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Review

The Wistar Audiogenic Rat (WAR) strain and its contributions to epileptology and related comorbidities: History and perspectives

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ABSTRACT

In the context of modeling epilepsy and neuropsychiatric comorbidities, we review the *Wistar Audiogenic Rat* (WAR), first introduced to the neuroscience international community more than 25 years ago. The WAR strain is a genetically selected reflex model susceptible to audiogenic seizures (AS), acutely mimicking brainstem-dependent tonic–clonic seizures and chronically (by audiogenic kindling), temporal lobe epilepsy (TLE).
Seminal neuroethological, electrophysiological, cellular, and molecular protocols support the WAR strain as a suitable and reliable animal model to study the complexity and emergent functions typical of epileptogenic networks. Furthermore, since epilepsy comorbidities have emerged as a hot topic in epilepsy research, we discuss the use of WARs in fields such as neuropsychiatry, memory and learning, neuroplasticity, neuroendocrinology, and cardio-respiratory autonomic regulation. Last, but not least, we propose that this strain be used in "omics" studies, as well as with the most advanced molecular and computational modeling techniques.
Collectively, pioneering and recent findings reinforce the complexity associated with WAR alterations, consequent to the combination of their genetically-dependent background and seizure profile. To add to previous studies, we are currently developing more powerful behavioral, EEG, and molecular methods, combined with computational neuroscience/network modeling tools, to further increase the WAR strain's contributions to contemporary neuroscience in addition to increasing knowledge in a wide array of neuropsychiatric and other comorbidities, given shared neural networks.
During the many years that the WAR strain has been studied, a constantly expanding network of multidisciplinary collaborators has generated a growing research and knowledge network. Our current and major wish is to make the WARs available internationally to share our knowledge and to facilitate the planning and execution of multi-institutional projects, eagerly needed to contribute to paradigm shifts in epileptology.
This article is part of a Special Issue entitled Genetic Models–Epilepsy

1. Introduction

When discussing the etiologies of the epilepsies, we readily discover how difficult it is to detect and classify the highly heterogeneous and multifactorial causes associated with these neurological and neuropsychiatric entities. In a search for causality, we also realize that the study of human subjects, with respect to epidemiology, history, diagnosis, and response to therapeutics, is quite challenging. Further, neurologists and neuropsychiatrists commonly differ in their views, nicely summarized by Kanner and Barry [1] with the question "why do neurologists and psychiatrists not talk to each other?". We may also extend this to "why do basic neuroscientists and clinical epileptologists not talk to each other?"

With regard to studying the cause–effect relationships of epilepsy and related comorbidities by means of experimental or even computational models, some attempts have been made recently to define the main features of human epilepsy in order to develop reliable experimental models [2]. These include, for example, the necessary criteria for a model of mesial TLE (MTLE), such as seizures with non-convulsive behavioral signs, hippocampal sclerosis, and focal electroencephalographic (EEG) activity [3]. Depaulis and Hamelin [3] experimentally demonstrated that among three different MTLE models, only those resulting from the induction of focal status epilepticus (SE) appear to model such characteristics of human MTLE.

Indeed, to achieve a "paradigm shift" that addresses the urgent need for knowledge of underlying basic mechanisms and the detection of therapeutic targets, animal and computational models are required that

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mimic the necessary clinical features under more controlled conditions, facilitated by clinicians proposing testable hypotheses to basic neuroscientists for evaluation in their models [2,3].

With respect to experimental models, we need to choose between those based upon electrical, chemical or sensory stimuli (or combinations), as well as those produced with known genetic background, usually by inbreeding or genetic engineering, such as transgenics and knockouts [4–8]. Computational and network tools can model the complexity of the associated neural substrates [9,10].

This special issue of *Epilepsy & Behavior* is based on the international symposium "Audiogenic Epilepsies: From Experimental Models to the Clinic", held in September 2014 in Salamanca, Spain, where internationally recognized colleagues discussed their experience with genetically-developed models, especially audiogenic, in mice, rats, and hamsters (http://gredos.usal.es/jspui/bitstream/10366/125169/1/Programme%20book%20audiogenic%20epilepsy%20congress%202014.pdf).

In this paper, we first present selected data from different laboratories worldwide, including data that complements several articles in this special issue, based on several audiogenic seizure-susceptible strains, with comments on their historical development, as well as their main contributions to the epileptology literature from the perspectives of behavior, EEG, and cellular and molecular mechanisms. Next, we describe how studies with the WAR strain have contributed both to the neuroscience and the epileptology–neuropsychiatry research communities in elucidating the complexity of the epilepsies and their comorbidities. Whenever possible, we contrast WAR-related challenges, data, and perspectives with those of other models. We agree with Insel [11], who posed the question "animal models or model animals?", and who wisely recognized it is preferable to use the terms *"model organisms"* and *"model animals"* than models that try to mimic precisely the human condition, because we clearly know the former's limitations and their planned specific uses.

Making WARs available internationally is one of our highest priorities, because this will help in the design of multicenter protocols and facilitate the development of new knowledge and technology, including computational tools, for increasing the contribution of WARs to epileptology and, more broadly, to neuroscience.

2. Historical and comparative research priorities on the studies of the audiogenic seizure strains with emphasis on WARs

It is believed that in 1924, Studenzov [12] observed the first murine audiogenic seizure in Ivan Pavlov's laboratory when studying conditioning to sound in mice. Unfortunately, these observations were not known to the general scientific community because they were not published in English, though they are referred to in the literature [12–15].

Since then, in addition to known mouse strains such as the Frings [16–18] and the DBA/2 [19,20], several audiogenic rat strains were developed: the *Krushinsky–Molodkina* (K–M) strain in Russia [13], the *Genetically Epilepsy-Prone Rats* (GEPR) in the USA [21–23], the *P77PMC* in China [24], the *Wistar Albine Glaxo/Rijswijk* (WAG/Rij) in the Netherlands [25], the *Wistar Audiogenic Susceptible* (WAS) rats in France [26], the previously mentioned WAR strain in Brazil [4], and, more recently, the *Genetic Audiogenic Seizure-Prone Hamster* (GASH:Sal) in Spain [27–29].

There are several controversial aspects concerning the application of results produced with these audiogenic strains to human epileptology. For example, in this special issue, Wolf [30] reviews clinical aspects of reflex epilepsies and points out the difficulties in using results from audiogenic strains to understand these epilepsies. Audiogenic seizure strains do not fully mimic audiogenic seizures in humans. For example, Wolf [30] mentions that seizures in humans triggered from a simple acoustic stimulus are practically non-existent. Reflex auditory epilepsies are classified as idiopathic generalized, mostly with genetic origin, and are typically triggered by complex sounds or music with appropriate combinations of melody, harmony, and rhythm, and with associated impact on memory and cognition [31,32].

While animal strains susceptible to audiogenic seizures may not model a clinically-relevant form of audiogenic epilepsy in humans, they are nonetheless useful because they are genetically selected animals, with a known activation trigger and a clearly described phenotype, expressed either after acute acoustic stimulation (tonic–clonic seizures) or after chronic audiogenic stimulation (kindling), which itself is used as a model of TLE [33]. Further, depending on the strain, there is extensive information available about their behavior, EEG, and cellular and molecular aspects from laboratories worldwide. Therefore, these strains represent "*model animals*" rather than "*animal models*", after Insel [11], and we need to understand the limitations of these models on the one hand and what clinically germane issues they do model, on the other hand, such as seizure type, EEG correlates, brain regions/circuits involved, developmental aspects, and sex- and aging-related features. In this way, results/conclusions may be applicable even to the more complex human condition.

Initially, in this review we sought to qualitatively illustrate and contrast the contributions made by different laboratories working on genetic strains with susceptibility to audiogenic seizures. Therefore, we searched for publications in PubMed using appropriate terms to identify all relevant papers for three different audiogenic strains. We found 45 articles using the WAR strain developed in Brazil [4,36–38] with the terms [WAR], [Garcia-Cairasco N], [Doretto MC], and [Dutra Moraes MF]. We found 162 articles with the USA-developed strain, the Sprague–Dawley derived Genetically Epilepsy-Prone Rat [21,37], using the terms [GEPR] and [Genetically Epilepsy-Prone Rat]. Finally, we found 184 articles with the Europe-developed WAG/Rij rats [25] using the terms [WAG/Rij rats], [seizure], [epilepsy], and [absence].

After exporting the PubMed search results to the reference manager Zotero (https://www.zotero.org/download/), we inserted the block of text including title, abstract, and keywords (but without any authors' names) of all selected articles from each strain (WAR, GEPR, and WAG/Rij) in the notepad of Wordle (http://www.wordle.net/), which allowed us to make qualitative comparisons, represented visually as word clouds, between the three strains (Fig. 1), where the graphical depiction is based on word frequency (the most frequent words are displayed as the tallest). This qualitative (but not quantitative) method visually highlights the apparent research themes for publications involving the three strains. Based on the word clouds, it is obvious that the WARs are an audiogenic Wistar-derived strain of genetically-selected rats, and that their seizures mimic both tonic–clonic (acute) and limbic (chronic/kindled) seizures (Fig. 1, top). For the WAR strain, the predominant words in descending frequency (using only one word for cases of repeated words, such as *Wistar* and *wistars*) are Wistar, seizures, audiogenic, rats, WAR, animals, stimulation, acoustic, kindling, model, epilepsy, limbic, strain, and tonic–clonic; whereas the corresponding list for the GEPRs strain (Fig. 1, up-middle), also derived from the Sprague–Dawley line, are AGS, GEPR, seizure, genetically, GEPR-9s, IC, epilepsy-prone, neurons, colliculus, audiogenic, epilepsy, Sprague–Dawley, and neuronal. For the WAG/Rij strain (Fig. 1, down-middle), also Wistar-derived, but mostly a model of absence seizures mixed with audiogenic susceptibility, the predominant words in descending frequency are WAG-Rij, rat, absence, seizures, SWDs, epilepsy, discharges, SWD, Wistar, animals, spike–wave, cortex, model, and epileptic.

We further contrasted word clouds based on publications of these three audiogenic strains with those using another experimental non-audiogenic model, the classical amygdala electrical stimulation kindling model [38–40] (Fig. 1, bottom), using the PubMed search terms [amygdala] and [electrical kindling]. The predominant words for this non-audiogenic model, in descending frequency, are kindling, amygdala, seizures, rat, electrical, kindled, stimulation, neurologic, male, and animals.

This quite simple qualitative data analysis for the WAR, GEPR, and WAG/Rij strains can be readily applied to hundreds of articles reporting other audiogenic genetic or non-genetic models, and demonstrates a very conserved expression of features and methods that represent specific hallmarks or signatures of these strains when compared to the traditional amygdala kindling limbic seizure model. At present and in the future, mathematical or computational algorithms (probably as simple

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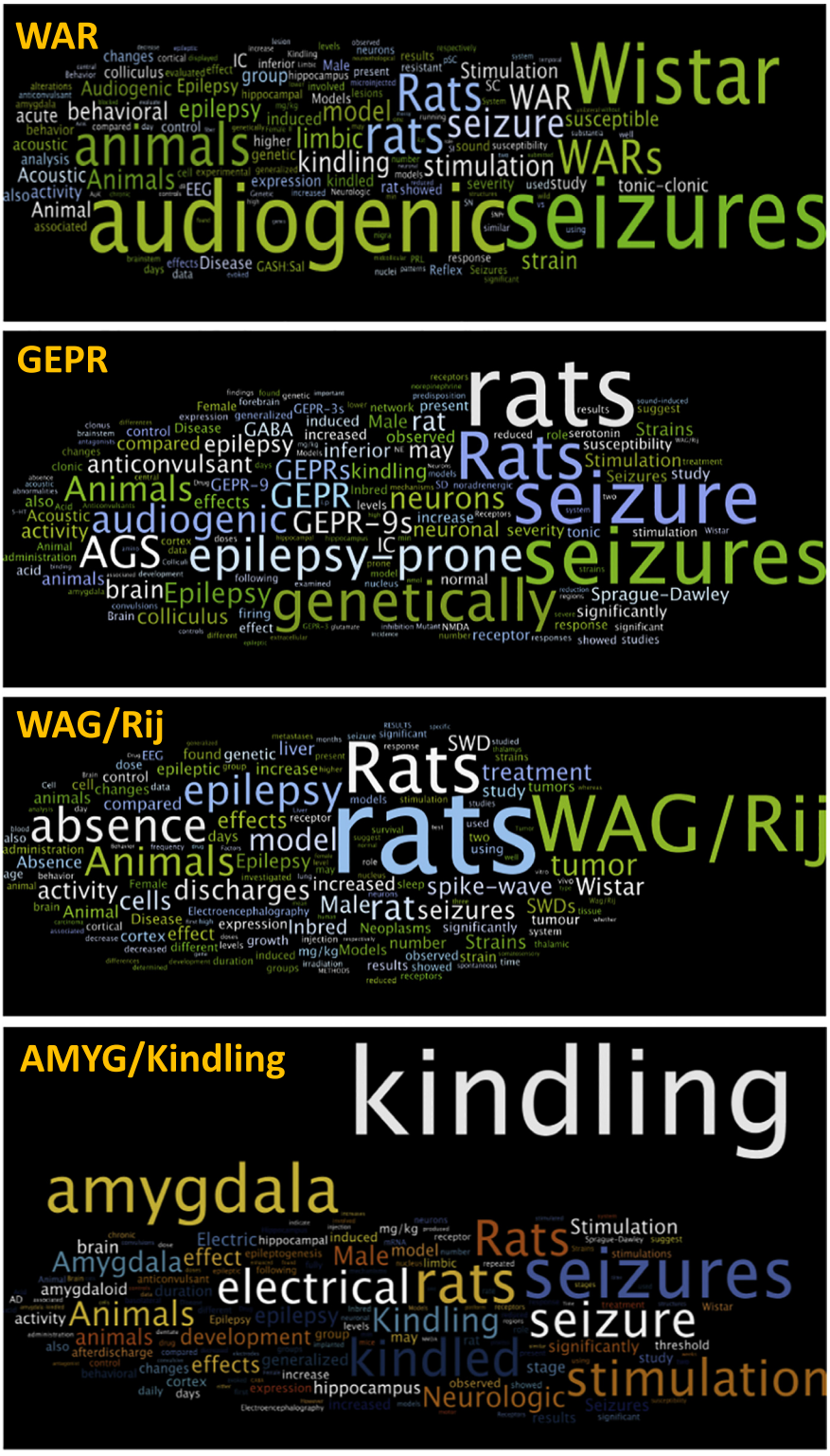

Fig. 1. Word clouds from Pubmed search (see details in the text) based upon Title, Abstract and Keywords (no authors) associated to the WARs (top), GEPRs (up-middle), WAG/Rij (down-middle) genetically developed strains, respectively, in contrast with the amygdala electrical kindling model (bottom).

as those contained in Wordle) can determine and visualize these associated characteristics by scanning terabytes of information (big data) far more efficiently than manual methods such as we used, thereby elucidating behavioral, electrophysiological, cellular, ultrastructural, and molecular features. In the meantime, to inform and educate interested researchers worldwide, we provide Table 1, which is a concise analysis of reports involving the Wistar susceptible rats and the WARs published over the past 34 years, including their use to model acute brainstem-mediated tonic–clonic seizures and chronic kindled seizures.

Table 1 clearly shows that early on, before WARs were genetically selected, we developed behavioral approaches to characterize the "audiogenic" phenotype, contrasting it with the "resistant" phenotype,

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Table 1
Summary of the studies, in chronological order of year of publication, with the original Wistar Audiogenic Rat (WAR) strain at the FMRP-USP at Ribeirão Preto-SP (#), as well as its secondary colony at the IBS-UFMG at Belo Horizonte-MG (@). References labeled as (%) are from WARs-RP used in collaborative studies with laboratories out of FMRP-USP.

Order	Year (Month)	Title [Reference]	Main contribution
1	1983#	Role of the substantia nigra in audiogenic seizures: a neuroethological analysis in the rat [41].	Before the existence of the WAR strain, "audiogenic seizure resistant" and "audiogenic seizure susceptible" phenotypes were described when Wistar rats were stimulated with high-intensity acoustic stimulation. This study is the pioneer neuroethological description of those phenotypes and of the detection of audiogenic-like seizures induced by unilateral electrolytical lesions of substantia nigra (SN) in Wistar audiogenic resistant rats.
2	1989#	Neuroethological evaluation of audiogenic seizures in hemidetelencephalated rats [42].	Previous research demonstrated the brainstem origin of audiogenic seizures. This study reveals that a massive lesion such as unilateral removal of telencephalon, forebrain, and diencephalon (hemidetelecephalation) induces strong asymmetric audiogenic seizures in audiogenic seizure resistant Wistar rats.
3	1991#	Possible interaction between the inferior colliculus and the substantia nigra in audiogenic seizures in Wistar rats [43].	Bilateral lesions of the inferior colliculus (IC) and lateral lemniscus (LL) abolish audiogenic seizures (induced by 120 dB acoustic stimulation) in Wistar susceptible male rats. Unilateral lesions of either SN or IC induce audiogenic-like seizures in resistant rats. Although the behavioral effects resulting from IC lesions are due to alterations in the primary structures involved in the origin of audiogenic seizures, unilateral SN lesions alter critical substrates of sensorimotor integration involved in their control and expression.
4	1992 (5)#	New insights into behavioral evaluation of audiogenic seizures. A comparison of two ethological methods [44].	Two classic methodologies for behavioral analyses of susceptible and resistant rats to audiogenic seizures are compared to a third and new method. The latter is proposed to graphically display frequency and temporal patterns simultaneously in a complex behavioral (sequential) cluster analysis.
5	1992 (8)#	Neuroethological evaluation of audiogenic seizures and audiogenic-like seizures induced by microinjection of bicuculline into the inferior colliculus. II. Effects of nigral clobazam microinjection [45].	Audiogenic resistant rats injected with bicuculline into the IC display audiogenic-like seizures with gyrations, jumping, and atonic falling, but no tonic–clonic components, and show postictal contralateral asymmetry/hyperreactivity. These audiogenic-like seizures are blocked by clobazam microinjection into SN. Vehicle or clobazam injected into SN of susceptible rats had no effect. These data are suggestive of GABAergic regulation of the development of audiogenic-like seizures in resistant rats and a defect in GABAergic neurotransmission in susceptible rats.
6	1993 (12)#	Midbrain substrates of audiogenic seizures in rats [35].	A comprehensive review of the contribution to knowledge of neurobiological midbrain substrates underlying seizures obtained from acute audiogenic seizures and to midbrain–forebrain interactions based on chronic (kindled) audiogenic seizures.
7	1994 (5)#	NMDA-dependent audiogenic seizures are differentially regulated by inferior colliculus subnuclei [46].	Behavioral neuroethological description of N-methyl-D-aspartate (NMDA)-dependent differential participation of IC subnuclei (central *versus* external/dorsal) on the development of audiogenic-like seizures.
8	1994 (10)#	Diuresis and natriuresis in non-seizing and in kindled rats from a genetically audiogenic susceptible strain [47].	Assessment of the water–electrolyte profiles of susceptible and resistant rats exposed to none, acute or kindled audiogenic seizures. Increased patterns of urinary flux, diuresis, and natriuresis are detected in susceptible animals, both naïve and those exposed to acute or kindled audiogenic seizures. These alterations are probably related to endogenous neuroendocrine alterations and to seizure experience.
9	1996 (3)#	Audiogenic and audiogenic-like seizures: locus of induction and seizure severity determine postictal prolactin patterns [48].	Identification of a positive correlation between seizure severity, site of seizure initiation (central or cortical IC nuclei), and postictal prolactin (PRL) patterns. Wistar susceptible audiogenic rats are proposed as a reliable model to study the neurochemistry of the postictal phase and the interaction between hormones and epilepsy.
10	1996 (12)#	Neuroethological and morphological (Neo-Timm staining) correlates of limbic recruitment during the development of audiogenic kindling in seizure susceptible Wistar rats [49].	First neuroethological demonstration that audiogenic kindling in susceptible Wistar rats effectively recruits forebrain structures. Briefly, clear-cut changes of behavioral sequences are detected from typical midbrain-dependent wild running/tonic–clonic seizures and from limbic seizures. Furthermore, morphological changes such as Neo-Timm + amygdala complex and perirhinal cortex rearrangements, in spite of the lack of mossy fiber sprouting, are associated with limbic seizures, depending on the number of seizures.
11	1997 (8)#	Anticonvulsant and proconvulsant roles of nitric oxide in experimental epilepsy models [50].	Inhibition of nitric oxide synthase (NOS) was assessed in chemically- and sound-induced seizure models. Although the effects of NOS inhibition are observed in pilocarpine (PILO) and pentylenetetrazol (PTZ) (dose-dependent) models, no effects are found in WARs.
12	1998 (7)@	Dipyrone, a novel anticonvulsant agent? Insights from three experimental epilepsy models [51].	Demonstration of the anticonvulsant effect of dypirone, a non-steroidal anti-inflammatory drug, in three experimental epilepsy models. Dipyrone blocks maximal hind limb extension in the electroshock model in Wistar rats, the tonic–clonic component of acute audiogenic seizures, and the limbic component of audiogenic kindling in WARs.
13	1998 (7)#	Reduced exploratory activity of audiogenic seizures susceptible Wistar rats [52].	Audiogenic seizure susceptible animals display reduced exploration in both the open field (reduced total distance moved) and the elevated plus maze (reduced number of enclosed-arm entries). In the latter, there was also a decrease in open-arm exploration, particularly of the distal part of these arms; therefore, the WAR strain is endogenously anxious.

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Table 1 (*continued*)

Order	Year (Month)	Title [Reference]	Main contribution
14	2000 (5)#	Audiogenic kindling in the Wistar rat: a potential model for recruitment of limbic structures [33].	Electrophysiological characterization of gradual and sequential involvement of the amygdala and then cortex during audiogenic kindling. All kindled WARs show very similar polyspike–wave activity in the amygdala, after behavioral limbic seizure patterns (by the Racine scale) occurred, with similar EEG morphology reported for electrical amygdala kindling. When audiogenic kindling continues, both IC (midbrain) and cortical electrodes show high-amplitude, synchronized epileptiform polyspike activity.
15	2002 (6)#	A critical review on the participation of inferior colliculus in acoustic-motor and acoustic-limbic networks involved in the expression of acute and kindled audiogenic seizures [36].	Reviews the key role of the IC in the expression of acoustic-motor and acoustic-limbic integration involved in both acute and chronic audiogenic seizures in WARs, including the behavioral characterization, search for their neuroanatomical substrates, and underlying neurochemistry, neuropharmacology, and electrophysiology, as well as known cellular and molecular mechanisms.
16	2002 (8)@	An effective anticonvulsant prepared following a host–guest strategy that uses hydroxypropyl-beta-cyclodextrin and benzaldehyde semicarbazone [53].	The effects of aryl semicarbazones, a class of compounds with anticonvulsant activity, are evaluated in two experimental models of seizures: electroshock and audiogenic seizures (WARs), either administered alone or in a 1:1 combination with benzaldehyde semicarbazone (BS) and hydroxypropyl-b-cyclodextrin (HP-b-CD). In both tests, the minimum dose of compound necessary to produce activity decreases from 100 mg/kg for the free semicarbazone to 35 mg/kg for the compound, indicating a significant increase in the bio-availability of the drug.
17	2002 (11)@	Zinc, magnesium and copper profiles in three experimental models of epilepsy [54].	Study of the effects of different type of seizures, including audiogenic seizures in WARs, on concentrations of zinc (Zn), magnesium (Mg), and copper in plasma and hair samples. Seizure type (limbic or generalized tonic–clonic) and number of seizures seem to determine changes in Zn and Mg levels, respectively.
18	2003 (1)#	Quantitative study of the response to genetic selection of the Wistar Audiogenic Rat (WAR) strain [4].	Analysis of 9450 observations in 1575 animals from the 3rd to 17th generations of genetic selection in WARs demonstrates significant effects of generation, parity, and litter on seizure severity index (SI; a marker of brainstem–midbrain activation) and of generation and litter on limbic seizure severity index (LI; a marker of forebrain recruitment). Using big data, the WAR strain from the 17th to 20th generations of quantitative genetic selection appears to be suitable and reliable for epilepsy studies.
19	2003 (1)@	Assessment of the seizure susceptibility of Wistar Audiogenic Rat to electroshock, pentyleneterazole and pilocarpine [55].	Evaluates seizure susceptibility of naïve female WARs to other (non-acoustic) pro-convulsant stimuli: transauricular electroshock (ES), PTZ, and PILO. Normal Wistar rats from the main breeding stock of the IBS-UFMG are controls and the results show that WARs have an inherited broader predisposition for seizures.
20	2003 (4)@	Changes in peripheral energy metabolism during audiogenic seizures in rats [56].	Plasma glucose and lactate, hepatic glycogen, and epididymal adipose tissue lipogenesis and lipolysis are studied in WARs, under three experimental conditions: before, 3 min after, and 10 min after seizures induced by intense sound exposure. Briefly, genetic selection for audiogenic seizure susceptibility in WARs results in pronounced alterations at multiple levels of metabolic regulation.
21	2003 (5)#	Effect of lactation on the expression of audiogenic seizures: association with plasma prolactin profiles [57].	Female Wistar rats and WARs are used to investigate the potential roles of PRL and progesterone in the modulation of seizure expression. Briefly, a post-ictal PRL peak after tonic seizures is demonstrated with a decrease in seizure severity in female lactating WARs (with and without pups). A long-term role of PRL modulating seizure activity related to both pregnancy and lactation is discussed.
22	2003 (6)#	Hippocampal cell proliferation and epileptogenesis after audiogenic kindling are not accompanied by mossy fiber sprouting or Fluoro-Jade staining [58].	Behavioral changes after audiogenic kindling in WARs correlate with potential alterations in neuronal proliferation, cell death, hippocampal mossy fiber sprouting, and electroencephalographic (EEG) patterns. Audiogenic kindling increases hippocampal mitotic rate, measured with bromo-desoy-D-uridine (BrdU), without promoting neuronal death or mossy fiber sprouting in the dentate gyrus.
23	2004(2)#	Limbic epileptogenicity, cell loss and axonal reorganization induced by audiogenic and amygdala kindling in Wistar Audiogenic Rats (WAR) strain [59].	Audiogenic kindling in WARs induces limbic epileptogenicity, measured as behavioral alterations (and facilitation of amygdala kindling), strongly associated with lack of hippocampal cell loss and increase (or reorganization) of Zn-positive fibers (gluzinergic terminals) in amygdala but not in the hippocampus. A small number of amygdala kindling-induced seizures are associated with broader and more numerous hippocampal cell loss than a higher number of acoustically-induced seizures.
24	2004 (8)#	Neuroethological study of status epilepticus induced by systemic pilocarpine in Wistar Audiogenic Rats (WAR) strain [60].	Pioneering neuroethological description of SE induced by PILO in WARs. The amount of PILO needed to induce SE in WARs is lower than in Wistar animals and the proportion of animals dying is greater. WAR-plus-PILO combination is suggested to be a suitable protocol to study the combination of genetic background and seizure experience (two hits) in experimental temporal lobe epilepsy.
25	2004 (10)#	Evidence for augmented brainstem activated forebrain seizures in Wistar Audiogenic Rats subjected to transauricular electroshock [61].	Electrophysiological data show that WARs have enhanced susceptibility to electroshock-induced seizures. These data support the hypothesis that the acoustic-limbic circuitry is facilitated even in unkindled WARs.

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Table 1 (*continued*)

Order	Year (Month)	Title [Reference]	Main contribution
26	2005 (3)#	Electrophysiological properties of cultured hippocampal neurons from Wistar Audiogenic Rats [62].	Using the whole-cell patch-clamp technique to record both active and passive membrane responses, the electrophysiological properties of cultured hippocampal neurons from naïve (no seizure experience) WARs are analyzed and compared to Wistar rats. Glutamatergic and GABAergic alterations are found in WARs, potentially the basis of neurophysiological and behavioral alterations detected in these animals with hyperexcitable brains.
27	2005 (3)@	Vasopressinergic hypothalamic neurons are recruited during the audiogenic seizure of WARs [63].	Arginine vasopressin (AVP) immunohistochemistry in the hypothalamus and radioimmunoassay in plasma and in hypothalamic and hypophysial tissues are performed on both controls and WARs to evaluate the dynamics of AVP release due to seizure induction. AVP-releasing profiles indicate that vasopressinergic hypothalamic neurons are recruited during audiogenic seizures of WARs.
28	2006 (12)#	EEG wavelet analyses of the striatum–substantia nigra pars reticulata–superior colliculus circuitry: audiogenic seizures and anticonvulsant drug administration in Wistar Audiogenic Rats (WAR) strain [64].	Behavioral and EEG analysis of the striatum–SN-pars reticulata–superior colliculus (SC) circuitry in the expression of audiogenic seizures in WARs. In the context of endogenous anticonvulsant systems, it is discussed why, although systemic phenobarbital injection blocks audiogenic seizures, intranigral muscimol or phenobarbital does not.
29	2008 (2)#	Modulation of B1 and B2 kinin receptors expression levels in the hippocampus of rats after audiogenic kindling and with limbic recruitment, a model of temporal lobe epilepsy [65].	Demonstration of the modulation of B1 and B2 kinin receptor expression levels in neonatal, as well as in adult, WARs subjected to audiogenic kindling. Based on those results, the authors propose that both B1 and B2 kinin receptors have a pivotal role in this TLE model, although their participation is not related to inflammation.
30	2008 (3)@	Peripheral glucose metabolism is altered by epileptic seizures [66].	Investigation of the status of jejunal absorption and peripheral metabolism of glucose in WAR after seizures. The concentration of GLUT4 in the gastrocnemius muscle of WAR is higher than that observed in control rats and the audiogenic stimulus leads to decreased concentration of this receptor in the muscle tissue of WARs.
31	2009 (2)#%	Sexual differentiation of cortical spreading depression propagation after acute and kindled audiogenic seizures in the Wistar Audiogenic Rat (WAR) [67].	Cortical spreading depression (CSD) is characterized in adult male and female rats from Wistar controls compared with WARs with and without audiogenic kindling. Besides other general data, in some Wistar and WAR females in which the estrous cycle status on the day of the CSD-recording is determined as being either estrous or diestrous, no cycle-phase-related differences in CSD-propagation velocities are detected. In contrast to other epilepsy models, such as SE induced by PILO, despite the CSD-velocity reduction, CSD propagation is not blocked in WARs. The results suggest a gender-related, estrous cycle phase-independent modification in the CSD-susceptibility of WAR rats.
32	2009 (12)#	Role of the superior colliculus in the expression of acute and kindled audiogenic seizures in Wistar Audiogenic Rats [68].	Description of the effect of disconnection between deep layers of the SC and adjacent tissues in the expression of acute and kindled audiogenic seizures in WARs. Although this study firstly demonstrates the involvement of the deep layers of SC in the expression of acute and kindled audiogenic seizures, it is also observed that cerebral cortex is essential for audiogenic kindling development in WARs.
33	2010 (1)#	Increased expression of GluR2-flip in the hippocampus of the Wistar Audiogenic Rat strain after acute and kindled seizures [69].	In order to identify genes involved in molecular mechanisms underlying epileptic processes, suppression-subtractive hybridization and normalized cDNA library enriched for transcripts expressed in the hippocampus of WARs are used. Differential upregulation of GluR2-flip isoform in the hippocampus of WARs displaying audiogenic seizures is observed for the first time, in agreement with and extending previous immunohistochemistry data for GluR2 data obtained in the Chinese P77PMC audiogenic rat strain, reinforcing the association of limbic AMPA alterations with epileptic seizures.
34	2010 (8)#	Inhibition of the renin–angiotensin system prevents seizures in a rat model of epilepsy [70].	Characterization in the WAR strain of the hippocampal renin–angiotensin-system (RAS), namely angiotensin-converting enzyme (ACE) and angiotensin II type 1 receptor (AT1), indicating their up-regulation (2.6- and 8.2-fold respectively) following audiogenic kindling. Centrally acting drugs that target the RAS may represent an additional strategy in the management of seizures in patients with epilepsy.
35	2011 (1)#	The non-coding RNA BC1 is down-regulated in the hippocampus of Wistar Audiogenic Rat (WAR) strain after audiogenic kindling [71].	Detection in WARs of down-regulation of the non-coding RNA sequence (BC1), a known repressor of the fragile-X-associated protein FMRP. Functional results recently obtained in a BC1 −/− mouse model and current data are supportive of a potential disruption in signaling pathways, upstream of BC1, associated with the seizure susceptibility of WARs.
36	2011 (3)#	Functional characterization of the hypothalamic–pituitary–adrenal axis of the Wistar Audiogenic Rat (WAR) strain [72].	Hypothalamic–pituitary–adrenal axis (HPA) responses to exogenous adrenocorticotropin hormone (ACTH) stimulation are used together with 15 min of restraint stress and circadian variation under rest conditions in WARs. Plasma measurements of ACTH and corticosterone concentrations demonstrate that, despite lower body weight than Wistars, WARs have adrenal gland hyperplasia and enhanced pituitary and adrenal responsiveness after HPA axis stimulation.
37	2011 (10)#	Behavioral and EEG effects of GABAergic manipulation of the nigrotectal pathway in the Wistar Audiogenic Rat strain [73].	Bicuculline ($GABA_A$ antagonist) and muscimol ($GABA_A$ agonist) are microinjected into the deep layers of either the anterior (aSC) or posterior (pSC) superior colliculi of WARs. This demonstrates that pSC makes a pro-convulsant contribution to audiogenic seizure activity in WARs, suggesting that this phenomenon may be a consequence of the genetic selection of this strain.

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Table 1 (*continued*)

Order	Year (Month)	Title [Reference]	Main contribution
38	2011 (10)@	Reduced hippocampal GABAergic function in Wistar Audiogenic Rats [74].	Evaluation of the inhibitory γ-amino-butyric acid (GABA)ergic modulation in the CA1 region of the hippocampus of male Wistar rats and WARs. A functional reduction of GABAergic neurotransmission in hippocampal slices from WARs is detected.
39	2011 (12)#	Changes in autonomic control of the cardiovascular system in the Wistar Audiogenic Rat (WAR) strain [75].	Autonomic cardiovascular modulation and baroreflex control of heart rate (HR) are measured in WARs, as well as spontaneous baroreflex sensitivity and reflex changes in HR evoked by phenylephrine/nitroprusside-induced changes in arterial pressure. Atropine and propranolol are used to measure cardiac autonomic tone. Higher arterial pressure and HR, as well as autonomic imbalance (sympathetic predominance), are detected in WARs, which could conceivably increase the risk of life-threatening cardiovascular events in this strain.
40	2012 (5)#	Role of endothelium on the abnormal angiotensin-mediated vascular functions in epileptic rats [76].	Description of angiotensin I (AngI) and angiotensin II (AngII)-mediated vascular responses and their contractile responses to the presence of endothelium and protein levels of the components of the renin–angiotensin system (RAS) (AT1, AT2, Mas receptor and ACE) in aorta isolated from the genetically-selected WAR strain. The vascular contractile response induced by AngI and AngII is endothelium-dependent and the endothelium impairs the contractile response induced by angiotensin in WAR, suggesting that endothelial relaxing factors play an important role on aortic contraction.
41	2012 (8)#	Behavioral and EEG effects of GABAergic manipulation of the nigro-tectal pathway in the Wistar Audiogenic Rat (WAR) strain II: an EEG wavelet analysis and retrograde neuronal tracer approach [77].	Searching for mechanisms associated with the susceptibility of WARs to audiogenic seizures, two different subcortical loops within the basal ganglia, an important part of the endogenous anticonvulsant system, are detected, probably a consequence of the WAR genetic background. The retrograde tracer fluorogold (FG) is used, microinjected into the aSC and pSC, in conjunction with quantitative EEG analysis (wavelet transform).
42	2012 (11)@	Anticonvulsant and antiarrhythmic effects of nifedipine in rats prone to audiogenic seizures [78].	Nifedipine, a calcium channel blocker, is studied for epileptic seizures and on reperfusion arrhythmias in WARs and in normal Wistar rats. Nifedipine may be considered as a potential adjuvant drug for epilepsy treatment, especially in those cases associated with cardiac rhythm abnormalities.
43	2013 (5)@	Cardiac dysfunction in rats prone to audiogenic epileptic seizures [79].	Cardiac and electrocardiographic parameters are evaluated in WARs. Chronic disturbances in sympathetic tone in WARs may increase the risk of life-threatening arrhythmias. Provides support for the usefulness of WARs as a model to study the relationship between seizures, cardiac dysfunction, and cardiac arrhythmias, which may contribute to the occurrence of sudden unexpected death in epilepsy (SUDEP).
44	2013 (11)#	Angiotensin II-independent angiotensin-(1–7) formation in rat hippocampus: involvement of thimet oligopeptidase [80].	Characterization of the possible role of the Ang-(1–7)-receptor Mas pathway in naïve and kindled WARs, the latter known to recruit limbic areas. It is demonstrated that Ang-(1–7) is the main metabolite of Ang I in rat hippocampi, and, strikingly, that thimet oligopeptidase is the main enzyme involved in the generation of Ang-(1–7). Data describe a new preferential biochemical pathway for the generation of Ang-(1–7) in the central nervous system and an increase in the levels of various elements of the related thimet oligopeptidase–Ang-(1–7)-receptor Mas pathway in WARs, unveiling potential new roles of the RAS in central nervous system pathophysiology.
45	2015 (6)#	Evaluation of cardiovascular risk factors in the Wistar Audiogenic Rat (WAR) strain [81].	Long-term ECG recordings in conscious, one-year-old WAR and Wistar counterparts are used to evaluate spontaneous arrhythmias and heart rate variability, a tool to assess autonomic cardiac control. The autonomic imbalance observed previously at a younger age is also present in aged WAR. Additionally, cardiac dysfunction was also observed and the findings taken together make the WARs model a valuable tool to study risk factors for cardiovascular events in epilepsy.
46	2015 (6)@	Wistar Audiogenic Rats (WAR) exhibit altered levels of cytokines and brain-derived neurotrophic factor following audiogenic seizures [82].	Interleukines, TNF, and BDNF are studied in WARs after audiogenic seizures and experimental evidence demonstrates that IL-1, IL-6, TNF, and BDNF are increased in WARs after audiogenic seizures. The potential involvement of these mediators in the pathophysiology of epilepsy is discussed.
47	2015 (10)@	Wistar Audiogenic Rats display abnormal behavioral traits associated with artificial selection for seizure susceptibility [83].	Behaviors in forced swim test, open-field test, sucrose preference test, elevated plus maze, social preference, marble burying test, inhibitory avoidance, and two-way active avoidance are characterized in WARs. Briefly, WARs present behavioral despair traits but no evidence of anhedonic behavior or social impairment. In addition, WARs are unable to demonstrate appropriate degrees of aversiveness. The particularities of the WAR model open new avenues to further untangle the neurobiology underlying the comorbidity of behavioral disorders and epilepsy.
48	2015 (12)#	Inhibition of long-term potentiation in the Schaffer-CA1 pathway by repetitive high-intensity sound stimulation [84].	Long-term potentiation (LTP) of hippocampal Schaffer-CA1 synapses and spatial navigation memory are altered by a repeated high-intensity sound stimulation (HISS) protocol in normal Wistar rats and in WARs. Repeated HISS prevents LTP of Schaffer-CA1 synapses from Wistar rats, without affecting spatial memory. This effect is not seen in hippocampi from WARs. In WARs, the link between auditory stimulation and hippocampal LTP appears to be disrupted, which could be relevant for the susceptibility to seizures in this strain.

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Table 1 (*continued*)

Order	Year (Month)	Title [Reference]	Main contribution
49	2016 (1)#%	Overexpression of the immediate-early genes Egr1, Egr2, and Egr3 in two strains of rodents susceptible to audiogenic seizures [85].	Comparative study of gene expression in the IC in WARs and GASH:Sal., Both models are exposed to high-intensity auditory stimulation, and 60 min later, the IC are collected. Among the common genes that are altered in both models was Egr3. This suggests that the overexpression of the Egr3 gene in both models might contribute to neuronal viability and development of the comorbid lymphoma in GASH:Sal in response to stress from audiogenic seizures.
50	2016 (5)#	Behavioral, ventilatory and thermoregulatory responses to hypercapnia and hypoxia in the Wistar Audiogenic Rat (WAR) strain [86].	WARs have important alterations in their ability to compensate for changes in levels of various arterial blood gases, presenting an attenuated ventilatory response to increased $PaCO_2$ (hypercapnia) or decreased PaO_2 (hypoxia). Those respiratory alterations are coupled to behavioral changes, making WARs a suitable model to further study respiratory risks associated with epilepsy.
51	2016 (9)#%	Impaired central respiratory chemoreflex in an experimental genetic model of epilepsy [87].	The central respiratory chemoreflex and the role of serotonergic (5HT) neurotransmission in the retrotrapezoid nucleus (RTN) are studied in WARs. Naïve or kindled WARs have reduced resting ventilation and ventilatory response to hypercapnia (7% CO_2). Both the number of chemically-coded (Phox2b+/TH−) RTN neurons, as well as the 5HT innervation to the RTN, were reduced in WARs. Ventilatory response to 5HT within the RTN region is significantly reduced in WARs.

as selected initial responses to the auditory stimulation of Wistars. Years later, the WAR strain was developed, and efforts were undertaken to characterize it compared with Wistar controls. More recently, publications with WARs have focused on specific networks, for example integrated sensory-motor networks or limbic networks, that are recruited by chronic audiogenic seizures, and their association with endogenous anticonvulsant systems, as well as the characterization of comorbidities such as anxiety, stress, depression, and cardiovascular and respiratory alterations.

As can be seen in Table 1, advancing knowledge about the main features of WARs came from and contributed to a number of productive scientific collaborations. At the Ribeirão Preto School of Medicine - University of São Paulo, Ribeirão Preto, São Paulo, Brazil (FMRP-USP-WAR), a number of studies explored potential neural substrates in WARs responsible for processing seizures and the underlying hyperexcitability, while at the Institute of Biological Sciences at the Federal University of Minas Gerais - Belo Horizonte, Minais Gerais, Brazil (IBS-UFMG-WAR), researchers studied behavioral responses in WARs in specific situations and associated endogenous hormonal and metabolic alterations, and also evaluated the potential of this strain to test anticonvulsant agents.

The collaborations also developed in parallel with the availability of animal strains, such as FMRP-USP-WAR, coded as #, used since the early 1990s as the original strain; IBS-UFMG-WAR, coded as @, and developed since 1992 as the second branch of this strain; and an additional (small) group of WARs, produced at the FMRP-USP in Ribeirão Preto, and evaluated in research laboratories in collaborative studies outside of its place of origin (coded as %).

Chronological analysis of the contributions contained in Table 1 shows that the WARs were selected at a time when other audiogenic strains of rats, such as the K–M [12,13], GEPRs [21], and WAG/Rij [25,88], were already well established and used widely by the scientific community.

Our original studies in the 1980s were done by first developing and applying standardized behavioral tools (neuroethology) to characterize what, at that time, we called *audiogenic-susceptible* and *audiogenic-resistant* animals (based on their positive or negative seizure response to high-intensity acoustic stimulation), all taken from the main breeding stock of rats of the University of São Paulo at Ribeirão Preto. At that time, no WARs were genetically selected. In addition to the small percentage of Wistars from the Main Vivarium (near 10%) [41] that displayed audiogenic seizures, we were able to produce audiogenic-like seizure animals, either by lesions of or applications of drugs to specific brain regions. Briefly, studies used a combination of lesions, for example in, substantia nigra (SN) and inferior colliculus (IC), as well as drugs such as agonists or antagonists of glutamate and GABA neurotransmitters, respectively [41,42,45,88–90].

Seizures have been traditionally quantified in rodent models of epilepsy with behavioral scales such as the Racine limbic scale [40], with its further extension by Pinel and Rovner [91], who included brainstem components such as wild running/bouncing, tonic–clonic seizures, and spontaneous recurrent seizures. Almost at the same time, the Jobe scale [21] was developed for brainstem seizures arising from audiogenic seizures in GEPRs in two subcolonies: the GEPR-9 and the GEPR-3. While these two GEPR subcolonies manifest important differences in severity and neural substrates, further comments are beyond the scope of this review. We developed a brainstem audiogenic seizure severity scale [44,49] for WARs, which was modified later by Rossetti et al. [64]. Depending on the situation, we have used a combination of the Garcia-Cairasco scale [44], modified by Rossetti et al. [64], together with the Racine scale [40]. Below, we describe in detail the use and limitations of these different seizure severity scales for the characterization of experimental models of epilepsy such as audiogenic kindling [26,49,92].

Our initial contribution based on studies of the WAR strain was the first detailed quantitative description of the behavioral sequences of acute and chronic (kindled) audiogenic seizures [41,49]. This new approach to behavioral evaluation of seizures was further applied by our group to chemically- and electrically-induced epilepsy models [59,92–95], to an experimental model of compulsive behavior [96], and to the evaluation of anticonvulsant drugs in the GASH-Sal (audiogenic hamster) model developed at the University of Salamanca, Spain [97,98]. More recently, these methods were applied to the semiological study of TLE [99,100] and frontal lobe epilepsy (FLE) [101]. Internationally, this method is known as neuroethology, and it is based on identifying neural substrates/mechanisms underlying the observed behavioral sequences [101–103]. Similar applications can also be found in clinical settings [104–106].

Specifically, several of the first articles cited in Table 1 deal with neuroethological studies of the WAR strain in a combination of protocols, mostly using flowcharts displaying behavioral sequences and complemented by behavioral scales. The scales are categorical, *a priori* descriptions of the behavioral phenomena from which arbitrary seizure severity scores are derived. More recent studies, also described in Table 1, deal with the search for cellular and molecular markers of epileptogenicity or demonstrations of neuroendocrine, cardiovascular, and respiratory alterations in WARs, several of them providing methods for studying the associated comorbidities of epilepsy.

While these studies of WARs were underway [36], GEPRs were preferentially studied in the Jobe laboratory to characterize the neurochemistry of specific regions such as the locus coeruleus and its noradrenergic

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(NA)-producing neurons [107] and the raphe nuclei and its serotonergic (5-HT)-producing neurons [108]. The Jobe laboratory published the pioneering demonstration of the intriguing impairment of endogenous NA and 5-HT neurochemistry in GEPRs [21–23,108–111].

Almost simultaneously, other studies of GEPRs focused on the circuits and networks [37] underlying seizures. The Faingold laboratory described the electrophysiology of the major networks and circuits responsible for audiogenic seizures, including for either the naïve condition (no seizures) or for acute seizures both the inferior and superior colliculi and the central periaqueductal gray [37,112–115]; and in the chronic condition (kindling), the medial geniculate body (acoustic thalamus) and the amygdala [116]. A collaborative study between the Jobe and Browning laboratories showed that in GEPR-9s exposed to audiogenic kindling, severe tonic–clonic seizures, typical of this sub-strain of rats, hamper the ability of the GEPR-9 forebrain to express behavioral limbic seizures, even when the same region displays spike–wave discharges [112].

In parallel, studies were conducted in Russia and the Netherlands with quite complex paradigms for K–M and WAG/Rij strains, respectively; a comprehensive historical review of the K–M strain is included in this special issue [12].

Pioneering anatomical studies with GEPRs done in the Ribak laboratory (as reviewed in this special issue) [117] found increased GABAergic neurons in the IC (as well as in superior colliculus (SC) and cerebellum) of GEPRs, in addition to increased numbers of cells that express glutamate decarboxylase (GAD67) mRNA [117–120]. This unexpected result was resolved later by Faingold and colleagues when they demonstrated that those excessive neurons and GABA-associated molecules were non-functional [121–123].

Complementary studies with GEPRs [124], using either microinjections in SC of excitatory substances or blockade of inhibitory neurotransmitters and lesions or transections (knife cuts) separating IC and SC [68,124,125], supported previous data with WARs [68], thereby confirming the importance of the SC in the expression of acute and kindled audiogenic seizures in GEPRs.

3. Triggering acute and chronic (kindled) audiogenic seizures with high-intensity auditory stimulation

In animals susceptible to audiogenic seizures, a single acoustic stimulus reflexively triggers a seizure that usually begins with wild running progressing to a tonic–clonic phase [21,41,126,127], mimicking generalized seizures in humans. Although each nucleus of the acoustic pathway should reasonably be involved in the expression of audiogenic seizures, most of the nuclei studied to date have been in the lower brainstem up to the midbrain [37,89,128]. Several studies have demonstrated that diencephalic and forebrain regions and circuits are not needed for the expression of acute audiogenic seizures in DBA mice [128] and GEPRs [37] (for a review, see Garcia-Cairasco [36]). An intriguing and interesting case is the GASH:Sal hamster, which exhibits functional and morphological alterations in the peripheral auditory system. Sanchez-Benito et al. [129] showed that the GASH:Sal strain has an auditory brainstem response threshold that is asymmetrical and higher than controls for several frequencies. In addition to alterations at the cochlear level (basal to apical cochlear turns), nuclei of the superior olivary complex are also altered.

Although there is no doubt that brainstem regions and circuits are associated with acute audiogenic seizures [36,37], the audiogenic models that seem to be relevant to TLE are those with chronic protocols or audiogenic kindling, which affect behavior, EEG, and neuroanatomical structures involving cortical and limbic networks [26,33,92]. Therefore, a brief discussion of the development of kindling models is provided.

From the 1950s to the 1970s, several studies designed to evaluate memory paradigms and their associated circuits used the globally accepted model of electrical stimulation of limbic structures, among them the amygdala. This protocol was named “kindling” by Goddard et al. [39]. The main feature of this model was the use of a subthreshold electrical stimulation, one that did not initially evoke EEG alterations, which over time after repeated stimulations evoked so-called primary afterdischarges accompanied by increasing behavioral alterations. These behavioral alterations became the basis for Racine's seizure severity scale [40] (see details in Table 3). Further studies by Pinel and Rovner [91] established a chronic paradigm in which 360 daily electrical stimulations of the amygdala produced spontaneous recurrent seizures (SRS). Shorter protocols with close to 100 amygdalar stimulations also evoked SRS [130] (Table 4).

Therefore, by analogy to amygdala kindling, Marescaux et al. [26] exposed WAS animals from Strasbourg to 40 daily auditory stimulations and described recruitment of cortex using EEG recordings from surface electrodes, thereby showing, for the first time, “audiogenic-kindling”. Some years later, Naritoku et al. [92] described the same phenomenon in GEPR-9s and GEPR-3s and together with Hirsch et al. [131] studying WAS rats from Strasbourg and Romcy-Pereira and Garcia-Cairasco [58] and Dutra Moraes et al. [33,58] studying WARs from Brazil, showed that recruited areas also included hippocampus and amygdala complex.

In consonance with the behavioral and EEG data, research groups in France [132] and the US [133], using c-Fos expression as a marker of neuronal activation, anatomically demonstrated the altered circuits after chronic acoustic stimulations. In WARs, our laboratory showed that with the initial stimulations of the audiogenic kindling protocol, WARs display severe mesencephalic seizures (Garcia-Cairasco's scale [49], Table 2) and no limbic seizures (Racine scale) [40] (Table 3). However as the audiogenic kindling progresses, the severity of mesencephalic seizures decreases whereas limbic seizures appear [49] and recruit amygdala, hippocampus, and cortex, as shown by EEG [33,58,61,64,77].

Needless to say, those video-EEG studies were fundamentally important to understanding the coupling between behavior and EEG activity. Some years later, we applied the video-EEG technology developed in our laboratory to GEPRs [134,135] in a collaborative project with the Jobe laboratory.

At the same time that experiments with audiogenic kindling were published, Parent and colleagues demonstrated that PILO-induced SE [136] as well as amygdala kindling [137] were associated with the appearance of 5-bromo-2-deoxy-uridine (BrdU)+ neurons, indicating a process normally known as neurogenesis, but which to that time had primarily been detected during normal development and not associated with seizures. While adult neurogenesis had already been demonstrated by Altman [138], Parent et al. used immuno-histochemistry for BrdU, a timidine analog, rather than the tritiated carbon used by Altman's group. Parent et al. [136] argued that these newly-produced neurons were responsible for the presence of another aberrant feature of the dentate granule cells, namely mossy fiber sprouting [139,140]. However, his team went on to demonstrate [141] that X-ray treatment, a procedure that abolished neurogenesis, was not able to impair mossy fiber collateral formation.

Table 2
Mesencephalic seizure severity indexes of Garcia-Cairasco et al. [49]* and Rossetti et al. [64]**.

Score*	Behavior	Score**
0	No seizures	0
0.11	Wild running	1
0.23	Wild running + jumps	2
0.38	2 wild runnings	3
0.61	Tonic seizure	4
0.85	Generalized clonic seizure	5
0.90	All the above plus head ventral flexion	6
0.95	All the above plus forelimb hyperextension	7
1.00	All the above plus hindlimb hyperextension	8

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Table 3
Racine scale [40] for limbic seizures.

Stage/class	Behavior
I	Mouth and facial movements
II	Head nodding
III	Forelimb clonus
IV	Rearing
V	Rearing and falling

The audiogenic kindling protocol elicits neuroplasticity in recruited brain areas that become part of the epileptogenic circuitry, especially in the cortex, amygdala, and hippocampus. Similarly to pivotal and recent studies using amygdala kindling [137,142,143], our group demonstrated that in WARs exposed to audiogenic kindling, hippocampal BrdU+ cell proliferation/neurogenesis are dependent on the presence of limbic seizures [58]. Specifically, WARs with more than six limbic seizures classified as Racine IV or V [40] had significantly more BrdU+ nuclei than animals that had none or 1–3 Racine IV or V seizures [58].

Interestingly, in contrast to amygdala kindling [144–146] or chemically-induced SE [147,148], the WARs undergoing audiogenic kindling did not show mossy fiber sprouting in the hippocampus, whether at one day or thirty days after the kindling; however, aberrant Neo-Timm staining was observed in the perirhinal cortex and several nuclei of the amygdaloid complex [49,59]. The potential role of mossy fiber sprouting as a main component of hyperexcitability in limbic networks associated with epilepsy is still under discussion [149–154].

Together with newly-produced neurons in non-audiogenic models of SE, there is also neurodegeneration and cell death [155–158]. While in audiogenic kindling in WARs, Fluoro-Jade (FJ+) C histochemistry, a known marker of neurodegeneration, failed to stain hippocampal neurons [58,59], there may be other markers for neuronal death or neurodegeneration yet to be studied, such as caspases, which are expressed in apoptotic processes associated with the epilepsies [159].

It is important to highlight that amygdala kindling is facilitated in WARs after the animals have already been exposed to audiogenic kindling [59] and that the stressful repetition of auditory stimulation, even without producing seizures, such as in Wistar control animals, also facilitates amygdala kindling [59]. Indeed, in the amygdala kindling model, it is well demonstrated that chronic stressful stimuli are epileptogenic [160,161].

Chronic audiogenic seizures *per se* are able to induce behavioral, morphological, and functional modifications such as neurogenesis [58], mild hippocampal cell loss [59], and electrophysiological evidence of limbic epileptogenesis [33,58]. However, we still need to evaluate the actual impact of the incorporation of newly-born neurons in the brains of WARs. In the case of more severe seizures, such as those from SE induced by PILO, it has been well documented that newly-generated neurons are incorporated aberrantly to the hippocampus network and thereby greatly contribute to further epileptogenesis [162–164].

Table 4
Pinel and Rovner scale [91].

Stage/class	Behavior
I	Mouth and facial movements
II	Head nodding
III	Forelimb clonus
IV	Rearing
V	Rearing and falling
VI	More than three fallings
VII	Wild running
VIII	Tonic–clonic seizures

4. The genetic selection of audiogenic-susceptible WARs and the consequent selection of comorbidities

The first time that WARs were introduced to the world community was at the *International Conference of Genetics of the Epilepsies* held in Minneapolis [34]. The pioneering studies with the *Wistar Susceptible Rats* (no inbred strain was available yet) were done at the Neuroethology Laboratory at the Ribeirão Preto School of Medicine at the University of São Paulo in the early 1980s, under the direction of Prof. Renato M. E. Sabbatini. The first characterization of the phenotype "*susceptible to audiogenic seizures*" for Wistar animals housed in the main Vivarium of the University of São Paulo in Ribeirão Preto was part of Norberto Garcia-Cairasco's Master's degree dissertation.

The first publication [41] based on acute auditory stimulation studies described two quite complex phenotypes: "*Wistar-Susceptible Rats*" and "*Wistar-Resistant Rats*". Garcia-Cairasco and Sabbatini [41] produced the first quantitative description of those phenotypes using flowcharts of behavioral sequences. Indeed, the sequences were of fundamental importance for the recognition of quite conspicuous clusters of behaviors such as oro-facial automatisms and dense exploratory and grooming behaviors in *Wistar-Resistant Rats*, particularly associated with the sound stimulation period. This was in contrast to the stronger startle response and decrease in exploratory clusters and grooming behaviors, as well as the presence of wild running cluster and tonic–clonic seizure clusters in "*Wistar-Susceptible Rats*". These behavioral sequences were described not only for the first time in audiogenic seizures but for experimental models of epilepsy in general, and contrasted with the behavioral scores or scales widely used at the time in epilepsy laboratories worldwide, which as noted earlier are arbitrary, categorical, and usually linear measurements of seizure severity.

While studies of *Wistar-Susceptible Rats* (out of the outbred Wistars) and the so-called *"audiogenic-like seizures"* in Wistar rats that were either lesioned in the IC or the substantia nigra pars reticulata (SNr) [43,45,89] but not the substantia nigra pars compacta (SNc) [165] proved to be fruitful, we decided to develop our own genetically-selected epileptic strain. To do so was a team effort, beginning with Maria Carolina Doretto, at that time a PhD student; José Antonio Cortes Oliveira, Research Technician; and Vera Cristina Terra, an undergraduate medical student, working with Garcia-Cairasco in the early 1990s. The team inbred Wistar-susceptible sisters and brothers, assuring the parturition of pregnant females, identified males and females in the litters, weaned the offspring, and separated males and females as soon as they were sexually mature.

After completing her PhD in 1992, Doretto took, as a donation from the Garcia-Cairasco laboratory, some WAR males and females to launch the second branch of WARs at the IBS at the Federal University of Minas Gerais, where it is still maintained under the supervision of Dutra Moraes, also a former PhD student from the Garcia-Cairasco laboratory. Oliveira, 28 years later, is still the main responsible person for the inbreeding program and the care of the WARs at University of São Paulo.

As of this writing, several thousand FMRP-USP-WARs and IBS-UFMG-WARs have been generated over more than 56 generations of brother × sister inbreeding. The first matings were done between animals that developed what is today called an intermediate seizure severity index [49,64], because at that time the outbreeding protocol did not identify the maximum seizure severity (tonic–clonic seizures, fore and hindlimb hyperextensions) that was seen, for example, in other strains such as the GEPRs, genetically developed initially by Jobe at the University of New Mexico [21] and later on at the University of Illinois College of Medicine at Peoria [110]. Currently, GEPRs are still maintained at the Pharmacology Department at the Southern Illinois University, Springfield, Illinois, under the direction of Prof. Carl Faingold.

The WAR strain was developed by mating brothers with sisters based on their behavioral seizures in response to acoustic stimulation. Animals that displayed tonic seizures are considered eligible for mating

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and only animals born from a dam's first delivery are elegible for screening.

Briefly, 70-day-old male and female rats are exposed to three acoustic stimulations at 48-h intervals. They are placed into the acrylic stimulation chamber (32 cm height × 30 cm diameter), which is located in a wooden, sound-proof box (45 cm × 45 cm × 40 cm) with a glass door. On top of the acrylic chamber is located a speaker (tweeter), connected to an amplifier which receives digital signals provided by a computer to produce pseudo-random sounds with frequencies between 5000 and 20,000 Hz at a sound intensity as measured inside the chamber of approximately 110–120 dB. Typically, the initial behaviors seen when a susceptible animal is exposed to acoustic stimulation are startle and withdrawal, eventually followed by wild running, which in fact is a composite of running and bouncing, jumping, and atonic falling [41,49]. The latency until wild running is one of the parameters measured to evaluate seizure susceptibility. The wild running occurs with or without jumps and atonic falls and can occur more than once during the same acoustic stimulation. Typically 1 or 2 episodes of wild runnings are observed. A tonic seizure (*opisthotonus*) occurs after the wild running phase and is usually followed by a generalized clonic seizure. In animals with high sensitivity to acoustic stimulation, head ventral flexion is seen after the tonic seizure, which can be followed by forelimb and hind-limb hyperextension. As noted above, based on the occurrence of these brainstem-dependent behaviors, an audiogenic seizure severity index was proposed by Garcia-Cairasco et al. [49] which was modified and categorized years later by Rossetti et al. [64] (Table 2). For detailed information regarding characteristics of audiogenic seizures in different strains (rats and mice), readers are referred to Ross and Coleman [15].

The first substantial quantitative evaluation of the genetically-selected WARs at our laboratory comprised 9450 observations of 1575 animals from the 3rd to 17th generations of genetic selection. That study demonstrated significant effects of generation, parturition, and litter on the Seizure Severity Index and of generation and litter on latency of wild running and tonic–clonic seizures [27].

More recently, we have detected several behavioral and molecular alterations in WARs. While this analysis was not an aim in the initial genetic selection of the audiogenic seizure phenotype, the endogamy/consanguinity throughout the generations produced an enormous increase in homozygosity and gene linkage. Therefore, the study of comorbidities is currently one of the objectives of our studies with the epilepsy genetic phenotype. To that end, we are developing a joint project between the FMRP-USP and the IBS-UFMG (under the supervision of Dutra Moraes), in order build a plataform/database of sufficient size for a comparative WAR study that will allow quantitative evaluations of both branches of WARs for the current 56 generations and for future generations. This platform will give us sufficient preliminary data to plan behavioral, EEGraphic, pharmacological, genetic, and epigenetic studies, among others, to compare the two colonies of WARs.

5. Endogenous anticonvulsant systems and the WARs strain: an example of translational value

Although the main interest of our laboratory at the start was to select susceptible animals to further investigate mechanisms involved in epileptogenic phenomena, we were also interested in characterizing endogenous anticonvulsant properties of brain networks.

We were intrigued that seizures have an onset (with or without a known trigger), a variable dynamic evolution, and, except for SE, an inevitable offset. Molecules such as adenosine [166], enkephalins, endorphins and opiate peptides [167], and oxytocin [168], among others, had been strongly implicated as endogenous anticonvulsant substances in several epilepsy models. Several laboratories had also suggested that specific brainstem circuits or networks could be part of so-called "endogenous anticonvulsant systems". The Gale laboratory at Georgetown University [169] produced pioneering experimental protocols that clearly demonstrated a potent anticonvulsant action of microinjections of muscimol, a GABA agonist, into the SNr of rats treated with either bicuculline or electroshock. Several other laboratories confirmed these findings, including the McNamara laboratory, which at that time was working with electrical kindling of the amygdala [170].

As a Master degree student, Garcia-Cairasco was aware of the classic experiments with SNc lesions induced by 6-hydroxydopamine (6-OHDA) in which the associated rotational or circling behavior was used as an experimental model of Parkinson's disease [171]. With that background, we first thought that the asymmetry of the *wild running* behavior, typical of the early phase of audiogenic seizures, was a consequence of alterations of circuits involving either SNr or SNc, but we did not know which one. Therefore, we proceeded with manipulations in Wistar resistant rats that interestingly became susceptible to audiogenic seizures after unilateral electrolytical lesions of the SNr [89,172], but not with 6-OHDA lesions of the SNc [165]. Using the latter protocols (with SNc) to prove that this could be a selective effect, we were able to induce clear amphetamine-dependent ipsilateral classical rotations (experimental *Parkinson-like* behavior) to the lesion side [171], but acoustic stimulation was not able to induce audiogenic-like seizures [165]. The experiments that followed were a collection of specific manipulations in either IC or both IC and SN, with either inhibitory neurotransmission blockade, for example with the $GABA_A$ receptor antagonist bicuculline [45,90] or by activation of glutamatergic excitatory neurotransmission with N-methyl-D-Aspartate (NMDA) [46], and both were able to induce audiogenic-like seizures in Wistar resistant animals.

In collaboration with the Jobe laboratory, we then demonstrated with brain microdialysis that perfusion with 100 mM of KCl into SNr induced the release of several neurotransmitters, among them aspartate, GABA, glutamate, and taurine in Sprague–Dawley controls but not GABA in GEPR-9s [173]. Although we did not confirm the lack of endogenous GABA release in nigral circuits during an actual audiogenic seizure in GEPRs and have not evaluated the status of SNr GABA in WARs, we are nonetheless confident that both sets of findings are strongly associated with the susceptibility of these strains to seizures.

Since then, several other laboratories contributed information on the potential role of selected regions of the nigral complex system to endogenous anticonvulsant effects. Findings from the Gale laboratory suggested that the most critical pathways were likely those from SNr to intermediate or deep layers of the SC or to the pedunculo-pontine nucleus, but not to the thalamus [174]. At the same time, the Moshe laboratory developed protocols with the fluorothyl model, showing paradoxical pro-convulsant effects of muscimol, particularly in young (P16) animals [175]. Over time, they proposed that anterior and posterior regions of the SNr could have anticonvulsant and pro-convulsant effects, respectively [176], acting (without specific anatomic or track-tracing demonstration) on their respective/analogous SC regions.

The identification of endogenous anticonvulsant systems benefited from the excellent and detailed mapping of intermediate and deep layers of SC by Redgrave et al. [177], who studied those circuits and their roles in fight or flight responses. They proposed that a polymodal sensory system facilitated synchronous or selective responses, depending on whether an event was perceived as non-dangerous or threatening.

It was already known [169] that at the peak of the GABAergic-dependent anticonvulsant effect, treated animals expressed choreic-like behaviors, typical of Hungtington's chorea hyperkinetic activity. Related clinical observations were made years later when lamotrigine, which is thought to inhibit the release of glutamate, was noted to induce tourettisms [178].

The contemporaneous description of choreic movements and tourettisms as side effects of experimental anticonvulsant treatments that target the basal ganglia suggested common underlying substrates for both anticonvulsant and pro-hyperkinetic effects. In clinical terms this is a problem, analogous to the situation with the anti-psychotic treatment haloperidol, a dopamine antagonist, which in addition to

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alleviating psychosis may cause Parkinsonian-like movements [179]. But from the basic science perspective, we viewed these "aberrant behaviors" as very specific biomarkers that indicated the anticonvulsant activity was occurring through mechanisms involving the basal ganglia and their connections.

Interestingly, we found that when patients with TLE have seizures that include dystonic postures (suggestive of basal ganglia involvement), they are twice as likely to not have secondary generalized tonic–clonic seizures compared to those without dystonic postures [99]. For that reason we coined the concept "*circuit antagonism*", which in our view is consistent with the contrasting behaviors described above.

We then began to study behavioral and EEG coupling in WARs associated with acute and kindled audiogenic seizures, with the main goal of determining alterations in SNr-SC connections of WARs. Rossetti et al. [64] had already demonstrated that systemically-applied phenobarbital completely blocked audiogenic seizures in WARs, but phenobarbital and muscimol microinjected into SNr did not. This suggested that WARs have endogenous alterations in their SNr, probably associated with their susceptibility to seizures, which is similar conceptually to GABA release alterations in the GEPRs SNr [173]. Using neuroethology, spectral analysis of EEG, GABA receptor imuno-histochemistry, and track-tracing techniques (fluorogold, a retrograde tracer, microinjected into SC), Rosseti et al. [64,73] had also showed that SNr neurons project fibers to both anterior and posterior regions of SC, and interestingly, that both sites exert pro-convulsant effects when microinjected with muscimol. What remains unclear is how to reconcile these data with those from Moshe's laboratory suggesting the differential expression of anticonvulsant activity of anterior SNr and the pro-convulsant activity of posterior SNr in flurothyl-induced seizures in young Sprague–Dawley rats [180].

Also controversial is the role of SNr in epilepsy-related comorbidities such as autism and obsessive–compulsive disorder (OCD). Velízek et al. [181] described circling behavior induced by unilateral application of muscimol, a potent $GABA_A$ and anticonvulsant agent, into SNr. This behavior is a conspicuous clinical expression of autistic/repetitive behavior, which experimentally appeared to Velízek et al. as due to activation of a nigral network with participation of both SNc (DA) and SNr (GABA).

An additional and interesting related stereotyped behavior – grooming – is accompanied by spiking activity in SNr [182]. In fact, the SNr is believed to code entire sequential patterns of grooming actions, not only elemental grooming movements. In that context, we developed an experimental model of compulsive behavior [96], induced by bilateral microinjection of oxytocin (OT) into the central nucleus of amygdala (OT-CeA-induced hypergrooming) of Wistar rats and showed (unpublished data) that at the peak of grooming behavior (hypergrooming) induced by microinjection of OT in the basolateral amygdala, rapid amygdala kindling is blocked in already-kindled animals. Our explanation is that circuit antagonism (probably by the SNr-SC pathway) is responsible for this intriguing effect, in agreement with the proposal of Meyer-Luehmann et al. [182] and Aldridge et al. [183], based upon Mink [184], that the basal ganglia are able to focus or select certain movements by dynamically inhibiting competing motor programs.

Recent studies with optogenetics, while challenging technically, have further advanced our understanding of endogenous anticonvulsant basal ganglia mechanisms. Optogenetic activation of the deep layers of the SC blocked or attenuated audiogenic seizures in GEPRs; seizures induced with neurochemical desinhibition of the deep pre-piriform cortex (area tempestas), with bicuculline, a $GABA_A$ antagonist; seizures evoked by gamma butyrolactone (thalamocortical/absence seizures); and seizures induced by the chemoconvulsant pentylenetetrazole [185]. In ongoing experiments, this group is using optogenetics to manipulate SNr [186], which sets the stage to further evaluate the role of SNr-SC pathways in the expression of audiogenic seizures in WARs.

Another recently developed anticonvulsant technique, direct electrical brain stimulation one form of which has been FDA-approved since 2013 [187], can be applied to the study of WARs over the next decade to further explore endogenous anticonvulsant systems. The long-term clinical impact of this therapy may also shed light on network plasticity and resulting clinical manifestations.

6. Autonomic control of the cardiovascular and respiratory systems in naïve and kindled WARs

Cardiovascular dysfunctions are well known to occur in patients with epilepsy [188,189]. Autonomic control of the cardiovascular function in WARs was investigated in a series of studies by Fazan et al. [75,81]. The first study evaluated the autonomic modulation of the cardiovascular system. Spontaneous baroreflex, as well as changes induced by phenylephrine/nitroprusside and propranolol, were compared in WARs and Wistars, indicating that WARs have a higher arterial pressure and increased heart rate. Moreover, when compared to Wistars, WARs have higher sympathetic and lower vagal modulation of cardiac function, as indicated by the low- and high-frequency (LF, HF) power of the pulse interval spectra [75].

Further cardiovascular alterations were evaluated in one-year-old WARs with long-term ECG recordings [81]. Spontaneous arrhythmias and HR frequency variability were analyzed in conscious rats while ventricular function (pressure-volume conductance) was performed in anesthetized animals. Autoregressive spectral analyses showed that the RR intervals do not differ between WARs and Wistars; however, WARs had higher RRi variability, increased LF, and increased LF/HF ratio. Hemodynamic results indicated that WARs also have alterations in the indexes of systolic and diastolic function, as well as higher occurrences of ectopic beats [81].

Additionally, Granjeiro et al. [86] used body plethysmography to obtain pulmonary ventilation (VE) measurements of WARs exposed to both acute hypercapnia (7% CO_2) and acute hypoxia (7% O_2). Ventilation of WARs was attenuated when compared to Wistar in both conditions, which was associated with alterations in the behavioral responses of these animals, demonstrating that WARs have alterated compensation for changes in levels of arterial blood gases [86]. Totola et al. [87] confirmed this attenuation of ventilation in WARs, and further demonstrated that naïve and kindled WARs have reduced rest ventilation and ventilatory response to hypercapnia. More interestingly, they showed that WARs have a reduced number of chemically coded (Phox2b+/TH−) retrotrapezoid nucleus (RTN) neurons, a key component of the medulla respiratory control, as well as a reduced number of 5-HT neurons in the midline medulla and reduced 5HT innervation to the RTN [87].

These findings suggest the possibility that WARs could serve as a model for SUDEP. Indeed, we have also found alterations of cardiovascular [75,81] and respiratory [86,87] functions in WARs. Yet no WARs died suddenly in our studies [75,81] or those GEPRs of our colleagues [78,79], though the WARs have been shown to display cardiovascular alterations, including hypertension, tachycardia, and more recently, 5-HT dysfunction in brainstem respiratory control nuclei [87], and all of these findings have been linked to SUDEP [190].

In a current model of SUDEP, DBA mice display an unusually increased mortality that is prevented by selective inhibitors of 5-HT re-uptake [191,192] (see Feng et al. [192] in this special issue). To further explore whether WARs may be a reliable and suitable model to study SUDEP, it is important to understand why WARs display attenuated respiratory frequency and ventilation when exposed to both hypercapnia and hypoxia [86,87], as well as their deficient 5-HT respiratory control mechanisms [87], and to include consideration of the endogenous stressful profile of WARs [52], occurrence of ectopic beats [75,81], and their hyperactive HPA axis [72] and increased sympathetic tone.

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By contrast, Sprague–Dawley-derived audiogenic strain GEPRs do not usually die after tonic–clonic audiogenic seizures (personal communication, Carl Faingold), even though they have profound 5-HT endogenous alterations, similar to WARs. However, the Faingold group has shown that after either ethanol withdrawal [193] or pre-treatment with adenosine 1 metabolism inhibitors [194], GEPRs have: (1) a substantial increase in the duration of post-ictal depression, (2) increased respiratory distress, and (3) increased mortality. Similar experiments need to be done with WARs.

Another approach to unraveling the mechanisms of SUDEP is suggested by the work of Richerson et al. [195], who demonstrated what is called "central apnea" in patients induced by electrical stimulation of amygdala, of which patients were unaware. The authors suggest that recruitment of the amygdaloid complex can be crucial to the consequent inhibition of brainstem central respiratory control nuclei as a potential a cause of SUDEP. Since we already demonstrated that audiogenic kindling recruits the amygdala in WARs [33] and facilitates subsequent amygdala kindling [59], studying the effect of amygdala electrical kindling in WARS would be a logical step forward in the study of respiratory alterations in WARs [87].

7. Modeling neuropsychiatric comorbidities in WARs

Kanner et al. [196] strongly stated that epilepsy and neuropsychiatric disorders, particularly depression, are bidirectionally associated. In other words, as clearly demonstrated over the decades, persons with epilepsy can become depressed [197], and as more recently documented epidemiologically, depression increases the risk of developing epilepsy [198]. This bidirectional effect is also supported in experimental models [199–204].

Kanner [204] recently reviewed the four major pathogenic mechanisms underlying depressive disorders that can contribute to epileptogenesis. In the neuroendocrine domain, HPA axis abnormalities are common findings in depressive disorders [205] and corticosterone is known to facilitate seizure susceptibility in experimental models of epilepsy [206]. In the structural domain, depressive conditions are associated with biomarkers commonly seen in epilepsy, such as altered neurogenesis and reduced hippocampal volume [207–209]. At the molecular level, multiple lines of evidence point to the involvement of monoamines in both depression and epilepsy [109,210–212], as well as glutamate, GABA, and pro-inflammatory cytokines [213].

A small number of studies have evaluated audiogenic strains and depression. The GEPR-3 colony, which has milder seizures than the GEPR-9 colony, has been suggested as a potential model for the neuropsychiatric comorbidities of epilepsy [109,210–212].

As detailed in this special issue, Castro et al. at the IBS-UFMG studied neuropsychiatric comorbidities in WARs. They compared WARs with Wistar audiogenic seizure resistant controls, and found that WARs displayed increased forced swimming test (FST) immobility, but no impairment in sucrose consumption preference or social exploration. In addition, WARs were unable to properly display appropriate degrees of aversiveness in the open-field test, the elevated plus maze, and the inhibitory avoidance test.

Additionally, the WAG/Rij strain, a mixed model of audiogenic seizures and absence seizures [25], has been used to test the combined potential of anti-depressant and anticonvulsant drugs [214,215].

8. Anxiety, stress and compulsion

People with epilepsy have an increased risk for anxiety disorders [216,217] among other psychosocial consequences [218], suggesting these too are comorbidities of epilepsy [219]. Several behavioral tests have been proposed to assess anxiety levels in rodents [220]. Garcia-Cairasco et al. [52] demonstrated that male and female naïve WARs, compared to their gender-paired non-susceptible Wistar controls, have reduced novel environment exploration as assessed by decreased distance traveled in the open-field test. Moreover, these rats showed an anxious profile in the elevated plus maze test, as assessed by decreased number of enclosed-arm entries, decreased percentage of time spent in the open arms, and decreased number of entries into the distal halves of the open arms.

Importantly, stress is often mentioned by persons with epilepsy as the most frequent seizure precipitant [221–223]. In addition, stress also appears to predispose to epilepsy, especially when it occurs early in life [224]. Studies with experimental models (for reviews, see [225,226]) are essential to shedding more light into the mechanisms underlying these clinical phenomena.

In this context, WARs may represent an interesting model to explore epilepsy–anxiety comorbidity inasmuch as they do not require exposure to chemicals or brain stimulation to induce seizures and they naturally display a stress-prone phenotype. Umeoka et al. [72] demonstrated that seizure-naïve WARs are considerably smaller than Wistars – at 70 days of age the body weight of WARs is almost half that of Wistars – and yet, WARs have a bigger adrenal gland, with a thicker *fasciculata* cortical layer and increased medullary volume. These morphological differences are associated with a hyperreactive HPA axis; WARs exposed to 15 min of restraint stress show higher plasma levels of ACTH than Wistars under the same conditions. Moreover, after exogenous ACTH intravenous injection, WARs release higher amounts of corticosterone than Wistars [72] and, consistent with this result, WARs have increased sympathetic cardiac tone compared to Wistars [81].

Furthermore, in several animal models, stress enhances vulnerability to seizures [160,208,227–230]. Likewise, in WARs, the endogenous hyper-reactive HPA axis seems to contribute to their seizure-prone phenotype. Data published only in abstract form from our laboratory [231] show that chronically stressed WARs present with more severe mesencephalic seizures throughout the whole audiogenic kindling protocol than non-stressed WARs, an effect that is blocked by gluco- and mineralocorticoid receptor antagonists, demonstrating that seizure severity and latencies for wild running and tonic seizures are modulated by corticosterone, most likely through genomic mechanisms.

Another psychiatric comorbidity of epilepsy, and in particular TLE and FLE, is OCD [232]. Modell et al. [233] discusses the two principal loops related to control of behaviors that may be dysfunctional in OCD: the glutamate-driven thalamo-orbitofrontal connection, and a collateral circuit, the striatal-orbitofrontal-thalamic, mediated additionally by serotonin, dopamine, and GABA. In that regard, and as mentioned earlier, we demonstrated that bilateral micro-injections of oxytocin induce hyper-grooming, which we propose as a model of compulsive behavior [96]. It is intriguing that WARs display even more pronounced grooming behavior when exposed to a novel environment [234,235], which suggests that the WAR strain is a genetic model of epilepsy with the behavioral comorbidity of hyper-grooming.

9. Memory and cognition

The quality of life of patients with epilepsy is often compromised due to cognitive impairment [236,237], especially memory difficulties, which can be easily assessed in rodents with tests such as the classic Morris water maze (MWW) [238] and the novel object recognition test (ORT) [239].

Recently, 60-day-old WARs were evaluated with these behavioral paradigms by Cunha et al. [84]. Naïve WARs, when compared to Wistars, performed slightly worse in the MWW. Although WARs naturally swim faster and travel shorter distances to reach the platform location, during the probe trial, they required more time than Wistars to complete the task. Moreover, WARs that were exposed to audiogenic kindling and had at least 3 limbic seizures four days prior to the MWW tests traveled significantly longer distances to find the platform location than WARs that did not experience limbic seizures. However, no significant difference was observed for the latency to reach the platform location [84].

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Cunha et al. [84] also showed that chronic audiogenic stimulation in Wistars hampered the LTP of the Schaffer-CA1 pathway; however, this effect was not observed in WARs exposed to audiogenic kindling.

Unpublished data from our lab suggest that cognitive impairment in WARs starts earlier than in Wistars. Naïve rats from both strains were submitted to the novel ORT. Briefly, while Wistars stopped distinguishing between novel and familiar objects at 12 months of age, WARs did so at the age of 7 months [240]. This result is in line with preliminary findings showing increased hippocampal levels of beta amyloid in naïve WARs compared to Wistars, and additionally with the finding that after audiogenic kindling of WARs, p-Tau is overexpressed when compared to the naïve condition [241].

10. Endogenous and seizure-dependent cellular and molecular alterations in WARs: possible biomarkers of epileptogenic networks and comorbidities

10.1. Hippocampal renin–angiotensin system

The renin–angiotensin system (RAS) is well known for its role in blood pressure control [242]; however, it is also involved in processes that control body temperature, water–electrolyte balance, and release of hormones [243,244]. Interestingly, in WARs exposed to audiogenic kindling that have not yet had their first seizure, increased expression of RAS mediators such as ACE and AT1 are detected in the hippocampus, but not in the heart. Curiously, treatments with enalapril (an ACE inhibitor) and losartan (an AT1 blocker) during audiogenic kindling reduce the severity of mesencephalic and limbic seizures [70].

Further biochemical studies on the RAS of WARs showed that, in the hippocampus, angiotensin 1–7 is the main metabolite of angiotensin-I and thimet oligopeptidase is the main enzyme responsible for this cleavage. Hippocampal levels of thimet oligopeptidase, the most important endo-oligopeptidase for the synthesis of Ang (1–7), as well as Ang (1–7) itself and its receptor Mas, were elevated in WARs after audiogenic kindling [80].

10.2. Hippocampal expression of BC1, GluR2, and Erg3

Molecular analyses of gene expression of the non-coding RNA sequence BC1, a known repressor of Fragile X modulatory repressor protein (FMRP) [245,246], identified decreased levels of BC1 mRNA in the hippocampus of WARs experiencing audiogenic kindling when compared to naïve WARs or to resistant naïve Wistars, demonstrating that this decrease is associated with repeated seizures and not with the stimulus *per se* [71]. Interestingly, quantitative *in situ* hybridization showed that this effect is region-specific and significant only in the hilus of the dentate gyrus [71]. It is worth mentioning that mice lacking the BC1 gene (BC1 −/−) are hyperexcitable and have heightened epileptogenic susceptibility both *in vitro* and *in vivo* [245].

Based upon these data, our expectations are that, at least in the hippocampus, WARs would have an up-regulation of FMRP. Given that young WARs have increased expression of beta amyloid [240,241], it is important to look for potential associations between our data and those from Westmark et al. [246] that support roles for amyloid β precursor protein (ABPP) in the determination of seizure threshold, measured as an increase in audiogenic seizure susceptibility and coupled synaptic plasticity, in FMRP knockouts. Further studies are needed because BC1 is a known repressor of FMRP and highly associated with autism [245–248]. In fact, APP, FMRP, and mGLUR5 are proposed to be the molecular links between autism, Alzheimer's disease, and fragile X syndrome [247].

Moreover, mRNA expression of the splice-variant GluR2-flip is overexpressed in the hippocampal CA1 region of WARs exposed either to acute or chronic audiogenic seizures (kindling). Similar findings on GluR2 overexpression were previously reported in the hippocampus of a different audiogenic strain developed in China (P77PMC) [24,249].

As part of a collaborative project between the Neuroscience Institute of Castilla y León at the University of Salamanca, Spain and our laboratory, Lopez-Lopez et al. [85] further investigated similarities in gene/protein expression in the IC after a single audiogenic seizure in two audiogenic susceptible strains, the WARs and the GASH:Sal. Among the altered genes detected in a microarray, there was significant (>2-fold) upregulation of 38 genes and downregulation of 47 genes in WARs compared to Wistars. A lower number of upregulated and downregulated genes was found when comparing control hamsters and GASH:Sal. Of particular interest is the zinc finger immediate-early growth response gene Egr3, which codes for a transcription factor induced by stress, which has been validated by immunohistochemistry of the protein in the cochlear nucleus complex, the IC, and the hippocampus of GASH:Sal and WARs [85].

Further explorations should be done with microarrays to look for potential clusters or cascades of genes and their codified proteins as important mediators of the audiogenic susceptibility of these strains and their associated comorbidities. In the case of the GASH:Sal, the gene Egr3, for example, is also associated with comorbid lymphoid tumors [250].

11. Making WARs available internationally

Taking into consideration all the above-described findings of WARs, chronologically summarized in Table 1, it is evident how valuable this

Fig. 2. Seizure severity mesencephalic (A_1) and limbic (A_2) indexes, of male audiogenic susceptible Wistar rats (n = 12) in a 30-day, 60-stimuli (twice daily) audiogenic kindling protocol. It is a clear reduction of the mesencephalic severity index is observed, coupled to an increase of the limbic index over the progression of the kindling protocol. Both events look as a mirror image, suggesting potential opposite interactions between them. After the two-month period without stimulation, the mesencephalic index almost come back to the initial high values, but the limbic index never returned to zero, indicating a clear memory effect of the kindling protocol. Taken with permission from [49]. B_1 illustrates the calibration of the rectangles (behaviors) and arrows (log X^2 values, where $X^2 > 3.84$; $p < 0.05$) of the flowcharts (behavioral sequences; clusters of behaviors are indicated by specific colors and ellipses [49]. In (B_2) and (B_3) are illustrated flowcharts of behavioral sequences of female WARs (n = 9) acoustically stimulated (110–120 dB) 30 days (once daily). Observation windows are PRE (before), SOUND (during) and POST (after) sound stimulation, respectively. Top flowchart (B_1) illustrates the acoustic 1st stimulation with predominance of exploration and grooming clusters (blue symbols) at the PRE phase. At the SOUND phase, beginning with startle (STA) there is also a clear exploratory cluster followed at some point with wild running behaviors (yellow symbols) and tonic seizures (*opistothonus*, CVT) in the limit between the SOUND and the POST phases. After the sound is off, a behavioral sequence or cluster of tonic–clonic seizures appears (red symbols), followed by post-ictal depression features (PIM, AP, DYS) and some behaviors such as those of a fragmented exploratory cluster, typical of recovery after the seizures. Bottom flowchart (B_2) illustrates the 30th acoustic stimulation. The PRE phase is characterized by the presence of an exploratory cluster, similar to the 1st acoustic stimulation, but a stronger grooming cluster (blue symbols). At the SOUND phase, after the startle response, in addition to exploratory behaviors, there is the co-existence of wild running behaviors (yellow symbols) and the limbic seizures cluster (green symbols). At the limit between the SOUND and the POST phases, the tonic (*opistothonus*, CVT) seizures are followed by generalized tonic–clonic seizures (red symbols) quite fragmented, when compared with the 1st stimulation (B_1). The post-ictal depression (PIM, AP, BR,TCP and VOC) is more prolonged. Furthermore, the high severity of those seizures, in fact a composite of brainstem and limbic seizures, is reflected also by the total absence of exploratory behaviors, which are usually associated, at the POST phase, with recovery after the post-ictal depression. **Behaviors Glossary/Dictionary.** *Wild running cluster* (yellow), Atonic Falling (AF); Gyrus Left (GL), Gyrus Right (GR), Jumping (JP). *Tonic–clonic seizures cluster* (red), Clonic Convulsion forelegs (CCV_1), Clonic Convulsion hindlegs (CCV_2), Clonic Convulsion generalized (CCV_g), Clonic Spasms (CLS), Hindlimb Hyperextensions (HLE), Head Ventral Flexion (HVF), Tonic Convulsion (TCV); *Limbic seizures cluster* (Green), Galloping (GAL), Myoclonus - generalized (Myo_g), Myoclonus of Head (Myo_h), Myoclonus of trunk (Myo_t). **Other behaviors** (empty rectangles): Startle (STA), Withdrawal (WI); Tonic Neck and Body Turning (Left) (TNBL); Tonic Neck and Body Turning (Right) (TNBR). *Exploratory cluster behaviors:* Sniffing (SNF), Walking (WA); Erect Posture (ER); pause (immobility) (IM); Scanning (SC); *Grooming cluster behaviors:* Grooming of Face (GRF), Grooming of Head (GRH), Grooming of Body (Left) (GRL), Licking of Claws (LIC), *Post-ictal depression cluster:* Postictal Immobility (PIM); Apnea (AP); Bradypnea (BR); Tachypnea (TCP); Vocalization (VOC). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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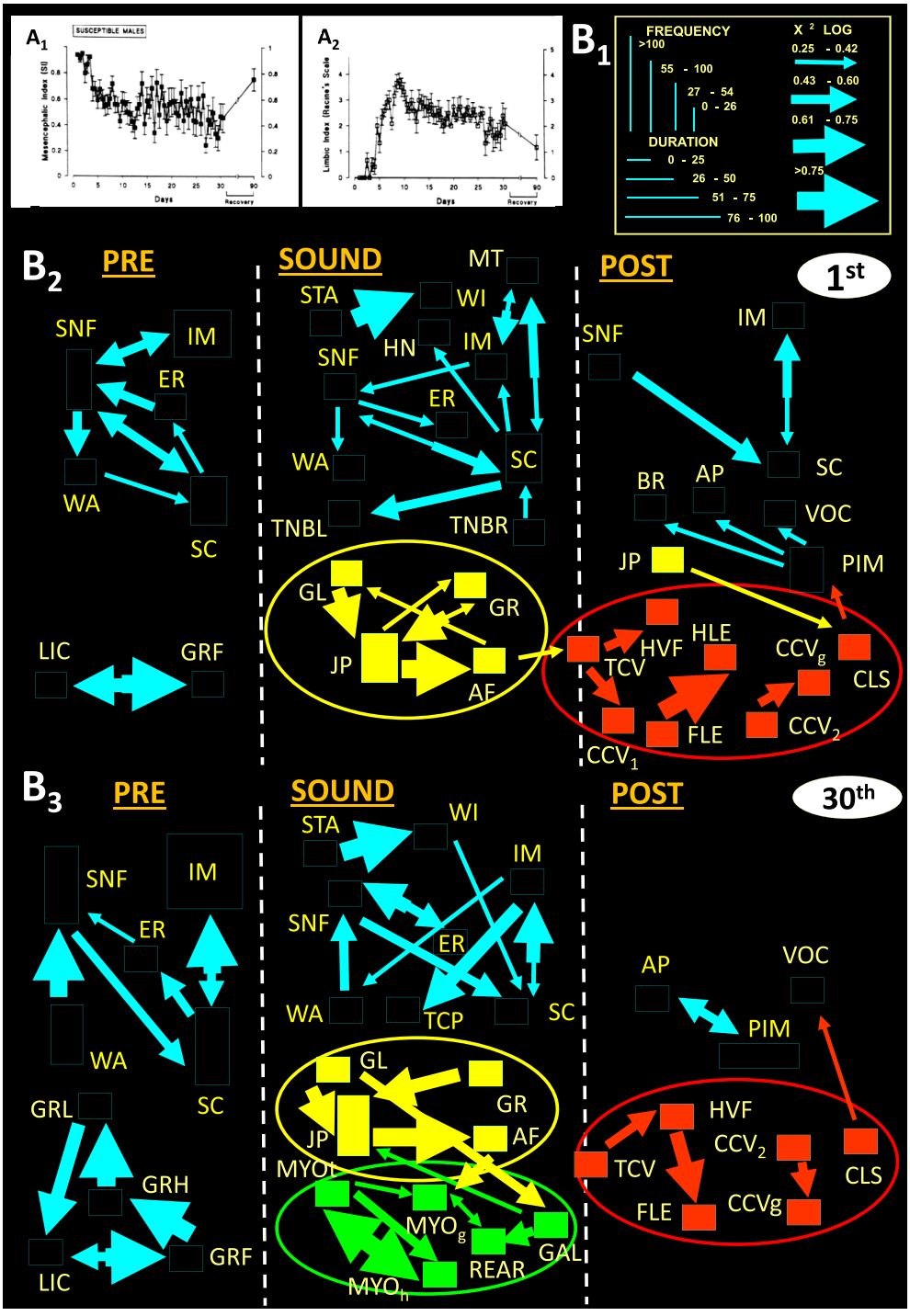
strain is, not only for the study of epilepsy but also for some of its most common comorbidities.

The restricted availability of WARs is, perhaps, the major limitation of the WAR model. Generation and maintenance of animals for experiments require considerable space, as well as efforts from devoted technicians and students. However, actions are being taken to solve this limitation.

Currently, WARs are maintained at the University of São Paulo in Ribeirão Preto and at the Federal University of Minas Gerais in Belo Horizonte. Although in recent years many efforts have been taken to maintain the colonies, it is still a challenge to supply enough animals for researchers interested in using WARs for their studies. We just began a third, still small, but promising production of WARs in the Gynecology Department of the University of the State of São Paulo (UNESP) in Botucatu, São Paulo under the supervision of Prof. Débora Damasceno. This colony is being used with animals from the FMRP-USP-WAR colony, together with Prof. Paula Navarro's laboratory in the Gynecology Department of the FMRP-USP, in order to make further studies on embryos and fetuses.

In addition to having the second branch of the WAR strain at the IBS-UFMG in Belo Horizonte, we have had good experiences sending WARs to other laboratories within Brazil and building a collaborative network



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out of the two main colonies (indicated by % on Table 1). However, doing so demands considerable additional time and work from our staff to assure safe and ethical animal transportation, with attention to the necessary paperwork and regulations. To offer WARs to a wider group of researchers and to allow execution of highly complex and sometimes technically demanding experiments with potential collaborators abroad, we have worked with our technology transfer office at the University of São Paulo to donate WARs for biological research under a Material Transfer Agreement. We have now talked with officials at the Rat Resource and Research Center (RRRC) in Missouri, an important NIH-funded repository of specific rat strains. In addition to working with Reproduction Laboratories from the Gynecology Department of FMRP-USP and the Gynecology Department of UNESP-Botucatu to characterize the reproductive profile and performance of WARs, together with the staff at the RRRC we are working to establish a core facility at the Cryopreservation Laboratory of our campus from which viable cryoprotected or vitrified embryos can be made available to the interested international neuroscience and epileptology research communities. Preliminary (unpublished) studies with WARs embryos and dam pregnancies and delivery profiles suggest this is quite feasible.

12. Limitations, current challenges, and perspectives: looking for paradigm shifts in epileptology

Despite the well-documented behavioral, EEGraphic, histological, and molecular characterization of WARs, which reinforces its use as a model for tonic–clonic seizures (acute) as well as for limbic epilepsy (chronic), there are important issues that remain to be addressed, such as a detailed description of its genetics and all the "omics". After more than 56 generations of selection, we would expect that WARs would be genetically different than their Wistar ancestors, but this remains to be confirmed.

The advantage of being able to trigger seizures acoustically in WARs can also be considered a limitation for the study of some types of epilepsy in which seizures occur spontaneously. Moreover, there are common findings in other epilepsy models that are not found in WARs, such as neurodegeneration and mossy fiber sprouting. Nonetheless, although originally genetically selected for an epilepsy phenotype, WARs have also been, probably by genetic linkage, non-intentionally selected for neuropsychiatric comorbidities that are seen clinically as well as for cardio-respiratory alterations that may represent potential risk factors for SUDEP. Further, we have recently detected potential biomarkers of Alzheimer's disease in WARs.

Historically, Wistar audiogenic-susceptible rats (before the genetic selection) and then WARs were used in our laboratory to describe, for the first time, behavioral sequences that subsequently became tools in the field of audiogenic seizures and experimental models of epilepsy in general and which contrasted with behavioral scores/scales. Interestingly, and in agreement with our observations, recent studies have not demonstrated any correspondence between seizure severity as measured particularly by the Racine scale with either PILO- [251] or kainate-induced [252] SE, nor with the associated EEG abnormalities as recorded by video-EEG. To further overcome limitations in quantifying seizure behavior, Bergstrom et al. [252] recognized that visual (behavioral) scoring of murine EEG signals is time-consuming, with low inter-observer reproducibility, and that the Racine scale for measuring seizure severity does not provide information about interictal/sub-clinical epileptiform activity. They therefore developed an automated wavelet algorithm based on single-channel EEG to identify spikes, seizures, and other abnormal signals and collected data from kainic acid-treated mice to validate the algorithm with a 36-cortical electrode montage using a model of absence (c-butyrolactone), demonstrating that the algorithm had 99% accuracy and 91% precision. They further showed that the wavelet transform method for algorithms was superior to other methods such as Fourier transforms or windowed Fourier transforms [252].

Similarly, we have used wavelet transform to analyze of EEG from WARs [64,73] and have evaluated seizure severity in GEPR with Jobe's brainstem seizures scale [134,135] and in WARs with the brainstem seizures scales of Garcia-Cairasco's [49] and Rossetti et al. [64,73] and Racine's [40] limbic seizures scales. However, in addition to that we have used flowcharts to illustrate sequential analysis of behaviors. Therefore we can put together quantitative behavioral analysis with EEG dynamics, and this coupling has helped and will continue to help us develop integrated information critical for the understanding of the actual complexity of the phenomena of epilepsy.

As typical examples of these integrated approaches, in Fig. 2 (A) are illustrated seizure severity indexes (brainstem and limbic) expressed over the progression of audiogenic kindling in male WARs (30 days, 60 stimuli, twice a day) and after another stimulation, two months later [49]. The brainstem index, initially high at first stimulation, goes down over the evolution of kindling, while the limbic index (initially zero) increases, almost as a mirror image of the brainstem seizure scores. After the two-month interval without stimulation, the brainstem seizures recover, while the limbic seizures did not go back to zero, suggesting a memory of those behavioral changes. As a complementary and more detailed evaluation, in Fig. 2 (B) are behavioral sequences, represented as flowcharts, of female WARs during the progression of audiogenic kindling (30 stimuli, once a day). In Fig. 2 (B_1) are represented the calibration parameters of the flowcharts. Behavioral sequences are built based upon pairs of behaviors (dyads) with probabilistic interactions detected after video capture analysis using the program *Ethomatic* [44,49]. In Fig. 2 (B_2) at the 1st stimulus (PRE-sound phase), WARs express exploratory and grooming clusters (blue symbols). These patterns are altered with the presence of the acoustic stimulation (SOUND). In fact, together with a decreased amount of exploratory and grooming behaviors, there is appearance of wild running (yellow symbols) and tonic seizures (*opisthotonus*, CVT, red symbol). At the POST-sound phase, animals display exuberant tonic–clonic seizures (red symbols), post-ictal immobility, and some exploratory behaviors. At the 30th stimulation in Fig. 2 (B_3) wild running and tonic-seizures are expressed at the SOUND phase, mixed with limbic seizures (green symbols) clusters, and they are similar to those found in other models, such as amygdala electrical kindling [39] and PILO-induced SE [157], which suggest that those behaviors are the product of activation of areas such a cortex, hippocampus, and amygdala. At the POST phase, initiated with the presence of tonic seizures (*opisthotonus*), the behavioral sequences evolve from tonic–clonic seizures to post-ictal immobility, respiratory alterations, and weak or absent exploratory behaviors cluster.

Further, in Fig. 3 are illustrated both the EEG activity before and after audiogenic kindling in male WARs [33,58] and the immunohistochemistry of BrDU, a marker of neurogenesis [58]. Briefly, audiogenic kindling induces EEG recruited activity in cortex, hippocampus, and amygdala, coupled to the behavioral alterations shown in the flowcharts (Fig. 2B_2 and B_3). Additionally, audiogenic kindling induces BrDU + neurogenesis, only when a certain amount of behavioral and EEGraphic limbic seizures, consequent to forebrain recruitment, are detected [58], indicating that behavioral and EEG alterations found in audiogenic kindling are also coupled to plastic cellular alterations.

Having developed a second colony of WARs at the IBS-UFMG, derived from the original strain at the FMRP-USP, we can design comparative studies between the WAR colonies. This type of comparison has been fruitful in the case of GAERs [253], which were originally derived from a Wistar rat strain, some of which displayed spontaneous absence-type seizures. A recent study [254], for example, compared seizures, behavior, and brain morphology in controls (NEC) with geographically-separated GAERs colonies. Briefly, although quite similar in terms of their genetic profile, they showed differences in seizure severity and the expression of some comorbidities that accompany the GAERs, including anxiety- and depressive-like behaviors, relative to NEC. Consequently, while there is a challenge for researchers studying GAERs in different countries and institutions given the heterogeneity

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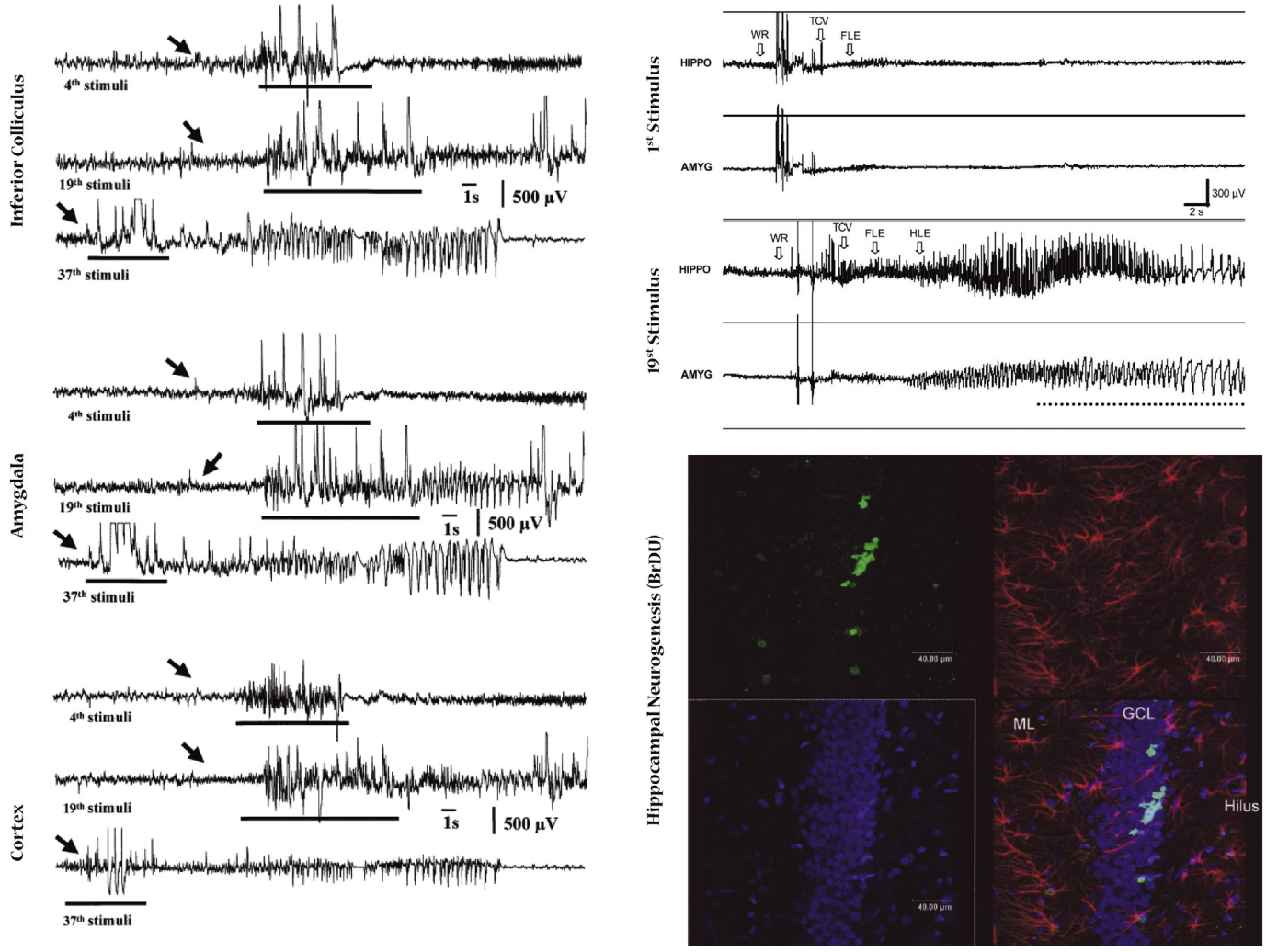

Fig. 3. EEG and cellular plastic changes after audiogenic kindling in WARs. On the left panel are EEGraphic recordings from WARs exposed to audiogenic kindling. Inferior colliculus, amygdala, and cortex signals (top to bottom) are displayed for the 4th 19th and 37th stimuli. Arrows represent the acoustic stimulus onset and the bars represent the wild running phase (movement artifact might be present). On the top right panel are displayed the 1st and the 19th hippocampal and amygdala EEGraphic recording from WARs exposed to audiogenic kindling. On the bottom right panel are BrdU + cells (green) in the granular layer of the DG of the hippocampus of WARs exposed to 28 stimuli; cell nuclei stained with DAPI (blue) and astroglial cells stained with GFAP (red) are also shown. EEG recordings and BrDU images were taken with permission from Dutra Moraes et al. [33] and Romcy-Pereira & Garcia-Cairasco [58]. Authorized reuse license numbers 3755890141380 and 3755890495121, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

of responses/phenotypes, this represents a quite interesting setting for comparative studies, for example in epigenetics that could be done either with GAERs or WARs.

Finally, in light of the contemporary views that epilepsy is a disease of hyperexcitable, highly interactive, dynamic networks [255–257], we need to move forward in our study of any epilepsy model, including WARs, to better understand the complexity and emergent properties of epileptogenic networks [258–260].

Zhang et al. [261] also emphasize a complex networks view, in which we need to wisely use, as much as possible, complementary approaches from several disciplines, as well as highly-developed technology and computational neuroscience tools. As a natural consequence, we hope that clinical diagnosis and treatment would eventually be advanced.

It is our further opinion that we need to use models that cause less massive lesions, because current experimental models, usually prolonged SE, more likely model epilepsy due to severely lesioned brains, rather than more subtle/specific protocols (*e.g.*, temporal or frontal) which, for example, would model regional structural or functional dysfunctions. In both experimental models and clinical settings, the future appears to be heading towards more selective lesions or removals, addressing network disturbances, using nanotechnology (*e.g.*, nanoparticles), developing more technically precise detection and stimulation closed-loop devices, and applying techniques such as optogenetics/fMRI and CRISPER/Cas9 DNA editing, among others.

In the case of new anti-epileptic drug (AED) development, certainly we need to move forward also from a perspective of concepts of seizure definitions and pharmacological targets based upon traditional animal models (PTZ, MES, 6 Hz) and the recurrent discussion between acute *versus* chronic seizures models [262] to concepts of models with less massive lesions [3], combinations of hits, including genetic predisposition plus seizure experience, with biologically promiscuous entities, such as those contained in multiple variations of receptor families and differential expression of alternative splices, the general concept of systems biology [263–265]. Those features will be only detectable when we clearly recognize that complex systems are behind the enormous variations in the epilepsies and their comorbidities. Therefore, because usually these approaches are quite scarce in AED development, we strongly suggest that complexity measurements and recognition of emergent properties of these systems need to be applied to the rational development of new AEDs, representing the quite new concept of systems pharmacology [266–267]. Pioneer experiences in this arena have

been discussed in our laboratory [259–261], in the context of complex systems and emergent properties, when contrasting, for example, the use of non-linear multi-variate methods such as behavioral sequences or flowcharts (neuroethology) against linear behavioral scales of seizure severity (see above sections), to evaluate AEDs in animal models such as WARs [64] and GASH/Sal [97,98]. Although still not applied to AED development in humans, we have applied these neuroethological techniques to seizure semiology in patients with TLE and FLE [260,268].

New research avenues and appropriate achievements are likely to arise mostly from multi-disciplinary, multi-institutional, multinational teams as joint venture global projects. We are now seeing the first steps towards this vision, among others, with the USA-Brain Initiative (https://www.braininitiative.nih.gov/funding/index.htm), the EU-Human Brain Project (https://www.humanbrainproject.eu), the National Institute of Neurological Disorders and Stroke (NINDS) Center without Walls for SUDEP (*https://www.nih.gov/news-events/news-releases/nih-initiates-centers-without-walls-study-sudden-unexpected-*

Timeline of WAR-GEPR-GASH:Sal Research Network

1982	NGC MSc FMRP-USP - Neuroethology of Audiogenic Seizures - RMES Supervision	WAR
1984	NGC PhD FMRP-USP - Neural Substrates of Audiogenic Seizures - RMES Supervision	WAR
1985	NGC received 2nd place in Iberoamerican Epilepsy Award, Madrid, Spain	WAR
1985	NGC at UVal School of Medicine, Department of Anatomy - Host MEGC	GPG/Vall
1988	JACO joined LNNE as Research Technician	
1989	NGC at UIC at Peoria, IL - Lecture "Neuroethology of Audiogenic Seizures" - Host PCJ	GEPR; WAR
1990	NGC introduced WARs internationally at Genetics of Epilepsy Congress, Minneapolis, MN	WAR
1991	MCD 9 months PhD sandwich program at UIC at Peoria, IL (CNPq) - PCJ Supervision	GEPR
1992	MCD settled 2nd branch of WAR colony in Belo Horizonte, MG at BSI-UFMG	WAR
1992	NGC at UIC at Peoria, IL - Lecture "Neurochemistry and Audiogenic Seizures" - Host PCJ	GEPR; WAR
1993	NGC at UIC at Peoria, IL - Lecture "Neurobiology of Audiogenic Seizures" - Host PCJ	GEPR; WAR
1993	NGC at SIU at Springfield, IL - Lecture "Audiogenic Kindling" - Host CF	GEPR; WAR
1997	MFDM 12 months sandwich PhD program at UIC at Peoria, IL (CNPq) - PCJ Supervision	GEPR
1997	PKM visited FMRP-USP – "Course on Brain Microdialysis"	GEPR; WAR
1998	LNNE 1st Symposium "Integrative Neurosciences"	GEPR; WAR
2001	INCyL Symposium on "Inferior Colliculus" - NGC at USal, Spain	GASH:Sal; WAR
2003	MCD et al published pivotal paper on WAR genetic selection	WAR
2003	NGC at USal PhD Neuroscience Program - Lecture "Experimental Models of Epilepsy"	GASH:Sal; WAR
2003	LNNE 2nd Symposium "Neuro-Arts"	WAR
2005	JACO and NGC at USal PhD Neuroscience Program, Spain - courses and training	GASH:Sal; WAR
2006	LNNE Workshop "Neuroscience on the Cutting Edge"	WAR
2008	NGC approval of FAPESP Program Project mainly dedicated to WARs	WAR
2008	LNNE 3rd Symposium "*NEW*roscience 2008 - Contemporary Neuroscience, Epilepsy and Arts"	WAR
2009	E&B Supplement Volume *NEW*roscience 2008	WAR
2010	Brazil-Spain Cooperation Project (CAPES) NGC, JACO and FDV at USal, Spain	GASH:Sal; WAR
2011	Research Cooperation Agreement University of São Paulo - University of Salamanca	GASH:Sal; WAR
2011	BBB 3 months PhD sandwich program at FMRP-USP - NGC Supervision	GASH:Sal
2011	FMRP-USP held 1st USP-USal Symposium	GASH:Sal; WAR
2012	CS and DELG at FMRP-USP Physiology Graduate Program - courses and training	GASH:Sal; WAR
2012	MAH and AM at USal, Spain - training and experiments	GASH:Sal; WAR
2013	LNNE 4th Symposium "*NEW*roscience 2013 - Epilepsies: Complexity and Comorbidities"	WAR
2014	E&B Special Issue *NEW*roscience 2013	WAR
2014	INCyL 2nd USP-USal Symposium in Salamanca, Spain	GASH:Sal; WAR; GEPR
2014	INCyL 1st Congress Audiogenic Epilepsy	GASH:Sal; WAR; GEPR
2014	NGC awarded "Distinguished Guest of the City of Salamanca", Spain	
2014	PN, NGC and CF published Chapter in Faingold and Blumenfeld Book	GEPR; WAR
2014	Brain tissue of WARs sent to DELG at INCyL for confection of gene microarrays	GASH:Sal; WAR
2015	PF at FMRP-USP Physiology Graduate Program – Lecture "Optogenetics"	GEPR; WAR
2016	PF at FMRP-USP Physiology Graduate Program - "Advanced Neuroscience Tools Course"	GEPR; WAR
2016	Brains of WARs sent to PF at GUW for MRI and DTI	GEPR; WAR
2017	E&B Special Issue Genetic Models of Epilepsy	K-M; DBA/2J; GEPR; WAG/Rij; WAR; GASH:Sal

Fig. 4. Timeline of LNNE and WAR history. It took decades to build a multi-national, multi-institutional solid epileptology network. Selected events from the past 33 years are highlighted in this chronological scheme. It is evident that travel exchange missions between research groups working mainly with WARs, GEPRs, and GASH:sal audiogenic seizures susceptible strains were essential to build such a solid network. Many people visited our laboratory but we also sent students, staff, and PIs to visit other laboratories and institutions, particularly in US and Spain. Scientific meetings, such as regional and International Symposia, were a key strategy to successfully enhance our collaborations; we have organized five Symposia at FMRP-USP including the 1st USP-USAL Symposium. The current special issue of *Epilepsy & Behavior* is based on the International Symposium "*Audiogenic Epilepsies: From Experimental Models to the Clinic*", held in September 2014 in Salamanca, Spain, and corresponds also to the 2nd USP-USal collaborative Symposium. Current and former members of the LNNE directly involved with WARs' development, breeding, and maintenance, as well as those involved on the travel missions are named in this timeline. **Institutions and Researchers:** Ribeirão Preto School of Medicine - University of São Paulo (FMRP-USP): Renato M.E. Sabbatini (RMES); Norberto Garcia-Cairasco (NGC); Miguel Ângelo Hyppólito (MAH); José Antonio Cortes de Oliveira (JACO); Flávio Del Vechio (FDV); Adriana Murashima (AM); Biological Sciences Institute - Federal University of Minas Gerais (BSI-UFMG): Maria Carolina Doretto (MCD); Márcio Flávio Dutra Moraes (MFDM); University of Valladolid (UVal): Maria Eugenia Gómez Carretero (MEGC); College of Medicine at Peoria - University of Illinois (UIC): Phillip C. Jobe (PCJ); Pravin K. Mishra (PKM); Southern Illinois University at Springfield (SIU): Carl Faingold (*CF*); Instituto de Neurociencias de Castilla y León (INCyL) - University of Salamanca (USal): Dolores E López Garcia (DELG); Consuelo Sancho (CS); Biviana Barrera-Bailon (BBB); Georgetown University - Washington, DC (GUW): Patrick Forcelli (PF); Prosper N'Gouemo (PN); **Audiogenic Strains:** K–M; DBA/2 J; GEPR; WAG/Rij; WAR;GASH:Sal. **Grant Foundations:** United Nations Developing Program (UNDP-UNESCO); Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES); Projeto USP/USal & Junta de Castilla y Leon (JCyL); Programa USP/USal para la Promoción de la Cooperación Bilateral em Materia de Investigación.

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death-epilepsy), and the NINDS Common Data Elements [269] (*https://www.commondataelements.ninds.nih.gov/#page=Default*). The Working Groups and the Task Forces of the ILAE, AES, NINDS, among others, have been of enormous importance in establishing these large-scale efforts.

The biggest driver for the present and future of neuroscience and of course epileptology will be data sharing, particularly of non-encrypted data. As wisely said by James Bower [270]: *"...For our field to advance, we must move from a point of view in which each of us is working with our own personal, unquantified, and therefore largely untestable model of how "our" part of the brain works, to shared, quantifiable testable models. It is my view that realistic neuronal models are ideal for this purpose..."*. Although he was referring to computational realistic modeling, certainly his statement is of universal value.

Along the same, one of the best examples of data sharing in neuroscience is Giorgio Ascoli's *Neuromorpho* plataform (http://neuromorpho.org), where the morphologies of 50,356 reconstructed neurons have been deposited from 227 different laboratories all over the world. As stated by Ascoli, *"Morphological data are essential for understanding the cellular complexity of the nervous system and are used for analysis, visualization, and modeling. NeuroMorpho.Org was established to facilitate access to such data and to encourage data sharing within the neuroscience community. A centrally curated and annotated inventory provides the opportunity to access accurate and verified data that is presented in a unified format. Deposition and distribution of reconstruction files ultimately prevents data loss and minimizes effort required by data owners. It also provides a "one-stop" entry point for all available reconstructions, thus maximizing data visibility and impact"*.

Accordingly, we have deposited in *Neuromorpho* doublecortin + newly-generated granule cells after PILO-induced SE [271], uploaded as 3D reconstructions with Microbrightfield *Neurolucida*. These neurons were later downloaded and processed, together with others which were uploaded by other researchers in different laboratories using the same platform, and used by us to model complex epileptogenic circuits [272]. To make such platforms more automatic, broader, and capable of dealing with big neuromorphological data, Ascoli's team has recently proposed the *BigNeuron Project* [273].

Finally, and as illustrated by this special issue, we note that over the many years of developing, maintaining, and studying the WAR strain in our attempt to contribute to the knowledge of the complexity of the epilepsies, its neuropsychiatric comorbidities, and of neuroscience in general, we have built a network of multidisciplinary collaborators, mostly associated with GEPRs, GASH:sal and WAR studies, that together have produced a relevant knowledge network, as reflected by the timeline of cooperative endeavors highlighted in Fig. 4.

Our current and major wish is to make the WARs available internationally to share our knowledge and to facilitate the planning and execution of multi-institutional projects.

Acknowledgments and conflicts of interest

We are grateful to Dr. Renato M. E. Sabbatini for his original ideas in the 1980s about the use of the audiogenic model and neuroethology tools in neuroscience, to the members of the LNNE for their constant enthusiasm and collaborative work all over these years, and to the Brazilian Research Foundations FAPESP 2007-50261-4, FAPESP-Cinapce 2005/56447-7, CNPq 305883/2014-3, CAPES-PROEX, Project USP-USal 2011.1.23386.81.3 and FAEPA. Spanish Research Foundations Programa USP-USal para la Promoción de la Cooperación Bilateral en Materia de Investigación and Junta de Castilla y Leon. NGC is a Research Fellow from CNPq- Brazil. EHLU currently is a FAPESP Post-Doctoral Fellow and JACO is a Research Technician. Here we declare that there is no conflict of interest.

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