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Behavioral manifestations of seizures in rodent models of epilepsy

Behaviorální projevy záchvatů v hlodavčích modelech epilepsie

Bachelor thesis

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Prohlášení

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V Praze, 06.08.2024 Tereza Strupková

Poděkování

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Abstract

Epilepsy is a serious chronic neurological disorder affecting 0,5 - 1 % of the population in developed countries. The defining feature of epilepsy are epileptic seizures. In human patients, the behavioral manifestations of seizures can be extremely diverse. The milder ones include staring, confusion, or speech difficulties. The more serious manifestations include clonic or tonic convulsions of limbs or the whole body and loss of consciousness. In clinical practice, the seizure manifestations have high diagnostic value since they can be informative of the extent of the brain areas affected by the seizure. Therefore, they are also studied in rodent models of epilepsy. The content of this bachelor thesis is a literature review on the behavioral manifestations of epileptic seizures in rodents and their link to the other modalities used for studying the seizures, such as electrophysiology. Also, similarities between rodent and human seizure manifestations are discussed.

Keywords: epilepsy, rodent model, behavioral manifestation, seizure, Racine scale

Abstrakt

Epilepsie je vážné chronické neurologické onemocnění postihující 0,5 - 1% populace ve vyspělých zemích. Charakteristickým znakem epilepsie jsou epileptické záchvaty. U lidských pacientů mohou být behaviorální projevy záchvatů velmi různorodé. K těm mírnějším patří zahledění, zmatenost nebo potíže s řečí. Závažnější projevy zahrnují klonické a tonické křeče končetin či celého těla a ztrátu vědomí. V klinické praxi mají projevy záchvatů vysokou diagnostickou hodnotu, neboť mohou poskytnout informaci o rozsahu mozkových oblastí postižených záchvatem. Z tohoto důvodu jsou také studovány na hlodavčích modelech epilepsie. Obsahem této práce je literární rešerše o behaviorálních projevech epileptických záchvatů u hlodavců a jejich propojení s ostatními modalitami používanými pro studium záchvatů, jako například elektrofyziologie. Dále jsou diskutovány i podobnosti mezi projevy záchvatů u hlodavců a u lidí.

Klíčová slova: epilepsie, hlodavčí model, behaviorální projev, záchvat, Racinova stupnice

List of abbreviations

ASDs = Antiseizure drugs

EEG = Electroencephalogram

FCDII = Focal cortical dysplasia type II

GAERS = Genetic Absence Epilepsy Rats from Strasbourg

ILAE = International League Against Epilepsy

IUE = In utero electroporation

MTLE = Mesial temporal lobe epilepsy

mTOR = Mechanistic target of rapamycin

NTLE = Neocortical temporal lobe epilepsy

PTE = Post-traumatic epilepsy

PTZ = Pentylenetetrazole

RISE = Reduced Intensity Status Epilepticus

SE = Status epilepticus

SLEs = Seizure-like events

SRS = Spontaneous recurrent seizures

SUDEP = Sudden unexpected death in epilepsy

SWDs = Spike and wave discharges

TBI = Traumatic brain injury

TLE = Temporal lobe epilepsy

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1. Introduction

Epilepsy is a brain disorder identifiable by a tendency to generate epileptic seizures. These are defined as unpredictable interruptions in the normal functioning of the brain in which excessive and synchronized neural activity occurs. Epileptic disorder also means that the patient is more likely to have a recurrence of another seizure during life. In addition, epilepsy is associated with the presence of neurobiological, cognitive and psychological comorbidities, which can lead to social exclusion (Fisher et al. 2005).

The official classification of seizure types in epilepsy is provided by the ILAE (International League Against Epilepsy) (Fisher et al. 2017). The ILAE (International League Against Epilepsy) was founded in 1909, published the first classification in 1960, and since then, the organization has made a few upgrades in the terminology and classification of epilepsies and seizures. The most recent one has been dated to 2017. This classification is being used to evaluate whether a person suffering from seizures has epilepsy or whether the seizures are of a different kind. In a more concrete way, the classification helps determine what type of epileptic seizures the individual has, and from that, other more specific information can be obtained (such as triggers for seizures and the likely course of the condition for the patient) (Scheffer et al. 2017).

Based on anatomy, there are three types of seizure onset. Focal onset, generalized onset, and unknown onset (Fisher et al. 2017). Focal seizures originate only in one hemisphere of the brain, as opposed to generalized seizures, which affect both hemispheres at the same time (Berg et al. 2010). In generalized seizures, awareness is usually impaired. One of the reasons why there can be an unknown onset is that it is recommended to have at least 80% certainty of knowing the correct type of onset, which is not always the case. Nevertheless, the correct type of seizure onset can be classified later on, when there is more information available (Fisher et al. 2017).

Among other diagnostic tools, knowing the semiology (behavioral manifestations during seizures) can be very helpful for the classification of seizure types and choosing further approaches to cure this condition either by proper medication or surgical procedures.

Animal models, particularly rodents, play a crucial role in epilepsy research by providing a controlled environment to study the mechanisms underlying seizure activity and the effects of potential treatments. The semiology of seizures in animal models mirrors the diverse seizure types observed in human patients of epilepsy. They serve as tools for understanding the complexity of this disorder. Therefore, these models bring value for the development and testing of new therapeutic strategies before they are applied in clinical settings.

In comparison with animals, human behavioral manifestations during seizures are essential for the identification of the concrete regions of the brain involved in seizure activity. Learning this information is crucial for creating plans for treatment, such as choosing the correct medication or surgical procedures.

By presenting the manifestations observed in rodent models and human patients, this thesis aims to highlight the similarities and differences between them, providing insights that improve the development of effective treatments for epilepsy. This information is key to translating animal research into successful clinical applications for humans suffering with epilepsy.

2. Animal models

Both *in vivo* and *in vitro* animal models are significantly valuable in comprehending the mechanisms underlying epilepsy (Stables et al. 2003). Therefore, animal models are crucial for the development of antiseizure drugs (ASDs) (Smith, Wilcox, and White 2007). ASDs are in many articles also referred to as antiepileptic drugs, but the term antiseizure medication/drug is the most fitting due to the fact that it is treating the symptoms of epilepsy, which are seizures (French and Perucca 2020). The aim of using ASDs is for the patient to experience inhibition, or ideally, the elimination of seizure occurrence (Stables et al. 2003). Around 20-30% of humans suffering from epilepsy are pharmacoresistant and therefore not seizure free (Picot et al. 2008). Testing ASDs on animal models serves to prevent potential harm to humans and maximize the effectiveness of these drugs (Klitgaard et al. 1998), (Krall et al. 1978). In order to identify a novel therapy effective for human patients with refractory epilepsy, it is necessary to select an animal model that exhibits similar traits (Stables et al. 2003). With that being said, it is important to introduce a few of the most important animal models, which are useful in the discovery and study of ASDs (Grabenstatter and Dudek 2019). The kindling, pilocarpine, and kainic acid are well-characterized models. They mimic the pathophysiological processes seen in human epilepsy, particularly temporal lobe epilepsy (Kulikov et al. 2021), (Mello et al. 1993), (Duveau et al. 2016). Other models which provide different insights into epilepsy will also be mentioned in this chapter.

Furthermore, models offer the opportunity to evaluate not only the symptomatic ASDs, but also to facilitate the testing of novel drugs aimed at altering the progression of epilepsy itself. This represents a much needed shift in approach (Bertoglio et al. 2017).

2.1 The kindling animal model

The kindling effect is when repeated stimulation is applied to a certain brain region, which causes a gradual increase in susceptibility to seizures until eventually bilateral clonic motor seizure is induced by each stimulation (Goddard, McIntyre, and Leech 1969), (Girgis 1981).

One of the most commonly used methods of stimulation is electric impulses. The electrical kindling can be induced by implanting stimulation electrodes in parts of the brain such as the amygdala, hippocampus, or piriform cortex (McIntyre, Kelly, and Armstrong 1993), (Pinel, Mucha, and Phillips 1975). The stimulation frequency is the determining factor for the seizure threshold of the animals. Another crucial factor in the electric kindling process is the interval between stimulation trials (Goddard, McIntyre, and Leech 1969).

Chemical kindling involves the repeated administration of substances that trigger seizures. That can be achieved by injecting, for example, pentylenetetrazole (PTZ) intraperitoneally until the animal starts showing clonic seizures (Babaie et al. 2017).

Other methods of kindling, such as audiogenic and optical kindling, also exist, although they are not as frequent. Audiogenic kindling consists of the animal undergoing sound stimulation, whereas the optical one involves the repetitive use of light pulses to stimulate a specific brain region, such as the hippocampus (Vinogradova, Vinogradov, and Kuznetsova 2006), (Tescarollo et al. 2023).

Electrical kindling targets specific brain regions, which makes it a reliable model. However it can lead to undesirable tissue damage (Morales et al. 2014). Chemical kindling is less invasive, since it does not involve the implantation of electrodes. But it can be challenging to achieve the correct dosage (Ngoupaye et al. 2022). Animals subjected to audiogenic kindling exhibit higher seizure susceptibility due to the use of genetically predisposed rat strains (Vergnes et al. 1987). Optogenetic kindling targets defined populations of neurons with a lower likelihood of causing tissue damage compared to traditional electrical stimulation techniques (Shimoda et al. 2022).

People with focal epilepsy most frequently suffer from temporal lobe epilepsy (TLE), where a large portion of them are also drug resistant (Panina et al. 2023). Animal models of kindling play a crucial role in understanding the pathophysiological mechanisms of TLE, facilitating the discovery of new therapeutic strategies, which can also be helpful in regards to refractory TLE (Huang et al. 2018), (He et al. 2021). One such mechanism is the similarity between animal models of kindling and human TLE in the synaptic reorganization of the mossy

fiber axons in the dentate gyrus (Cavazos, Golarai, and Sutula 1991), (Sutula et al. 1989), (Kulikov et al. 2021).

2.2 The pilocarpine animal model

Pilocarpine is a cholinergic agonist that is used to induce status epilepticus (SE), after which chronic spontaneous recurrent seizures (SRS) eventually start to occur (Turski et al. 1984), (Mello et al. 1993). The most recent classification of SE by ILAE specifies it as a seizure lasting minimally 5 minutes or as more seizures in a row without the person returning to a normal state between them (Trinka et al. 2015). In animal models, the SE can persist for more than 30 minutes and can be stopped or decreased in severity using a drug, such as diazepam (Figure 1) (El‑Hassar et al. 2007), (Inostroza et al. 2012).

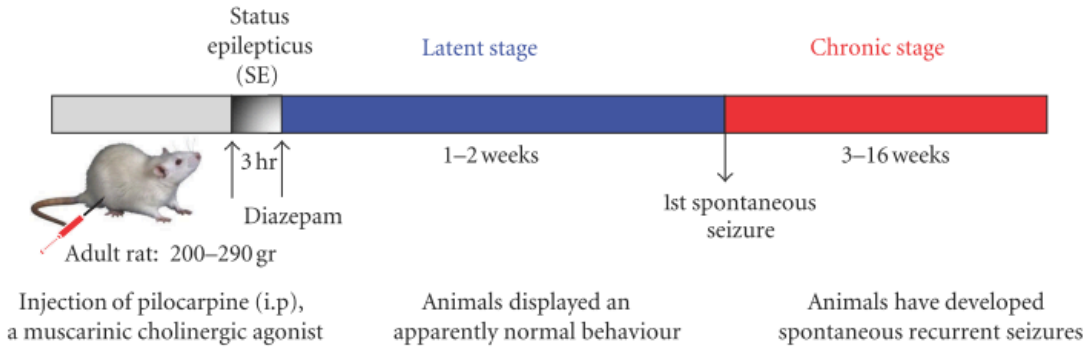

Figure 1. Intraperitoneal injection of pilocarpine in adult rat results in SE, which is then stopped by applying diazepam (which decreases the chance of the rat dying). A latent period of no abnormal behavior follows. The first spontaneous seizure marks the chronic stage, where SRS occur. Adopted from Ferhat 2012.

The SRS start to appear after a latent (seizure-free) period (Modebadze et al. 2016). This chemoconvulsant can be administered systemically (for example, intraperitoneally) or locally-intracerebrally (for example, intrahippocampal injections) (Mello et al. 1993), (De A. Furtado et al. 2002).

The pilocarpine model shows similarities to human TLE, such as cell loss in the dentate gyrus and in CA1 and CA3 areas of the hippocampus and synaptic alterations called mossy fiber sprouting, being the main cause of SRS. The sprouting appears in supragranular and

intragranular layers of the dentate gyrus. These similarities are making it a suitable model for the study of TLE in humans (Mello et al. 1993). One of the more recent adaptations of this model includes the Reduced Intensity Status Epilepticus (RISE) model of temporal lobe. Very positive attributes of this model are a significant decrease in mortality to 1% and reduced levels of neuronal damage in the hippocampus (Modebadze et al. 2016).

2.3 The kainic acid animal model

Kainic acid (KA) is structurally related to glutamate and therefore has an excitatory effect on neurons (Shinozaki and Konishi 1970). In this animal model, SE, which precedes the appearance of SRS, is also being brought on by this chemoconvulsant (Bertoglio et al. 2017). The common target of injection of KA is usually intracerebral, such as the amygdala or hippocampus (Ben-Ari, Tremblay, and Ottersen 1980), (Raedt et al. 2009). But it can also be applied intraperitoneally or intranasally (Hellier and Dudek 2005), (Zhang et al. 2008). The chosen type of administration brings different advantages and disadvantages (Figure 2).

	Advantages	Disadvantages
A) Intracerebral	• focal precision • relatively low mortality • reliability	• invasiveness • high labor-intensity
B) Intraperitoneal	• low labor-intensity	• no control over bioavailability • great variability • high mortality
C) Intranasal	• low labor-intensity • low mortality • effective for resistant strains	• no focal precision • requires higher doses

Figure 2. The benefits and limitations of each type of administration of KA. The intracerebral route is quite invasive but provides reliable and precise outcomes. The intraperitoneal route is less difficult to perform but the results may be more inconsistent. The intranasal route has low mortality but is not focally precise. Adopted from Rusina, Bernard, and Williamson 2021.

KA also has different effects (mortality, sensitivity to KA,...) depending on the animal's age, gender, and other aspects (Mikati et al. 2003), (Zhang et al. 2008). This animal model also

serves as a model of TLE, because it replicates the behavioral aspects in humans and the neurodegeneration in the hippocampus (Berger et al. 1990). Moreover, the KA model of TLE (in many cases, Mesial temporal lobe epilepsy=MTLE) is relevant for evaluating therapeutic interventions in epilepsy thanks to the study of its pathophysiology (Duveau et al. 2016). This model can be useful for examining how different treatments might influence the mechanisms of the development of this disease. By examining the different stages of epileptogenesis (SE, the acute phase immediately following SE, the latent phase, which is then followed by chronic epilepsy), researchers can observe how interventions affect the progression of the disease and potentially prevent its onset (Bertoglio et al. 2017).

2.4 Other animal models

As opposed to the pilocarpine and KA models, the tetanus toxin model exhibits an absence of SE (Ferecskó et al. 2015). As it was already mentioned, pilocarpine and KA can be administered systemically, but tetanus toxin requires a precise intracerebral injection, which might not always be as practical (Mello et al. 1993), (Hellier and Dudek 2005), (Ferecskó et al. 2015), (Nilsen, Walker, and Cock 2005). Even though the primary site of onset is focal (toxin is injected, for example, in the hippocampus), secondary generalization can occur (Ferecskó et al. 2015). The tetanus toxin model is useful for examining the mechanisms of seizures as well as new treatment strategies (Nilsen, Walker, and Cock 2005).

Another model worth mentioning is the Genetic Absence Epilepsy Rats from Strasbourg (GAERS). As the name already indicates, GAERS is a model of absence epilepsy (Islam and Abdullah 2014). Absence seizures are a type of generalized seizures, mostly affecting children (Scheffer et al. 2017), (Wirrell et al. 1997). They are characterized by episodes of impaired consciousness (Fisher et al. 2017). The electroencephalogram (EEG) of GAERS displays spike and wave discharges (SWDs) (Figure 3), (Islam and Abdullah 2014).

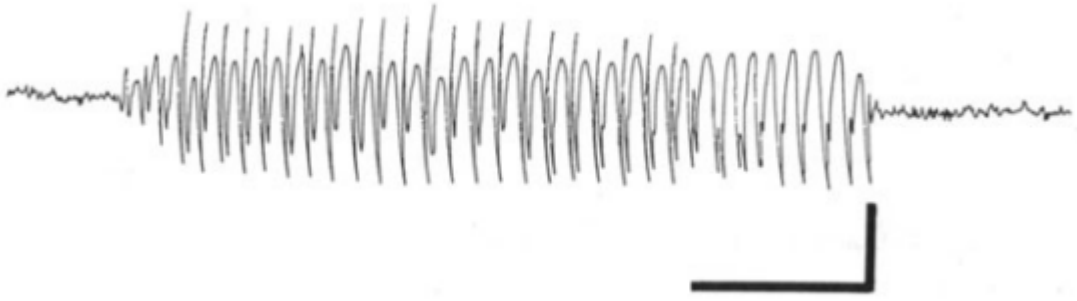

Figure 3. ,,Spontaneous cortical spike-and-wave discharge recorded in a GAERS. Calibration 1 s, 400 μV". Adopted from Marescaux, Vergnes, and Depaulis 1992.

This makes it a relevant model for investigating the mechanisms underlying absence seizures (Pinault, Vergnes, and Marescaux 2001). GAERS is a good subject for research on comorbidities related to absence epilepsy (Roebuck et al. 2020).

In utero electroporation (IUE) is a technique used to manipulate gene expression in the developing brain. It involves the delivery of plasmids into the embryo's ventricles via microcapillary pipettes, followed by the application of electrical pulses (Figure 4) (Ribierre et al. 2018), (Meyer-Dilhet and Courchet 2020). The plasmids encode fluorescent proteins that are introduced into the neural progenitor cells, which allows for the visualization of the morphology and migration of those cells (Hand and Polleux 2011). Depending on the positioning of the electrical field during electroporation, targeted transfer is enabled as the negatively charged DNA moves towards the positive electrode (Dal Maschio et al. 2012).

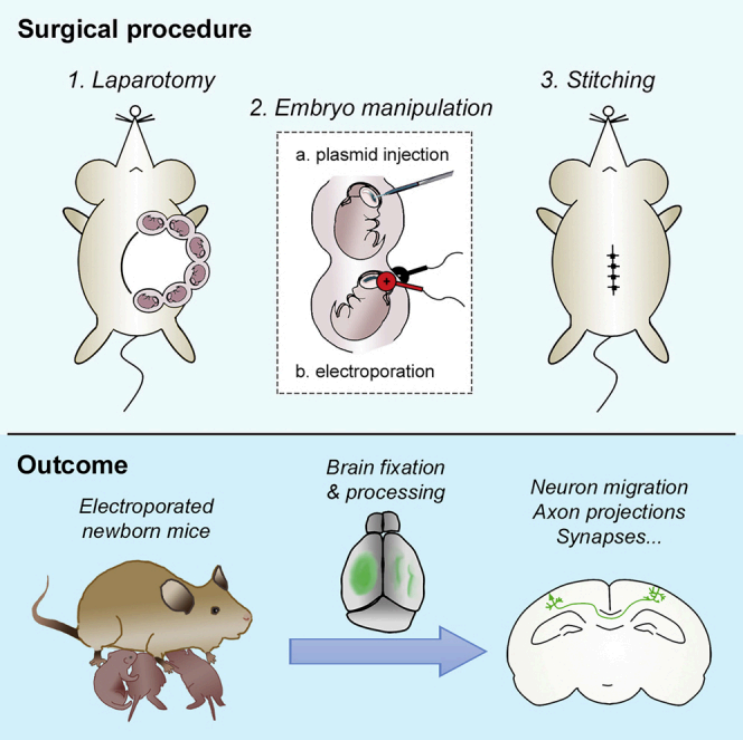

Figure 4. The procedure: 1) Embryos are carefully taken out of the abdominal cavity. 2) DNA plasmid is being injected into the lateral ventricle of the embryo, which is then electroporated (it is important that the anode is placed on the injected side). 3) The embryos are placed back into the abdomen, which is subsequently sewn together. The outcome: Electroporated mice are born. The migration of neurons with axonal and synaptic development can be then studied in brain slices. Adopted from Meyer-Dilhet and Courchet 2020.

During electroporation, the hippocampus or cortex are often the targeted regions (Pacary et al. 2012). Targeting the cortical region and electroporating genes that interfere with the mechanistic target of rapamycin (mTOR) pathway results in a malformation that mimics the pathology of FCDII (Ribierre et al. 2018). Focal cortical dysplasia type II (FCDII) is a lesion where dyslamination of the cortex appears and neurons take on a dysmorphic character, which mostly results in epilepsy (Blümcke et al. 2011). IUE based models are helpful for studying the neuropathological characteristics associated with this disorder (Ribierre et al. 2018).

Animal models of traumatic brain injury (TBI) are used to study post-traumatic epilepsy because they mimic the mechanisms of epilepsy development in humans after TBI. Despite the high mortality, they are quite important because epilepsy is likely to occur after some brain damage and injury (Kharatishvili et al. 2006).

2.5 *In vitro* models

In vitro models can be used for the research of epilepsy mechanisms and for studying the effects of ASDs. For example, rodent hippocampal slices can be used to test the efficacy of some ASDs. In a specific study, seizure-like events (SLEs) were triggered either by lowering the magnesium level in the liquid in which the slices were submerged or by blocking potassium channels in neurons (Albus, Wahab, and Heinemann 2008).

In another study, the entorhinal cortex slices of kainate-treated rats showed varying sensitivities to different ASDs. The ASD that has proved to be the most effective, was Ezogabine, which targets the potassium channels of neurons (West et al. 2018).

These techniques are useful for the study of mechanisms of the efficacy of ASDs, but they are limited to a small area of the tissue or even one synapse. In contrast, *in vivo*, the neurons are connected on a larger scale and can therefore respond differently. However, the effects of ASDs *in vivo* cannot necessarily be determined from their activity in *in vitro* systems (Hovinga 2002).

3. Behavioral manifestations of seizures in rodent models of epilepsy

Through observing and analyzing the behavioral responses of rodents during seizures, researchers can gain insights into the relationship between neural activity and behavior in the context of epilepsy (Powell et al. 2003). The way seizures manifest in animals in laboratory research often mirrors the diverse seizure types seen in humans, with behavioral expressions in

rodents sharing numerous similarities with human clinical seizure manifestations. Different seizure types in rodents exhibit distinct behavioral patterns, and assessing these manifestations allows for characterizing and differentiating between seizure types (Velíšková and Velíšek 2017).

By using a scoring system, the severity of seizures can be determined, aiding in understanding the progression and network involvement during seizures. Monitoring behavioral manifestations helps evaluate the efficacy of treatments in controlling or reducing seizure activity (Velíšková and Velíšek 2017).

3.1 Methods used to assess data

Data on the behavior of rodents during seizures can be acquired in various ways. One of those involves a person observing the animal within a strict time window and writing the behavior down on a scoring table. This table contains predetermined behavior that is expected to be observed (such as rearing or jaw tremor), as well as blank spaces for any unexpected behavior that may occur. Subsequently, the collected data from the scoring tables is then further evaluated (Kelley 1998).

Another way of obtaining data about the behavior is by simultaneously using the EEG activity and video recordings of the rodent during seizures. This helps assess the correlation between behavior and brain activity (Van Erum, Van Dam, and De Deyn 2019). Therefore, the significance of EEG cannot be omitted.

Certain behavioral manifestations may not necessarily indicate epileptic seizures. For instance, while injections of KA serve as a tool for animal models of epilepsy, they are also utilized in animal models of dystonia. Dystonia presents with abnormal postures and twisting motions that lack synchronicity. EEG is helpful for distinguishing dystonia from epileptic seizures, as it does not show any epileptiform activity during dystonic episodes (Pizoli et al. 2002).

Relying solely on the behavioral aspect of seizures without EEG recordings might result in misinterpretation of the epileptic condition and not identifying the onset of seizures correctly as well as the spread of seizure activity in the brain. Correlating EEG patterns with observable behaviors likely reflects the underlying pathophysiology and can provide valuable insights into seizure mechanisms (Phelan et al. 2015).

3.2 Behavioral manifestations of seizures in the kindling model

Thanks to the data obtained from the electrical kindling of the amygdala, a scale was created by Ronald J. Racine. This scale is divided into five categories based on the severity of the semiology. These are the following stages introduced by Racine (1972): „(1) Mouth and facial movements. (2) Head nodding. (3) Forelimb clonus. (4) Rearing. (5) Rearing and falling." This scale is still in use with numerous alterations in various studies, as certain seizure behaviors may differ from the original descriptions or may not be observed at all (Van Erum, Van Dam, and De Deyn 2019). For example, in a study where rapid kindling, utilizing only a subthreshold stimulation intensity of 50 Hz, was applied, the Racine scale was updated. In this study, the scale was expanded by adding R0, representing a stage where there is no disruption of usual behavior. Additionally, the forelimb clonus was further divided into phases R3, representing the unilateral clonus of the limbs, and R4, representing the bilateral clonus with rearing. In R5, it was also specified that tonic-clonic movements of all limbs occur (Morales et al. 2014). The tonic part is usually considered to be the most severe part. It is characterized by flexing and extending the limbs (Van Erum, Van Dam, and De Deyn 2019), (Sabnis et al. 2024).

In chemically (specifically PTZ) induced kindling in mice, a revised scale of behavior and EEG correlation was created (Figure 5).

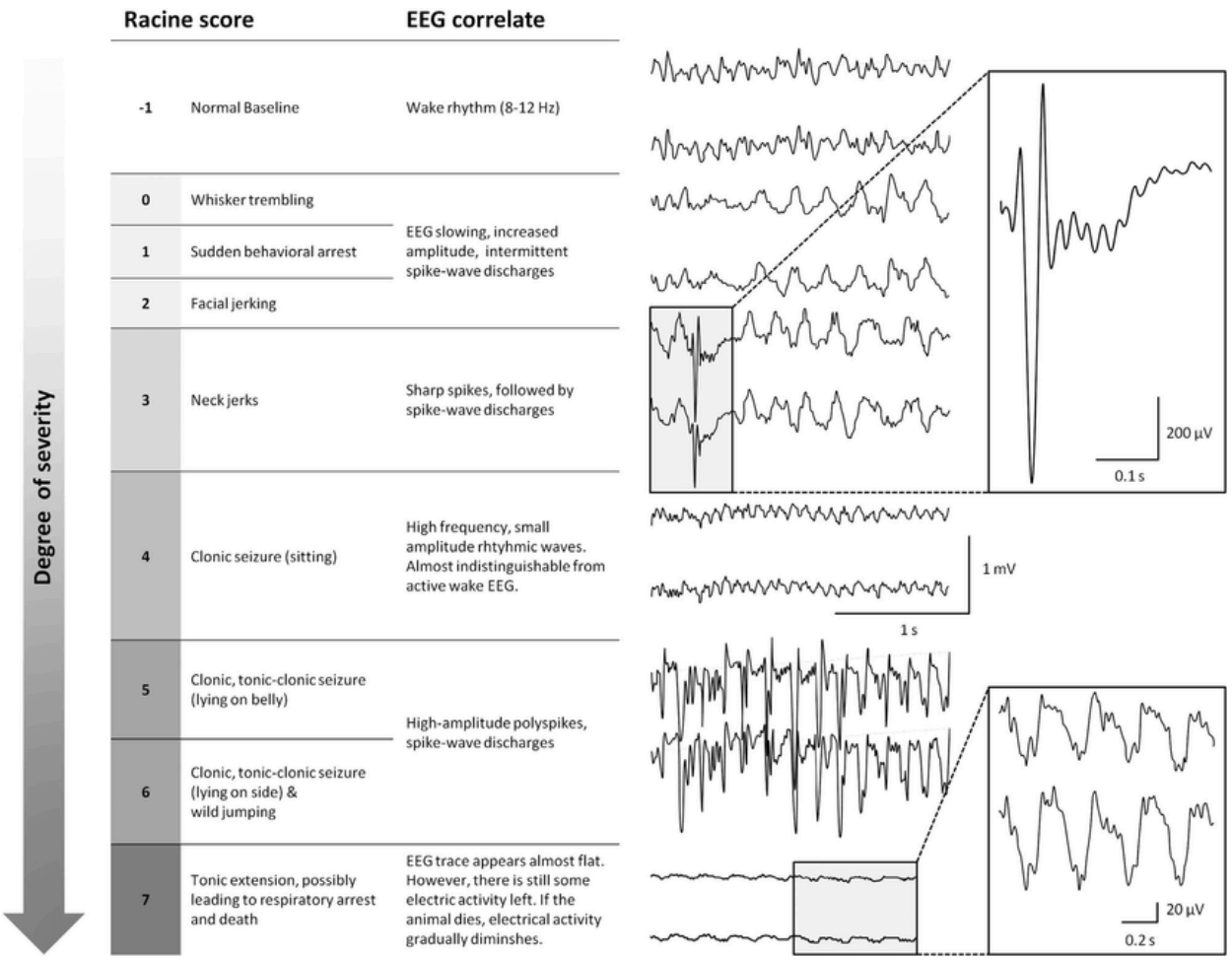

Figure 5. On this scale, scores 0-2 signify focal seizures, while stages 3-6 signify generalized seizures. The highest phase, 7, can be fatal for the animal. Adopted from Van Erum, Van Dam, and De Deyn 2019.

Wild running can also be observed in rats that have been kindled by audio stimulation. This time, the running phase is one of the early manifestations, which can then progress into a clonic phase, which consists of the same features that were established by Racine. The audiogenic kindling process involves a combination of focal and generalized seizure characteristics in rats. The focal aspect is characterized by the direction of running, which corresponds to the unilateral neuronal depolarization cascade in the cortex (Vinogradova, Vinogradov, and Kuznetsova 2006).

Kindling can also be used to create a model for neocortical epilepsy through optogenetics. The rodents in this model exhibit similar semiology to the previously mentioned

ones. The most severe score, labeled as number 6, includes wild running and vocal sounds (Cela et al. 2019).

3.3 Behavioral manifestations of seizures in the pilocarpine model

The pilocarpine animal model is distinguished by inducing SE, during which behavioral arrest, facial automatisms, and head bobbing occur (Phelan et al. 2015). When it comes to a site of administration, when animals are injected locally, their seizures can get generalized less often, as they are more localized for example in the hippocampus and other limbic areas, (Clifford et al. 1987). The Racine scale (which can be modified) is often used to score the behavioral manifestations of the pilocarpine model. A score of 3, bilateral forelimb clonus, can be used as a threshold to indicate that an animal is experiencing SRS (Modebadze et al. 2016). The scale can also be enriched with grooming, scratching, and wet dog shakes for score 1 and trembling for score 2 (Meurs et al. 2006). The tonic phase of the seizure is often connected to the death of the animal (Phelan et al. 2015).

3.4 Behavioral manifestations in the kainic acid model

As it was already mentioned, animals injected with KA initially experience SE, during which they exhibit behavioral arrest and clonic seizures (Raedt et al. 2009), (Bertoglio et al. 2017). However, the behavioral aspects of SE can become severe, including behaviors like wild running and jumping, and SE must be stopped by ASDs (which should prevent the rodent from dying) (Raedt et al. 2009).

The semiology of spontaneous seizures after the latent period can be assessed using a modified version of the Racine scale (Raedt et al. 2009). Once again, the seizures are categorized into groups based on their severity. Severity stages 1 and 2 contain immobility, automatisms (such as chewing), head nodding, or facial clonus. Stage 3 involves the unilateral clonus of a forelimb; stage 4 involves a clonus that occurs symmetrically on both of the forelimbs and rearing; and stage 5 involves tonic-clonic seizures and falling. The numbers of the stages can slightly differ, depending on a concrete study (Raedt et al. 2009), (Mouri et al. 2008). Rats injected locally with KA can also experience barrel rolling (the body twists around its length, where the back turns toward the side of the injection = ipsilaterally) (Vécsei and Flint Beal 1991). Straub tail (erect tail) can also occur during seizures (Mouri et al. 2008).

Gender and age differences can be observed, with older female mice experiencing a more severe course of seizures, characterized by severe clonic seizures and an increased frequency of rearing and falling (Zhang et al. 2008).

3.5 Behavioral manifestations in other animal models

In the tetanus toxin animal model, seizures typically begin to manifest after a latent period of approximately one to two weeks. The behavioral characteristics of the seizures include staring and automatic mouth or sniffing movements. These seizures develop into unilateral or bilateral forepaw clonus, rearing, falling, and tonic-clonic episodes. Eventually, the rodents can often finish by having wet dog shakes (Jiruska et al. 2013).

In rodent models exhibiting absence epilepsy, seizures are characterized by behavioral arrest, which consists of a sudden stop of activity and a reduction in consciousness (Taylor et al. 2019). Stargazer mutant mice resemble absence epilepsy with additional dyskinetic motor characteristics. These characteristics include circling to the sides, hyperactivity, and head swinging horizontally and vertically (Khan et al. 2004).

In animal models of cortical malformations, for example, the telencephalic internal structural heterotopia mutant (tish) rat, the behavior during seizures was described as twitching of the face and limbs and one-sided turning of the rat's body, with occasional cases of falling followed by convulsions (Chen et al. 2000).

One study demonstrated that in rodents with FCD II pathology, the focal origin of seizures is the electroporated cortical region, but they manifest contralaterally as tonic limb contractions.(Ribierre et al. 2018). Other semiology can also be behavioral arrest, tonus of the body, and contralateral clonus, but the manifestations can be quite variable (Hu et al. 2018). The spontaneous tonic-clonic seizures of these rodents can lead to sudden unexpected death in epilepsy (SUDEP). Research on SUDEP highlights the importance of uncovering the physiological pathways behind this condition, which may later help to develop preventive strategies for human patients (Ribierre et al. 2018).

The animal models of TBI can have a very similar semiology of spontaneous seizures to the one described in the Racine scale (Kharatishvili et al. 2006). But that is not always the case. The behavioral manifestations of seizures can also begin with jumping, followed by clonic and tonic clonus, and in some cases, running; whisker and tail spasms can also be present (Komoltsev et al. 2020).

4. Behavioral manifestations of seizures in human epilepsy

Evaluating the behavioral manifestations during seizures in epilepsy patients helps classifying them into seizure types (focal, generalized and unknown onset). The observed seizure semiology combined with possible additional neurological medical disorders, EEG, neuroimaging, and other diagnostic tests can help achieve a more accurate classification (Boßelmann 2021). This helps direct the choice of appropriate ASDs and helps identify suitable candidates for epilepsy surgery, which may be undergone by drug refractory patients (Boßelmann 2021), (Sutula et al. 1989).

A seizure can either be observable (motor signs), or as a subjective sensation, called an aura. Subjective seizure symptoms can only be described by the patient themselves. The symptoms exhibited during a seizure offer insights into the seizure onset site and the site where the observable symptoms arise from, which are components of the epileptogenic zone. This lateralizing and localizing is valuable when assessing epilepsy patients for potential surgical treatment (Boßelmann 2021).

4.1 Temporal lobe epilepsy

The first type of human TLE, mesial temporal lobe epilepsy (MTLE), usually involves hippocampus and amygdala (entorhinal and perirhinal cortex can also be affected) (Bernasconi 2003). MTLE is often characterized by hippocampal sclerosis (Figure 6), which consists of reorganization of mossy fibers and their synapses, neuronal loss and hypertrophy of glial cells (Cavazos, Golarai, and Sutula 1991), (Zhu et al. 2023).

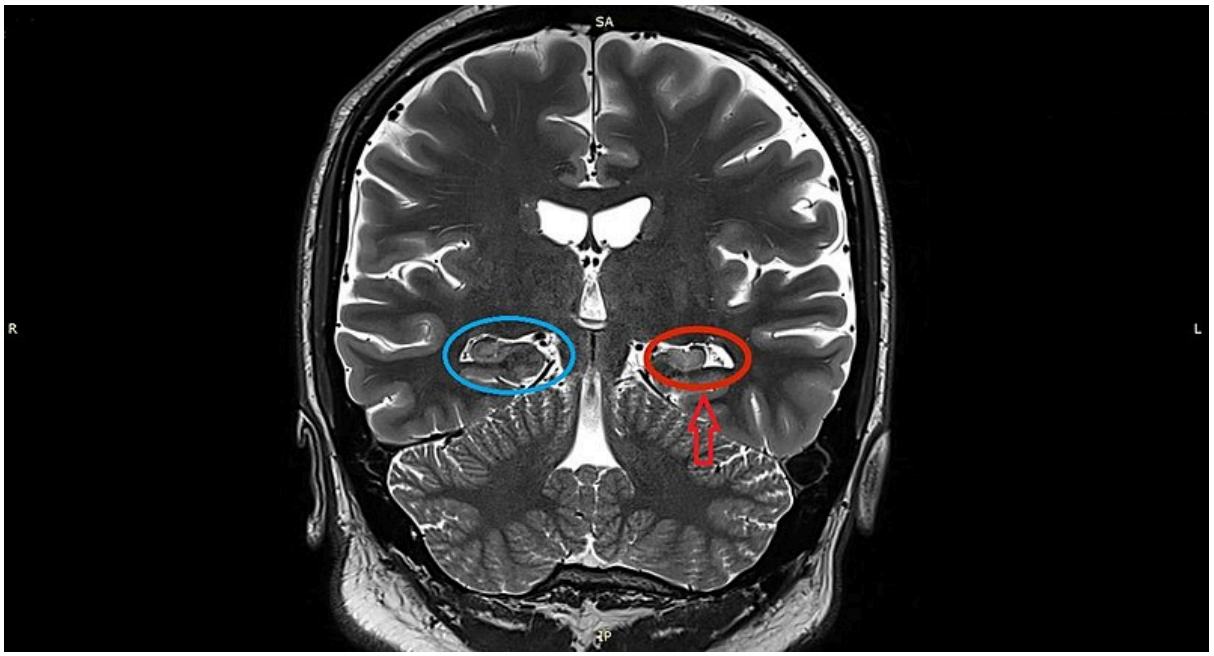

Figure 6. The hippocampal sclerosis on the left side of the brain (red circle) depicted on MRI. The hippocampus is visibly smaller. Adopted from Uhomachinky, CC BY-SA 4.0 <https://creativecommons.org/licenses/by-sa/4.0>, via Wikimedia Commons

In the second case, the site of onset can also be in the temporal neocortex (NTLE) (Zhu et al. 2023).

At the onset of a seizure, there may be an occurrence of an aura, which can consist of an epigastric and chest feeling, warmth spreading upward the arms, unpleasant emotions (fear, anger, guilt), dreamy state, déjà vu, and sensory illusions or hallucinations (Gloor et al. 1982), (Maillard et al. 2004). The reason why there is an emotional component in an aura is because the limbic structures such as the amygdala, which are responsible for emotions, are commonly involved (Biraben 2001). An aura is then often followed by a loss of responsiveness and consciousness. During the seizure, patients can also experience a variety of automatisms, such as involuntary movements involving the mouth, which can be eating-related; arm movements; and vocal automatisms. Eye or head version and tonus of the arms can also be present (Biraben 2001), (Maillard et al. 2004). Secondary generalization with tonic-clonic seizures is more frequent in males (Janszky 2004). Postictally, language impairment and the inability to recall the event can occur (Maillard et al. 2004).

The semiology can differ based on the side of the brain affected and whether neocortical or medial sides of the lobe are affected. For example, patients experience fear and exhibit verbal

or vocal automatisms only when the medial temporal lobe is affected. Moreover, seizures in MTLE tend to have a longer duration compared to those in NTLE (Maillard et al. 2004).

When it comes to the laterality, in a study involving 60 patients researchers examined where symptoms occurred within the brain in relation to their focal onset. For those suffering with MTLE, the dystonic posturing was mainly contralateral to the site of onset, whereas motor automatisms were mostly ipsilateral to the site of onset of the seizures. In patients with NTLE, the dystonic posturing was ipsilateral and the motor automatisms were contralateral. These differences in laterality may be helpful for distinguishing between those two types of TLE (Dupont et al. 1999).

4.2 Absence epilepsy

Although absence seizures are typically considered a type of generalized seizure with spike-and-wave patterns on EEG, they do not affect all parts of the brain equally. These seizures can be bilateral but may not engage every brain network (Scheffer et al. 2017). There are also instances where they can manifest with a focal onset. The epileptogenic zone includes the cortical networks, primarily in the frontal areas of the brain, which have extensive connections with the thalamus (Aguilar-Fabré et al. 2022).

Besides a loss of consciousness, one of the most significant characteristics of absence seizure is eyelid myoclonia (Thomas, Valton, and Genton 2006), (Fisher et al. 2017). The seizure manifestations can also include automatisms and head and eye versions. More rarely, the motor seizure activity, such as myoclonic jerks and tonic-clonic phases, can also appear during seizures (Thomas, Valton, and Genton 2006).

Childhood absence epilepsy is more frequent in females than males (Asadi-Pooya, Emami, and Nikseresht 2012). The SWD rhythmicity in human patients is of approximately 3Hz, whereas in rodent models of absence epilepsy, it is around 8Hz (Thomas, Valton, and Genton 2006), (Medvedeva et al. 2020).

4.3 Focal cortical dysplasia type II

FCD II is a lesion with cortical dyslamination, which has two subdivisions, in which the first one, type a, is characterized by neurons with disrupted morphology, such as enlarged soma and nucleus of the cell, and neurofilament protein buildup in the cytoplasm. In addition to the dysmorphic cells, type b is also characterized by balloon cells, which have enlarged soma as

well and more than one nuclei (Blümcke et al. 2011). The boundary between white and gray matter can be observed as blurred in FCD II (Figure 7) (Sheikh et al. 2023).

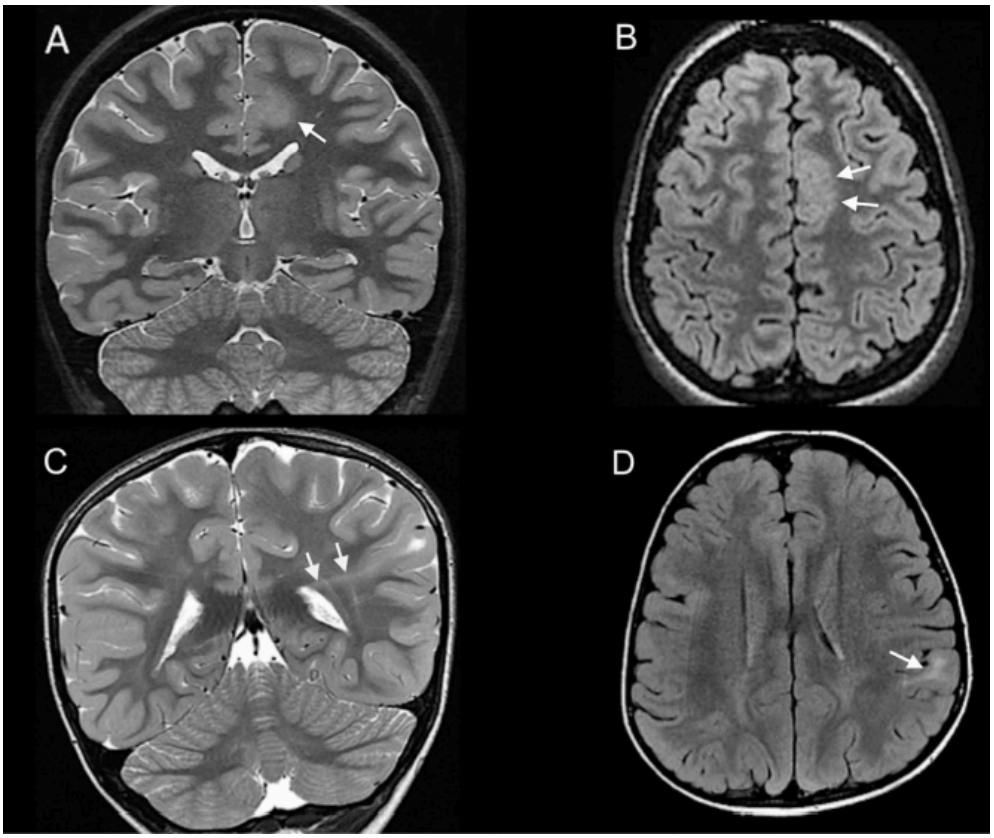

Figure 7. The FCD II type a is depicted in A and B, where the white arrows point on the zones where the white and gray matter lineage becomes blurred. In panels C and D, FCD II type b is depicted with T2 hypersensitivity - structural abnormalities, again, shown by white arrows. Adopted from Desikan and Barkovich 2016.

The behavioral manifestations during seizures vary depending on the location of the lesion within the cortex (Chassoux et al. 2012). Most frequently, the lesion occurs in the frontal lobe (Widdess-Walsh et al. 2005), (Schuch et al. 2023).

The common characteristics among patients of FCD II are that the seizures often arise during sleep (Jin et al. 2018), (Sheikh et al. 2023). The seizures can manifest as secondarily generalized tonic-clonic convulsions, but in some patients it can happen only a few times a year (Sheikh et al. 2023), (Mao et al. 2019). At the beginning of a seizure, there may be an appearance of an aura (Jin et al. 2018). Some patients may also experience numb feeling in arms and legs, uncomfortable feeling in the stomach, loss of consciousness, vocal manifestations, lateralized clonic movements of one hand, tonic extension of one arm creating a „figure of four“

appearance and post-seizure exhaustion (Mao et al. 2019), (Sheikh et al. 2023). The way seizures manifest in a patient can change over the years (Mao et al. 2019).

4.4 Post-traumatic epilepsy

The most frequent causes of TBI are by car accidents and injuries by falling (Gupta et al. 2014). If patients develop epilepsy from head trauma, the onset of seizures can occur anywhere from days to over a year after the injury (Vespa et al. 1999), (Gupta et al. 2014). The highest risk of developing epilepsy after a TBI is during the first year (Yeh et al. 2013).

Epilepsies resulting from brain trauma most usually affect the temporal lobe or the frontal lobe. But there also can be an occurrence of more than one epileptogenic zone, where the other zones create microseizures, which do not manifest behaviorally and cannot be identified by scalp electrodes (Gupta et al. 2014).

The behavioral manifestations during seizures in post-traumatic epilepsy (PTE) patients can be presented by rapid movement of the eyes, flickering of the eyelids, facial automatisms, and rhythmic muscle spasms. A focal seizure may evolve into a secondary generalized tonic-clonic seizure (Vespa et al. 1999). Some patients may also experience SE, which can last for several minutes and may be fatal, especially when it is combined with brain injury (Arndt et al. 2013), (Vespa et al. 1999). In a study of TBI in children, the seizure semiology most frequently consisted of clonus of the arms and legs, eye and head version, automatic motor movements, and tonic-clonic convulsions (Park, DeLozier, and Chugani 2021).

4.5 Semiology similarities in humans and animal models of epilepsy

As it is visible in the chapter about the semiology in distinct animal models, the severity of seizures in rodent models for TLE is measured by the Racine scale and its modified versions. The essence of the progression remains the same, meaning that the least severe manifestations are often facial movements and behavioral arrest, whereas the most severe are tonic-clonic seizures (Raedt et al. 2009), (Ngoupaye et al. 2022). In humans with TLE, we can observe a similar progression, where seizures can start with aura and focal seizures and progress to far more severe manifestations of generalized seizures (Maillard et al. 2004).

Genetically predisposed rodents that are exposed to audio stimulation experience seizures characterized by wild running, tonic-clonic seizures, and high seizure susceptibility (Vinogradova, Vinogradov, and Kuznetsova 2006), (Kulikov et al. 2021), (Vergnes et al. 1987). Reflex epilepsy in humans triggered by sound leads to similar seizure types, with tonic-clonic

seizure type included (Al‐Attas, Al Anazi, and Swailem 2021). There are also other animal models for reflex epilepsy, such as photosensitivity, but these are usually not rodent models (Douaud et al. 2011).

When it comes to absence epilepsy, the presence of SWDs and similar behavioral symptoms in both rodents and humans represent the validity of these models for studying absence epilepsy (Thomas, Valton, and Genton 2006), (Medvedeva et al. 2020).

In humans, FCD II manifests with motor patterns and frequent nocturnal seizures (Sheikh et al. 2023), (Jin et al. 2018). Animal models mimic the structural abnormalities and seizure patterns, which is ideal for studying the genetic and developmental aspects of FCD (Ribierre et al. 2018). These models exhibit a variable semiology, highlighting the variability also observed in human patients. But there is a need for further research to explore the complexities of FCD and the seizure variability associated with it (Hu et al., 2018).

Post-TBI epilepsy in humans can lead to a variety of seizure types, including SE (Arndt et al. 2013). Animal models replicate the injury and subsequent epileptogenesis, helping to understand the mechanisms (Kharatishvili et al. 2006).

5. Conclusion

Epilepsy is a disorder that profoundly affects the life of those who suffer from it, not only during seizures, but also socially due to the possible comorbidities, yet current ASDs are only effective in ⅓ of cases. Therefore there is a considerable amount of ASDs that are available, and new ones are continually being developed.

Animal models play an important role in the research and drug development process. They offer a controlled environment to study the progression of epilepsy from the insult to chronic epilepsy. By replicating specific etiologies (such as genetic mutations, trauma, or cortical malformations) and targeting specific brain regions, these models provide valuable insights into the mechanisms of epilepsy.

The aim of this thesis was to compare the behavioral semiology of seizures in animal models (experimental observations) and human patients (clinical observations), focusing on well characterized models such as electrical and audiogenic kindling, chemical induction (using pilocarpine, KA and tetanus toxin), those with cortical malformations and TBI. These and many other models show a variety of seizure types, many of which parallel the semiology in human epilepsy.

In the animal models, most often the Racine scale was used to categorize severity of the seizures. In some cases, there can be an occurence of additional behavior, such as wild running or wet dog shakes. Human behavioral manifestations during seizures in conditions such as TLE, absence epilepsy, FCD II and PTE, provide information for localizing seizure onset and planning future treatment strategies.

This thesis provides similarities (seizure severity, the main seizure stages) and differences (more detailed manifestations such as whisker trembling for animals or aura for humans) between the observed semiology of rodent models and human patients. This comparative approach is essential for translating animal research into successful clinical applications, ultimately benefiting patients with epilepsy by improving diagnostic accuracy and therapeutic efficacy.

In addition to addressing the treatment of epilepsy symptoms, the potential for treating epilepsy as a whole was also mentioned in this thesis. Current scientific research is also focused on the discovery of possible effective treatments of epilepsy. Understanding the mechanisms of epilepsy development is fundamental for this achievement, and luckily animal models do provide these insights. Although it is still in early stages for applying these findings on human treatments, a promising approach is to administer preventative treatments to patients who have suffered from TBI and are at high risk of developing epilepsy. Therefore, one of the targets for future studies could be the identification of a reliable biomarker that would predict, as early as possible, the development of epilepsy following an initial insult and prevent the progression to chronic epilepsy.

Though animal models of epilepsy cannot fully mimic the natural condition of human epilepsy (as they are more stereotyped and not as complex), they are still useful in understanding the disease's mechanisms and in testing treatment options. Continued development in research into these models of epilepsy is crucial to advancing our ability to treat epilepsy and to improve the quality of life of those living with such a debilitating condition.

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