A Review on the Pathomechanism of Interictal Psychiatry Comorbidities in Epilepsy

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Abstract

Epilepsies, especially mesiotemporal epilepsy in adulthood, are frequently associated with chronic cognitive loss, psychiatry symptoms and conditions. We aim to present the pathophysiology of interictal psychiatric comorbidities interlocked with cognitive loss; severely compromising the quality of life of epilepsy patients. We will present the mechanism of cognitive harm related to interictal spiking; and the abnormalities of brain networks in epilepsy, especially of the default mode network, briefly looking into psychosocial and pharmacology effects, too.

In addition to seizures, interictal epileptic activity, mainly in sleep, may exert chronic cognitive harm, increasing the risk for primarily non-cognitive psychotic conditions as well. Intercital spikes and pathological high frequency oscillations curiously resemble normal memory traces; enabling them to “behave” and be mistaken for engrams by the memory process. Epileptic activity impairs the white and grey matter of the brain; likely contributing to brain network changes. The epileptic network changes resemble those seen in non-epileptic psychiatry conditions, offering a network-interpretation of psychiatric comorbidity.

Keywords: Epilepsy; Cognitive loss; Memory; Default mode network; Psychosis; Depression

Introduction

The flagship symptom of epilepsies is the epileptic seizure, but cognitive and behavioural changes, psychiatry symptoms and conditions intimately associate with it. We aim to present the putative mechanism of interictal epileptic psychiatric comorbidities, with special attention to cognitive changes. Because the temporo-limbic system has paramount importance in the regulation of emotional and mood-related functions as well as in the processes of memory and learning – cognition -, mesiotemporal lobe epilepsy out of the adulthood epilepsies, carries the highest risk for developing mental symptoms. Through its rich connections, the temporo-limbic system participates in the shaping of psychopathology symptoms of extra-temporal epilepsies as well; making mesiotemporal lobe epilepsy a proper model for studying the cognitive and mental comorbidities of epilepsies in general. Therefore, in our work we pay most attention to mesiotemporal lobe epilepsy.

Classification of mental comorbidities in epilepsy

The mental disturbances that are the complications of epilepsy belong to the group of ‘Organic, including symptomatic, mental disorders’ (ICD-10; F00-F09) [1]. In the classification system of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [2], epilepsy-related disturbances fit into several additional groups: Group 20. ‘Other clinically significant disturbances’ or group 17, ‘Neurocognitive disturbances’. Childhood developmental epileptic encephalopathies may be consistent with DSM-5 1. ‘Neurodevelopmental disorders’. The depressive, psychotic, anxiety and compulsive disturbances belong to DSMS 2-6: 2. Schizophrenia spectrum and Other Psychotic Disorders; 3. Depressive Disorders; 4. Bipolar and Related Disorders; 5. Anxiety Disorders; 6. Obsessive-Compulsive and Related Disorders.

However, the epileptic variants of psychiatry conditions are usually different compared to the non-epileptic forms: they are shorter, non-familial and leave no mental deficits, contrasting schizophrenia. They may brittle from one type to another in one patient, carrying mixed features. Recognizing the atypical, epilepsy-specific presentation of some mental disorders, the International League against Epilepsy has built a classification system [3], discriminating typical versus atypical epileptic forms.

Based on the adoption of the existence of atypical forms by ILAE, we venture not to use detailed psychiatry nosology categories in our work; rather, we refer to groups based on leading symptoms such as depressions-mood disorders,
anxiety syndromes, psychoses and schizophreniform psychoses in general.

The background of interictal psychopathology disturbances in epilepsy

While the cognitive damage of seizures and the instant harm of interictal discharges, called transient cognitive impairment, are relatively easy to interpret, the mechanism of enduring psychiatry symptoms and conditions far away from clinical seizures is less clear [4-8]. The following data demonstrate the proportions of such comorbidities.

More than half of the epilepsy population suffer from low moods and each epilepsy patient develops at least one episode of clinically significant depression, contrasting with just 16% of patients with diabetes, 17% with asthma and 9% of the general population [9-11]. Forty percent of epilepsy patients suffer with anxiety conditions [12]. The risk of suicide is elevated several-fold compared to the general population; twenty-fivefold in temporal lobe epilepsy [11,13-16]. The prevalence of psychosis is sevenfold of the general population, and the schizophreniform psychoses affect more than half of TLE patients [17-20]. During ten years of follow-up, 10% of children suffering in temporal lobe epilepsy have developed an episode of schizophrenic psychosis [21].

There are several concepts on the causes of chronic psychiatry comorbidity in epilepsy.

1. The unforeseen seizures maintaining uncertainty and defenselessness together with the complex psychosocial handicap related to epilepsy may have a psychopathology impact

2. Are the antiepileptic drugs responsible? Sometimes, but likely not essentially: we see the mental harm before introducing antiepileptic treatment and in spite of drug changes as well.

3. The interictal epileptiform activity causes chronic cognitive harm [22].

4. It has long been suspected that the abnormal sensoro-limbic connections in mesiotemporal lobe epilepsy might cause pathologic hypersensitivity to external stimuli. Connectivity studies, especially those on resting state networks have confirmed such possibilities.

Ad 1. The unexpected seizures causing uncertainty and defenselessness may have a psychopathology impact

Epilepsy is a source of traumatic experiences, restrictions, defenselessness and stigmata. Most patients have social difficulties; are lonely and single. A seizure occurring in a community may be disgraceful, leading to embarrassment and repudiation, causing the isolation of the patient. Stigmatization may cause abnormal development of the self, and security restrictions increase shyness.

The repeated seizure-related loss of control is another specific traumatizing factor: experiencing doom may foster suicidal propensity and maladaptive strategies. Female gender, family stressors or the lack of family support are additional psychological risk factors.

Ad 2. The cognitive and psychopathology effects of antiepileptic drugs (AEDs)

Old AEDs as barbiturates and phenytoin typically cause psychopathology. Phenytoin and phenobarbione are independent risk factors of suicide [23]. Vigabatrine, an irreversible gamma amino butyric acid (GABA)-transaminase inhibitor causes depression in 10% of patients [24], similarly to tiagabine; inhibiting GABA-uptake. Topiramate may aggravate depression [24]. Based upon one study; oxcarbazepine is an independent risk factor of depression; while other studies found its mood-improving effect [15,25,26]. Levetiracetam may cause irritability and fatigue, aggressive behaviour [27-29] and even psychosis [23,30]; 16% of patients treated with levetiracetam suffer psychiatry complications [31]. At the same time, due to its excellent antiepileptic properties, it is a good option in treating peri-ictal psychoses. Carbamazepine, lamotrigine and sodium valproate have an anti-depressive and mood stabilizing effect [24]. Lamotigine and gabapentine cause less mental adverse effects than the rest of AEDs [31]. Carbamazepine has a protective effect against psychosis [23].

The cognitive harm of AEDs correlates with the number administered in poly-therapy: the increase of AED-numbers given in combination correlates with an impairment of executive functions: “each additional drug matters” [32]. The excellent cognitive effects of lamotrigine and the less favorable ones of topiramate are well known. The cognitive spectrum of lacosamide is similar to LAM [33]. Levetiracetam improves the performance in visual memory and attention tests [27]. Only topiramate has caused any language-related functional network deactivation and dysphasia [34].

In summary, when dealing with mental changes in epilepsies, one needs to consider the potential impact of antiepileptic drugs, especially, if given in combination. Older antiepileptic drugs and topiramate may have cognitive harm, levetiracetam frequently compromises mood and might cause agitation, and lamotrigine is a mood-stabilizer sometimes also causing agitation. The drug interactions of AEDs (exceeding the frameworks if this review), especially with psychotropic drugs need special consideration when both types of drugs need to be administered together.

Ad 3. The chronic cognitive harm of interictal epileptiform activity: the memory impairment caused by spikes

Cognition has strong impact on apparently independent psychopathology conditions, even acting as their risk factors [35-37]. The memory process - encoding, consolidation and retrieval - may be compromised in several types of epilepsies; mildly and not perceived in some, or at a tragic and dramatic
speed and extent in other ones e.g. in early childhood developmental encephalopathies.

The physiology of learning - encoding and consolidation of memory - associates to the hippocampi, the thalamo-cortical system and to nREM sleep [38-46].

Memory encoding

Based on animal experiments, the site of the activated CA1 and CA3 pyramidal cells is the presently known clue for the transcription from external stimulus to nervous signal, called encoding [47].

Synaptic plasticity

Learning depends on synaptic enhancement and weakening. Cellular learning, consistent with long-term potentiation is under the control of N-methyl-D-aspartate (NMDA)-receptors and other neurotransmitters. Long-term potentiation [48] is a persistent strengthening of synapses based on recent patterns of activity, marked by the decrease of synaptic stimulus-threshold, the increase of the intensity and frequency of discharges, postsynaptic depolarization and the rate of calcium influx [42,43,49-52]. It develops due to repeated high frequency (tetanic) stimulation of a synapse, so that the involved neurons learn to convey a given stimulus.

Memory replay

One of the basic elements of memory consolidation [the stabilization of an engram] is the replay of daytime impulses. The incoming impulse activates the specific cortex, which in turn stimulates the granular cells of the hippocampus causing delayed activation of the hippocampal pyramidal cells during sleep and other off-line states of the brain [53]. The discharges of hippocampal pyramidal cells repeat the sequence of daytime impulses in an accelerated and condensed form; this is called replay [42,43,54-57]. The replay reinforces the unstable engrams and projects them to the frontal cortex, where they join stored memories and consolidate. e.g., the place-cells activate in a certain order at the time of the spatial orientation then the sequence of these discharges reoccurs in the hippocampal pyramidal cells with a10-20-fold speed during the next sleeping period; consolidating ultimately in the cortex [53,54]. Thus, memory consolidation occurs in a cortico-hippocampo-cortical loop, broken if the hippocampus is damaged [43,55,56,58-60].

Sharp wave-ripple complexes

The key electrophysiology actor of memory-replay is the hippocampal sharp-wave ripple complex. It is made of a sharp wave arising from the excitatory system of the CA3 region [42,43,53-61] and an 80-200 Hz network ripple in the CA1 region [42]. The sharp-wave ripple complex emerges during off-line states: nREM sleep, resting and consummator periods [59-62]. Those studies where the abolishment of sharp-wave ripple complex hindered rats’ space learning; have proven its essential role in memory consolidation [60,63].

The sharp-wave ripple complex and the interictal epileptic activity

Animal and human studies show that temporal epileptic spikes link with hippocampal ripples, suggesting that the sharp wave component of the complex suffers an epileptic derailment to an epileptic spike. This transcript (sham) of the sharp wave is unfit for memory consolidation [43,57-59,64,65]. In addition, the ripples of the complex may undergo an epileptic conversion as well, developing into pathological high frequency oscillations [43,66]. Thus, the epileptic spikes and pathological high frequency oscillations occupy the normal plastic process, making the system unserviceable [64,67]. Due to the sleep dependency of SPW-Rs, this conversion links to nREM sleep and favours after-learning periods.

Sharp-wave ripple complex and schizophrenias

In a schizophrenic, calcineurin-deficient mouse model (calcineurin is a forebrain specific phosphatase enzyme involved in synaptic plasticity) the hippocampal replay is abnormal: there are many sharp-wave ripple complexes, but their sequential pattern repeating daytime stimuli is absent. This links schizophrenia to cellular level synaptic dysfunction and cognitive harm [68,69].

The triad of slow waves, spindles and ripples in sleep

Within nREM sleep, sharp-wave ripple complexes link to neocortical slow (<1 Hz) waves, more so with the higher amplitude ones, emerging in the transition-zones of slow waves when the waves are turning from their up to their down states [61,70]. There is a coupling between sharp-wave ripple complexes and sleep spindles as well. In nREM sleep, those three patterns interlock under the direction of slow waves. The ripples of sharp-wave ripple complexes, carrying the reactivated engrams, fit into the sleep spindles feeding the hippocampal information into the neocortical networks, resulting in persistent synaptic enhancement called learning [61,71,72].

The homeostatic control of sleep slow waves

Sleep slow waves are under homeostatic control. Their number increases in the site of, and proportionally to the pre-sleep exertion of the brain; then it decreases again after fulfilling the task [73-75]: recovering the exhausted synapses facilitated by pre-sleep daytime exertion. The name of this recovery process with slow wave decay overnight is synaptic downscaling; refreshing the saturated synapses and making them workable again. After a hard requisition, our sleep is “deeper”, containing more slow waves [41]. Slow waves are abundant in periods of high sleep-pressure (the first sleep cycle of the night, deep slow wave sleep and cyclic alternating pattern (CAP) A1), then they attenuate overnight [72,74-76].
Slow waves and spikes

The slow wave-tie of sharp-wave ripple complexes and their propensity to an epileptic derailment involve, that spikes and pathological high frequency oscillations couple with sleep slow waves [56,67,77-79]. Therefore, the highest spike-density is due in the periods of high homeostatic pressure during sleep, correlating with pre-sleep cortical requisition [77-80].

The spikes “mimic” engrams

The epilepti derailment of sharp-wave ripple complexes results in “senseless” spikes and pathological high frequency oscillations: Due to the spikes' similarity to the sharp waves of sharp-wave ripple complexes, the residual normal plasticity “mistakes” daytime spikes for memory traces. The condensed sequence of pre-sleep interictal spike-discharges could be detected during the subsequent sleep period over wide cortical regions meaning that spikes are replayed and processed, as normal engrams are [66,81]. Thus, spikes “behave” as normal engrams, enhancing the homeostatic restitution. A high daytime spike-number was followed by less slow-wave decay than normal learning during the subsequent sleep period [66]. In encephalopathy with electrical status epilepticus in sleep encephalopathy with status epilepticus in sleep (ESES), the continuous interictal discharges in sleep inhibited night-time slow wave decay, reducing next day’s learning capacity [73,82].

Summary: The multiple ways of memory-impairment caused by interictal spikes

- During sleep, spikes and pathological high-frequency oscillations, as dysfunctional shams of sharp-wave ripple complexes are unfit to replay and consolidate normal memory (Figure 1).
- Daytime spikes behave as engrams: annexing synaptic capacity, they obstruct the elaboration of normal engrams.
- While daytime spikes cause homeostatic slow wave increase in sleep, they block slow wave decay overnight thus decreasing synaptic receptivity the day after.
- The distortion of the default mode network in mesiotemporal lobe epilepsy interlocks with spiking.

Clinical evidence on the harm of interictal spikes

Children: The prevalence of epilepsy is 30% in children with learning difficulties, and epileptic children without any IQ deficit may perform more poorly than controls in distinct learning domains, which justifies screening for such weaknesses in epileptic children [83,84]. The mood disorders seen in 34% of epileptic children can simulate cognitive deficits [85].

Sleep-related spikes and spike-wave pattern found in non-epileptic children is associated with cognitive deficits and behavioural changes, and the decrease of spike numbers resulted in behavioural improvement [86,87].

In mixed-type childhood epilepsies, attention- and short-term memory deficits were seen [88]. The information processing and visuo-motor integration was poorer in those with interictal epileptic activity covering at least 10% of the daytime EEG [89].

In age-related childhood epilepsies, behavioural anomalies and cognitive loss [90,91], language and short-term memory deficits were detected [92-94], e.g. in benign centro-temporal epilepsy, proportionally with spiking the recognition of scary faces was deficient [95]. In another group of idiopathic focal epilepsy children, the memory consolidation related to nREM sleep correlated negatively with spiking [96-98].

The most severe forms of epilepsy-related cognitive loss are seen in the epileptic encephalopathies [82,99-101] with abundant epileptic activity during sleep. Electrical status epilepticus in nREM sleep presenting with global or patchy cognitive deterioration and its focal variant Landau-Kleffner syndrome with acquired aphasia are specific sleep-dependent forms [102-107]. No seizures or just sparse ones may occur with them; proving the independent harm of sleep related interictal activity [104]. Without the orienting lead of clinical seizures, these conditions cannot be diagnosed except with sleep EEGs [105-107].

Thirty percent of children with epilpsies suffer with attention-deficit hyperactivity syndrome. Both attention-deficit hyperactivity syndrome and autism spectrum disorder link with epilepsy, as shown by the presence of interictal discharges carried by the affected non-epileptic children; epilepsy is an “autism sibling comorbidity disorder” [108-110].

Adults: The prevalence of dementia in epilepsy varies in a wide range: 8-17% [84]. Mesiotemporal lobe epilepsy may importantly compromise memory, negatively correlating with hippocampus volume and interictal activity [111-117]. The most affected field is executive functioning including verbal

Figure 1 The multiple harm of epilepsy on the memory process, the 24 hours cycle and the homeostatic drive (HD). [SW: Slow Waves <1 Hz in nREM sleep; HD: Homeostatic Drive; MC: Memory Consolidation; Sy: Synaptic up-, and down scaling; SPW-R: Sharp wave-Ripple; pHFO: Pathologic High Frequency Oscillations; --> : Derailment or Malfunctioning; Day and night].

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fluency and IQ [22]. “Everyday” memory - phone-numbers and dates - is impaired [114].

The role of interictal epileptic activity in the pathogenesis of dementia in adult neurodegenerative conditions, e.g. Alzheimer’s disease, has been raised [116,117].

Clinical consequences

The severe cognitive complications of interictal epileptic activity during nREM sleep [97,118-120] call attention to the lack of and need for a “spike-killing” treatment. Sleep EEG is indispensable in epilepsy practice in general, and especially in searching for the cause of mental deterioration of childhood with no clinical seizures [76,80].

Ad 4. Aberrant sensoro-limbic connections in the mechanism of psychiatry comorbidities

Background

Brain functioning is related to the co-activation of interconnected nodes, outlining brain networks. The whole of functional and structural brain networks is called ‘connectome’ [analogue wording ‘genome’]; it is modelled by sophisticated mathematical methods [121-123]. The functional networks flexibly change their patterns depending on the context e.g. state, age, mood, pains etc., mutually influencing each other [123,124]. Somatic diseases also transform them; and their conversions are causes and markers of mental conditions [125-130]. The recognition of brain networks accompanies the development of the network-concept of epilepsies and mental conditions [131-133]; e.g. taking into account the long reach of mesiotemporal lobe epilepsy involving wide spread bilateral regions; not just one mesio-temporal focus [105,134].

Methodology

Functional MRI, diffusion tensor imaging, tractography: Functional connectivity is the term describing the connected [in time and frequency] activation of brain nodes in a network. EEG-based sophisticated calculations and functional MRI allow the modelling and imaging of brain networks [135]. Functional MRI traces out the regional oxygen consumption [BOLD signal-blood-oxygen-level dependent contrast imaging], which is proportional with the metabolism of a region scrutinized [136]. Thus, functional MRI can localise those regions co-activated by a task, allowing the mapping of the connected regions, constituting a functional network [137-139].

MRI tractography, based on diffusion tensor imaging [DTI] is the tool of mapping structural connectivity

MRI tractography images the neural pathways and tracts in the white matter, anatomically interconnecting the nodes [140]. DTI measures the diffusion of water molecules through white-matter bundles; which is necessarily slower across high-density structures. Its measure is anisotropic diffusion, depending on the thickness and wholeness of myelin [141].

The default mode network (DMN)

We have learned the networks of elementary somatosensory functions [142], and those of sophisticated mental activities [143]. The latter are strongly related to the task-negative networks activating during resting states and inhibited by tasks; which had seemed artefacts-noises- initially [144-147]. The pattern of those networks related to attention [146], reward [147], mathematics [148] etc. determine our moods, level of anxiety, thinking and pathologic mental brain conditions.

The default mode network is one of the resting state networks, involved in the brain’s floating, non-specific-default-activity [145,149]. Out of all other networks, the concordance of functional and structural connectivity is the strongest in this one [150], the “neurology base of self” [151]; related to a wide range of cognitive, mood-related and emotional functions.

Its main nodes are the posterior cingulate cortex and precuneus, the medial prefrontal cortex, the angular gyrus, the temporo-parietal junction, the temporal pole and hippocampus, the retrosplenial cortex, and the posterior inferior pariet “https://en.wikipedia.org/wiki/Parietal_lobe”al lobe [149,152-155].

Epileptic networks

Epilepsy spreads across self-generating tracks - epileptic networks- in the brain producing new spikes, seizures and additional epileptic regions (foci) on its way [156-158]. In this sense, epilepsies are progressive conditions. Typically, mesiotemporal epilepsy spreads to the contralateral hippocampus, the homo-lateral temporal neocortex and the ipsilateral frontal lobe [104,159].

Interaction between interictal epileptic activity and the default mode network

Immediately before spikes occur, there is an increase of default mode network-activity, while spikes associate with a decrease of the activity of several default mode network nodes [138], suggesting an interaction [137,160]. This mutual effect might explain why in encephalopathy with electrical status epilepticus in sleep the spiking regions show an increased default mode network activity, while outside the epileptogenic area, it deactivates pathologically [82].

Abnormal functional connectivity in mesiotemporal lobe epilepsy

There are several epilepsy-specific functional connectivity changes [161]. The network changes persist after seizure freedom is reached, i.e. chronic epilepsy leads to a permanent network distortion (and likely related mental symptoms); making early treatment vital [162]. The pattern of functional connectivity changes helps to discriminate mesiotemporal
epilepsy cases with or without hippocampal sclerosis, right and left, poor and good prognosis, easy- and difficult-to-treat ones [163-170] and those ones developing after-, versus those without a febrile convulsion (Table 1).

The default mode network undergoes a transformation in mesiotemporal epilepsy. There is an intra-hippocampal increase of connectivity and a decrease of connectivity between the hippocampus and the default mode network [171-180]. The limbic-neocortical connectivity is low as well (Table 1).

### Table 1: Network changes shared by mesiotemporal epilepsy and non-epileptic psychoses (schizophrenia and schizophrenia spectrum disorders -ICD10-5 F20-29; DSM5-2; depressions and bipolar disorders -ICD10-5 F30-39; DSM5-3,4) (C= connectivity, H= hippocampus, hippocampal, DMN: default mode network, SMA: Supplementary sensory-motor area).

<table>
<thead>
<tr>
<th>Mesiotemporal epilepsy</th>
<th>Schizophreniform psychosis</th>
<th>Depression/bipolar disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased C between H and DMN [163-165]</td>
<td>Decreased C between H and DMN [187]</td>
<td>Decreased medial prefrontal cortex C [186]</td>
</tr>
<tr>
<td>Hyperconnectivity between H and DMN [166]</td>
<td>DMN hyper-, [132,187] or hypo-connectivity [155,180,188].</td>
<td>Decreased DMN C in the left caudate nucleus, right anterior cingulate cortex, right angular gyrus, bilateral medial prefrontal cortex and right prefrontal cortex [190].</td>
</tr>
<tr>
<td>Increased C between the occipital and cingulate cortex [134,171]</td>
<td>C changes between H-DMN and H-SMA correlating [180,188] with positive symptoms.</td>
<td>Increased C between the DMN and the subgenual region [192, 193]</td>
</tr>
<tr>
<td>Increased neocortico-limbic C [193]</td>
<td>Distorted cortico-subcortical networks: thalamocortical, frontolimbic and cortico-cerebellar [194-197].</td>
<td>Inter-hemispheric and limbic C changes; increased amygdala-medial prefrontal C [186]</td>
</tr>
<tr>
<td>Hippocampo-limbic C changes correlating with the depressive symptoms positivity in left mesiotemporal epilepsy, negativity in right mesiotemporal epilepsy [198].</td>
<td>C changes in hearing and language networks, in the frontopolar network, in basal ganglia [199].</td>
<td></td>
</tr>
<tr>
<td>Changes of C in amygdalar emotional face recognition networks, mainly in right temporal epilepsy [167,168]</td>
<td>changes of C between nucleus accumbens-DMN, and cingulo-opercular network [201]</td>
<td></td>
</tr>
<tr>
<td>Increased intra-H C [134, 171]</td>
<td>Abnormal intra-H C [189]</td>
<td></td>
</tr>
</tbody>
</table>

The functional connectivity changes found in non-epileptic psychoses and affective conditions are similar to those in epilepsy

There are default mode network excitation/inhibition changes and imbalance in psychotic and affective disorders, affecting mentally intact relatives as well [180-185]. Although due to methodology issues, the data on network changes are hard to summarize there is growing evidence on the change of the default mode network or some of its nodes in non-epileptic mental conditions.

In Table 1 and Figure 2, we present those connectivity changes strikingly shared by non-epileptic psychoses and epilepsies, to highlight the similarities, which are in line with structural changes and might contribute to the development of psychoses in epilepsy.

Epilepsy causes structural connectivity changes

There are unexpected structural changes in non-lesional epilepsies [164-172]. The volume of white matter decreases in childhood epilepsies. In surgical tissue samples of mesiotemporal epilepsy patients, there were significantly more excitatory and inhibitory neurones both in the white and grey matter, than in non-epileptic controls [173].
mesiotemporal epilepsy, the axonal calibres were decreased and the myelin-sheets abnormal [151] and in humans, the degree of the anterior temporal, uncinate and lower longitudinal fasciculus abnormalities correlated with the severity of mesiotemporal epilepsy [173].

In summary, because the degree of white matter impairment correlates with the frequency of partial seizures and the duration of mesiotemporal epilepsy, the causative role of epilepsy seems likely [186-200].

How does epilepsy cause white matter damage?

The over-use of epileptic networks by spiking and seizures may not be responsible in itself, because generally, the excess use of brain systems - practice - improves functioning: e.g., vision, movements, thinking etc. do not cause harm; rather, they improve performance and lead to the anatomic enlargement of the involved system, contrasting epilepsy.

Structural connectivity-changes in non-epileptic psychoses and mood disorders (ICD10-5 F20-29; DSM5-2; ICD10-5-F30-39; DSM5-3,4)

Schizophrenias develop white matter disorganisation. Schizophrenia and bipolar disorders share frontal white matter anomalies, more marked in the former [186]. The fronto-temporal pathways are abnormal early, even in the prodromal phase and in adolescents. The decrease of white matter volume correlates with the duration of the disease [140].

There are grey matter volume changes as well, affecting the frontal, temporal and anterior cingulate cortices [200,201]. The volume-increase of the thalamus, and the decrease of the left middle and superior frontal gyrus, significantly link with cognitive deficits [194,195].

In summary, it is possible that epileptic psychoses and mood disorders are related to the structural changes caused by epilepsy, partially resembling those seen in genuine mental conditions.

Summary of the chapter ‘Aberrant sensoro-limbic connections in the mechanism of psychiatry comorbidities’

Epilepsy, especially mesiotemporal epilepsy

- Changes the default mode network.
- It causes structural damage affecting both grey and white matter especially the tracts and nodes of the default mode network.

These network changes and structural alterations resemble those seen in genuine, major psychiatry conditions probably contributing to the appearance of their atypical forms in epilepsies.

Summary Considerations

Mechanism of psychopathology in epilepsy

Depressions and epilepsy: Psychosocial factors do certainly affect patients’ mood and some of the antiepileptic medications may contribute as well, but the remarkably frequent depressive co-morbidity compared to the rest of chronic conditions suggests an additional biological background of depression in epilepsy [202-206]. There are pathogenic factors shared by depressions and epilepsies e.g. the overlapping functional and structural connectivity changes [207-212]. The harm of temporal lobe epileptic activity exerts on plastic functions is another major contributing factor [35-37,212,213] while conversely, depression impairs memory [214].

In epileptic animal models, low levels of serotonin, noradrenaline, dopamine and GABA promote the production of new epileptic areas - epileptic kindling- increasing seizure frequency and disease severity. Some antidepressants may inhibit or reverse this [209,215,216].

Higher serotonin levels allow long lasting long-term potentiation in response to external stimuli, while lower ones support the replay of engram [54]: the serotonergic disturbances related to depression have multi-lateral impacts on memory consolidation. The triangle of epilepsy, depression and cognitive loss interact, mutually augmenting each other [9,215,217].

Epilepsy and psychoses: Based on the frequently seen interictal psychoses in patients with complex partial seizures, Gibbs and Gibbs [218] presumed the existence of common mesio-temporal mechanisms. Several data support this suspicion.

- Connectivity studies [134,219]: epilepsies lead to atypical psychotic disorders, though distorting the default mode network.
- There are shared genetic factors of temporal lobe epilepsy and schizophrenia [220].
- In surgical samples of TLE patients suffering also in psychoses or major depression, the accumulation of neuro-inflammatory molecules resembled those in non-epileptic psychiatry conditions discriminating temporal lobe epilepsy with or without a psychosis [216].
- We have known since Kraepelin and Bleuler that schizophrenia associate with cognitive harm, even before the actual onset of psychosis. The cognitive loss is not a complication of psychosocial factors and occurs in the normal relatives as well; it might be a risk factor and harbinger of poor prognosis in schizophrenias [221].

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References

35. Bora E, Murray RM (2014) Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: Do the
cognitive deficits progress over, or after, the onset of psychosis? Schizophrenia Bull 40: 744-755.


behavior via the block Akt/GSK3β signaling pathway. Behav Brain Res 323: 38-46.


