Neuro-Cognitive Comorbidities in Rats with Absence Epilepsy

Subjects: Neurosciences

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Absence epilepsy is a non-convulsive type of epilepsy characterized by the sudden loss of awareness. It is associated with thalamo-cortical impairment, which may cause neuropsychiatric and neurocognitive problems. Rats with spontaneous absence-like seizures are widely used as in vivo genetic models for absence epilepsy; they display behavioral and cognitive problems similar to epilepsy in humans, such as genetic absence epilepsy rats from Strasbourg (GAERS) and Wistar Albino rats from Rijswijk (WAG/Rij). Depression- and anxiety-like behaviors were apparent in GAERS, but no anxiety symptoms were found in WAG/Rij rats. Deficits in executive functions and memory impairment in WAG/Rij rats, i.e., cognitive comorbidities, were linked to the severity of epilepsy. Wistar rats can develop spontaneous seizures in adulthood, so caution is advised when using them as a control epileptic strain.

genetic animal models | spontaneous absence epilepsy | drug-naive rats

1. Introduction

The International League Against Epilepsy and the International Bureau for Epilepsy define epilepsy as a neurological disorder characterized by an ongoing propensity to experience epileptic seizures and by the neurobiological, cognitive, psychological, and social implications of this condition [1][2][3]. Consequently, there is a considerable concern regarding the link between epilepsy and a range of neuropsychiatric comorbidities, such as anxiety, depression, and attention-deficit/hyperactivity disorder.

Absence epilepsy is a non-convulsive type of epilepsy characterized by the sudden temporary loss of awareness or consciousness [4][5]. Absence epilepsy is less common than the convulsive type of epilepsy, but it can be just as dangerous if not treated. In view of the fact that absence seizures can occur without warning, they can be extremely frightening for patients and their families [4][6][7][8].

Absence seizures are caused by excessive excitation and hyper-synchronization of the thalamocortical system [9][10][11][12][13][14][15]. This system is incredibly complex and huge, containing over a million neurons and with connections to over a hundred different areas of the brain [10][16][17][18]. **Figure 1** shows the schema of the thalamo-cortical system. There are three major parts in the cortico-thalamo-cortical loop [17][19][20][21][22][23]: the pyramidal cells of the neocortex (**Figure 1**, green pyramids), which are excitatory neurons; the thalamocortical neurons of the relay and high-order thalamic nuclei, which are also excitatory neurons; the inhibitory neurons of the reticular thalamic nucleus. Cortical pyramidal neurons excite neurons in the relay thalamic nuclei (brown neurons in **Figure**

1) and inhibitory neurons of the reticular thalamic nucleus (blue neurons in **Figure 1**). The reticular thalamic nucleus intermittently inhibits thalamocortical cells. Thalamocortical cells provide excitatory feedback to the cortex and to the reticular thalamic nucleus [23][24]. Thus, the thalamocortical system generates sleep spindle oscillations and spike-wave discharges (SWDs) [10][12][21][22][25][26]. Dysfunction of the thalamocortical network could underlie cognitive comorbidities, as suggested by the concept of thalamocortical dysrhythmia [27][28] and the concept of the cognitive thalamus.

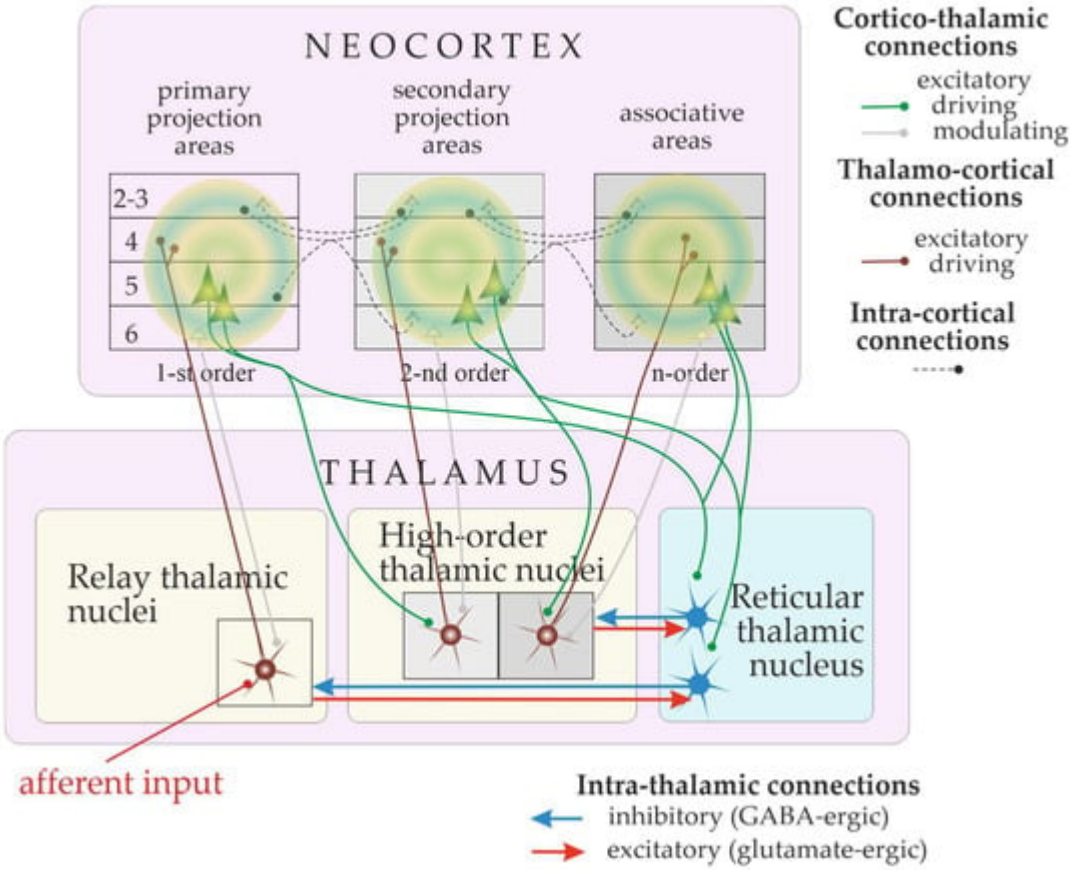

Figure 1. Schematic representation of the thalamocortical system. The loop is activated by external stimulus (afferent input). Thalamo-cortical ascending connections are shown in brown. Cortico-thalamic descending connections are shown in green (driving inputs) and gray (modulatory inputs). The terminology is from [16].

SWDs are recognized as hallmarks of absence epilepsy in human and rat models [3][29][30][31][32]. The primary dysfunctions in information processing in the thalamocortical circuitry are associated with a variety of cognitive problems, such as executive function problems, attention deficit, thought problems, and many others [6][33][34][35][36].

A number of clinical studies have demonstrated that absence epilepsy is associated with some cognitive comorbidities, such as executive dysfunction, memory deficits, and impairment of visual-perceptual skills [6][34][35][36]. It is challenging to determine the effect of absence seizures on cognitive functioning, as the outcomes in various patient groups are inconsistent and may be influenced by medication. Therefore, genetic rat models with

spontaneous absence seizures offer a valuable opportunity to better understand the neurocognitive comorbidities associated with absence seizures in humans.

Spontaneous absence seizures in genetic rat models could only be detected using electroencephalogram (EEG) through the presence of high-voltage spike-wave discharges (SWDs) [37][38][39]. The monitoring of EEG in freely moving rats requires chronically implanted electrodes, which is rather invasive.

2. Genetic Rat Models

In vivo animal models are essential for basic research on human diseases, preclinical studies, and the development of new medications [37][40][41][42][43][44]. There are two major types of animal models of neuropsychiatric disorders [40] and epilepsy: (1) the induced/experimental models, in which a pathological condition is induced through mechanical, chemical, or electrical means (e.g., kindling and pharmacological models of epilepsy); (2) the natural/genetic models, in which pathological processes are genetically predetermined, e.g., genetic rat models of absence epilepsy. Both types of animal models display behavioral and cognitive comorbidities. For the induced/experimental animal models of acquired epilepsy (i.e., the first type), neurobehavioral comorbidities have recently been systematically reviewed by W. Löscher and C. Stafstrom [45].

Some rat strains are known to display inheritable disorders of the nervous system and are used as models for human diseases, like depression (Wistar–Kyoto rats [46][47][48][49] and Flinders Sensitive Line rats [50][51]), schizophrenia (Brattleboro rats, spontaneous hypertensive rats, apomorphine-susceptible rats [52]), and absence epilepsy (GAERS and WAG/Rij rats [32][38][53][54]). Belzung and Lemoine (2011) proposed a logical schema for validating animal models of psychiatric disorders and outlined five criteria for validity [55]: homological validity, pathogenic validity, mechanistic validity, face validity, and predictive validity. As early as 1984, Willner introduced three criteria for model validity that are well accepted in the area of translational neurology: face validity, predictive validity, and construct validity [56]. "*Face validity [is] the phenomenological similarities between the model and the condition being modeled… Predictive validity concerns the success of predictions made from the model, and construct validity concerns its theoretical rationale*" [56]. Willner introduced these criteria in order *"to assess animal models of depression*", and these criteria have been widely used to validate various animal models of human diseases [55][57][58], including absence epilepsy [32][37]. Willner defined the face and predictive validities in relation to the antidepressant effects of drugs.

GAERS and WAG/Rij rats are widely used as reliable animal models of absence epilepsy with behavioral and cognitive comorbidities. In 1986, van Luijtelaar and Coenen introduced WAG/Rij rats as a genetic rat model of absence epilepsy [30]. They reported electrophysiological and behavioral signs of absence epilepsy in these rats [32][59]. WAG/Rij rats were proposed as a model for studying the epileptogenesis of absence epilepsy [60] in conjunction with neurological and psychiatric comorbidities [61].

A well-recognized genetic rat model of absence epilepsy, GAERS, has been selected from the Wistar strain. As early as 1982, Vergnes et al. reported that 6–12-month-old Wistar rats in their 20-year-old breeding colony in

Strasbourg (France) spontaneously exhibited absence seizures [62] and started selectively breeding subjects with spontaneous SWDs, GAERS and control NEC strains. GAERS were derived from an outbred Wistar colony and displayed a 100% incidence of SWDs. NEC rats were also derived by selective inbreeding for the lack of absence seizures.

3. Investigation of Behavioral and Cognitive Functions in Rats

Absence epilepsy is associated with *behavioral comorbidities*, which are expressed as depression- and anxiety-like symptoms [60][63][64][65][66][67][68], and with *cognitive comorbidities*—poor learning abilities [65][67][69][70][71]. A variety of behavioral tests can be conducted on rats to evaluate their behavioral functions. Listed below are some tests that are commonly used (**Figure 2**): the Forced Swimming test, the Tail Suspension test (developed for mice, and less commonly used for rats), the Sucrose Preference test, the Light–Dark choice test, the Elevated Plus maze, and the Open Field test [49][58][64][65][66][72][73].

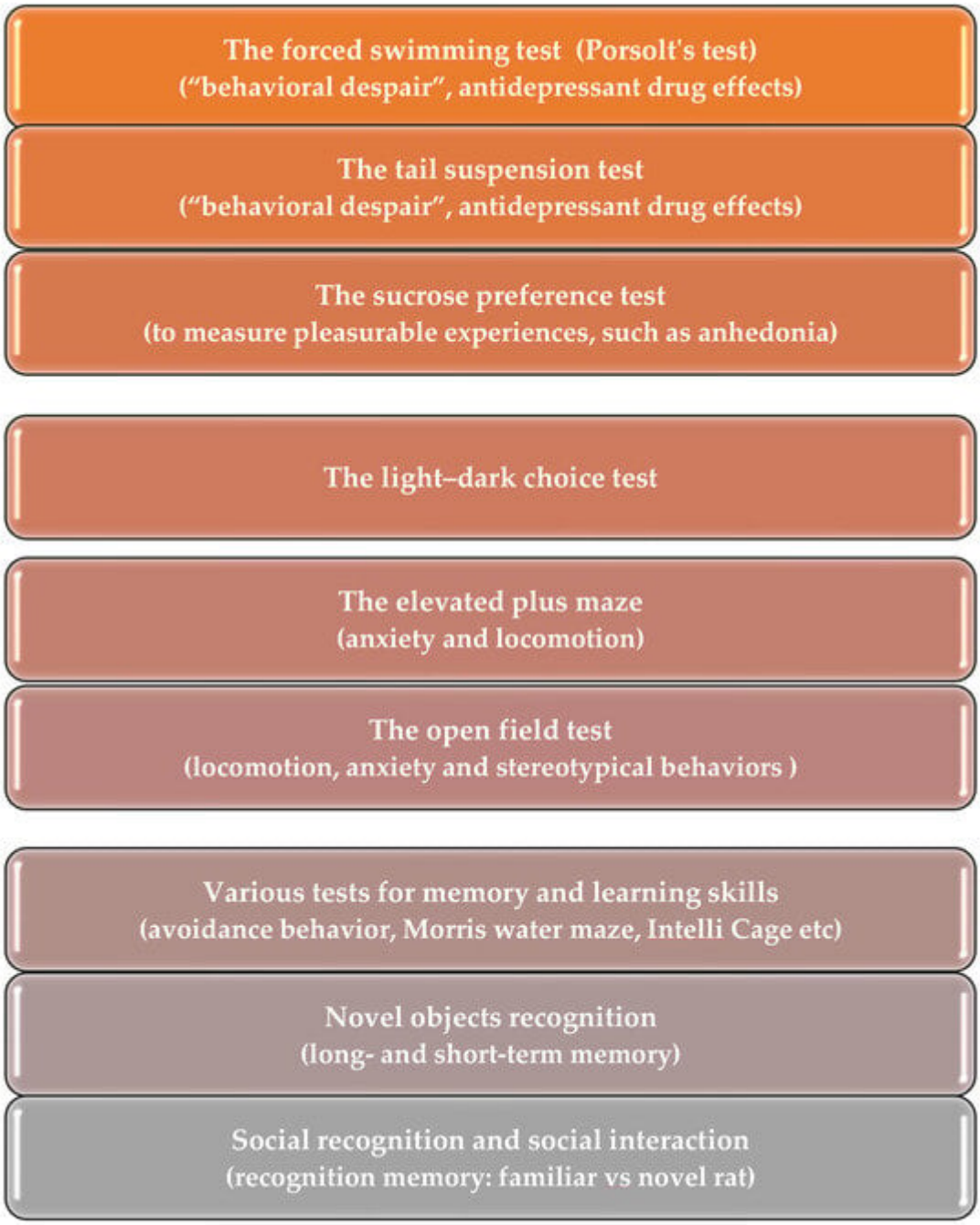

Figure 2. Behavioral test battery used to assess behavioral comorbidities in genetic rat model of absence epilepsy.

The Forced Swimming test, also known as Porsolt's test, is the gold standard for screening antidepressant drugs in rats [72][74][75]. The rat is placed into a tank of water from which it cannot escape. It shifts between actively trying to escape and staying passive. In this test, the rat's immobility is used as an indicator of depressive-like behavior (or "behavioral despair" in terms of Porsolt [75]).

The Tail Suspension test, which was developed for mice [48][68] and adapted for rats [57][76][77], is a behavioral test used to measure an animal's reaction to stressful situations. The rat is suspended by the tail from a lever, the movements of the animal being recorded for 6 min during which the animal shows periods of agitation and

immobility. In this test, the rat either attempts to escape through active movements or remains passive, similar to what is seen in Porsolt's test. The efforts to escape can be classified into three types: (1) running movements; (2) body torsion with attempts to catch the suspending bond; (3) body jerks. After several failed attempts, the subject finally stops moving and hangs motionless. The Tail Suspension test is analogous to Porsolt's test and produces "behavioral despair" [76][77]. The benefits of the Tail Suspension test can be summarized as follows: (1) rats do not experience hypothermia; (2) the recording of rat behavior is more accurate than with Porsolt's Test; (3) it is more sensitive to low doses of drugs and provides a more distinct dose-effect relationship.

The Sucrose Preference test is the most commonly used method for measuring pleasurable experiences and hedonic drivers of consumption as well as anhedonia [78][79]. Chronic stress reduces rats' physiological preference for sweet solutions, which is thought to be analogous to the anhedonic behavior observed in depressed patients and indicative of a decreased rewarding effect of sweet tastes.

The Open Field test is a quick and simple way to evaluate locomotion, anxiety, and stereotypical behaviors such as grooming and rearing [80]. There is a lot of debate about the interpretation of behavior in the Open Field test due to uncertainty about the motivation of rats' behavior. Some believe that it is fear-induced escape behavior rather than anxiety. Anxiety can be measured in situations with both positive and negative outcomes, but the central area in the Open Field test is illuminated and considered to be aversive (i.e., a negative outcome). Rats become more averse to the central zone as their level of anxiety increases.

The Elevated Plus Maze is an established test for anxiety in rodents that has been used for more than 30 years [81]. This is a black plastic arena in the shape of a plus with two opposite arms enclosed by walls and two open arms. The rat is placed on the central platform and is allowed to explore three zones of interest: closed arms, open arms, and the central area. Rats with high levels of anxiety-like behavior tend to spend less time in the open arms of the plus maze.

4. Cognitive Comorbidities in WAG/Rij Rats

Over the past 10 years, the prevalence of cognitive comorbidities in WAG/Rij rats has been increasingly acknowledged. A. Leo et al. (2019) concluded that cognitive impairment and depressive-like behavior in WAG/Rij rats were secondary to the occurrence of absence seizures [65]. These authors also suggested that absence seizures are necessary for the expression of cognitive impairment.

Cognitive comorbidities of absence epilepsy in WAG/Rij rats included cognitive impairment, depression-like symptoms, and altered emotional responsiveness. K. Sarkisova et al.'s comprehensive studies performed in 2003–2011 [64][82][83] indicated that WAG/Rij rats display a range of behavioral signs of comorbid depression, as well as being particularly sensitive to stress, making them an ideal candidate for modeling chronic low-grade depression. An in-depth analysis of A. Leo et al. (2019) [65] indicated the following:

- Cognitive impairment in WAG/Rij rats was secondary to absence epilepsy and to depressive-like behavior;

- Absence epilepsy, depressive-like behavior, and cognitive deficit may arise independently and separately in a lifetime from the same underlying network disease;
- Cognitive impairment in WAG/Rij rats was age-dependent and was linked to the age-dependent increase in spike-wave discharges (i.e., the electroencephalographic sign of absence epilepsy).

Fedosova at al. (2015) [84] found that WAG/Rij rats display increased anxiety and higher stress responses compared to Wistar rats, which precedes the emergence of absence epilepsy, depression-like behavior, and cognitive impairments.

Midzyanovskaya et al. (2005) tested WAG/Rij rats in the Light–dark Choice test and the Open Field test [66]. The Light–dark Choice test, in contrast to the Open Field test, allows an option to escape to a dark compartment. Therefore, the Light–dark Choice test is considered less stressful for rats than the Open Field test. In the Light–dark Choice test, WAG/Rij rats showed an increased locomotor activity (i.e., more entries into the light compartment and more rearings) and more emotional responses (i.e., defecation and urination) than Wistar rats. In contrast, in the Open Field test, WAG/Rij rats were more passive than Wistar rats, and showed reduced exploration and more episodes of grooming [66]. The authors stated that *"mild environmental stressors can stimulate the hyperresponsive nucleus accumbens of absence-epileptic rats and produce exaggerated behavioral response"* [66]. In the WAG/Rij rats, an exaggerated behavioral response to a novel environment was observed, which somewhat contradicted the findings of depressive-like behavior. Increased grooming in the Open Field in WAG/Rij rats might indicate an increased level of anxiety.

5. Behavioral and Cognitive Comorbidities in the GAERS

As well as WAG/Rij rats, the GAERS also share some similarities with human patients in terms of anxiety and depressive-like behavior. Some of the most significant findings, observations, and conclusions are noted below.

Jones et al. (2008) examined behavioral comorbidities of absence epilepsy in the GAERS [73] and reported that the GAERS differed from NECs by the following:

- Reduced consumption of 20% sucrose solution;
- Spending less time in the open arms of the Elevated Plus Maze;
- Reduced exploratory activity in the Open Field test;
- Spending less time in the inner area of the Open Field test.

In summary, all measures presented in this study revealed significantly greater levels of both depression- and anxiety-like behaviors in the GAERS [73].

Marques-Carneiro et al. (2014) compared the locomotion and anxiety in the GAERS at the age of 3–6 months, in the NECs as the first control group, and in Wistar rats as the second control group [63]. This study indicated the following:

- All three strains showed similar levels of locomotor activity as measured in their home cages during the lights-on period;
- The NECs and the GAERS were slightly less active in their home cages than Wistar rats during the light-off period;
- In the beam-walking test, the GAERS and the NECs showed good sensorimotor abilities. Among the three strains, Wistar rats showed the poorest sensorimotor abilities, likely because the body weight in Wistar rats exceeded that in the GAERS and the NECs;
- The GAERS showed a higher anxiety than NECs in the Open Field test (lower activity scores in both central and peripheral areas, and a lower number of rearings) and in the Plus Maze test (a lower number of entries in open arms). However, the results of the GAERS did not differ from those of the Wistar rats;
- When exposed to higher novelty in the Open Field, the GAERS showed a reduced exploration, as compared to the NECs and Wistar rats.

Marks et al. (2016) investigated anxiety, sensorimotor gating, and cognitive performance in male and female GAERS and NECs during the prepubescent age (P35) and young adult age (P56) [85]. The GAERS spent less time in the open arms of the Elevated Plus Maze and showed an elevated startle response, and this was interpreted as an anxiety-like behavior. Furthermore, increased footshock reactivity in the GAERS rats as well as enhanced freezing to conditioned fear-associated cues confirmed anxiety-like responses. The GAERS showed the following differences from the NECs:

- During prepuberty, both sexes spent less time in open arms and had fewer total open and closed arm entries in the Elevated Plus Maze;
- During prepuberty and young adulthood, both sexes traveled less distance in both the inner and outer areas of the Open Field;
- During young adulthood, females spent less time in open arms in the Elevated Plus Maze, with no difference between the males;
- During pre-puberty and young adulthood, both sexes exhibited higher startle responses;
- During pre-puberty and young adulthood, males showed increased freezing relative in the low-intensity fear conditioning;

- Exaggerated cued and contextual Pavlovian fear conditioning and impaired fear extinction;
- An impairment of latent inhibition in a paradigm using Pavlovian fear conditioning.

6. Some Translational Issues

The application of the translational approach has become more and more common due to its potential to link animal studies with clinical practice, and to incorporate the latest breakthroughs in human medicine. Rats are nocturnal animals. They are more awake during the dark period and less active during the light period. Despite this, behavioral studies are usually done during the light period, in a lighted environment. This might not be a crucial issue, because rats have a polyphasic sleep pattern, which means it is natural for them to be awake during the light phase of the day. An important issue is the endogenous circadian mechanism, which controls the timing of spontaneous SWDs in rats [86][87][88]. SWDs in WAG/Rij rats were most frequent in the middle of the dark period [88]. Behavioral experiments are usually conducted during the light phase, when the number of SWDs varies between medium and high [87][88].

Attention deficits have been recognized as the most common comorbidity, affecting an estimated 35–40% of patients with absence epilepsy [89][90]. Most seizure-free patients experienced some cognitive difficulties after successful pharmacological treatment with ethosuximide, valproic acid, and lamotrigine [91][92]. Ethosuximide is a first-choice anti-absence drug that also prevented seizures in WAG/Rij rats and improved cognitive and behavioral functions in these rats to healthy levels [61][82].

Next to difficulties in executive function (more generally, attention) [71], poorer associative learning in WAG/Rij rats [67][69][70] might be accounted for by a lack of motivation to explore the environment resulting from depressive-like symptoms [61][64][68][82]. It is an open question for future research whether the slower acquisition of learning seen in WAG/Rij rats is primarily caused by a deficit in executive function or by a motivational impairment.

Another issue is a putatively high level of emotionality in WAG/Rij rats, which makes them more likely to have negative experiences. WAG/Rij rats demonstrated behavioral signs of emotional excitation in the Ligh-Dark choice test, such as an increased locomotion and defecation/urination [66]. "*It is likely that genetic absence epilepsy, especially when a mixed pathology is present, is accompanied by a high vulnerability to stressors*" [66].

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