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Review
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Feline Temporal Lobe Epilepsy: Review of the Experimental Literature

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Accumulating evidence suggests that epileptic seizures originating from the temporal lobe (TL) occur in cats. Typically, affected animals have clinically focal seizures with orofacial automatisms including salivation, facial twitching, lip smacking, chewing, licking, and swallowing. Motor arrest and autonomic and behavioral signs also may occur. Many affected cats have magnetic resonance imaging (MRI) changes within the hippocampus or histopathologically confirmed hippocampal sclerosis or necrosis. From the 1950s to the 1980s, cats frequently were used as animal models for neurophysiological experiments and electrophysiological studies, from which important basic knowledge about epilepsy originated, but which has been rarely cited in clinical veterinary studies. These studies were reviewed. Experimental research on cats showed the widespread anatomical connections among TL structures. The ictal clinical signs originating from the hippocampus, amygdala, or lateral temporal cortex are similar, because of their dense interconnections. The ictal signs can be divided into autonomic, somatic, and behavioral. For research purposes, a 6-stage system was established, reflecting the usual sequential progression from focal to generalized seizure: attention response (1), arrest (2), salivation, licking (3), facial twitching (4), head turning or nodding (5), and generalized clonic convulsions (6). Knowledge of this data may help in recognizing low-stage (stage 1 or stage 2) epileptic seizures in clinical practice. Early experimental research data are in accordance with recent clinical observations regarding ictal clinical signs of TL epileptic seizures in cats. Furthermore, the research data supports the idea that TL epilepsy represents a unique clinical entity with a specific seizure type and origin in cats.

Key words: Electrical stimulation; cat; Kindling model; Review; Temporal lobe.

Accumulating evidence suggests that epileptic seizures originating from the temporal lobe (TL) occur in cats. Clinically, affected cats experience focal seizures (FS) with orofacial automatism including salivation, facial twitching, lip smacking, chewing, licking, and swallowing (Fig 1). Motor arrest and autonomic and behavioral signs also may occur.[1–4] Many cats with such seizures have a lesion within the TL, mainly in the hippocampus. These clinical observations suggest that the TL is the main source of epileptic discharges, but electroencephalographic confirmation usually is absent. Feline temporal lobe epilepsy (FTLE) is a well-known model based on experimental research. Until recently, very little knowledge from experimental research in FTLE was used in clinical veterinary epileptology. However, important basic knowledge about epilepsy was acquired experimentally from cats. Better knowledge of these experimental results may help clinicians to understand more about FTLE.

The goal of our review was to emphasize the importance of experimental research in FTLE in veterinary medicine in order to gain additional and better knowledge about the anatomical and functional mechanisms underlying the disease. Consequently, we summarized the literature on experimental research regarding FTLE. The years from 1950 to 1980 received special focus, because cats were frequently used as animal models for neurophysiological experiments and electrophysiological studies during that time period.

Abbreviations:

AD	after discharge
CPA	complex partial seizure
ECS	electroconvulsive shock
EEG	electroencephalography
FTLE	feline temporal lobe epilepsy
MRI	magnetic resonance imaging
NE	norepinephrine
NREM	nonrapid eye movement
TL	temporal lobe

Database Search

Our review is based on literature searches in online medical databases, as well as a few selected specialized books on epilepsy and the important anatomical

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Fig 1. A cat with a typical temporal lobe seizure: orofacial automatism with head turning upwards, salivation, facial twitching, mastication, and licking.

structures involved.[5,6] The research involved medical databases such as PubMed, Europe PubMed Central, Scopus, Ovid, and ScienceDirect. The following search criteria were used: "epilepsy cat," "TL epilepsy cat," "FTLE," "experimental research cat epilepsy," and "experimental research TL epilepsy cat." To increase the specificity, "kindling TL cat," "kindling kitten," "electrical stimulation TL cat," and "chemical stimulation TL cat" were added. Finally, the references of each publication were reviewed.

Electrical Stimulation Studies of Temporal Lobe Epilepsy in Cats

Amygdala Stimulation

Ursin and Kaada[7] described the "attention response" as one of the most common reactions after amygdala, as well as hippocampal, stimulation in cats. Kaada (1951) called it "arrest," and others called it "searching" or "attention response."[8–10] At the beginning of stimulation, cats stopped all spontaneous activities. Their facial expression and behavior changed to attention or alertness. Cats frequently seemed surprised and behaved as if they expected something to happen. The response usually included initial respiratory arrest, strikingly in expiration. The initial inhibition was followed by a movement resembling orientation. The cats raised their heads and sometimes their forelimbs as well. They seemed to be anxiously searching for something and looked backwards, usually contralateral to the stimulation side but ipsilateral turning also occurred. The eyes were widely opened, the pupils dilated, and directional movement of the ears sometimes occurred. Occasionally, sniffing movements were observed. During this period, cats reacted appropriately to different stimuli. The initial apnea was followed by tachypnea of low amplitude.[7] The contralateral searching sometimes continued into contralateral circling. The attention response sometimes was combined with other motor and autonomic signs. Most frequently, licking and ipsilateral facial twitching were observed (Fig 2).[8–10]

Studies from Delgado et al.[9] showed a clear correlation between electrical stimulation of the amygdala and direct ipsilateral facial motor effects. Similarly, Kaada et al.[10] showed that electrical stimulation of distinct parts of the amygdala in unanesthetized cats resulted in an immediate and strong contraversive turning of the head, eyes, and cranial part of the body. It usually was combined with backward-upward movement of the head and tonic extension of the forelimbs, culminating in a spiral movement of the head and upper body parts.[10]

Kaada et al.[10] stated that both motor and autonomic responses were obtained mainly from the same phylogenetically old anteriomedial division of the amygdaloid nuclei. The animals also were looking or staring at a certain body area, which was interpreted as a change of bodily sensation. These responses were obtained mainly from the phylogenetically younger basolateral division. Furthermore, a study by Kesner and Doty[11] identified a link between electroconvulsive shocks (ECS) applied to the amygdala and some state of amnesia.

Hippocampal Stimulation

Delgado and Sevillano[9] observed the so-called "attention response," similar to the amygdala stimulation. When stimulation was carried out during sleep or dozing, animals opened their eyes, looked around, and stared. In contrast, in completely awake animals, there were no obvious effects, and spontaneous activity, such as walking, continued, seemingly undisturbed. Only with longer stimulation (>5 seconds) did the spontaneous activity of the animals stop and the typical "attention response" appeared, which lasted until the stimulation was finished. Afterward, the cats were frequently hyperactive, walking, or running around with increased vocalization. Approximately 10% of stimulations with recordable after discharges (ADs, discharges of neural impulses after an initiating stimulus) were asymptomatic in the hippocampus.

The hippocampal stimulation generally also had autonomic, motor, and behavioral effects.[8,9,12] The most frequently observed autonomic effects were mydriasis, salivation, gagging, and piloerection (Fig 2).[8,9,12] The main motor responses were arrest, staring, head turning, vocalization, facial twitching, and clonus.[8,9,12] Behavioral effects were attention or apprehensiveness, signs of fear or anger, searching behavior, and sniffing.[8,9,12] Immediately after hippocampal stimulation,

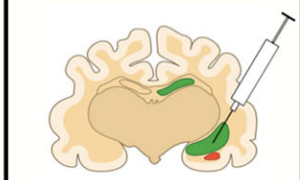
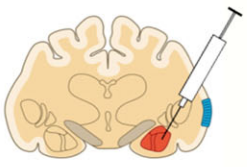
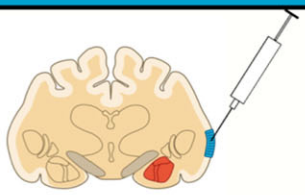
Injection Site	Hippocampus	Amygdala	Insula
	 B	 A	 A
Effect	• Psychomotor • Autonomic	• Psychomotor • Autonomic • Generalized motor seizures	• Psychic • Autonomic
Head Turning	Ipsilaterally to lesion	Contralaterally to the lesion	Contralaterally, upward with staring
Facial Twitching	Initially ipsilateral	Initially contralateral, remaining uni- and sometimes becoming bilateral	No
Pupillary Dilatation	Up to 80%	Up to 100%	Up to 50%
Salivation	Profuse, watery	Thick	No
Additional Ictal Signs	• Apprehensive crouching • Masticatory movements • Clonus of upper ipsilateral lip and face • Ipsilateral turning of body until it becomes twisted • Turning around	• Inital alertness, pre-occupation, staring • Excitement • Chewing • Clonus of head and forelimb • Generalization • Falling • Struggling • Postictal exhaustion	• Wide eye-opening • Head lifting • Searching • Sudden jumping • Looking sideways • Ipsilateral head jerking • Apprehensiveness • Vocalization • Swallowing
EEG	Spikes, sharp waves	Widespread spikes	Sharply localized higher voltage discharges

Fig 2. Seizure features in experimental temporal lobe (TL) epilepsy in cats using tungstic acid injection into the different TL regions according to Blum et al.[18]

motor signs similar to a "wet dog shaking" may occur.[13,14] The hippocampus generally is considered to have striking electrical features within the brain because discharges may be elicited easily after an initial electrical stimulation elsewhere.[9] Elul et al.[15] also found a regional differentiation of the hippocampus. The dorsal hippocampus exhibited lower AD thresholds than did the ventral part.[16]

In 1936, a study concerning the convulsion threshold of various parts of the feline brain noted that points with rather low thresholds were found along the course of the fornix, in the gyrus cinguli and in the TL.[17] The low threshold points close to the amygdaloid nucleus are of interest because the fornix and taenia semicircularis connect the amygdaloid nucleus and adjacent structures with the TL, and there is evidence that fiber connections to the gyrus cinguli run through the fornix.[17]

Insular Stimulation

The insula and peri-insular regions of the feline brain are thought to be substantially less developed than those of humans. Studies concerning the role of the insula and peri-insula in experimental epilepsy in cats were carried out in the early 1960s.[18] The main effects after stimulation of the insular region also can be divided into autonomic, motor, and behavioral. The

most frequent autonomic responses were mydriasis and salivation. Motor effects included head turning, looking sideways, jumping, and swallowing. Behavioral responses were apprehensiveness, searching, and vocalization (Table 1, Fig 2).[19,20]

Staging Systems in Feline Temporal Lobe Epilepsy by Kindling

A classification of certain stages emerged throughout the years of research in this field, and systems of the chronological development of seizure patterns were developed (Table 2). The early stages of 0–3 represent motionless staring, autonomic manifestations such as salivation and dilatation of pupils, focal (partial) seizures, and head turning. With progressive kindling and recruitment of more distant structures, stages 4 and 5 evolve and are represented by forelimb clonus and extension, and generalized seizures of different severity with falling and tonic–clonic convulsions. Some researchers even extended evaluation to stages 6–8, which occur after more intense stimulation and lead to progressively more severe seizures.[21] Most researchers continued stimulation until a stage 5 seizure state was achieved.[22] Wada et al.[23] used a similar classification system for their amygdala-kindled cats.

Table 1. Effects of hippocampal, amygdaloid, and insular stimulation.

Effects of Stimulation	Hippocampus	Amygdala	Insula
Autonomic	Mydriasis Salivation Gagging Piloerection	Mydriasis Urination Defecation Piloerection	Mydriasis Salivation
Motor	Head turn Facial twitching Arrest Staring Vocalization	Head turn Facial twitching Licking Sniffing Chewing Tonic stiffening Apnea	Head turn Looking sideways Jumping Swallowing Vocalization
Behavioral	Attention Searching behavior Fear Anger Sniffing	Attention Searching behavior Body sensation	Apprehensiveness Searching behavior

Kindling Model

Kindling is a widely accepted experimental animal model of epilepsy with a progressive and permanent character. It is used mainly as a model to study epilepsies[24] and as a method to study physiological changes in epilepsies. Kindling studies initially were performed in rats, but other mammalian species, such as dogs, cats, and primates,[25] and even amphibians,[26] soon followed. Kindling is based on repeated, low-intensity, initially subconvulsive, daily electric stimulation, resulting in focal AD at the electrode tip but without seizures.[27,28] Complex, widespread functional reorganization of the brain[29] and alternation of neuronal responses take place after kindling without gross morphological damage.[5,30] The repetition leads to a lengthening of ADs, which gradually elicits seizure activity. Once an animal has been successfully kindled, the increased response to the stimulus seems to be permanent, and spontaneous seizures can occur within a short period of time.[6] Once generalized seizures occur, the excitability of the stimulated brain area stays altered.[28] Kindling also can be induced by

Table 2. Two different staging systems of experimentally induced seizures and clinical observations of naturally occurring temporal lobe seizures.[1,30,32]

	Wada et al.[23] (Experimentally Induced Seizures)	Sato et al.[32] (Experimentally Induced Seizures)	Pakozdy et al.[1] (Naturally Occurring Seizures; Did Not Use Staging but Retrospectively Reconizable)
Stage 1	Unilateral ipsilateral face twitching	Attention response, looking around, sniffing	
Stage 2	Bilateral facial twitching	Immobility (staring and arrest)	Arrest
Stage 3	Head nodding	Autonomic manifestation: salivation, licking, pupillary dilatation	Hypersalivation, orofacial automatism, mydriasis, licking, lip smacking
Stage 4	Contralateral head turning, tonic extension of contralateral forepaw	Facial twitching, masticatory movements	Masticatory movements, facial twitching
Stage 5	Generalized clonic jerking while standing	Tonic extension of contralateral forepaw, head nodding, head turning	
Stage 6	Falling down with generalized convulsive seizure	Generalized clonic convulsions in lateral recumbency	May evolve into generalized convulsive seizures

chemical means, such as the systemic or intracranial periodic application of drugs.

The progress of clinical seizures proceeds through a distinct sequence of events, and the behavioral manifestations of kindled seizures strongly depend on the stimulated site and on the animal species used.

The kindling stimulation usually begins with 100 μA, followed by daily increases of 200 μA until a localized AD is elicited.[30] The kindling process depends on ADs, as without them kindling is not possible.[22] Subsequently, the stimulation is decreased by 50 μA daily, until no AD can be evoked. The lowest current intensity at which an AD can be produced is called the AD threshold. The AD threshold also can be taken as an index for the local epileptogenicity of a brain area and how susceptible it is to the kindling technique.[5] The average number of daily required electrical stimulations to reach the final stage of generalized convulsions is 36 days (range, 9–91 days) in cats.[31]

A study by Sato et al.[32] in 1975 showed an entirely independent AD and interictal discharge in the bilateral globus pallidus and amygdala with secondary site convulsions after hippocampal kindling, suggesting a response potency in these secondary sites equal to that in the primary site.

Chemical Stimulation Studies of Temporal Lobe Epilepsy in Cats

Kainic Acid Model

In the late 1970s and early 1980s, the kainic acid model became a valued experimental model for focal epilepsy.[33] Kainic acid, an analog of the neuro-excitatory amino acid glutamate, has excitatory effects.[34] It can be applied to various regions of the brain, but TL structures have a very high susceptibility.[33] It mainly produces limbic seizures (arrest, mydriasis, hypersalivation, facial twitching), which occur within minutes after application and strongly resemble those seen in TL epilepsy in humans.[33] They can decrease after hours or days, but may reappear spontaneously after a silent period.[33] In 1982, Tanaka et al. studied the electroclinical features of kainic acid-induced status epilepticus in freely moving cats by microinjection into the dorsal hippocampus. Three different dosages were administered to 3 different groups in order to show a dose-dependent and substantial effect of kainic acid. The injection of 1 μg induced focal status epilepticus for 2–3 days. With 4 μg of kainic acid injection, limbic status epilepticus was observed for 3 days and continuous interictal discharges persisted throughout the observation period. After the injection of 12 μg, however, independent amygdaloid seizures (alerting, mydriasis, hypersalivation, facial twitching, head turn, head nodding, limb clonus) accompanied by strong rage reactions and secondary generalized convulsions evolved, and the cats died in status epilepticus. The change in the behavioral status suggests an influence of the hippocampus on the behavioral reaction of the cat.

Tetanus Toxin Model

The tetanus neurotoxin, produced by the gram-positive bacteria *Clostridium tetani,* was first used as an experimental model for recurrent chronic focal (partial) seizures in the 1960s.[35] Its effect involves the synaptic blocking of the release of inhibitory neurotransmitters such as γ-aminobutyric acid (GABA),[36] as shown when applied experimentally to hippocampal slices.[37] In 2 studies by Louis et al.,[33,38] tetanus toxin was applied to the cerebral cortex of 60 dogs and the left primary motor cortex of 5 cats. In both studies, the administration of tetanus toxin induced epileptogenic foci, which lasted up to 2 months.[33,38] A clinical and electroencephalographic (EEG) onset occurred after a relatively short latency period that varied from hours to several weeks and remained chronically active.[33] In the 5 cats with tetanus toxin lesions of the motor cortex, clonic motion of contralateral shoulder and forepaw initially occured. When the tetanus toxin was injected into the hippocampus, behavioral, autonomic, and motor signs were observed similarly to those described during direct electrical stimulation of the hippocampus.[38,39] The toxin seemed to be an ideal agent for producing highly localized lesions after local injection, because of its large molecular size and its rapid binding to receptors.[33] Tetanus toxin lesions are relatively small and well confined, consisting of necrosis and reactive gliosis.[33] Another advantage of tetanus toxin is the wide range of susceptible telencephalic application areas (e.g., the hippocampus, substantia nigra, thalamus, orbital frontal cortex, cerebral cortex, and motor cortex).[33]

Tungstic Acid Model

In the studies of Blum et al.,[19] a characteristic TL type of epilepsy was induced by the unilateral injection of tungstic acid in the hippocampus and lateral amygdala of cats. In the new tungstic acid method, by the injection of minute quantities of tungstic acid gel, discrete lesions in 3 selected areas of the TL were produced: the ventral hippocampus, the amygdala, and the insula.[20] The pathological findings were the same in the different parts of the TL. Epilepsy with different clinical signs occurred within 12–24 hours after the injection, but generalized seizures only were observed after amygdaloid injection. Both the hippocampal and insula-peri-insula-type seizures were described as being behavioral and autonomic. The clinical signs after injection of the 3 different sites overlapped, which is not surprising because they all belong to the limbic system. With unilateral ablation of the amygdala in cats, ipsilateral motor manifestations disappeared and did not return, even during kindled generalized seizures.[9]

Sleep and Epilepsy in Cats

From 1980 to 2005, Shouse[40–43] performed FTLE studies using a different premise. She proposed that studying sleep and arousal disorders coexisting with FTLE might identify common underlying mechanisms

for the onset or expression of secondary generalized seizures. She produced 3 major sets of findings:

1 Temporal lobe epilepsy in humans and cats shows similar, sleep-related timing of secondary generalized TLE seizures and of sleep disorders. Peak TLE seizure manifestations occur in nonrapid eye movement (NREM), also called slow-wave sleep (SWS) in cats.[42]
2 Shouse was the first to show the physiological factors for rapid eye movement (REM) suppression and NREM activation of generalized seizure manifestations when compared to waking.[42,44,45] Identical findings were obtained in evoked seizure measures using feline models of primary generalized epilepsy (PGE) (ECS and systemic penicillin epilepsy) and TLE (amygdala kindling). Atropinized cats displayed REM sleep with a selective presence of a synchronized, NREM-like EEG and selective increase in seizure discharge generalization without motor seizure accompaniment. The epileptic spikes usually originated from the amygdala and could be recognized during stages 1 and 2 seizures. After stage 3, the EEG discharges were so pervasive that no distinction was possible. Independent interictal spikes also occurred not only arising from the amygdala but also the locus coeruleus, motor cortex, piriform and entorhinal cortex, and lateral geniculate nucleus. Interestingly, these multifocal interictal discharges were very prominent during SWS and during cluster seizures between the convulsive periods. Strikingly, in some cases, such interictal spikes were completely absent in kittens with severe spontaneous seizures, even during SWS.[41] The absence of motor signs was attributed to profound lower motor inhibition, also called atonia, in REM. This was confirmed by lesions of the pontine tegmentum which selectively abolished the atonia of REM. Cats without atonia had motor seizures in REM as readily as in waking.
3 Lastly, Shouse's group discovered the first model of developmental FTLE and of spontaneous, convulsive "sleep" epilepsy by amygdala kindling in kittens. Microdialysis showed early postkindling depletion of norepinephrine (NE) in the brainstem and amygdala and subsequent increase of NE with low concentrations predicting evoked and spontaneous seizures and sleep disorders in cats kindled as kittens.[40] Also, microinfusion of NE agonists delayed, whereas antagonists accelerated, kindling in kittens.[43]

From the 1950s to the 1980s, cats frequently were used as animal models for neurophysiological experiments and electrophysiological studies. Electrical discharges are easily elicited in the hippocampus within the TL. For functional testing of the TL, different methods were used in cats. The most frequent method to investigate TL function was electrical stimulation. Stimulation electrodes were placed in different parts of the TL, and the behavioral, motor, or EEG changes were documented. Other studies involved injections of different chemical substrates into discrete TL structures, usually the amygdala, hippocampus, or TL cortex. Another type of research involved a special kind of stimulation called "kindling." Based on the experimental data, it can be concluded that epileptic activity within the TL in cats has characteristic ictal signs. Experimentally elicited ictal signs were best described in a staging system by Sato et al.[32] (Table 2). Knowledge on that literature is important because there is accumulating evidence that epileptic seizures originating from the TL occur spontaneously in cats worldwide. The initial signs can be summarized as orofacial automatism, which is the main clinical feature of the TL seizure in cats. This is so characteristic that it can be recognized clinically, and it is very likely that these early stages (1–3) were observed by clinicians.[1,46–48] Looking more closely at the different stages: arrest (stage 2), orofacial automatism (stage 3), facial twitching (stage 4), and generalized clonic convulsions (stage 6) were recognizable as epileptic by Pakozdy et al.[1] based on clinical observation. Tonic extension of the contralateral forelimb (stage 5) was not observed clinically because it is less obvious and it could have been overlooked. More importantly, the clinical recognition of stage 1 signs (looking around, attention response, sniffing movement) is more challenging. However, knowledge of the experimental literature may enable recognition in the future. The clinical rediscovery of the experimentally well-known TLE in cats is summarized in Table 2.

The clinical antemortem diagnosis of TLE in cats can be supported by magnetic resonance imaging (MRI) changes, but electrophysiological confirmation, usually is lacking. Epileptic discharges, however, were detected in experimental cats, and detailed clinical observations were provided. The experimental studies clearly show that orofacial automatism is the main feature of TL epilepsy, which sequentially can evolve into generalized motor convulsions. However, orofacial automatism is not necessarily always an epileptic phenomenon and obsessive-compulsive disorder may be a differential diagnosis. Furthermore, many epileptic discharges may not manifest themselves clinically.

Abnormal, excessive, or synchronous neuronal activity in the brain is the main feature of epilepsy.[49] Epileptic discharges can be detected by EEG, which is the main diagnostic procedure in the study of epilepsy in people, whereas in cats it is rarely used.[50] A drawback in the study of epilepsy in animals is that EEG data are not consistent and there is neither agreement about the appropriate technique and sedation protocol nor about the EEG features that are associated with epileptic seizures. The consequence of these limitations is 2-fold. First, it is usually not possible to confirm epilepsy in clinical practice. Secondly, localization of the epileptic discharge within the brain cannot be achieved. Consequently, whether an episodic event is epileptic and where it is localized can only be suspected based on clinical, laboratory, and neuroimaging findings.[50] This limitation underlines the importance of knowledge about the ictal signs of experimental epilepsies in cats.

This feature was widely studied during early experimental research. The EEG recording usually was a central part of the studies, and epileptic discharges were recorded and simultaneous behavioral changes were observed and noted. The electrodes used frequently were intracranial, and were able to detect epileptic discharges in deep brain structures. For this reason, this method is more sensitive than the EEG with its surface electrodes. These data are important for clinicians because the evidence for epileptic discharge is much higher than in clinical cases. On the other hand, it is not clear whether these epileptic discharges reach the cerebral surface and are recordable by surface EEG during sedation or general anesthesia.

Temporal lobe epilepsy seizures occur most frequently in SWS in amygdala-kindled cats, but these aspects were not investigated in clinical cases. However, different aspects could be interesting in the future. Electroencephalography could be performed in a subgroup of cats during natural sleep, which could help in understanding more about sleep and awake states in this species. Secondly, sleep (REM versus SWS) could be influenced by different drugs, increasing diagnostic value in epileptic animals.

In conclusion, early experimental research data are in agreement with recent clinical observations regarding the ictal clinical signs of TL epileptic seizures in cats. When summarizing these results, it seems that TLE represents a unique clinical entity with a specific seizure type that can be recognized clinically. Knowledge of the earlier research supports the recognition and interpretation of epileptic signs. However, challenging cases still may occur, and confirmation usually is not possible.

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