

## Seizures (mice)

*Behavior name: Seizures / Convulsions*

### *Description of behavior:*

A seizure or convulsion is generally defined as a sudden, violent, uncontrollable contraction of a group of muscles. However, a seizure can also be more subtle, consisting of only a brief "loss of contact" or a few moments that can be characterized as "daydreaming".

Because of the wide variety of seizures and convulsions that exists in humans and the direct relation between seizures and epilepsy, the International League Against Epilepsy (ILEA) defined and grouped the seizures according to an internationally accepted scheme in 1981. The main classifications are currently:

1. Partial Seizures or Focal Seizures (indicating that it originates in a part of the brain)
2. Generalized Seizures (indicating that the entire brain is involved)
3. Continuous Seizures (indicating a continuous state of seizures)

### *Limbic seizures in mice*

When limbic seizures are observed in rodents (such as rats and mice), the classification of the seizures is often done on the Racine grading scale (called after Ronald J. Racine who was one of the first to classify the seizure intensity by grading the seizures in 1972). The Racine scale has 5 grades, although some researchers refer to 6 grades by including grade 0 on the grading scale. The Racine grading scale for limbic seizures is defined as follows:

- 0 = **Immobility**  
No presence of visual seizures. In seizure related tests, the animal is sitting still and without motor manifestations.
- 1 = **Mouth movements and facial movements**  
The animal shows small twitches in the orofacial region which can be characterized as involuntary mouth and facial movements. The last one is often referred to as facial twitches.
- 2 = **Head nodding / clonic head movements**  
The animal shows slow involuntary and repetitive up and backward head movements (nodding) which is often referred to as Clonic Head movements.
- 3 = **Forelimb clonus / clonic forelimb movements**  
The animal shows uncontrolled repetitive movements of the forelimbs while in a sitting position. The movements start with unilateral forelimb movements, which are normally followed by contra-lateral or bilateral movements of the forelimbs.
- 4 = **Rearing with bilateral forelimb clonus**  
The animal is rearing (standing up position) and shows clonic bilateral forelimb movements (kangaroo posture).
- 5 = **Rearing and falling with bilateral forelimb clonus**  
The animal is rearing and making clonic bilateral forelimb movements, but is losing postural control and balance and falling-down (often tumbling backwards). This category of full-grown seizures is also called generalized motor convulsions because they affect many muscles and involve the entire brain.

*\* during grade 2 & 3 the animal can also produce sounds (this can be normal or ultrasound)*

### *Tonic-clonic seizures in mice*

The tonic-clonic seizure is a generalized seizure (sometimes also called the grand mal seizure) that has a tonic and a clonic phase and is the most commonly seizure that is associated with epilepsy. In the tonic phase the body of the animal is entirely rigid (when rearing the animal often falls backwards), and in the clonic phase there is uncontrolled jerking of the forelimbs and often also the hind limbs.

To score the different stages preceding and occurring during the tonic-clonic seizure, an adjusted Racine scale is sometimes applied.

### *Barrel-rolls in mice*

Barrel rolls are an extreme form of generalized seizures in which the animal is rolling over the head-tail axis, often combined with running and jumping behavior. It is the most severe form of seizures that can be observed and can be evoked by PTZ or electrical stimulation.

LABORAS is validated to detect the Racine grade 4 and grade 5 seizures in a reliable and consistent way. The validation was based on corneal electroshock induced seizures.

A separate software module was developed for LABORAS to detect tonic-clonic seizures and barrel roll seizures. The detection of these seizure types was validated and found reliable, based on PTZ induced seizures.

### *Context to other behaviors:*

If the seizures evolve in Racine type 5 (full-grown generalized seizures) they can lead to extreme movements and often occur together with running, jumping and rolling-over.

The smaller, Racine type 2 (orofacial seizures) can show similarities with some aspects of purposeless chewing

Depending on the cause of the seizure, the seizures often evolve from a less to a more extreme type of seizure over time, but not necessarily reach the most extreme form.

### *Pharmacological relevance:*

Seizures are often investigated in relation to epilepsy. Epilepsy is one of the most common neurological disorders and shows major clinic syndromes such as spontaneous recurrent seizures (SRS). A common form of epilepsy is temporal lobe epilepsy (TLE), with about two-third of the patients having intractable seizures and memory problems while its mechanism is unclear.

There are many animals models for epilepsy that are based on induced seizures. Classical screening tests are:

#### 1) **Kindling model**

In the Kindling model, the duration and behavioral involvement of induced seizures increases after seizures are induced repeatedly. After repeated subconvulsive stimuli seizures begin to occur spontaneously. The animal is then called a fully kindled animal. The stimuli are often electrical (electrode connected to parts of the brain, often the Amygdala, but also the Cortex and Hippocampus) or with chemicals (most often pentylenetetrazol –PTZ).

Although the Kindling model is used in many epilepsy studies, it is heavily debated how

- this models furthers our understanding of human epilepsy (such as contribution of genetics, seizure susceptibility, and the underlying pathophysiology of epilepsy).
- 2) **Electroshock induced seizures**  
A few electrical induced seizures are the Corneal Electroshock on the eyes (electrodes have corneal cups at the end that soaked in saline), the Transauricular Electroshock (same but electrodes connected from ear to ear) and the Supramaximal Electroshock – MES (corneal electroshock that is 5 to 7 times the threshold current, leading to severe tonic-clonic seizures).
  - 3) **Subcutaneous Pentylentetrazol (sc-PTZ) induced seizures**  
PTZ when administered in a sufficiently high dose can produce a continuum of seizure activity that progresses from mild to full tonic extension of both forelimbs and hindlimbs. The behavioral seizure is quite consistent with the human seizures and provides a reproducible and predictable seizure that can be quantitated.
  - 4) **Subcutaneous Bicuculline and Picrotoxin induced seizures**  
In addition to PTZ, two other commonly employed chemoconvulsants include bicuculline and picrotoxin. The seizures that are evoked are for the most part indistinguishable from that produced by sc. PTZ. Despite this similarity it is known that the efficacy of some drug against PTZ seizures is not the same for Bicuculline and PicroToxin induced seizures even though their effect exerts through an interaction with the GABA receptor.
  - 5) **Kainic Acid (KA) and Pilocarpine induced seizures**  
Two more compounds that are used to induce seizures are Kainic Acid and Pilocarpine . Both are able to mimic complex human partial seizures when systemic administration in a high dose. A single injection of a convulsive dose of KA results in limbic status epilepticus, which is followed by longterm SRS as well as spatial learning impairments.
  - 6) **Sound induced or Audiogenic seizures**  
Sound-induced or audiogenic seizures are generalized convulsions elicited by intense auditory stimulation. Although rarely observed in humans, they have been reported to occur in a variety of rodent species and are currently one of the most widely studied animal models of human reflex epilepsies.