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Review

Amygdaloid complex anatomopathological findings in animal models of *status epilepticus*

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ABSTRACT

Temporal lobe epileptic seizures are one of the most common and well-characterized types of epilepsies. The current knowledge on the pathology of temporal lobe epilepsy relies strongly on studies of epileptogenesis caused by experimentally induced *status epilepticus* (SE). Although several temporal lobe structures have been implicated in the epileptogenic process, the hippocampal formation is the temporal lobe structure studied in the greatest amount and detail. However, studies in human patients and animal models of temporal lobe epilepsy indicate that the amygdaloid complex can be also an important seizure generator, and several pathological processes have been shown in the amygdala during epileptogenesis.

Therefore, in the present review, we systematically selected, organized, described, and analyzed the current knowledge on anatomopathological data associated with the amygdaloid complex during SE-induced epileptogenesis. Amygdaloid complex participation in the epileptogenic process is evidenced, among others, by alterations in energy metabolism, circulatory, and fluid regulation, neurotransmission, immediate early genes expression, tissue damage, cell suffering, inflammation, and neuroprotection. We conclude that major efforts should be made in order to include the amygdaloid complex as an important target area for evaluation in future research on SE-induced epileptogenesis.

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1. Introduction

Epilepsy is one of the most common neurological conditions in the world, affecting all ages, ethnicities, and social classes, imposing a major burden in psychological, physical, social, and economic areas [1–3]. Worldwide, it is estimated that about 85 million people live with epilepsy, and its annual incidence reaches 61.4 per 100,000 inhabitants [4].

Epileptic seizures are transitory electrophysiological events characterized by synchronous and excessive neuronal activity in the brain [5]. They are accompanied by abnormal, subtle, and transitory alterations of consciousness and/or motor, sensitive, autonomic, or psychic symptoms, perceived by the patient or an observer [6]. The process by which pathological alterations gradually occur in the brain, leading a previously normal neural network to evolve to an epileptic one is referred to as epileptogenesis [7–9]. Temporal lobe structures, such as the hippocampus, the amygdaloid complex, and the pyriform cortex, when lesioned, are some of the most susceptible regions to the maladaptive epileptogenic plasticity [7,10].

The epileptogenic process is studied preclinically mostly utilizing rodents as subjects, divided in two groups of experimental models [11–14]. In the now classical kindling model, repeated subthreshold electrical stimuli result in progressive behavioral and electrographic (electroencephalogram (EEG)) epileptiform response, leading to the consistent occurrence of stimulus-induced generalized seizures [8,13,15,16]. Epileptogenesis can also be induced in animals that are submitted to *status epilepticus* (SE), an abnormally prolonged seizure that occurs after a single insult [10,13,17–19]. Convulsive SE can endure several hours, depending on the chosen post-SE treatment protocol and SE refractoriness to medication [14,19]. SE is followed by a latent period, when several neuroplastic alterations occur in the brain while no

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seizures are observed [10,13]. In animal models, one to two weeks after SE, the chronic stage starts, characterized by the presence of spontaneous recurrent seizures [10,13].

A great number of studies using animal models of SE focus on pathological alterations in the hippocampus as the main area involved in epileptogenesis [20–22]. Nonetheless, many other studies implicate the amygdaloid complex in seizure generation, seizure activity, and epileptogenesis [15,23–29]. For example, inflammatory processes related to seizures evolve jointly or even faster in the amygdala, when compared with the hippocampus [30,31]. Furthermore, electrode implantation in the amygdala alone increases epileptogenesis [32]. Interictal epileptic discharges tend to be initiated in the amygdala or in the nearby cortical areas, such as the piriform cortex [23,24,33,34]. Additionally, in most of the cases, patients with epilepsy submitted to surgical ablation of the temporal lobe can only obtain full control of seizures if the amygdala is also resected [35]. Occasionally, removal of only the amygdala is enough to decrease seizures [36].

The amygdaloid complex modulates cognitive functions and plays a central role in the processing of emotional memories, emotionally driven behaviors, and mood/affective perturbations [37]. Furthermore, it presents rich network connections with other temporal lobe structures [38]. Consequently, the epilepsies involving this area are important not only for their role in specific kinds of seizures but also in the expression of psychiatric comorbidities that are associated with this disease [39].

The amygdala participation and importance in temporal lobe epilepsy and its comorbidities have been reviewed, most recently with focus on emotional disturbances, electrophysiological phenomena, computational network analysis, and pathophysiology [40–43]. Conversely, there has been no recent structured and comprehensive review on amygdala pathology in animal models of SE. We believe that the summarized data from the literature allow an increased perception on the amygdala participation in epileptogenesis, providing opportunities to formulate new hypothesis, discuss about diverging and convergent views, and draw new perspectives and insights.

2. Methods

A search in PubMed Medline® database was performed using the following terms, without any date restriction: ("*status epilepticus*"[MeSH Terms] OR "*status epilepticus*"[All Fields]) AND ("amygdala"[MeSH Terms] OR "amygdala"[All Fields] OR "amygdaloid complex"[All Fields]) AND ("pilocarpine"[MeSH Terms] OR "pilocarpine"[All Fields]) OR ("kainic acid"[MeSH Terms] OR "kainic acid"[All Fields]) OR ("electric stimulation"[MeSH Terms] OR "electric stimulation"[All Fields] OR "electrical stimulation"[All Fields]) AND ("rats"[MeSH Terms] OR "rats"[All Fields] OR "rat"[All Fields]).

Only articles written in English that used young adult and/or adult male rats with SE induced by electrical or chemical stimulation were used. The articles should describe amygdala alterations during or consequent to SE. Publications based on protocols that induced direct mechanical, chemical, or electrical damage to the amygdala were excluded. Other criteria for exclusion were lack of appropriate controls for the purpose of this review (sham/vehicle-treated animals), inclusion of areas adjacent to the amygdala in evaluations, and diverging data/conditions described. Some types of articles were not included: review articles, articles that were based on human studies only, those that did not use rats or used only modified rat strains, and those that did not show anatomopathological or related findings. Additionally, female (young and adult) and young (male and female) rats were not included, given that such animals have specific modifying factors to be considered, such as hormonal cycle influences and central nervous system developmental processes [44–49]. Subsequent searches were performed in order to verify the addition of new publications between the first list of publications and the finalization of this review (last search date was June, 2019).

Research papers were selected or excluded based on three phases. In the first phase, we excluded only those articles that could be ruled out undoubtedly by their Abstracts. If any uncertainty remained, the article was left to the second phase. In this phase, all articles that remained were read entirely, and the decision was taken for their maintenance or not in the review. Two authors (CQT and LRF) evaluated all Abstracts (first phase) and papers (second phase) and decided if they would be included in the current review. In the third phase, all the relevant information was collected: age and strain of the rats, method for SE induction and termination, duration of SE, and main anatomopathological results presented.

3. Results

3.1. Publications included in the review: general characterization

The sequence of procedures for the selection process of the articles to be included in this study is presented in Fig. 1. The oldest article found in the search was from 1975. The total number of articles screened was 243. One hundred and two (102) did not reach inclusion criteria during the first phase (screening by Title and Abstract reading), leaving 141 to be completely read. We did not obtain access to 2 articles, so they were excluded as well. After complete reading, another 74 articles were excluded from this review. Therefore, in total, 178 articles were excluded from the review, and 65 articles were considered adequate for our study. All references in the final search are divided in 2 tables: Table 1, with the articles included in the review and their main data, and the Supplemental Table, where the articles excluded from the review are listed with the reason for their exclusion.

Articles included in the review were published between 1983 and 2018. The majority of them presented data from SE induced by systemic injections of pilocarpine or kainic acid (55 publications). SE could also be induced systemically by soman or MK-801 followed by pilocarpine injections, or locally by kainic acid or carbachol injections, or by electrical stimulation of limbic areas outside the amygdaloid complex. We classified each data according to the following categories: energy metabolism-, neuroprotection-, circulatory and fluid regulation-, neurotransmission-, immediate early genes-, tissue damage-, inflammation-, plasticity-, and cell suffering-related data. Using the classified data from Table 1, it was possible to create a timeline or kinetics with the main anatomopathological processes identified in the amygdaloid complex after SE in young adult and adult male rats (Fig. 2).

3.2. Current literature on amygdaloid complex anatomopathological processes after SE: detailed description

Brain regional metabolism quantification during seizures and interictal periods can be used to identify the nervous system structures responsible for the generation, maintenance, propagation, and control of the epileptic activity [112,113]. Once SE is initiated, the first alterations observed in the amygdala are metabolic. There is an immediate (3 min) increase, followed by a decrease (15–120 min), in brain perfusion rate (BPR) and in the apparent diffusion coefficient (ADC) signal [62–64]. Regardless of the behavioral and electrographic differences in SE observed between animals [28,29], those initial alterations are accompanied by an increase in local glucose uptake [28,29,84,97,110]. High-energy phosphates (adenosine triphosphate, phosphocreatine) are reduced in about 50% 1–2 h after SE onset [69,70], suggesting that the increased glucose uptake is not sufficient to provide the amount of energy demanded by the amygdala during SE. Blood–brain barrier leak starts, especially in the medial amygdaloid nucleus [80]. Subsequently, at 24 h after SE, vascular endothelial growth factor (VEGF) is increased [87], possibly as an attempt to compensate the increased demand for energy. In fact, 14 days after SE, the blood vessel density is increased in the amygdala [73]. On the other hand, during the first 2 h of SE, morphology shown by magnetic resonance images (MRI) is normal, neuronal

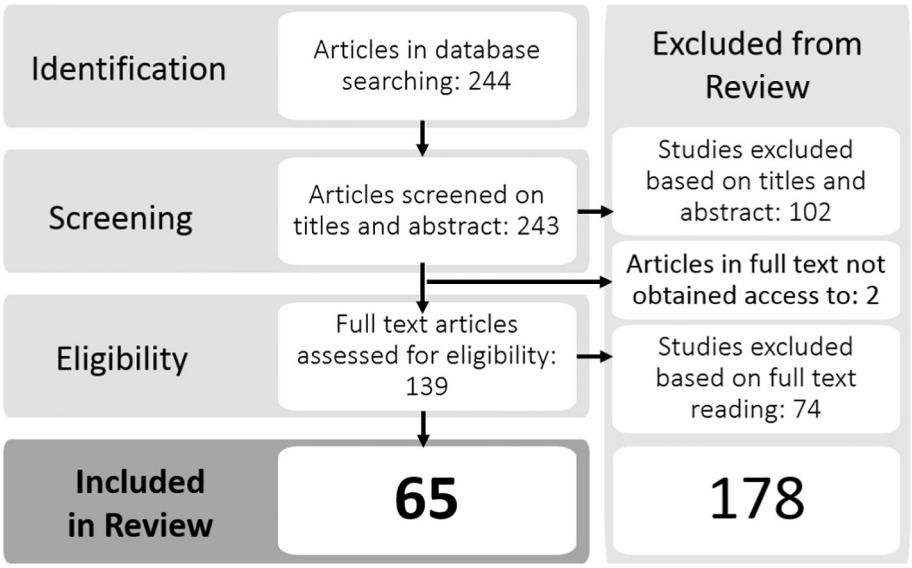

Fig. 1. Flowchart of the articles' selection process.

survival is maintained, and most cell damage and inflammation markers are sparsely or not observed [62,67,79,85,86,92,96,103,108].

The genomic reprogramming in response to the damage caused by SE includes the expression of hundreds of genes, and this is coincident with the distribution map of Fos protein expression [60,84]. Fos is one of the most reported immediate early genes that are expressed after an epileptic seizure, activated because of excessive neuronal activity [114–116]. Immediate early genes start to appear 2 h after SE onset (and after SE termination, depending on the study), in several amygdaloid nuclei [52,60,74,84,90]. Fos and Fos B proteins are expressed in superposing time points after SE. Fos-positive strongest immunoreactions are observed 2–4 h after SE, while Fos B protein expression peak occurs up to 2 days later [90]. Nonetheless, they can be both observed concomitantly between 2 and 24 h after SE in the medial amygdaloid nucleus after SE [60,90]. Other immediate early genes-positive (jun D proto-oncogene and c-jun) neurons are increased as well [59,60]. All the above phenomena are described in the first minutes to hours after SE, indicating a great amount of activity in the amygdala and related areas. Conversely, one study showed that there are no alterations in dopamine and catecholamine metabolites' levels in the amygdala 30 min after SE onset [50]. Glucose uptake remains increased for several hours as compared with the baseline [28,98,99]. However, the high-energy phosphates are maintained in lower levels in the amygdala up to 3 days after SE [70].

Several studies have also shown that the later appearance of neuronal lesions in the amygdala can be directly associated with local hypermetabolism and increased T2-weighted signal intensity in the MRI during the first minutes to hours after SE onset [28,61,65,92,96]. Correspondingly, as early as 2.5 h after SE induced by pilocarpine (but not by kainic acid), some silver-impregnated neurons are seen in the amygdala [56]. On the other hand, inflammatory process markers and gliosis were not seen before 4–12 h after SE [79,81,86,92,103,111]. Epileptic seizures can increase the expression of inflammatory mediators in the brain regions involved in the generation and in the propagation of epileptic activity [117–120].

Neuronal damage is evident in the amygdala starting 4 h and peaking 12–48 h after SE [56,57,108,111,74,75,79,81,86,92,94,100]. Markers of inflammation and oxidative stress such as histamine, caspase 3, and cytochrome c oxidase activity present a similar pattern [81,86,94,108,111]. In addition, microglia activation, gliosis, and tissue edema are also observed [56,57,75,86,92].

An increase in citrulline, a determinant of nitric oxide presence in the tissue, is observed in the amygdala at this time [70]. Accordingly, cyclooxygenase-2, an enzyme that may be induced by nitric oxide, start to rise in several amygdaloid nuclei as well: lateral, basolateral, basomedial, and cortical [74]. In the lateral nucleus of the amygdala, there is an increase in the number of neurons immunoreactive to the proapoptotic B-cell lymphoma 2-associated X (Bax) protein, while no alterations are observed for the antiapoptotic protein B-cell lymphoma 2 (Bcl2) [103]. The underlying damage process in the amygdala also starts to be more evident about 12–24 h after SE in MRI studies. This is observed by an initial decrease in T2-weighted signal, with peak at 24–72 h after SE [61,65,92,95,96,101,105].

While peaks in neuronal damage occur between 8 and 48 h after SE, the degenerating process is progressive and lasts several weeks to months in the amygdala. The degeneration is shown through the observation of pyknotic neurons, FluoroJade-positive neurons [121,122], and neurons with deoxyribonucleic acid fragmentation [56,71,86,93,103,104,108]. Likewise, the amygdaloid complex showed reduced cell counts using thionin or immunohistochemistry for neuronal markers such as the neuronal nuclei protein Neu-N, microtubule-associated protein 2 (MAP2), and glutamic acid decarboxylase (GAD) [17,54,67,68,71,75–79,81,86,56,92,93,96,99,102–104,106,108,109,58,59,61,62,64–66]. Some amygdaloid nuclei such as the lateral, basal, medial, and cortical, are more prone to damage than others, for example, the dorsal lateral and the central amygdaloid nuclei [58,71,92,103,104].

Two to three weeks after SE, positive silver staining or argyrophilic neurons, known to be neurons in distress, are present in the amygdala [71,93,104]. Concomitantly, cell reorganization with synaptic plasticity are also part of the observed consequences to SE in the amygdala. Newly generated cells are detected and are later (42 days after SE) observed with neuronal or glial phenotypes [75]. Interestingly, such cells do not migrate from other areas but are generated locally [75]. Additionally, during this same time range, the metabotropic glutamate receptor mGluR5 availability and zinc-containing fibers (Timm staining) are not altered or reduced [53,55,89]. Likewise, histamine receptors H1 and H3 binding and messenger ribonucleic acid (mRNA) expression decrease [81]. On the other hand, other molecules are increased, such as histamine and histamine-reactive fibers, the gamma-aminobutyric acid (GABA) transporters GAT-1 and GAT-3, neuropeptide Y immunoreactive neurons, mu-opioid receptors binding, microtubule-associated protein-2 (MAP2), stromal-derived factor 1 alpha (SDF-1 alpha), and synaptophysin [72,75,81,83,89,91,100]. The SDF-1 alpha and synaptophysin hyperregulation suggests cell synthesis, migration, and synaptic remodeling in the amygdaloid complex circuitry [72,123]. Furthermore, the increased expression of GAT-1 and GAT-3 suggests a

Table 1
Publications included in the review and main data collected (total 65).

Authors	SE induction method; SE duration	Data
Alam and Starr, 1996 [50]	Systemic lithium + pilocarpine or intrahippocampal carbachol; 30 min	■ 30 min after self-sustained SE started: no alteration in dopamine, DOPAC (dopamine metabolite) and HVA (catecholamine metabolite) levels (HPLC).
Atanasova et al., 2018 [51]	Systemic kainic acid; at least 3 h	■ 5 months: reduced angiotensin II receptor (type 1; AT1) expression at the temporal part of the basolateral amygdala.
Barone et al., 1993 [52]	Systemic pilocarpine; 2–4 h	■ 2–4 h: positive Fos staining, especially in the basolateral nucleus
Cavarsan et al., 2012 [53]	Systemic methyl-scopolamine + pilocarpine; 90–150 min	■ 2 and 8 h, 1 and 7 days: increased homer1a with peak at 24 h; mGluR5 not different from control
Chen and Buckmaster, 2005 [54]	Systemic kainic acid; at least 4 h	■ 7–12 months after SE: reduced amygdaloid complex volume, especially posterior portions
Choi et al., 2014 [55]	Systemic lithium + methyl-scopolamine + pilocarpine; at least 1 h	■ 24 h and 7 days after SE: mGluR5 availability is reduced, peak at 7 days (measured by [11C]ABP688 positron emission tomography tracer) ■ 4 weeks after SE: mGluR5 binding potential back to control levels
Covolan and Mello, 2000 [56]	Systemic methyl-scopolamine + pilocarpine or kainic acid; at least 90 min	■ 2.5 h: some silver-impregnated neurons are seen in the amygdala of pilocarpine-injected animals but not KA-injected animals. ■ 8 h: peak of silver-impregnated neurons in several amygdaloid nuclei (basolateral, anterior, basomedial, central, cortical, lateral), in both models; ■ 8–48 h: edema, with peak at 24 h, especially in the cortical nucleus
Dedeurwaerdere et al., 2012 [57]	Systemic kainic acid; at least 4 h	■ 7 days after SE: translocator protein and OX42 (markers of activated microglia) increased in the amygdala, higher in more severe SE.
Dos Santos et al., 2005 [58]	Systemic methyl-scopolamine + pilocarpine; at least 90 min	■ About 60 days after SE: reduced volume of the central amygdaloid nucleus; no reduction in the lateral and basolateral nuclei; Sprouting (NeoTimm staining) reduced in the central amygdaloid nucleus and not altered in the lateral and basolateral amygdaloid nuclei
Dragunow et al., 1993 [59]	Dorsal hippocampus electrical stimulation or MK801 + pilocarpine; "many hours"	■ 24 h: c-jun mRNA and protein expressed in the amygdala ■ 6 days: cell loss in the amygdala
Dube et al., 1998 [60]	Systemic lithium + methyl-scopolamine + pilocarpine; at least 2 h	■ 2 and 24 h after SE: high Fos staining ("early" and "late" waves, respectively) ■ 6 h after SE: high density of silver-stained neurons; ■ 24 h after SE: Jun-D moderately induced, low to moderate levels of HSP70; ■ 2 days after SE: no Fos was observed in the amygdala
Ebisu et al., 1994 [61]	Systemic kainic acid; 4–8 h	■ 3 days: reduced levels of n-acetyl-aspartate (MRI), high T2 signal intensity and high degree of cell loss; there was correlation between the parameters.
Engelhorn et al., 2005 [62]	Systemic methyl-scopolamine + pilocarpine; up to 8 h	■ 3 min after SE onset: brain perfusion rate increased (129 ± 16%); ■ 15, 30, 60, and 120 min after SE onset: brain perfusion rate reduced (maximal at 60 min, 62% from baseline); ■ 0.5 and 2 h after SE onset: no difference in surviving neurons ■ 24 h, 1, and 2 weeks: progressively reduced percentage of surviving neurons in the amygdala, 66, 54, and 38%, respectively.
Engelhorn, Hufnagel, et al., 2007 [63]	Systemic methyl-scopolamine + pilocarpine; SE duration not informed	■ 3, 5, 10, 15, 20, 30, 45, 60, 90, and 120 min apparent diffusion coefficient: peak increase at 3 min after seizure onset and reduced from 15 to 120 min (peak 30–90 min); no differences were observed 5 and 10 min after seizure onset. ■ 0.5, 2 h, 1, 7, 14 days: progressively reduced surviving neurons from 1 day to 14 days, reaching 38% from control (62% reduction).
Engelhorn, Weise, et al., 2007 [64]	Systemic methyl-scopolamine + pilocarpine; up to 8 h	■ 3 min after seizure onset: increased apparent diffusion coefficient; ■ 30, 60, 90, and 120 min after seizure onset: reduced apparent diffusion coefficient; ■ 5, 10, and 15 min after seizure onset: no alterations in apparent diffusion coefficient; ■ 2 weeks after SE: 38% surviving cells in the amygdala
Fabene et al., 2003 [65]	Systemic methyl-scopolamine + pilocarpine; at least 4 h	■ 12 h after SE: reduction of apparent diffusion coefficient (61%); increased T2-weighted MRI (22%); "numerous" FluoroJade B-positive neurons in the amygdala.
Figueiredo et al., 2011 [66]	Systemic hydroxyiminomethyl-pyridinium + soman + atropine; about 10 h	■ 1 and 7 days after SE: basolateral amygdala evaluated; 64% neuronal survival, score moderate for neurodegeneration (FluoroJade C staining); GABAergic neurons (GAD67) were not different at 1 day after SE but were reduced at 7 days after SE, in the same proportion of general neuronal loss.
Francois et al., 2011 [67]	Systemic lithium + methyl-scopolamine + pilocarpine; SE duration not informed	■ 0.5, 3, 8, and 24 h: FluoroJade B staining progressively increased with statistical significance at 24 h. ■ 14 days: basolateral amygdala 72% and median nucleus 38–52% neuronal loss.
Fritsch et al., 2009 [68]	Systemic kainic acid; at least 3 h	■ 7–10 days after SE: 15% reduction in total neuron and 43% reduction in GAD67 neurons (special vulnerability of inhibitory neurons in the amygdala); FluoroJade C-positive cells (basolateral, medial, lateral, posterior cortical, central amygdala nuclei); increased GAD65–67 protein in the amygdala (27.1 ± 7.8%); $GABA_A$ subunit alpha1 also increased (157 ± 19%); glutamate receptor GluK1 reduced to 73,0 ± 4,6% of control group.
Gupta and Dettbarn, 2003 [69]	Systemic kainic acid; at least 1 h	■ 2 h after KA injection: increased citrulline (300%); and decreased high-energy phosphates (55%, adenosine triphosphate, total adenine nucleotides, nicotinamide adenine dinucleotide, phosphocreatine, and total creatine compounds).
Gupta et al., 2000 [70]	Systemic kainic acid; SE duration not informed	■ 1 h and 3 days: high-energy phosphates – adenosine triphosphate, total adenine nucleotides (ATP + ADP + AMP), phosphocreatine and total creatine compounds (phosphocreatine + creatine) – reduced in about 50%.
Halonen, Nissinen and Pitkanen, 1999 [71]	Perforant path electrical stimulation; 40–60 min	■ 2 weeks after SE induction: neuronal damage observed in 15 of 18 amygdaloid areas evaluated (silver staining). Especially damaged: lateral, basal, and cortical nuclei.
Hanaya, Boehm and Nehlig, 2007 [72]	Systemic lithium + methyl-scopolamine + pilocarpine; 6–8 h	■ 1, 3, 7, and 21 days after SE: increased synaptophysin expression, peak at 1 day, tending back to normal, statistical significance lost at 7 days; GAP-43: reduced in all amygdala areas (laterodorsal, basolateral, centrolateral, medial), starting at 7 days and reducing more at 21 days
Handforth and Ackermann, 1995 [29]	Electrical stimulation of several brain areas; 40–50 min	■ Detailed study, based on behavior and EEG, different types of SE were suggested; 40–50 min after self-sustained SE started: amygdala was involved in all patterns of SE obtained in the experiments (^{14}C-2DG, slice radiography).

Table 1 (*continued*)

Authors	SE induction method; SE duration	Data
Handforth and Treiman, 1995 [28]	Systemic lithium + pilocarpine; 1–2 h	■ Detailed SE study based on EEG; different stages of SE were determined; increased signal in the amygdala in all stages evaluated (^{14}C-2DG, slice radiography)
Hayward et al., 2010 [73]	Systemic scopolamine + pilocarpine; SE duration was not informed	■ 2 and 14 days after SE: no alterations in cerebral blood volume; increased cerebral blood flow in the amygdala at 2 (16%) and 14 (30%) days; at 14 days, 27% increase in blood vessel density in the amygdala.
Joseph et al., 2006 [74]	Systemic dextrose + kainic acid; 4–5 h	■ 2, 6, 24 h: increased COX-2 in neurons at all time points, peak at 24 h (amygdala nuclei marked: lateral, basolateral, basomedial, and posterolateral cortical); ■ 2 h: Fos staining in several nuclei of the amygdala
Jung et al., 2009 [75]	Systemic lithium + methyl-scopolamine + pilocarpine; at least 1 h	■ 14 and 42 days after SE: 33% reduction in cell number in the amygdala; increased OX-42 (microglial activation marker), peak at 14 days; same pattern for proliferation (BrdU); at 42 days, newly generated cells were 20% neurons, 30% astrocytes, and 25% oligodendrocytes (at 42 days) ■ 1, 3, and 28 d: SDF-1a prominently increased in the amygdala, mainly astrocytes.
Kemppainen and Pitkanen, 2004 [76]	Systemic kainic acid; SE duration not informed	■ 6–7 weeks after SE: moderate to severe damage (medial division of the lateral nucleus, periamygdaloid cortex, posterior cortical nucleus, lateral division of amygdalohippocampal area); mild to moderate damage (lateral part of parvicellular division of the basal nucleus, accessory basal nucleus, anterior cortical nucleus, other areas of periamygdaloid cortex, medial division of amygdalohippocampal area). Reduced retrograde labeling of amygdala neurons by tracers injected in hippocampus.
Kemppainen, Nissinen and Pitkanen, 2006 [77]	Systemic kainic acid; SE duration not informed	■ 13–15 weeks after SE: the lateral nucleus of the amygdala was evaluated; dorsolateral division not affected; ventrolateral and medial divisions presented positive damage score (as compared with zero in control rats) and volume reduction of up to 23% from control.
Klitgaard et al., 2002 [78]	Systemic methyl-scopolamine + pilocarpine; 7.5–120 min	■ 21 days after SE: all animals with 90 min or longer SE duration presented necrosis in the amygdala; 3/9 and 9/17 animals presented necrosis in the amygdala after 7.5- and 15-min SE duration, respectively.
Lehtimaki et al., 2003 [79]	Systemic kainic acid; "several hours"	■ 1 and 3 h after SE onset: no difference in IL-6 or glycoprotein 130 (GP130) expression relative to control. ■ 6 and 12 h after SE onset: increased IL-6 expression; GP130 expression continues at normal levels. ■ 1 and 3 d after SE onset: no difference in IL-6 or GP130 expression relative to control. ■ 7 days after SE onset: no difference in IL-6 expression relative to control; GP130 hyperregulation.
Leroy et al., 2003 [80]	Systemic lithium + methyl-scopolamine + pilocarpine; 6–12 h	■ 90 min after SE onset: blood–brain barrier leak in the medial (66%), but not in the basolateral, amygdaloid nucleus; increased cerebral blood volume (generalized); ■ 2 months after SE: reduced cell count in the medial amygdaloid nucleus
Lintunen et al., 2005 [81]	Systemic kainic acid; at least 5 h	■ Histamine H1 receptor mRNA expression after SE: not altered at 3 and 6 h; reduced expression levels at 12 h, 1, 2, 3, and 7 days; back to normal levels at 4 weeks, 6 months, and 1 year. ■ Histamine H1 receptor binding after SE: not altered at 3, 6, and 12 h; reduced at 1, 2, 3, and 7 days; back to normal levels at 6 months and 1 year. ■ Histamine H3 receptor mRNA expression after SE: not altered at 3 and 6 h; variable at 12 h (depending on the isoform); reduced at 1, 2, and 3 days; isoforms return to normal levels between 7 days and 4 weeks and maintain in normal levels 6–12 months. ■ Histamine H3 receptor binding after SE: not altered at 3, 6, and 12 h; reduced at 1, 2, 3, 7 days, 4 weeks, 6 months, and 1 year. ■ Histamine levels (HPLC): increased at 6 h, 1, 3, 7 days. ■ Histamine-reactive fibers: increased at 6 h, 1, 2, 3 days, 4 weeks; back to normal levels 1 year after SE.
Liu et al., 2016 [82]	Systemic kainic acid; at least 4 h	■ 13 weeks after SE: reduced protein phosphatase 2A activity; reduced expression of its regulatory B unity PR55; increased ratio of phosphorylated tau epitopes Ser198 and Ser262.
Lurton and Cavalheiro, 1997 [83]	Systemic methyl-scopolamine + pilocarpine; 5–24 h	■ 4 and 60 days after SE: increased neuropeptide Y immunoreactivity in the amygdala.
Motte et al., 1998 [84]	Systemic lithium + pilocarpine; up to 10 h	■ 1 h after SE onset: 14C-2DG injected; 582% increase in local cerebral metabolic rate; ■ 4 h after SE: if 2 min SE duration, moderate intensity in Fos expression; if 30–240 min SE duration, strong Fos expression; ■ 24 h after SE: HSP72 and acid fuchsin strong in the amygdala in groups with 90 min or longer SE.
Nakasu et al., 1993 [85]	Systemic kainic acid; at least 1 h	■ Immediately after SE, 1 and 4 weeks after SE: no alterations in T1- and T2-weighted MRI (visual inspection)
Narkilahti et al., 2003 [86]	Systemic kainic acid; 6–12 h	■ 1, 2, 4, and 8 h after SE onset: increased levels of caspase 3 in the amygdala. Colocalized with both glia (higher quantity) and neurons; not with microglia. ■ 16, 24, and 48 h after SE: higher increase in caspase 3 (peak at 16 h) in the lateral, basal, and medial amygdala; not increased in the central amygdala; ■ 48 h: FluoroJade B and TUNEL positive neurons increase.
Nicoletti et al., 2008 [87]	Systemic atropine methylbromide + pilocarpine; 1 h	■ 24 h after SE: increased VEGF expression in the astroglia and neurons, particularly striking in neurons in the amygdala
Penschuck et al., 2005 [88]	Ventral hippocampus electrical stimulation; at least 2 h	■ 4 months after SE: increased number of KCNQ2-expressing neurons in the basolateral amygdala.
Pereno and Beltramino, 2010 [89]	Systemic kainic acid; at least 3 h	■ 10 days, 1, 2, 3, and 4 months after SE: medial amygdaloid nucleus evaluated; reduced Timm staining at 10 days, gradually recovering to normal levels, completely normal at 4 months; synaptophysin peak at 10 days, returning back to normal levels at 3 months; MAP2 increased expression that was maintained during all times evaluated.
Pereno, Balaszczuk and Beltramino, 2011 [90]	Systemic kainic acid; at least 3 h	■ 2, 4, 12, 24, 48 h: Fos staining increased between 2 and 12 h in anterior parts, and between 2 and 24 h in posterior parts of the medial amygdaloid nucleus; Fos B presented a progressive increase, with peak at 48 h, but starting at 2 h in posterodorsal, 4 h in anterodorsal

(*continued on next page*)

Table 1 (*continued*)

Authors	SE induction method; SE duration	Data
		and posteroventral, and 12 h in the anteroventral medial amygdaloid nucleus; silver impregnation was increased in all areas from 12 to 48 h, with peak at 24 h.
Perez-Cruz and Rocha, 2002 [91]	Systemic kainic acid; at least 2 h	■ 1 and 40 days after SE: μ-opioid receptors binding increased in all amygdaloid areas evaluated (anterior, medial, basolateral, and central)
Pirttila et al., 2001 [92]	Systemic kainic acid; SE duration not informed	■ 2 h and 4 h after SE induction: no neuronal loss. ■ 8 h after SE induction: the lateral nucleus starts to present reduced cell count. ■ 10 days, 4–8 weeks after SE: neuronal count less than 50% of control in the lateral nucleus ■ 10 days: gliosis peak in the lateral nucleus. ■ Central nucleus preserved. ■ MRI correlated to damage: reduced T2-weighted signal indicates medium to severe tissue damage.
Pitkanen, Tuunanen and Halonen, 1996 [93]	Perforant path electrical stimulation; at least 40 min	■ 14 days after SE: 25% reduction in number of somatostatin-positive neurons in the lateral and in the basal nuclei of the amygdala; some rats with high score silver impregnation in the lateral nucleus (4/9) and mild–moderate–severe (1 each) impregnation in the basal nucleus (total 3/9).
Raffo, Koning and Nehlig, 2004 [94]	Systemic lithium + methyl scopolamine + pilocarpine; up to 8–10 h	■ 4 h after SE: 13–16% reduced cytochrome c oxidase activity in the medial amygdala as compared with control. No alteration in lactate dehydrogenase. ■ 24 h after SE: cytochrome c oxidase activity in the medial amygdala, as compared with control, maintains reduced, not as much as previous time. No alteration in lactate dehydrogenase. ■ 2 weeks after SE: cytochrome c oxidase back to normal levels. No alterations in lactate dehydrogenase activity.
Righini et al., 1994 [95]	Systemic kainic acid; at least 1 h	■ 3 h, 1, 2, 3, and 9 days: T2-weighted MRI increased from 1 to 3 days in the amygdala. 1 day after SE, reduced apparent diffusion coefficient.
Roch et al., 2002 [96]	Systemic lithium + methyl scopolamine + pilocarpine; at least 2 h	■ 24 h, 2, and 9 weeks after SE: progressive cell loss detected in the amygdala. ■ T2-weighted MRI increased in 2 waves, one with peak at 24 h and other starting at about 3 weeks and persisting until 9 weeks. Data collected at 2, 6, 24, 30 h, 2, 3, 7, 14, 21 days, and 5, 7, 9 weeks
Sawamura et al., 2001 [97]	Local, unilateral kainic acid in *substantia nigra pars reticulata*; at least 3 h	■ ^{14}C-2DG injected 2 h after kainic acid, in rats presenting self-sustained SE; tissue collected 45 min later; autoradiography showed increased local cerebral glucose uptake in the amygdala ipsilateral to injection site.
Scorza et al., 2002 [98]	Systemic pilocarpine; 6 h	■ Increased local cerebral glucose uptake in the amygdala (about 30%)
Silva et al., 2011 [99]	Systemic methyl-scopolamine + pilocarpine; at least 4 h	■ 4 h: highly increased local cerebral glucose uptake in the medial, basolateral, lateral amygdala nuclei; cerebral blood flow increased in the same areas; ■ 24 h, 7 days: numerous FluoroJade B-positive neurons in the basolateral amygdala (other areas not evaluated)
Su et al., 2015 [100]	Local intracerebroventricular injection of kainic acid; 1–2 h	■ 3 days after SE induction: IL-1b, IL-6, and TNF-alpha levels increased when compared with control; GAT-1 and GAT-3 expressions increased when compared with control.
Suleymanova, Gulyaev and Abbasova, 2016 [101]	Systemic lithium + pilocarpine; at least 2 h.	■ 2 days after SE: increased T2 relaxation time (+17%); ■ 7 and 30 days after SE: T2 relaxation time not different from baseline; ■ 2, 7, and 30 days after SE: no amygdala volume alterations were observed.
Tchekalarova et al., 2017 [102]	Systemic kainic acid; at least 3 h	■ 10 weeks after SE: severe neuronal loss basolateral amygdala.
Turski et al., 1983 [17]	Systemic methyl-scopolamine + pilocarpine; 5–6 h	■ 1 day after SE: extensive damage to the amygdala.
Tuunanen et al., 1999 [103]	Systemic kainic acid; at least 7 h	■ Extensive study; amygdala divided in the deep nuclei (lateral, basal, accessory basal), superficial nuclei (medial, anterior cortical, posterior cortical, periamygdaloid cortex, nucleus of the lateral olfactory tract, and bed nucleus of the accessory olfactory tract), and remaining nuclei (anterior amygdaloid area, intercalated nucleus, central nucleus, and the amygdalohippocampal area). ■ TUNEL increased progressively in most areas, with the exception of the anterior amygdaloid area (not stained) and the central nucleus (peaks at 16 and 48 h) ■ Silver staining: progressive increase, with stabilization at 4 h in the central nucleus, medial nucleus, basal nucleus; and stabilization at 16 h in the anterior amygdaloid area. ■ Thionin staining showed progressive cell loss in most nuclei. ■ Dorsal part of the lateral, basal, central, and medial nuclei, anterior amygdaloid area, and bed nucleus of the accessory olfactory tract were less affected than others (as per silver and thionin evaluations) ■ Bax and Bcl2 were evaluated in the lateral and basal nuclei, with no alterations in both, except for a peak in Bax-ir neurons in the lateral nucleus at 2 h after SE and a loss of such neurons from 24 to 48 h.
Tuunanen, Halonen and Pitkanen, 1996 [104]	Systemic kainic acid or perforant path electrical stimulation; 10–16 h and 35–55 min, respectively	■ 2 days and 2 weeks after SE (kainic acid only, all animals presented damage), damage score based on silver impregnation, somatostatin, and GABA stainings: detailed evaluation; some data are as follows: virtually all nuclei from the amygdala had some degree of damage; noticeable lateral nucleus (ventrolateral and medial), basal nucleus (parvicellular division), accessory basal nucleus, ventral portion of the central division of the medial nucleus, periamygdaloid cortex, amygdalohippocampal area, and posterior cortical nucleus. ■ 2 weeks after SE (kainic acid), density of GABA-positive neurons: reduced to 56% in the lateral nucleus and to 25% in the basal nucleus; somatostatin-positive neurons: reduced to 48% in the lateral nucleus and to 33% in the basal nucleus. Specially, great loss of somatostatin-positive neurons was seen in areas apparently preserved by silver staining and Nissl, such as intermediate and magnocellular divisions of the basal nucleus. ■ 2 weeks after SE (perforant path; 4 out of 9 presented damage) was mostly preserved, with some degree of damage in the medial division of the lateral nucleus and ventral portion of the central division of the medial nucleus. Somatostatin-positive neurons were reduced to 76% in the lateral nucleus and to 75% in the basal nucleus.
van Eijsden et al., 2004	Systemic lithium + methyl scopolamine +	■ 3 and 5 h after SE onset: decreased T2-weighted MRI signal and apparent diffusion

Table 1 (*continued*)

Authors	SE induction method; SE duration	Data
[105]	pilocarpine; 7 h (under anesthesia)	coefficient at both times.
van Vliet et al., 2014 [106]	Systemic kainic acid; at least 4 h	■ 1 and 6 weeks after SE: blood–brain barrier leakage in the amygdala, peak at 24 h; Control is the same animal before SE. ■ 6 weeks after SE, neuronal loss confirmed by Nissl staining and blood–brain barrier leakage confirmed by fluorescein detection.
van Vliet et al., 2016 [107]	Systemic kainic acid; at least 2 h.	■ 1, 4, 8 days, 3 and 6 weeks after SE: blood–brain barrier leakage (MRI) in the amygdala in all time points. Control is the same rat before SE.
Weise et al., 2005 [108]	Systemic methyl scopolamine + pilocarpine; 6–8 h	■ 30 and 120 min: no alterations ■ 1, 7, 14 days: number of neurons reduced progressively; caspase 3 marked predominantly in neurons, at 1 and 7 days (peak), and back to normal levels at day 14; TUNEL presented the same pattern as caspase 3.
Wolf et al., 2016 [109]	Systemic lithium + methyl-scopolamine + pilocarpine; at least 2 h	■ 47 days after SE induction: reduced neuronal survival (Neu-N positive cells counted), maintenance of parvalbumin-positive neurons, increased optical density parvalbumin reading.
Yamada et al., 2009 [110]	Systemic lithium + methyl-scopolamine + pilocarpine; 91–136 min	■ 1 and 45 min after SE: local cerebral glucose uptake increased in the amygdala at 45 min, but not at 1 min (313%).
Yang et al., 2016 [111]	Local, intracerebroventricular kainic acid injection; "at least 1–2 h"	■ The same day as SE: no differences were observed for hypoxia-inducible factor 1 (HIF-1); 1, 3, and 7 days after SE: HIF-1 significantly increased, peak at 3 days. ■ 3 days after SE: increased proinflammatory cytokines IL-1 beta, IL-6, and TNF-alpha, and increased caspase 3.

Abbreviations: DOPAC: 3,4-dihydroxyphenylacetic acid; HVA: homovanillic acid; HPLC: high-performance liquid chromatography; KA: kainic acid; ATP: Adenosine-5'-triphosphate; ADP: adenosine diphosphate; AMP: adenosine monophosphate; TUNEL: terminal deoxynucleotidyl transferase dUTP nick end labeling (dUTP = deoxyuridine 5-triphosphate).

higher receptor recycling process [100]. The synaptic reorganization in the amygdala neuronal terminals is also evidenced 7–10 days after SE. In this time range, glutamatergic receptors such as kainate type 1 (GLUK1) are reduced [68], while levels of GAD65/67 isoforms [68], and of cytokine receptor GP130 [79], are increased.

The progressive loss of amygdala neurons and of amygdala volume, as mentioned before, starts hours after SE and reaches maximal intensity months later, with profound modifications been reported [54,58,77,78,80,89,90,92,96,102,104,108,59,109,62–64,67,71,75,76]. Among the lost neurons, there is a preferential reduction of GABAergic neurons immunoreactive to somatostatin, but GABAergic neurons in general are lost in the same proportion as the total population [66,68,93,104]. Still in the long-term, blood–brain barrier integrity is compromised in the amygdala [106,107]. Additionally, blood vessel density is increased [73], and eventual alterations in T2-weighted signal are observed [96]. Four to six months after SE, the amygdala presents increased number of neurons expressing the member 2 of the subfamily Q (KCNQ2) voltage-gated potassium channels [88]. In addition, protein phosphatase 2A activity and its regulatory B unity PR55 are reduced, with concomitant increase in phosphorylated tau epitopes [82]. Furthermore, angiotensin II receptor type 1 is reduced [51]. Gliosis is still observed [124], but microglia marked by OX42 [75] and histamine receptor H1 [81] return to normal levels. Lastly, the H3 receptors stay reduced up to one year after SE [81].

4. Discussion and concluding remarks

Epilepsy and epileptogenesis are emergent properties of complex systems made of multifactorial phenomena [7,125,126]. They can involve different brain areas and occur because of genetic and developmental factors, or they can develop after diverse brain insults, stimulations, injuries, and infections [127–129]. A great number of animal models have been developed, allowing for the better understanding of epilepsy, the discovery of new and better treatments, and the elucidation of morphological and molecular mechanisms underlying seizures and epileptogenesis [13,130–135]. Despite the above statements, a significant parcel of the patients with temporal lobe epilepsy remains pharmacoresistant [136–138].

In the current study, we aimed to organize the data on the participation of the amygdaloid complex as a whole and its nuclei in epileptogenesis, considering histopathological, morphological, and imaging techniques. We were able to classify several alterations in the amygdala during and after SE: energy metabolism, neuroprotection, circulatory and fluid regulation, neurotransmission, immediate early genes, tissue damage, inflammation, plasticity, and cell suffering. It is important to note that any conclusions are hindered by the lack of details in most results descriptions (amygdaloid complex's several nuclei become simply "amygdala" or "amygdaloid complex"), great variability in protocols for SE induction and duration, and animal's age and strain. Besides, there is concentration of results in some time points after SE. For example, there is a great amount of data 2 h and 24 h after SE, while much less is known about the other time points. Additionally, nonexpected alterations were scarcely investigated. For example, if Pereno and collaborators [90] did not immunostain Fos and Fos B in materials that were not produced specifically to the optimal time range of those molecules' expression (Fos peaks at 2–4 h after SE and Fos B peaks at 48 h after SE), it would not be possible to know that both can be observed 24 h after SE in the medial amygdaloid nucleus. Thus, in general, there is little negative data and even less unexpected data been generated in epilepsy research.

As can be seen in Fig. 2 of the current review, several alterations are observed in the amygdaloid complex during and after SE induction in young adult and adult rats. For example, among all the categories classified in our review, there is strong evidence for plastic changes that lead to altered circuitry and functionality in the amygdala. The neurotransmission systems involved with the activation, propagation, and/or maintenance of epileptic seizures are complex and relate to regulatory processes of excitation and inhibition in several brain areas [139]. SE physiopathology involves a failure in the mechanisms that normally prevent the occurrence of an isolated epileptic seizure; caused by excessive excitation and/or inefficient inhibition [140–142]. The plastic manifestations in the adult CNS are characterized by dendritic alterations, synaptic restructuring, axonal outgrowth, dendritic reorganization, synaptogenesis, and neurogenesis [143–146], all those observed in the amygdala. It is suggested that spontaneous recurrent seizures in temporal lobe epilepsy models result from this excessive, dysfunctional plasticity, leading to pathological expressions of the neuronal function [22,147,148]. The great plastic ability of neural tissue given by SE-induced gene expression, concurrent with cell loss and therefore, clearance of local connective sites, is accepted as part of the mechanisms underlying epileptogenesis in SE models of temporal lobe epilepsy [149]. All the data categorized in the current review, referring to the amygdaloid complex, indicate that this structure is deeply involved in the pathophysiology of epilepsy.

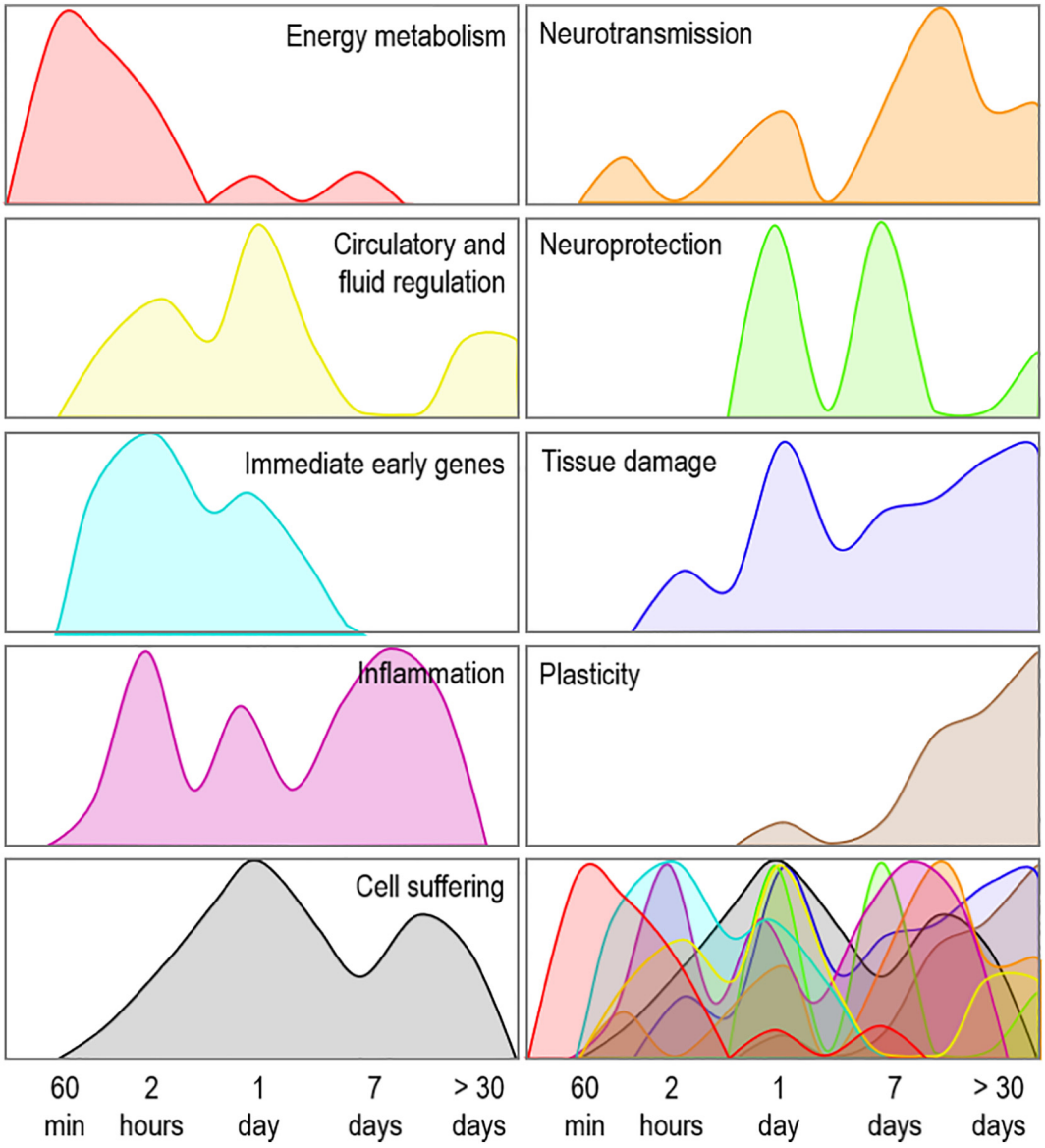

Fig. 2. Timeline of anatomopathological alterations observed in the amygdala after status epilepticus. Note that the time axis is nonlinear, since the amount of data in each time point is variable. This figure illustrates a qualitative evaluation of the evidence found for each pathological process category listed below. Higher curves indicate greater evidence, based on the intensity of the described alterations, in the underlying time point. Pathological process categories: Energy metabolism, Circulatory and fluid regulation, Immediate early genes expression, Inflammation, Cell suffering, Neuroprotection, Neurotransmission, Tissue damage, and Plasticity. Y-axis: arbitrary scale.

It is important to note, however, that the translation of research findings in animal models to the human context is complex. For instance, current animal models of epilepsy do not reflect the diverse etiologic nature of epilepsy, nor are the new drugs discovered using animal models more effective in avoiding pharmacoresistance [150–152]. Moreover, a parallel between human and rodent amygdaloid nuclei may be hampered by its several morphofunctional differences or poor data availability [40,153,154]. Comparison between both species have revealed differences in amygdaloid complex nuclei volumes, neuronal sizes, neuronal density, neuropil volume, interneuron composition and distribution, and monoamine transporters [154–156], implying greater functional complexity in human amygdala than in rats. Nonetheless, many other evidences support similarities between human and rat functional and epilepsy-related anatomopathological characteristics [12,40]. For instance, human and rodents' amygdala have the same function of identifying threatening situations, emotional learning, and fear conditioning [157–160]. Specifically, amygdala atrophy in human patients with epilepsy have been consistently shown, such as in animal models [36,40,41,161]. In fact, amygdala volume was inversely correlated to the number of epileptic seizures in chronic temporal lobe epilepsy in humans [162].

Nonetheless, there is a much greater number of studies considering hippocampal alterations after SE [163,164], when compared with those in the amygdala. The reasons why this happens are not clear, but one possible explanation is the neatly organized and well-known hippocampal anatomy, as opposed to the amygdala complex and less conspicuous anatomical and functional organization [165–170]. Despite the above, amygdaloid complex's contribution to epileptogenic process is demonstrated by the accumulating evidence reviewed here and elsewhere [40–43]. In general, the process starts with metabolic alterations, followed by inflammatory process development. Neurotransmission and genetic expression are changed, together with plastic and proliferative phenomena. Finally, cell death leads to the long-term atrophy and loss of functionality. This consequently results in seizures and in disturbances of mood, of emotional memories, and of cognition. Considering that the amygdala is extensively connected to several other brain areas besides hippocampus, it is critical that research be reexamined in order to include other substrates in the exploration of the circuits

that take part in epilepsy and epileptogenesis. Thus, we suggest that attention should be directed to other areas besides hippocampus, in the characterization of pathophysiology of epilepsy.

It is interesting to highlight, additionally, that the amygdaloid complex is distributed in rat brains mostly in the same anteroposterior range as hippocampal formation [171]. Actually, in the exact same areas included in histopathological slices obtained for hippocampus evaluation, not only the amygdala can be observed, but also several cortices of interest for epilepsy (entorhinal, piriform, cingulate) and many other areas that may be of interest for epilepsy pathophysiology (the entire thalamus and hypothalamus, *substantia nigra*, periaqueductal gray matter, superior colliculus, mesencephalic tegmentum). Thus, it is probable that research laboratories that focus on hippocampal alterations consequent to SE may have, in their archives, histopathological material that can be used to investigate alterations in several other brain areas. Since it was not the purpose of this review, we did not compare results from the amygdala with those from hippocampus. However, a rapid inspection in the articles included in this review indicates that pathophysiology of epilepsy develops differently in both structures. Such differences have been described on intensity [66,83,99], time of presentation after the onset of SE [56], presence or absence of the studied variables [53,70,95], and even opposite findings between both structures [51,65]. In times when ethics in animal use for research raise concerns and the 3R strategies gain more attention [172–174], going back to high quality material stored in research laboratories could generate original shared research data on epilepsy and epileptogenesis, giving rise to new hypotheses for future investigations. This kind of approach and effort will be fundamental for actual multinational and multicenter research in Global Cooperation in epileptology.

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