endeavor, deciphering the neural mechanisms which underlie disorders as TLE is key to be able to act on those specific mechanisms. Towards this aim, studying neurological and neuropsychiatric diseases sharing common dissociative disorders and comorbidities at different levels of integration, i.e., at the micro- and macro-scale level, is one critical step to embrace [125].

Finally, if several studies recently identified changes in functional connectivity during TLE [50,73,84–86,88,126,127], not many have highlighted correlations between impaired functional connectivity during TLE and its associated comorbidities, at the cognitive and behavioral levels, except few (for example, see [11,12]), and mostly using neuroimaging. Therefore, it is yet necessary to detect aberrant network dynamics underlying TLE cognitive comorbidities at early stage of the disease, i.e., ahead of the first ictal episode, and at a much faster timescale, in order to reflect functional dynamic changes in brain function relevant for dynamic coordination between functional TL networks. The ultimate goal would be to identify preventive biomarkers of the disease [128,129] in high-risk patients, as it has been already done in epilepsy-associated and related brain (neurodegenerative and neuropsychiatric) disorders [130–133].
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Figure 1. **Epileptogenesis profile during TLE.** In human TLE, epileptogenesis starts from an initial insult (e.g., a stroke, febrile seizures, focal cortical dysplasia) which marks the onset of TLE development. In animal models, this initial insult is mimicked by a status epilepticus (SE) which can be induced by several ways (e.g., injection of pilocarpine, kainate, or the repetition of an electrical stimulation in a specific brain structure). This initial insult/SE is usually followed by a seizure-free period, at least in TLE animal models, considered the early stage of epileptogenesis, and characterized by the absence of spontaneous and recurrent seizures.
seizures (SRSs) but already by the presence of EEG-pathological activity, called interictal activity (IA) and by cognitive deficits. This seizure-free period will end with the occurrence of spontaneous and recurrent epileptic seizures defining epilepsy per se, i.e., a seizure-prone state (also called the chronic stage). This seizure-prone state is still characterized by IA and (persistent) cognitive comorbidities. Epileptogenesis thus characterizes the development of the disease, from its onset and throughout the whole epileptic period.

**Figure 2. Potential causes of TL-dependent cognitive deficits.** Resume of the different TLE variables which can directly or indirectly negatively impact onto the functional connectivity of brain circuits and therefore lead to cognitive alterations: (from the top right corner to the bottom right corner, counterclockwise): TLE structural reorganizations, the initial precipitating injury (i.e., the SE in animal models), epileptic seizures (SRSs), a deficit in the E-I balance, a deficit in synaptic plasticity (at the level of its mechanisms, synaptic connections and/or synaptic strength), paroxystic activity (IA/post-ictal activity), and AEDs. TLE: temporal lobe epilepsy; SE: Status Epilepticus; SRS: Spontaneous and recurrent (epileptic) seizures; IA: interictal activity; E-I: excitatory-inhibitory; AEDs: anti-epileptic drugs.

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**DISCLOSURE OF CONFLICTS OF INTEREST**

The author has no conflict of interest to disclose.
**Initial insult**: TLE patients: FCD, stroke, FS, cortical malformations, ...

**TLE animal models**: SE to mimic this initial trigger, often via a chemoconvulsivant injection (pilocarpine, kainate) or electrical stimulation.

**SZ1**: Occurrence of the first spontaneous seizure
E-I balance

SE/SRS

TLE reorganizations

Cognitive deficits

AEDs

Synaptic strength / connectivity / plasticity