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► **To cite this version:**

T. Marissal. An inventory of basic research in temporal lobe epilepsy. *Revue Neurologique*, 2021, 10.1016/j.neurol.2021.02.390 . hal-03328575

HAL Id: hal-03328575

<https://amu.hal.science/hal-03328575>

Submitted on 5 Jan 2024

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1 **An inventory of basic research in Temporal Lobe Epilepsy.**

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5

6 **Abstract:**

7 Temporal lobe epilepsy is a severe neurological disease, characterized by seizure
8 occurrence and invalidating cognitive co-morbidities, which affects up to 1% of the adults.
9 Roughly one third of the patients are resistant to any conventional pharmacological
10 treatments. The last option in that case is the surgical removal of the epileptic focus, with no
11 guarantee for clinical symptom alleviation. This state of affairs requests the identification of
12 cellular or molecular targets for novel therapeutic approaches with limited side effects. Here
13 we review some generalities about the disease as well as some of the most recent
14 discoveries about the cellular and molecular mechanisms of TLE, and the latest perspectives
15 for novel treatments.

16

17 **Keywords (maximum 6): Temporal Lobe Epilepsy; Preclinical Research; Therapeutical**
18 **perspectives.**

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1. Temporal Lobe Epilepsy: Generalities

Temporal lobe epilepsy (TLE) affects up to 1% of people from Western countries [1,2]. TLE is the most prevalent type of epilepsy in adults, accounting for 30-40% of epileptic patients. The precise causes of TLE are difficult to identify with certainty. It is postulated that patients undergo an initial trauma (e.g., febrile seizure, infectious disease, head injury, or status epilepticus [3]), which induces remodeling of the temporal lobe neuronal network. One of the most salient histological manifestations of these changes is abnormal hardening and a decrease in the size of the hippocampus, called hippocampal sclerosis, which is observable using magnetic resonance imaging and was developed by two-thirds of patients with TLE [4].

After a latent period that can last years, the temporal lobe becomes susceptible to unpredictable and recurrent epileptic seizures. The latter include focal aware seizures that manifest through an ensemble of clinical symptoms, called "auras", which are sometimes hard for patients to describe. It seems that auras are associated with uncomfortable sensations from the stomach and the chest and are transiently accompanied by abnormal emotional (e.g., fear, anxiety), sensory (e.g., hearing or olfactory hallucinations), or mnemonic (e.g., amnesia, déjà-vu feeling) perceptions, most of the time without loss of consciousness.

Complex partial seizures can also occur (lasting a few minutes at maximum), notably characterized by a fixed stare and motor manifestations such as abnormal arm positioning and typical repetitive lip-smacking movements. In extreme cases, seizures can evolve into generalized tonic-clonic seizures accompanied by behavioral convulsions or even status epilepticus during which seizure activity lasts more than 30 minutes without recovery of consciousness.

From an electrophysiological point of view, the symptoms detailed above can coincide with the pathological, sometimes hypersynchronous, activity of the neurons from the temporal lobe of the brain, called "ictal" events, which can be monitored using electroencephalogram (EEG) recordings. In patients suffering from TLE, ictal event onset is characterized by the

28 emergence of rapid discharges, sometimes preceded by rhythmic spiking [5]. Interestingly,
29 EEGs can also detect abnormal patterns of activity during periods between seizures called
30 “interictal” events, which are brief episodes of rhythmic epileptiform activity. These activity
31 patterns are commonly considered a distinguishing signature of an epileptic network. As
32 interictal events are not necessarily correlated with abnormal behavior, their impact on
33 hippocampal function is still debated: some experimental evidence suggests that they could
34 disturb cognitive performance [6–8] by interfering with the underlying physiological
35 mechanisms, notably hippocampal-cortical coupling [9]. Conversely, the observation that
36 interictal activity results in the inhibition of glutamatergic cells [10] supports the hypothesis
37 that those activity patterns could be protective phenomena [11].

38 Last, ictal and interictal periods can also be accompanied by pathological high-frequency
39 oscillations [12,13] that are concurrent with physiological ripples of lower frequencies [14].
40 EEG signals are used as a tool for the identification of the epileptogenic zone in the temporal
41 lobe [15]. The ability of the different regions from the temporal lobe to act as epileptogenic
42 foci is still debated. Although temporal lobe structures such as the amygdala complex and
43 the entorhinal cortex are able to initiate ictal discharges [5,15–17], the hippocampus is still
44 considered a major ictal generator [18], particularly in the case of TLE accompanied by
45 hippocampal sclerosis [19].

46 In addition to seizures, patients suffering from TLE must cope with numerous invalidating
47 comorbidities. Among them, psychiatric disorders are very common: TLE is associated with a
48 high prevalence of mood disorders such as anxiety, major depression or suicidal ideation
49 compared with the general population [20]. In addition, patients exhibit an increased risk of
50 developing serious cognitive impairments: alterations in social processing [21], deficits in the
51 recognition of emotional expression [22], and executive dysfunctions [23] have been notably
52 observed in patients suffering from TLE. Furthermore, one of the most prominent side-effect
53 cognitive disorders in TLE (and probably the most studied) is memory disruption. More than
54 half of the patients with TLE present mild or severe memory alterations [24], affecting diverse

55 domains of mnemonic function, such as spatial [25], episodic [26], or working [27] memories.
56 For the generation of seizures, the hippocampus might play a key role in the cognitive
57 impairments that are associated with TLE. First, various lines of evidence suggest that
58 physiological hippocampal theta and gamma band rhythms, which are substrates for several
59 cognitive functions, are disturbed in TLE [28–30]. Second, hippocampal sclerosis seems to
60 be an important correlate for the severity of memory decline [31,32]. Notwithstanding, TLE
61 pathology is unlikely to rely on the hippocampus alone. In contrast, cognitive impairments
62 extend far beyond the epileptic zone(s) from which seizures originate, even beyond the
63 temporal lobe itself [33]. It was demonstrated that hippocampal epileptiform events could
64 perturb network activity patterns in “remote” brain regions and that abnormal coupling could
65 disrupt the related cognitive functions [9,34–36]. Importantly, the aberrant connectivity
66 between the epileptic foci and distal brain regions seemed to be correlated with TLE severity
67 (cognitive impairments, seizure frequency) and postsurgical outcome [35].

68 In summary, patients with TLE suffer from numerous disorders that dramatically dampen
69 their quality of life. The disease burden from epilepsy (based on life expectancy disability
70 weight and other factors) was estimated to be heavier than those for Alzheimer’s and
71 Parkinson’s disease combinations [37]. To control seizure occurrence, multiple anti-epileptic
72 drugs (AEDs) can be prescribed. Classically, these pharmacological agents tend to block
73 specific ionic channels to reduce excitatory glutamatergic transmission or potentialize
74 inhibitory GABAergic transmission [38]. Unfortunately, these therapeutic strategies present
75 numerous inconveniences. First, as a symptomatic treatment, AEDs do not prevent or
76 reverse the pathological processes underlying the disease. Second, controlling seizures
77 using AEDs is not always sufficient to alleviate the associated clinical comorbidities. Even
78 worse, these drugs may contribute to aggravating cognitive disorders in some patients [39].
79 In addition, interactions may occur between AEDs and the other medications the patient
80 takes, resulting in reductions in their effects. That said, the pharmacological agents that were
81 most recently developed display less adverse cognitive effects and cause fewer drug

82 interactions [38]. Last, a high fraction of patients with TLE in developed countries are
83 resistant to any available pharmacological therapy [40]. For intractable TLE, surgical
84 resection of the epileptic focus is a strategy of last resort. However, only 25-50% of adults
85 are cured after surgery in TLE with hippocampal sclerosis (e.g., at least five years seizure-
86 free and off drugs, [38,41]). Moreover, this type of surgery is capable of permanently
87 damaging cognitive functions in some patients [42]. Therefore, epilepsy surgery is still
88 underutilized even though growing lines of evidence suggest that surgery remains the best
89 option for patients with refractory TLE [43].

90 In conclusion, not only do the current therapeutic strategies not guarantee the relief of the
91 symptoms associated with TLE (including seizure generation), but the socioeconomic burden
92 is heavy: the estimated cost per patient was evaluated at €2000-11,500, representing a total
93 expense of €15.5 billion in Europe in 2004 [44]. Therefore, in terms of public health, it is
94 particularly important to better understand the pathophysiological mechanisms underlying
95 TLE to identify targets for novel treatments.

96 **2. The molecular and cellular bases of temporal lobe epilepsy: lessons from basic** 97 **research.**

98

99 **2.1 Substrates for basic research: from patients to animal models**

100 A few basic studies were conducted directly on patients, notably to decipher the network
101 connectivity at the macroscale level [45]. However, those strategies were not able to capture
102 the cellular and microcircuit alterations that can impact TLE pathology [46]. A growing
103 number of basic researchers have used living tissues surgically removed from the brains of
104 patients with intractable TLE. These samples could be used to conduct cellular and
105 molecular biology experiments or proteomic studies [47]. In addition, surgically resected
106 tissues allowed the preparation of both acute, and organotypic slices with longer lifespans
107 [48,49]. These slices displayed several molecular and histological features of the epileptic
108 hippocampal network in vivo [48]. In addition, those preparations maintained the ability to

109 spontaneously generate epileptiform activity in vitro, resembling interictal discharges, which
110 could be recorded using electrophysiological or calcium imaging strategies [48–51].
111 Pharmacologically induced ictal-like patterns [48], along with theta and gamma rhythmic
112 activities [52], which were distinct from epileptiform discharges but similar to the behavior-
113 related oscillations recorded in vivo, could also be monitored. Thus, human tissues appear to
114 be a powerful tool for the screening of innovative approaches based on drugs or gene
115 therapy. However, they have many limitations [53]. In addition to the inconveniences that
116 were applicable to in vitro preparations in general [54], the interpretation of the results might
117 be precluded by the absence of “normal” controls and by the variability of each patient e.g.,
118 (age, sex, history of seizure and medication). Consequently, the use of rodent models of TLE
119 remains essential [55,56]. In this review, I will focus on two rodent models in which the initial
120 brain injury was reproduced by the systemic or intrahippocampal administration of the
121 glutamatergic agonist kainate [57,58] or by injecting the muscarinic agonist pilocarpine [59].
122 The injections rapidly lead to status epilepticus that initiates epileptogenic processes. During
123 a period with few clinical signs, called the “latent phase”, numerous changes at the
124 molecular, synaptic, and cellular levels occur within the temporal lobe (summarized in part
125 2.3 below). These pathological phenomena are reflected by the emergence of nonictal
126 pathological activity patterns generated in future epileptic foci [60] and beyond [61]. After a
127 few weeks in rodents (weeks to years in patients), the latent period is followed by a chronic
128 period that manifests with the occurrence of recurrent seizures generated by the temporal
129 lobe. Pilocarpine and kainate status epilepticus induction procedures are widely used due to
130 their high similarity to human TLE [62]. First, both models exhibited EEG electrophysiological
131 signatures of epilepsy during the chronic period, such as ictal and interictal discharges, along
132 with pathological high-frequency oscillations. Interestingly, classical AEDs reduced seizure
133 occurrence in most animals, but a fraction of animals remained pharmaco-resistant, similar to
134 patients with TLE [63]. Second, kainate and pilocarpine models of TLE displayed several
135 histological changes in the temporal lobe and, more particularly, alterations in the

136 hippocampus that were reminiscent of hippocampal sclerosis in patients [64,65]. Last, they
137 presented anxiety and depression-like behavior [66], social deficits and memory impairment
138 [64,65], and decreases in the associated physiological rhythmic activity patterns [67,68],
139 mimicking the principal functional alterations accompanying seizure generation in humans
140 with TLE. Overall, the two models display quite similar manifestations. Notably, pilocarpine-
141 treated animals seem to develop a higher seizure rate [69] and more marked behavioral
142 alterations [64,65] than kainate models. Thus, the pilocarpine model reliably replicates the
143 symptoms associated with the most severe TLE forms. In contrast, the intrahippocampal
144 application of kainate better reproduced the unilateral lesions observed in most humans with
145 TLE [70]. Originally established for rats [57,71], kainate and pilocarpine administration
146 protocols were also efficient in inducing TLE in mice, which became indispensable for their
147 ability to undergo genetic engineering. Nonetheless, the experimenters had to deal with a
148 higher mortality rate during TLE induction and a lesser likelihood of developing seizures after
149 kainate injections in some mouse strains compared with rats [72].

150 In brief, kainate- and pilocarpine-based rodent models of TLE satisfy the requirements for
151 valid models of human TLE [60]. Consequently, they are a good substrate for the study of the
152 cellular and molecular bases of the disease.

153 **2.2 Cellular and molecular bases of temporal lobe epilepsy**

154 One of the most characteristic changes observed using TLE models, but also in humans,
155 was severe neuronal degeneration. More particularly, pyramidal neurons from the CA1 and
156 CA3 areas [73], hilar mossy cells [74] and, to a lesser extent, granule cells from the dentate
157 gyrus [75] degenerate. In the latter brain area, a dispersion of granule cells was also
158 observed [76], along with an increase in the number of adult-born granule cells displaying
159 aberrant locations and properties [77]. These histopathological processes were first observed
160 in the hippocampus and were associated with hippocampal sclerosis. However, evidence of
161 neuron loss has also been reported in other structures from the temporal lobe, such as the
162 entorhinal cortex and the amygdala [78]. Moreover, the damaged areas were colonized by

163 glial cells, a phenomenon called gliosis [79]. It was postulated that gliosis might participate in
164 TLE pathology by promoting an immune and inflammatory response [80] that could
165 participate in neuronal death [81] and a perturbation of the properties of glial cells
166 themselves [82]. In addition, a perturbation of glial cell function could also take part in the
167 alteration of physiological oscillations and the generation of synchronized pathological
168 activity patterns [83–87].

169 The remaining excitatory neurons developed aberrant properties, notably via changes in ion
170 channel properties [88]. For instance, the downregulation of Kv1.1 [89] and A-type [90]
171 potassium ion channels amplified CA1 pyramidal neuron intrinsic excitability. Furthermore,
172 surviving neurons form abnormal excitatory connections in each hippocampal area. Among
173 them, the most emblematic in TLE is the sprouting of mossy fibers, which are granule cell
174 axons [91]. These fibers normally contact hilar neurons and CA3 pyramidal cells. Under TLE
175 conditions, granule cells form recurrent connections that are very rarely observed otherwise
176 [92,93]. Similar aberrant recurrences were also observed in CA1 regions [94]. CA3-to-CA3
177 connections, which are more common in the healthy hippocampus, and CA3 to CA1
178 projections (called Schaffer collaterals) were shown to be denser in a model of chronic
179 epilepsy [95]. Again, the reorganization of the excitatory synaptic network is not restricted to
180 the hippocampus; it has been recently demonstrated that other temporal lobe regions, such
181 as the entorhinal cortex, might also be affected by axonal sprouting in TLE [96]. TLE-related
182 synaptic rewiring, which leads to the formation of aberrant recurrent connections or the
183 strengthening of pre-existing connections, might play a key role in seizure generation since it
184 has been shown that recurrent excitatory networks can act as a “pacemaker” for synchrony
185 in the hippocampus [97,98]. In addition, some aberrant synapses display unusual properties
186 that lead to an increase in neuronal excitability. More specifically, our research group
187 reported the presence of slow kinetic GluK2/K5-containing kainate receptors at the level of
188 aberrant mossy fibers established between dentate gyrus granule cells [99,100]. These
189 receptors, which are absent in nonepileptic conditions, interact with the persistent sodium

190 voltage-dependent channel I_{NaP} , facilitating the sustained and rhythmic discharges of
191 hippocampal neurons [101].

192 Because GABAergic interneurons are less numerous than excitatory neurons and because
193 they are subdivided into numerous heterogeneous populations [102,103], the exhaustive
194 characterization of each inhibitory neuron subtype property in TLE conditions appears to be a
195 dauntingly long task. However, numerous alterations concerning GABAergic neurons have
196 been documented [104]. For excitatory neurons, some specific interneuron subpopulations
197 are vulnerable to neuronal death in the hippocampus [105,106] but also in other temporal
198 lobe structures [107]. In the hippocampus, some interneurons degenerate at very early
199 disease stages (e.g., CA1 parvalbumin-expressing axo-axonic cells and somatostatin-
200 positive O-LM cells), whereas other subtypes (e.g., parvalbumine basket cells, long-range
201 projecting GABAergic neurons) appear quite well preserved [108–111]. Surviving neurons
202 display aberrant intrinsic properties, notably changes in their excitability [108]. In addition,
203 they undergo substantial axonal reorganization [112]. As a consequence, reductions in both
204 perisomatic [113] and dendritic [108,114] inhibition of leftover excitatory neurons in the
205 hippocampus are observed.

206 The acquired hyperexcitability of the hippocampal excitatory network, combined with deficits
207 in inhibition, may act as a “detonator” for epileptic seizures [115]. In addition, such alterations
208 could interfere with cognitive functions [67,68,116,117], which are encoded by the precise
209 and coordinated firing of excitatory neurons, themselves orchestrated by the cooperative
210 actions of specific subpopulations of inhibitory neurons [118–122]. Therefore, numerous
211 attempts have been made (and are still ongoing) to reverse cardinal molecular and cellular
212 alterations (i.e., cell loss, gliosis, altered intrinsic and synaptic properties, excitatory/inhibitory
213 imbalance), to reduce the pathological symptoms associated with TLE.

214 **3. Therapeutic strategies explored using models related to temporal lobe epilepsy**

215 Hereunder, I report some of the latest basic research breakthroughs that open new
216 possibilities concerning TLE treatment. Various unconventional approaches have been
217 shown to provide beneficial actions on epileptic networks, including the modulation of
218 neuropeptide Y [123] and the opioid system [124,125], the design of seizure-regulatory
219 miRNA targets [126,127], and the delivery of neuroprotective substances using genetically
220 engineered cells encapsulated in a grafted device [128,129] or using organic electronic ion
221 pumps [130]. Here, I will specifically focus on strategies that attempt to restore the
222 aforementioned molecular and cellular alterations that were actually observed in temporal
223 lobe epilepsy.

224 **3.1. Strategies aimed at circumventing neuronal loss**

225
226 There are two potential approaches aimed at reducing the impact of neuronal loss on TLE
227 pathology: a) preventing neuronal death at the earliest disease stages and b)
228 counterbalancing cell loss at later stages. For instance, the inhibition of the TrkB pathway
229 [131] or the use of NMDA receptor antagonists [132] in narrow time windows following status
230 epilepticus showed a protective effect against brain damage. In some cases, these strategies
231 could even decrease subsequent cognitive impairments and epileptogenesis [131,132]. In
232 some other notable cases, the neuroprotective effect was unable to prevent the development
233 of epilepsy [133]. A possible explanation is that neurons that were spared from death could
234 develop aberrant properties, promoting network hyperexcitability and seizure generation
235 [134].

236 An alternative approach is to replenish the epileptic temporal lobe neuronal pool with cells
237 that actually display intrinsic and synaptic properties similar to those that are normally
238 present in nonepileptic conditions [135]. Pursued since the late 1990s [136,137], that goal
239 was successfully achieved for inhibitory neurons by grafting stem cell-derived medial
240 embryonic eminence (MGE) neuroprogenitors originating from mice [138–140] or humans
241 [141]. These cells differentiate into GABAergic neuron subtypes, are well integrated in the

242 pre-existing hippocampal network, and display typical neurochemical and
243 electrophysiological properties [138–141]. The implantation of MGE-derived cells leads to the
244 diminution of abnormal neurogenesis and aberrant mossy fiber sprouting in TLE models
245 [141]. More importantly, it causes a marked reduction in spontaneous seizure occurrence
246 and improves depression-related and cognitive behaviors [138,139,141,142]. Therefore, a
247 cell strategy targeting inhibitory neurons appears to be a promising therapeutic approach for
248 TLE.

249 Unlike interneurons, replacement strategies aimed at refilling the decimated population of
250 glutamatergic neurons have been poorly explored to date [143]. Obviously, if glutamatergic
251 neuron loss is detrimental to hippocampal function, the addition of new excitatory neurons in
252 a hyperexcitable network would constitute a certain risk.

253 **3.2. Approaches targeting gliosis**

254 Targeting glial function and neuroglial interactions was explored quite recently as a possible
255 therapeutic strategy for epilepsy [144,145]. Accordingly, it has been highlighted that
256 pharmacologically or genetically manipulating glia-related processes, such as inflammation
257 [146,147], cellular interactions via gap junctions [148] or gliotransmission [149], can delay the
258 development of seizures and attenuate abnormal behavior in models related to TLE. More
259 recently, a research group focused on pannexin-1, which is expressed by neuronal and glial
260 cell channels [150]. These channels, which are activated under pathological but not basal
261 conditions [151], are thought to potentiate neuronal excitability [152]. Pharmacological
262 blockade or genetic inactivation of pannexin-1 strongly decreases seizure frequency in
263 mouse models of TLE. More interestingly, blocking pannexin-1 using probenecid and
264 mefloquine dramatically reduces ictal discharges generated in cortical slices resected from
265 patients with glioma or malformations of cortical development [151]. Further experiments
266 should be performed to determine whether probenecid and mefloquine are also efficient in
267 alleviating the pathological symptoms observed in patients suffering from TLE. However,
268 these results are encouraging in the prospect of developing a therapy applicable to humans

269 since these two drugs are already approved by the United States Food and Drug
270 Administration (FDA) for treating gout and malaria.

271 **3.3. Methods aimed at re-establishing the excitatory/inhibitory balance**

272 The hypothesis of a dysregulation of the excitatory/inhibitory equilibrium in favor of excitation
273 is traditionally exposed to explain the mechanisms of epilepsy in both models [153] and
274 patients [154]. In line with that assumption, numerous cellular and molecular defects
275 associated with TLE might lead to the perturbation of the inhibitory and/or excitatory
276 component of the temporal lobe. Therefore, a particular effort has been made to directly
277 decrease excitation or increase inhibition using various strategies. For instance, a gene
278 therapy strategy aimed at re-establishing the normal expression of the Kv1.1 potassium
279 channel that participates in glutamatergic neuron hyperexcitability in epileptic conditions [89]
280 has been recently developed. That genetic approach, which is based on a harmless virus
281 that was optimized for further clinical development, was effective at diminishing seizures in a
282 rat TLE model [155,156]. In addition, light-based optogenetic tools have been used to
283 manipulate the activity of genetically defined populations of inhibitory or excitatory neurons
284 with fine temporal precision in the context of epilepsy [46,157]. The inhibition of the main
285 population of excitatory glutamatergic neurons delayed seizure onset in a rat model of TLE
286 [158]. Combined with a closed loop system enabling the control of the activity as soon as
287 seizures are detected using EEG monitoring, light-assisted inhibition of hippocampal
288 pyramidal cells was efficient at stopping the seizures in vivo [159]. In contrast, the activation
289 of some peculiar glutamatergic neuron subclasses, i.e., dentate gyrus mossy cells,
290 surprisingly reduces convulsive seizures [160]. However, that “enigmatic” subtype of locally
291 projecting excitatory neurons can indirectly provide powerful inhibition to principal granule
292 cells by exciting surrounding inhibitory interneurons [161]. As specific interneuron subtypes,
293 notably parvalbumin and somatostatin cells, play a key role in shaping network activity and
294 behavior under “normal” conditions [118–122], the effect of optogenetic manipulation of these
295 inhibitory neuron subpopulations on TLE pathology has been tested. In particular, direct

296 excitation of the parvalbumin-expressing interneuron subclass interrupts behavioral and
297 electrographic seizures in TLE mice [159,162] and improves spatial memory [163]. However,
298 it is still uncertain whether each functionally diverse parvalbumin-expressing neuron subset
299 [164] that survives TLE [109] actually displays alterations in excitability and firing [108] and
300 whether they need to be overexcited. Notably, it seems that the activation of a peculiar
301 parvalbumin neuron subpopulation, which is involved in the disinhibitory nigra-parafascicular
302 pathway, aggravates seizures in kainic acid and kindling models of epilepsy [165]. In
303 addition, a strategy based on specific interneuron manipulation could collide with the fact that
304 some interneuron subsets may have paradoxical pro- and anti-epileptic effects as a function
305 of the stage of seizures (interictal period, ictogenesis initiation, maintenance of ictal activity,
306 [166–168]). The “double agent” role of interneurons may depend on GABA polarity and
307 chloride homeostasis dynamics, which are thought to be perturbed in TLE [169,170].
308 Accordingly, the photostimulation of subicular GABAergic neurons aggravates secondary
309 generalized seizure expression via depolarized GABA signaling [171]. Last, it appears that
310 activating larger, mixed populations of inhibitory neurons is more effective than activating
311 only a subset of parvalbumin or somatostatin interneurons in the hippocampus [172,173], but
312 similar manipulation exhibited a poor effect in the entorhinal cortex [173]. Consequently,
313 additional experiments should be performed in the future to better understand the timing,
314 region specificity and subtype dependence of neuron optogenetic manipulation effects on the
315 epileptic brain.

316 Even though those results raise considerable optimism, the use of an optogenetic approach
317 in humans is confronted with several technical and ethical hurdles, as it implies the surgical
318 implantation of devices enabling light delivery and an EEG recording system in the case of a
319 closed-loop system [174]. An alternative strategy is the use of chemogenetic strategies (also
320 called pharmacogenetic approaches) to selectively control the activity of genetically defined
321 populations of neurons with no invasive light delivery [175,176]. Chemogenetic strategies are
322 based on the neuron subtype-specific expression of designer excitatory or inhibitory

323 receptors that are activated by designer inert ligands (i.e., drugs that have no biological effect
324 but that activate the chemogenetic receptor). In conformity with optogenetic, the
325 chemogenetic excitation of excitatory neurons in the neocortex has a robust effect against
326 seizures generated in a rat model of chronic epilepsy [177]. Conversely, the chemogenetic
327 activation of hippocampal parvalbumin-expressing interneurons and, to a lesser extent,
328 somatostatin-containing inhibitory cells diminishes epileptiform discharges and compulsive
329 behavior in vivo, whereas the stimulation of VIP-expressing interneurons has little effect
330 [178]. An important restriction with the use of chemogenetic technology is the capacity of the
331 most common designer ligand, clozapine-N-oxide (CNO), to be back-converted in vivo into
332 pharmacologically active metabolites such as clozapine, which could lead to potentially
333 undesirable off-target effects [179]. However, it appears that the injection of designer drugs
334 [180], olanzapine [181] and a low dose of clozapine [179] could activate chemogenetic
335 receptors with little, if any, nonspecific behavioral effects. The possible use of clozapine and
336 olanzapine increases the translational potential of chemogenetic approaches, as FDA-
337 approved molecules are clinically used as atypical antipsychotics for treating schizophrenia.
338 However, the possible life-threatening adverse effects of these drugs must be taken into
339 consideration, particularly in the case of clozapine [182].

340 Despite their specific limitations, the optogenetic or chemogenetic control of neurons of
341 interest, particularly interneurons, seems to be a credible lead from the perspective of
342 developing innovative treatments for TLE [183]. Another recently developed strategy could
343 maintain some of the main advantages of the methods detailed above (detection of seizures,
344 specific neuronal manipulation) while circumventing some of their major inconveniences
345 (e.g., surgical implantation of recording and/or manipulation devices) [184]. This
346 autoregulatory genetic approach is based on the virally induced expression of glutamate-
347 gated chloride channels (GluCl) that open only in response to pathological elevation of
348 extracellular glutamate, therefore biochemically “sensing” the initiation of seizures [185]. Cl-

349 conductance is sufficient to robustly reduce the frequency of seizures in a chronic model of
350 neocortical epilepsy, presumably by shunting inhibition [184].

351 A common point of each strategy described above is the fact they are based on the
352 compensation of the pathological alterations by virally delivering genes that are not normally
353 expressed in the targeted cell type, sometimes not even in the human brain [155,158–
354 160,162,172,177,178]. Those approaches might be associated with various ethical and
355 safety concerns, which have to be overcome prior to clinical application [186,187]. However,
356 genetic modification of the epileptogenic area in an intractable adult patient, which would be
357 otherwise surgically removed in last resort, is clearly not ethically out of the question.
358 Besides the expression of ectopic genes, an alternative strategy would be to suppress the
359 acquired pathological molecular and cellular features of TLE. For instance, granule cells form
360 abnormal recurrent synapses in the epileptic dentate gyrus [99,186], which express aberrant
361 GluK2/K5-expressing kainate receptors (KARs [99–101]). These synapses participate in the
362 elevation of granule cell excitability [99,101], participating in the generation of epileptiform
363 discharges [100,187]. It has been shown that the selective pharmacological blockade of
364 GluK2/K5-expressing receptors efficiently reduced KAR-mediated postsynaptic currents
365 [188] and robustly decreased the frequency of interictal and ictal discharges in a reliable
366 mouse TLE model, reproducing the effect of a complete genetic knockout of GluK2 [100].
367 Further investigations should be performed to determine if those strategies could relieve the
368 comorbidities associated with TLE and if they can efficiently alleviate seizures in patients.
369 Notwithstanding, the modulation of KAR opens exciting perspectives [187].

370 Regardless of the method used, which is associated with specific pros and cons,
371 manipulating excitation and/or inhibition seems to be an efficient method of controlling
372 seizures in chronic models of epilepsy.

373 **4. Future challenges**

374

375 Basic researchers worldwide initiated a true arms race to fight against temporal lobe
376 epilepsy, using their most powerful bioengineered weapons to control seizures. Some of the
377 state-of-the-art strategies detailed above are already undergoing translation towards clinical
378 applications [189], sometimes with the financial support of local health agencies [190].
379 However, the battle against TLE is likely not even close to being won. First, bridging the gap
380 between the bench and the bedside is obviously a difficult task [191]. Second, these
381 techniques are confronted with at least one of the following major limitations and challenges
382 that, if they are not necessarily crippling, should be addressed before sliding towards
383 translational research:

384 a) *Insufficient human data*: A significant proportion of intractable patients with TLE have
385 little alternative but to undergo surgical removal of the epileptogenic focus. With a
386 collaboration between academic laboratories and local clinical settings and patient
387 permission, resected tissues from epileptic temporal lobe structures can be used for
388 research purposes [48,49]. As slice preparations originating from those tissues
389 maintain the ability to generate epileptiform activities, they could constitute an ideal
390 substrate for testing the effect of a given strategy on seizure occurrence and for
391 monitoring seizure toxicity in humans. However, very few studies have attempted to
392 test a strategy targeting epilepsy in human brain tissues [151], even less so in
393 temporal lobe structures from patients suffering from TLE.

394 b) *Lack of specificity*: A fraction of the strategies detailed in part 3, particularly those that
395 target glutamatergic neurons [155,184], are able to differentiate between neurons
396 involved in pathological processes and those underlying normal brain function; the
397 two cell types are likely to be engaged in distinct subnetworks [14]. In a way, those
398 approaches are not so different from existing therapies that do not discriminate
399 across cell types and brain structures [192].

400 c) *Missing information concerning functional alterations in addition to seizures*: Ictal
401 activity is probably the most prominent symptom associated with TLE. Therefore,

402 most research groups have focused on suppressing seizures or at least
403 interrupting/reducing them. However, ictal activity is not the only macroscopic
404 pathological trait associated with TLE. First, other pathological patterns, such as
405 interictal activity and abnormal high-frequency oscillations, can also be recorded in
406 the temporal lobe from TLE patients and animal models. Although they are not
407 directly associated with any behavioral manifestation (unlike ictal activity), they could
408 mediate functional processes [6,14]. Second, physiological activity, such as
409 hippocampal oscillations, is deeply perturbed in TLE conditions [193]. Third, and
410 probably as a consequence of the points described above, TLE is accompanied by
411 severe mood and cognitive disorders that are very disabling for the patients. An ideal
412 treatment would not only interrupt seizures but also restore normal temporal lobe
413 activity (by reducing each pathological activity pattern and restoring physiological
414 activity) and alleviate the neuropsychiatric comorbidities associated with TLE.
415 Unfortunately, only limited effort was made in general to determine if those strategies
416 could be efficient on the multiple facets of the disease.

417

418 **Declarations of interest:** none

419

420 **Acknowledgments:** TM thank Valérie Crépel for helpful discussions and comments on the
421 manuscript. This work was supported by the Agence Nationale de la Recherche (ANR-17-
422 NEU3-0003-02), the Institut National de la Santé et de la Recherche Médicale (INSERM) and
423 Aix-Marseille Université (AMU).

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