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REVIEW

# Modelling epilepsy in the mouse: challenges and solutions

Grant F. Marshall<sup>1,2</sup>, Alfredo Gonzalez-Sulser<sup>2,3</sup> and Catherine M. Abbott<sup>1,2,\*</sup>

## ABSTRACT

In most mouse models of disease, the outward manifestation of a disorder can be measured easily, can be assessed with a trivial test such as hind limb claspings, or can even be observed simply by comparing the gross morphological characteristics of mutant and wild-type littermates. But what if we are trying to model a disorder with a phenotype that appears only sporadically and briefly, like epileptic seizures? The purpose of this Review is to highlight the challenges of modelling epilepsy, in which the most obvious manifestation of the disorder, seizures, occurs only intermittently, possibly very rarely and often at times when the mice are not under direct observation. Over time, researchers have developed a number of ways in which to overcome these challenges, each with their own advantages and disadvantages. In this Review, we describe the genetics of epilepsy and the ways in which genetically altered mouse models have been used. We also discuss the use of induced models in which seizures are brought about by artificial stimulation to the brain of wild-type animals, and conclude with the ways these different approaches could be used to develop a wider range of anti-seizure medications that could benefit larger patient populations.

**KEY WORDS:** Mouse, Epilepsy, Induced seizures, Genetic models

## Introduction: what is epilepsy?

Epilepsy is one of the most common neurological conditions worldwide, with an incidence of just under one in every hundred people in the UK, and a peak in occurrence in very young and very old people (Beghi and Giussani, 2018). It is a condition that results from disruptions in network activity in the brain that manifests as seizures. Although anti-seizure drugs [ASDs; also known as anti-epileptic drugs (AEDs); see Glossary, Box 1] can be used to treat patients, these have very variable efficacies and are palliative, as there is no cure for epilepsy.

There are many different types of seizures with different origins and frequencies. The three main categories of epilepsy, as defined by the International League Against Epilepsy (ILAE), are based on the origin of onset: seizures of generalised onset involve large bilateral brain areas, focal onset seizures arise in a specific region on one side of the brain, and the remaining category comprises seizures of unknown onset. Sudden death in epilepsy (SUDEP; Box 1), when an individual dies during or after a seizure and often while they are

sleeping, occurs in one in 1000 people with epilepsy who are otherwise healthy each year.

The causes of epilepsy range from purely environmental, such as traumatic brain injury, through multifactorial causes like brain tumours, to purely genetic, like inherited single-gene disorders or *de novo* heterozygous dominant mutations (Fig. 1). Epilepsy frequently starts in later life and is usually associated with underlying cardiovascular or neurodegenerative disease or with physical insults such as head injury. The worldwide incidence in over 65s is 240 in every 100,000 (Liu et al., 2016). However, epilepsy is more common in childhood, with a particularly high incidence in children under 2 years old (Wirrell et al., 2011). Multiple monogenic epileptic encephalopathies (Box 1) have been identified (for a detailed review, see McTague et al., 2016). Importantly, in these cases, the epileptiform activity (Box 1) may, in itself, be harmful to development and contributes to additional cognitive and behavioural impairment.

Over a hundred single-gene causes of epilepsy have now been identified, with no one gene underlying more than 1% of total cases (reviewed in Helbig and Ellis, 2020). Initially, many of these were inherited mutations in genes encoding ion channels. However, the advent of exome and later whole-genome sequencing fostered the discovery of many new epilepsy genes. Trio sequencing, which entails sequencing of the exomes of both parents and the affected child, has been a particularly successful approach for pinpointing mutations that have arisen *de novo*. Without sequencing, these cases would, of course, not have been diagnosed as genetic as they manifest sporadically rather than running in families. Many of the newly discovered epilepsy genes overlap with those found to be causative of autism, intellectual disability and other neurodevelopmental disorders. These genes encode not just ion channels, but proteins with roles ranging from synaptic vesicle recycling (Dhindsa et al., 2015) and protein synthesis (de Ligt et al., 2012; Lam et al., 2016) to basic metabolic functions like glucose transport (Seidner et al., 1998). The underlying mechanisms by which these newly identified mutations result in network disorders often remain to be identified, depending on the function of the gene and the ease with which mutations can be modelled. However, there are some notable exceptions for which different mutations in a single gene can lead to either a loss or gain of function, depending on whether the mutation is a nonsense or deletion, as opposed to a missense, mutation. This distinction can be very important for therapy, as discussed in more detail below.

How then, with this complex picture, can we best model epilepsy in animals? Although we limit the discussions in this Review to modelling epilepsy in mice, researchers also use other model systems with their own advantages and disadvantages (Box 2).

## Modelling epilepsy

In order to rationally design and test novel treatments for epilepsy, researchers require whole-animal models that capture the relevant human pathology. Animal models must have construct validity, recapitulating the aetiology of the human disorder within a homologous neurobiological context; they must have face

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**Box 1. Glossary**

**Anti-seizure drug (ASD):** medication to treat seizures in people with epilepsy; these drugs are also known as anti-epileptic drugs (AEDs).

**Electrographic seizures:** seizures that are only identifiable by monitoring with electroencephalography (EEG), with no outwardly observable signs.

**Epileptic encephalopathies:** disorders in which epileptic activity in the maturing brain contributes to severe progressive cognitive and behavioural impairments beyond that predicted from the underlying pathology.

**Epileptiform:** specific discharges in the brain, usually detected via EEG.

**Interictal:** the periods between seizures in a patient or animal model.

**Lennox–Gastaut syndrome:** a complex, rare and severe childhood-onset epilepsy characterised by multiple and concurrent seizure types and cognitive dysfunction.

**Kindling:** repeated induction of seizure activity leading to progressively more severe seizures in terms of behaviour and duration.

**Overt, convulsive or behavioural seizures:** visually obvious seizures that can be accurately and reliably detected without the need for EEG. Examples include tonic-clonic seizures, convulsions and wild running.

**Maximal electroshock seizure test:** a highly effective test for detecting novel ASDs in which an electrical pulse is given either through mouth or scalp electrodes to induce generalised tonic-clonic seizures.

**Myoclonic jerk:** a brief and involuntary muscle spasm with irregular muscle twitching.

**Racine stages:** a widely used observational system for categorising seizure severity in animal models, originally proposed in the 1970s.

**Sudden death in epilepsy (SUDEP):** when an individual with epilepsy dies suddenly and unexpectedly with or without evidence of a seizure and where no other obvious cause of death can be found.

**Temporal lobe epilepsy (TLE):** is characterised by focal seizures that originate in the temporal lobe of the brain. One-third of patients with TLE have drug-resistant seizures.

validity, exhibiting the same or similar phenotypes as patients; and they should ultimately have predictive validity, only responding to treatments that are effective in patients with the modelled disorder (Garner, 2014; Willner, 1984). Such models provide an indirect window into human pathology, allowing us to identify novel drug targets and to test the efficacy of therapies through preclinical trials.

Although there are fundamental differences between human and mouse neurobiology at all levels of organisation (Hodge et al., 2019), mice nevertheless represent strong candidate organisms for modelling human neurogenetic disorders. Over 99% of mouse genes have human homologues (Mouse Genome Sequencing Consortium et al., 2002), and, within the brain, the spatial pattern of gene expression is at least grossly conserved (Strand et al., 2007). In terms of epilepsy, focal mouse models of temporal lobe epilepsy (TLE; Box 1) mimic patients, in that ictal seizures emerge from the hippocampal formation and then spread to the rest of the brain (Riban et al., 2002). Similarly, cortical and thalamic structures are responsible for generalised seizures in both humans and mouse models (Cao et al., 2020).

Mouse models of epilepsy can be divided into genetic and induced (Fig. 2). In genetic models, genetic lesions (or spontaneous mutations) result in the emergence of spontaneous seizures. In induced models, chemical, electrical or acoustic stimulation result in either acute or chronic seizures, depending on the induction method and protocol.

**Genetic models**

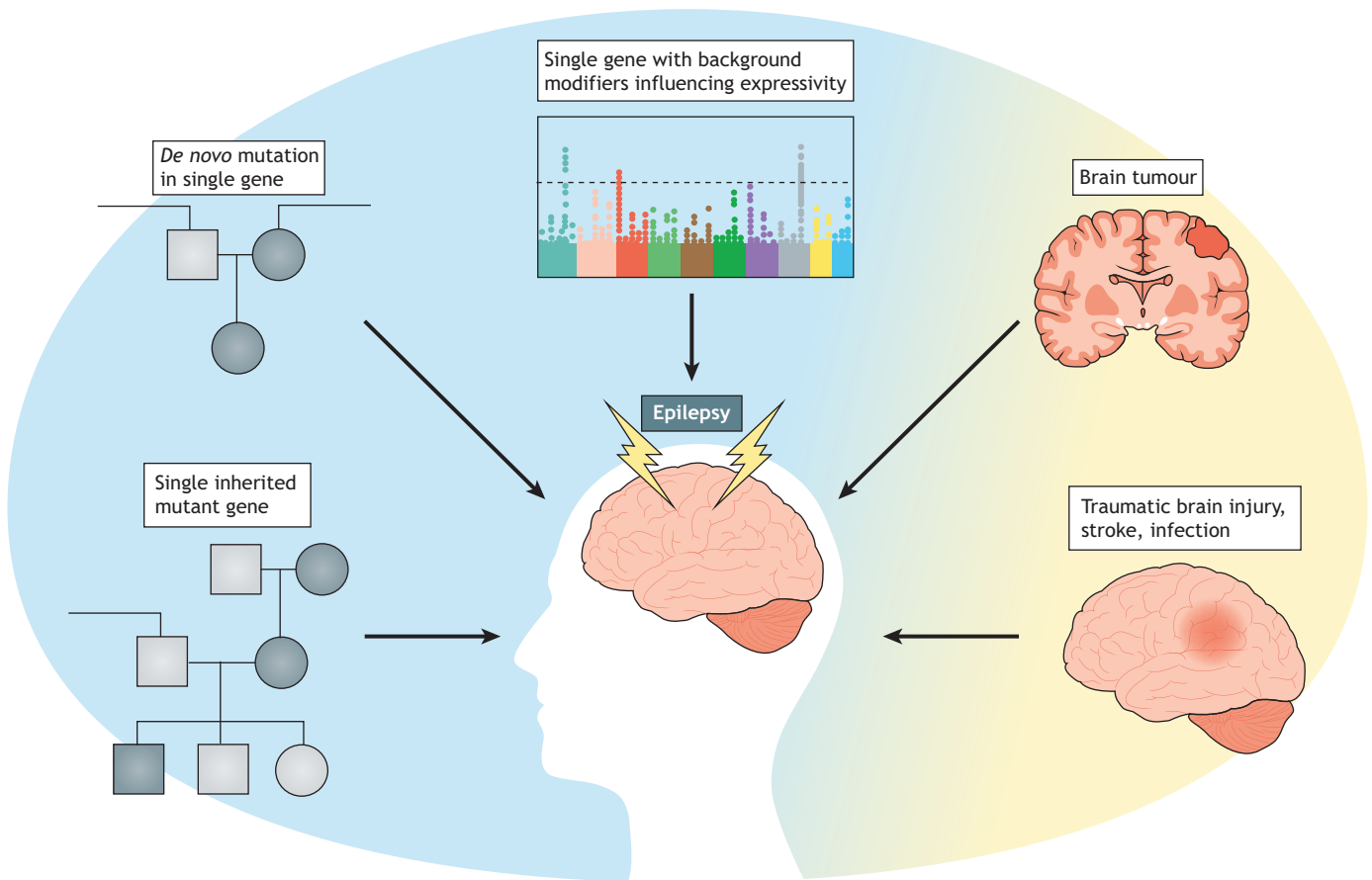
The development of programmable endonuclease-based genome editing such as CRISPR/Cas9 has significantly streamlined the

generation of clinically relevant genetic mouse models (Gurumurthy and Lloyd, 2019). Of course, if we want to model genetic epilepsies, CRISPR/Cas9 enables us to generate models of specific missense mutations, as well as complete knockouts, with relative ease. These models are essential for understanding the underlying molecular mechanisms and phenotypic consequences of specific mutations, and can even be used as additional support where variants have been discovered in patients but have not yet been definitively shown to be causative. Genetic mouse models are also invaluable for studying the behavioural outcomes of network disruptions in early development, including the possibility of age-dependent reversibility, and are necessary for testing any gene-specific therapies, whether precision medicine-based therapeutics or gene therapy. There are, of course, challenges posed by the presence or absence of modifier loci in different inbred mouse strains, as discussed below. Similarly, extrapolating results from single-gene models on inbred backgrounds to human cases with highly variable genetic backgrounds will not always be straightforward, but is likely to be more successful in epileptic encephalopathies resulting from highly penetrant mutations in single genes.

The genetic background of mouse models of epilepsy, whether genetic or induced, can of course vary. This potential confounder needs to be considered when comparing results from different studies, even those using mice with apparently the same inbred strain background. However, these phenotypic differences can also be manipulated to identify genetic modifiers, and to modulate seizure severity to suit the purpose of the experiment. For example, the *Scn2a*<sup>Q54</sup> model displays different stage of onset of seizures, seizure frequency and survival, depending on whether the mutation is on a C57BL/6J or SJL/J background. These differences were exploited to identify *Cacna1g* as an epilepsy modifier gene (Calhoun et al., 2016). Similarly, SJL/J mice with an *Scn8a*<sup>N1768D</sup> mutation modelling an epileptic encephalopathy mutation seen in patients have later seizure onset and increased survival in comparison to mice with the same mutation on a C57BL/6J background. Intercross experiments showed that a hypomorphic mutation of *Gabra2* in the C57BL/6J strain increased seizure severity, suggesting that upregulation of the *Gabra2* product could be a future therapeutic strategy (Yu et al., 2020). Mouse models of different mutations in *Scn8a* (Table 1) have also been used for preclinical testing of drugs that have moved into clinical trials (Meisler, 2019).

Importantly, genetic models can also be used to establish whether mutations operate through a gain- or loss-of-function mechanism, which can, in turn, provide crucial context for determining the appropriate therapeutic approach. There are some notable cases where, for example, different mutations in a single gene can lead to either loss or gain of function, depending on whether the mutation is a nonsense or deletion, as opposed to a missense, mutation (Davies et al., 2020; Quraishi et al., 2020). This distinction can be very important for therapy. In a recent striking example, researchers found that epilepsy resulting from mutations in *SCN2A* usually had an onset at less than 3 months of age, when the mutations were missense, and that these cases responded well to sodium channel blockers. By contrast, cases with disease onset at over 3 months generally had truncating loss-of-function mutations and failed to respond to sodium channel-blocking drugs, illustrating the importance of understanding the underlying mode of action even within a single gene (Wolff et al., 2017).

Although genetic models are clearly more useful for studying the molecular mechanisms of specific epilepsies and for generating targeted therapies, their value as preclinical models can be limited



**Fig. 1.** The common causes of epilepsy, from purely genetic (blue) to purely environmental (yellow).

by their seizure phenotypes (or lack thereof). Later, we will discuss the limitations of genetic mouse epilepsy models in terms of seizure manifestation, before discussing how these disadvantages may be overcome.

#### Induced models

Induced models of epilepsy, in which otherwise healthy animals are made to develop seizures either by exposure to a chemical compound or to electrical stimulation (Fig. 2), have been utilised for over 75 years. They have been instrumental in the identification and development of treatments (Bialer et al., 2013, 2015, 2017, 2018; Fallah and Eubanks, 2020; Löscher, 2011, 2017). Electrical shock or systemic or intracerebral injection of a convulsant compound can trigger frequent and severe seizures in mice, making the phenotypes of these models relatively easy to visually quantify while also allowing for large throughput. From the antiepileptic properties of trimethadione in 1945, which eventually became a standard treatment for absence seizures, which present outwardly as a sudden behavioural arrest (Everett and Richards, 1945), to the maximal electroshock seizure test (Box 1; Toman et al., 1946), which is still the most commonly used initial readout for screens of new ASDs, induced mouse models have played a crucial role in the discovery of many of the major epilepsy treatments in use today (Löscher, 2017).

In so-called kindling (Box 1) protocols, researchers deliver electrical (Leech and McIntyre, 1976) or chemical (Schmidt, 1987) insults on multiple occasions. Once the animals are 'kindled', seizures can be elicited on demand and novel treatments can be

tested. Similarly, quantifiable motor seizures can be generated acutely by a systemic chemical injection of pilocarpine (Cavalheiro, 1995), kainate (Lévesque and Avoli, 2013) or pentylenetetrazole (Karler et al., 1989). In chronic epilepsy models, neuronal damage and reorganisation of connections lead to the emergence of spontaneously occurring seizures, which better mimic clinical epilepsy, as the seizures can occur at any time. For example, in the systemic pilocarpine (Cavalheiro, 1995) and intrahippocampal kainate (Riban et al., 2002) injection models, an initial insult leads to a status epilepticus event that eventually subsides and is followed by a refractory period lasting days to weeks. This coincides with the emergence of hippocampal sclerosis and spontaneous seizures. Furthermore, some ASDs are ineffective in these models, mimicking TLE, which is often difficult to treat. Induced models are therefore useful platforms for discovering new therapeutic strategies that are able to block intractable seizures (Klein et al., 2015; Lévesque and Avoli, 2013).

#### Challenges in finding new treatments

Despite progress in developing novel ASDs, a substantial proportion of epileptic patients have drug-resistant epilepsy, for which medication cannot manage the seizures. Under ILAE definitions, the prevalence of drug resistance has been estimated to range from 17% to 33% of all epilepsy cases (Kwan et al., 2010; Ramos-Lizana et al., 2012; Téllez-Zenteno et al., 2014). Large screening consortia, such as the Epilepsy Therapy Screening Program, are now utilizing the above-discussed chronic and kindling models, in which conventional ASDs do not block

## Box 2. Genetically manipulable model systems for epilepsy beyond the mouse

### iPSCs

Human induced pluripotent stem cells (iPSCs) were first generated in 2007 from fibroblasts and can now be efficiently generated from patients with neurological disorders and healthy controls (Kogut et al., 2018; Takahashi et al., 2007). Patient-derived iPSC lines are useful for modelling disorders with complex genetic architecture, which would be impractical to model in whole animals. Otherwise, control iPSC lines can also be edited using tools such as CRISPR/Cas9 to recapitulate mutations seen in monogenic disorders (Eggenschwiler et al., 2016).

Diverse neuronal and non-neuronal cell types can be differentiated from iPSCs (Wiegand and Banerjee, 2019), enabling mechanistic studies and drug screening in human tissue. The effect of candidate drugs on spontaneous neural activity can be assessed at high throughput using multi-electrode array setups (Tidball and Parent, 2016). Aside from differences in the differentiation potential of iPSCs from different donors (Kyttilä et al., 2016), human iPSC-derived neurons are slow to fully differentiate (Nicholas et al., 2013) and slow to develop mature electrophysiology (Prè et al., 2014). Moreover, human neuronal cultures do not consistently develop synchronous network activity unless co-cultured with human or murine astrocytes (Kuijlaars et al., 2016), limiting their usefulness for modelling network disturbances in epilepsy.

However, recent advances in three-dimensional culture techniques and differentiation methods have allowed the generation of cerebral organoids from single iPSC lines. These organoids comprise diverse neuronal and glial cell types, which show limited self-organisation and exhibit spontaneous, synchronised neural activity (Izsak et al., 2019; Trujillo et al., 2019; Zafeiriou et al., 2020), meaning that they could eventually model both network-level and cell-autonomous defects in epilepsy.

### *Caenorhabditis elegans*

The roundworm *C. elegans* has a relatively simple but exceptionally well-characterised nervous system consisting of exactly 302 neurons (in the adult hermaphrodite) with a highly stereotyped organisation (Chatterjee and Sinha, 2007). *C. elegans* neurons are morphologically similar to mammalian neurons and use conserved neurotransmitters, although there are important physiological differences – *C. elegans* neurons have ion channels but they do not have voltage-gated sodium channels (Bargmann, 1998; Risley et al., 2016). Nevertheless, it has been estimated that over 80% of protein-coding *C. elegans* genes have human homologues (Lai et al., 2000). Seizure-like activity in *C. elegans* typically includes convulsions or head bobbing. For example, worms with loss-of-function mutations in GABA<sub>A</sub> receptors are susceptible to pentylenetetrazol (PTZ)-induced head-bobbing convulsions (Williams et al., 2004; Wong et al., 2018). Head bobbing can also be induced in *C. elegans* by increasing their temperature above 26°C (Pandey et al., 2010).

*C. elegans* are cheap to maintain, reproduce rapidly, and can be treated with drugs via food (Kaletta and Hengartner, 2006). Combined with easily induced and assayed seizures, these features make them suitable for high-throughput drug screening (Wong et al., 2018). Electrophysiological recording is also possible in *C. elegans* (Goodman et al., 2012; Stawicki et al., 2013).

### *Drosophila*

Around three-quarters of human disease genes have orthologues in *Drosophila* (Bier, 2005; Pandey and Nichols, 2011). Researchers using *Drosophila* as a disease model can exploit a wide variety of assays and sophisticated genetic tools to understand gene function and disease mechanisms (Ugur et al., 2016).

*Drosophila* have been used extensively as epilepsy models, with a number of seizure-susceptible mutants available (Parker et al., 2011a). For example, *bang senseless* is a gain-of-function mutation of the *paralytic* gene, which encodes a voltage-gated-sodium channel subunit. *para<sup>bss1</sup>* is

associated with a stereotyped sequence of spasms and paralysis in response to various mechanical stimuli (Parker et al., 2011b). Mutations in voltage-gated sodium channels also cause seizures and epilepsy in humans (Feng et al., 2019), and several of these mutations cause seizures in *Drosophila* when knocked into *paralytic* (Kroll et al., 2015b). Seizures in *para<sup>bss1</sup>* flies can be partially suppressed with anti-seizure drugs (ASDs) or a ketogenic diet (Radlicz et al., 2019; Reynolds et al., 2004), suggesting shared underlying pathophysiology with patients. Furthermore, several *Drosophila* mutants have been identified that suppress seizures in *para<sup>bss1</sup>* flies (Kroll et al., 2015b; Saras and Tanouye, 2016). The identification of seizure suppressor or enhancer mutations in *Drosophila* can reveal novel therapeutic avenues.

*Drosophila* have low maintenance costs and a rapid life cycle, and can be administered with drugs via food, making them suitable for high-throughput drug screening. Moreover, electrophysiological recording and stimulation are routinely performed at various stages of the life cycle (Kroll et al., 2015a; Parker et al., 2011b; Ugur et al., 2016).

### Zebrafish

Over the past decade, zebrafish have surged in popularity as models of human neurological disorders (Fontana et al., 2018). It has been estimated that 76% of human disease genes have a zebrafish orthologue (Howe et al., 2013), and both larvae and adults are susceptible to seizures. Seizures can be elicited using convulsants such as PTZ or kainic acid, or by genetic manipulation, and typically involve hyperactive swimming followed by loss of posture (Afrikanova et al., 2013; Baraban et al., 2013). Electrographic seizures can be detected using EEG, which has been developed for use in both larval (Lee et al., 2020) and adult (Cho et al., 2017) forms. Seizure activity can also be directly visualised in the transparent larvae using transgenic reporters (Burrows et al., 2020).

Zebrafish have high fecundity and are relatively cheap to maintain (Avdesh et al., 2012). The larvae, arrayed in microtitre plates and video recorded, can be used for high-throughput ASD screening (Baraban et al., 2013; Griffin et al., 2016), with candidate drugs simply added to the water. For example, a zebrafish model of Dravet syndrome (with mutations in the *SCN1A* homologue *scn1lab*) shows face validity for behavioural and electrographic seizures. Drug screening using this model identified clemizole as a potential treatment for patients (Baraban et al., 2013).

### Rats

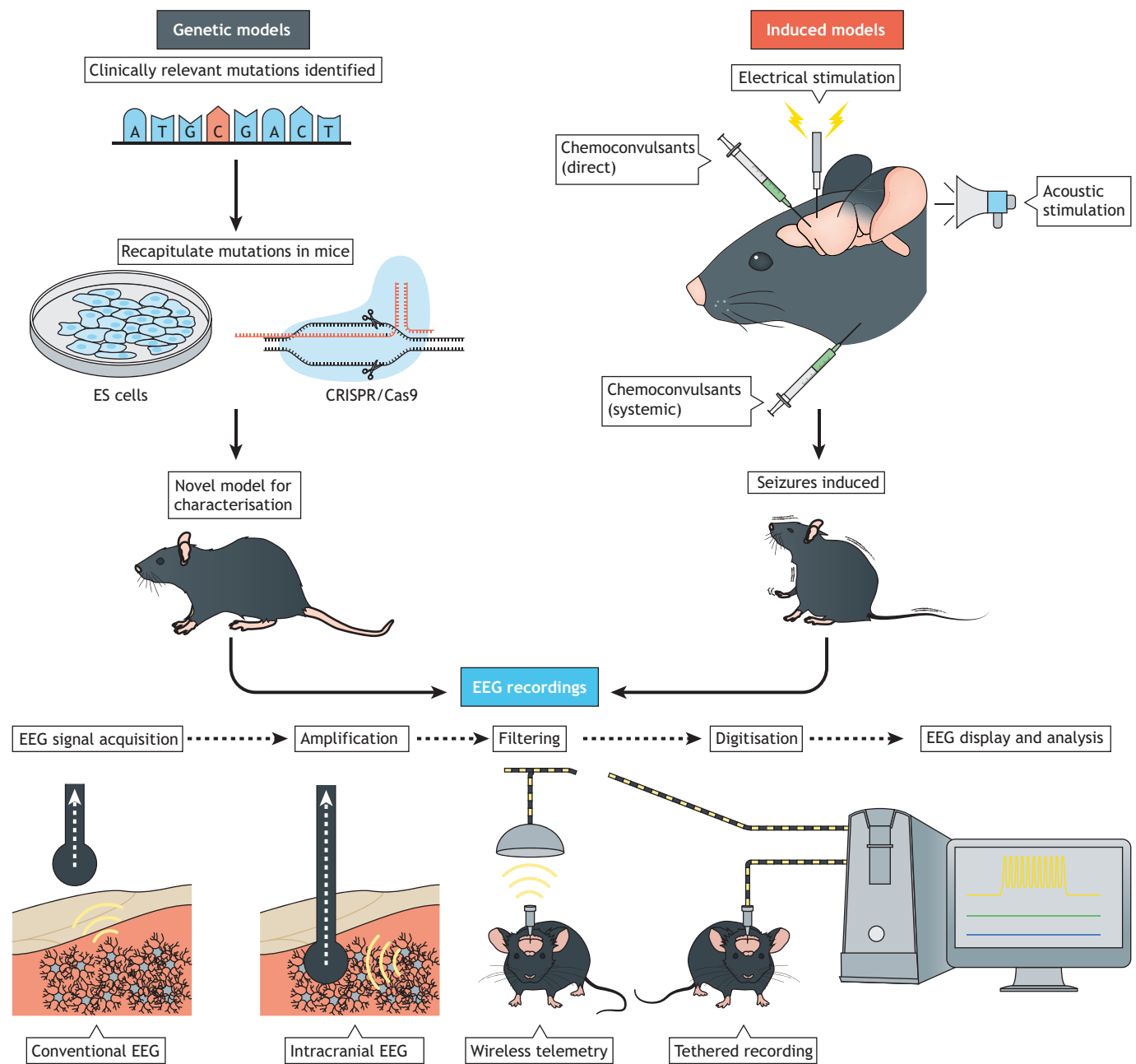
As well as having similar gross brain anatomy, rats possess neural circuits and patterns of network activity that are highly homologous to those in humans (Heilbronner et al., 2016; Lu et al., 2012). Around three-quarters of human disease genes have rat orthologues, and genes associated with neurological disease are particularly well conserved (Huang et al., 2004). Before the development of programmable endonucleases, the transgenic tools available for rats were lagging behind the more sophisticated tools available for mice. However, transgenesis and site-specific editing are now equally feasible in rats (Ellenbroek and Youn, 2016; Guan et al., 2014; Gurumurthy and Lloyd, 2019).

Rats have been extensively studied and are highly informative as acute seizure models, and as kindling models, and have been instrumental for ASD screening (Löscher, 2017). At present, the best-characterised genetic rat epilepsy models are inbred strains carrying spontaneous mutations, such as the GAERS and WAG/Rij strains (Danover et al., 1998). However, rats with clinically relevant mutations have also been studied (Ohmori et al., 2020). Diverse EEG setups have been developed for both tethered (Medlej et al., 2019) and wireless (McGuire et al., 2019) EEG in rats, and *ex vivo* brain slice preparations can be used to study seizure susceptibility (Accardi et al., 2018) and epileptogenesis (Dyhrfeld-Johnsen et al., 2010), and to screen ASDs (Hill et al., 2010).

seizures, to discover novel treatments for drug-resistant epilepsy (Löscher, 2017). However, these models are more relevant to adult TLE, for which disease mechanisms are likely to be very different from those of genetic epilepsy syndromes such as epileptic encephalopathies. As these syndromes often display drug-resistant

seizures in association with intellectual disability (Zhang et al., 2017), researchers face the challenge of developing treatment for drug-resistant epilepsies of vastly varying aetiologies.

Induced models can be relied upon to exhibit acute or chronic seizures ‘on demand’ and therefore have high face validity, but their



**Fig. 2. Generation and characterisation of rodent epilepsy models.** Genetic models are generated by knockout or knock-in mutagenesis. In induced models, seizures are typically elicited by chemical, electrical or acoustic stimulation of the brain. In both model types, the seizures are the key phenotypic readout and can be accurately and reliably detected using electroencephalography (EEG). Rodent EEG begins with the installation of electrodes or electrode arrays on the skull surface in the case of conventional EEG or beneath the skull for intracranial EEG or electrocorticography. Intracranial electrodes may be positioned at the brain surface or at a higher depth. Synchronised neuronal activity near the electrodes generates the EEG signal that undergoes various stages of amplification, filtering and digitisation before finally being displayed (Moyer et al., 2017). EEG signals may be transmitted from the animal to the computer via a cable (tethered recording) or wirelessly (wireless telemetry). ES cells, embryonic stem cells.

relevance to human epilepsies remains contentious. One may contend that, even though they trigger repeated seizures, chemical or electrical induction are not genuine causes of human epilepsy and will therefore fail to recreate the precise cellular and molecular pathology of any bona fide aetiology, limiting our ability to extrapolate findings to humans (Bertram, 2007; Löscher, 2011). Conversely, genetic models can precisely recapitulate the genetic mutations that cause epilepsy in patients and thus have high construct validity. Although it is clear that researchers need both induced and genetic models for maximal drug development efficiency, genetic models are likely to become

increasingly important for developing properly targeted therapies. Indeed, the concept of precision medicine has had some notable successes in epilepsy, albeit mainly in the field of metabolic epilepsies. The most striking example of this is seen in GLUT1 deficiency, where mutations in the *SLC2A1* gene, which encodes a glucose transporter in the blood brain barrier (GLUT1), lead to low glucose in the cerebrospinal fluid, resulting in seizures and developmental delay (Seidner et al., 1998). Treating affected children with a ketogenic diet so that their neurons use ketone bodies as an energy source results in good seizure control (Fujii et al., 2016). This progress in precision

**Table 1. Selected validated models of genetic epilepsies**

Mouse gene symbol	Mutation class	Name/function of gene product	Phenotype/key findings	References
<i>Arfgef1</i>	Frameshift (null)	ADP ribosylation factor guanine nucleotide exchange factor 1; intracellular vesicle trafficking.	No spontaneous seizures, increased susceptibility to induced seizures.	(Teoh et al., 2020)
<i>Arx</i>	Triplet repeat expansion	Aristaless-related homeobox; plays a role in developmental patterning.	Neonatal seizures, EEG abnormalities; treatment with E2 hormone reduces seizure burden if administered during first week of life.	(Siehr et al., 2020)
<i>Cdkl5</i>	Null and missense	Cyclin-dependent kinase-like-5; protein kinase.	Spontaneous seizures seen only in aged mice.	(Mulcahey et al., 2020)
<i>Chma4</i>	Null and missense	Cholinergic receptor nicotinic alpha 4 subunit; ion channel.	Frequent spontaneous seizures in heterozygous mice.	(Klaassen et al., 2006)
<i>Cntnap2</i>	Null	Contactin-associated protein-like 2; role in cell adhesion.	Spontaneous seizures after 6 months, induced by handling.	(Peñagarikano et al., 2011)
<i>Dnm1</i>	Null and 'fitful' missense	Dynamin 1; role in clathrin-mediated endocytosis.	Homozygous fitful mice have early lethal seizures, older heterozygotes have spontaneous mild seizures. Null mutation is lethal in homozygotes but no seizures seen in heterozygotes. Comparison between mutations demonstrates that the missense mutation has a gain-of-function/dominant-negative mechanism of action.	(Asinof et al., 2016)
<i>Eef1a2</i>	Null and missense	Translation elongation factor 1A2; crucial for neuronal protein synthesis.	Spontaneous audiogenic seizures (AGSs) seen in null homozygotes, no seizures observed in missense homozygotes or heterozygotes. Phenotyping revealed gain of function of missense mutants.	(Davies et al., 2017, 2020)
<i>Epm2a</i>	Null	Laforin; regulation of glycogen metabolism.	Spontaneous seizures by 9 months in knockout, which is a model for Lafora syndrome.	(Ganesh et al., 2002)
<i>Fmr1</i>	Null and triplet repeat expansion	Fragile X mental retardation 1; regulator of translation.	Increased susceptibility to AGSs but no spontaneous behavioural seizures observed; AGS susceptibility depends on age of animal, differs according to sex.	(Musumeci et al., 2000)
<i>Gabra1</i>	Truncation	Gamma-aminobutyric acid type A (GABA <sub>A</sub> ) receptor alpha 1 subunit; neurotransmitter receptor.	Homozygous null animals develop severe seizure phenotype by 19 days; homozygous phenotype is lethal soon after birth. Heterozygotes show increased levels of sudden death by 4 weeks.	(Vicini et al., 2001)
<i>Gabrg2</i>	Null and missense	GABA <sub>A</sub> receptor gamma 2 subunit; neurotransmitter receptor.	Both null and missense heterozygotes exhibit spontaneous seizures.	(Kang et al., 2015; Warner et al., 2016)
<i>Gabra3</i>	Missense	GABA <sub>A</sub> receptor alpha 3 subunit; neurotransmitter receptor.	Novel model of Lennox–Gastaut syndrome (Box 1). Fatal seizures in homozygotes after a few weeks; heterozygotes display spontaneous atypical absence seizures, as well as less frequent tonic, myoclonic, atonic and generalised tonic–clonic seizures. Absence seizures blocked by ethosuximide, clobazam and a cannabinoid.	(Qu et al., 2020)
<i>Gria2</i>	Null and editing defective	Glutamate ionotropic receptor AMPA type subunit; glutamate receptor.	Spontaneous seizures in both heterozygotes and homozygotes.	(Brusa et al., 1995)
<i>Grin2a</i>	Missense	Glutamate ionotropic receptor N-methyl-D-aspartate (NMDA) type subunit 2A; ion channel.	Fatal seizures in homozygotes by a few weeks of age, heterozygous animals show increased susceptibility to induced seizures. Treatment with NMDA receptor agonists delays, but does not prevent, seizure onset in homozygous pups.	(Amador et al., 2020)
<i>Iqsec2</i>	Null	IQ motif and Sec7 domain 2; guanine nucleotide exchange factor.	Fatal seizures in adult heterozygotes but paradoxical resistance to induced seizures.	(Sah et al., 2020)
<i>Kcnq2</i>	Null, missense	Potassium voltage-gated channel subfamily Q member 2; ion channel.	Early-onset generalised seizures in null homozygotes. No spontaneous seizures in heterozygous missense mice, but these animals show increased susceptibility to induced seizures and death during and after kindling.	(Singh et al., 2008; Otto et al., 2009)

Continued

Table 1. Continued

Mouse gene symbol	Mutation class	Name/function of gene product	Phenotype/key findings	References
<i>Kcnq3</i>	Null	Potassium voltage-gated channel subfamily Q member 3; ion channel.	Early-onset generalised seizures in null mice.	(Singh et al., 2008)
<i>Lgi1</i>	Null	Leucine-rich glioma-inactivated 1; secreted neuronal protein.	Early-onset spontaneous seizures and seizure-related death.	(Chabrol et al., 2010)
<i>Mecp2</i>	Null, missense and truncations	Methyl CpG binding protein 2; transcriptional repressor.	Progressive age-dependent spontaneous epileptiform discharge activity; handling-dependent behavioural seizures. Model used to test critical periods for gene reactivation.	(Chao et al., 2010; D'Cruz et al., 2010; Guy et al., 2007)
<i>Nlgn2</i>	Null	Neuroigin-2; cell adhesion.	Spontaneous absence seizures in homozygotes; blocking absence seizures pharmacologically and through gene therapy rescues motor and social impairments.	(Cao et al., 2020)
<i>Pcdh19</i>	Null (complex disorder of cellular mosaicism affecting females)	Protocadherin 19; cell adhesion.	No spontaneous seizures but animals show spike wave discharges on EEG.	(Gecz and Thomas, 2020)
<i>Scn1a</i>	Null and missense, many different alleles	Sodium voltage-gated channel, alpha subunit 1; ion channel.	Variety of seizure types plus SUDEP – these models have been reviewed extensively and largely phenocopy the human disorder well.	(Ogiwara et al., 2007; Yu et al., 2006; Martin et al., 2010; Fallah and Eubanks, 2020; Gu and Dalton, 2017; Gonzalez-Sulser, 2020)
<i>Scn1b</i>	Null	Sodium voltage-gated channel, beta subunit 1; ion channel.	Homozygotes show early-onset spontaneous seizures and sudden death at 3 weeks; heterozygous nulls have no spontaneous seizures or increase in susceptibility to induced seizures. If knockout is delayed until adulthood, the animals still develop spontaneous seizures and mortality within 20 days.	(Chen et al., 2004; Patino et al., 2009; O'Malley et al., 2019)
<i>Scn2a</i>	Null and missense	Sodium voltage-gated channel, alpha subunit 2; ion channel.	Absence seizures in heterozygous nulls.	(Miyamoto et al., 2019)
<i>Scn8a</i>	Missense	Sodium voltage-gated channel, alpha subunit 8; ion channel.	Spontaneous seizures develop by 2-8 weeks depending on mutation, followed by death within hours/weeks. Drugs have been tested on mice to good effect.	(Gu and Dalton, 2017; Papale et al., 2009; Wagnon et al., 2015; Meisler, 2019)
<i>Shank3</i>	Duplication/overexpression	SH3 and multiple ankyrin repeat domains 3; post-synaptic density scaffold protein.	Spontaneous seizures; 50% die by 12 weeks.	(Han et al., 2013; Jin et al., 2018)
<i>Stxbp1</i>	Null	Syntaxin binding protein 1; synaptic vesicle function.	Absence seizures and spike wave discharges in heterozygous nulls.	(Kovacevic et al., 2018; Miyamoto et al., 2019)
<i>Syngap1</i>	Null	Synaptic Ras GTPase activating protein 1; regulates receptor trafficking at the post-synaptic density.	No spontaneous seizures but increased interictal activity and increased susceptibility to induced seizures. Animals have been used to test critical periods for gene reactivation.	(Creson et al., 2019; Ozkan et al., 2014)
<i>Tsc1/2</i>	Null	Tuberous sclerosis complex 1/2; regulation of growth signalling.	Spontaneous tonic-clonic seizures found in null het mice at P16. GluN2C/D antagonists block seizures in <i>Tsc1<sup>+/-</sup></i> mice <i>in vivo</i> and <i>in vitro</i> .	(Zeng et al., 2011; Lozovaya et al., 2014)
<i>Ube3a</i>	Null; multiple alleles available	Ubiquitin conjugating enzyme 3a; targeting proteins for degradation.	No spontaneous seizures but increased susceptibility to AGSs or induced seizures. EEG abnormalities. Used to test gene reactivation critical periods.	(Jiang et al., 1998; Rotaru et al., 2020; Judson et al., 2016)

Note that some models comprise extensive allelic series and have been reviewed in depth recently (see Fallah and Eubanks, 2020; Gu and Dalton, 2017). We have omitted models of disorders that primarily manifest as cortical malformations or ataxia and those that rely on conditional knockouts to disrupt network activity. EEG, electroencephalography; SUDEP, sudden death in epilepsy.

medicine suggests that the availability of genetically altered mouse lines recapitulating specific clinical mutations could lead to the development of properly targeted, individualised therapies for groups of patients (Helbig and Ellis, 2020).

### Problems of two sorts with genetic mouse models

In the field of epilepsy research, the major challenge no longer lies in the generation of genetic models but in assessing their face

validity: do these mutant mice have seizures and, if so, how frequent and severe are they?

As in humans, seizures in mice are typically detected and classified using a combination of electroencephalography (EEG) and behavioural signs, such as convulsions or myoclonic jerks (Box 1). Although all seizures involve epileptiform brain activity, not all seizures have obvious behavioural manifestations. For specific models or classes of seizure, ordinal scales such as the



classical Racine stages (Box 1) have been developed to measure seizure severity (Chung et al., 2009; Racine, 1972; Singh et al., 2008). The duration of seizures can also be used as a measure of severity (Wu et al., 2020).

Frequent, overt (Box 1), but non-fatal, seizures represent ideal face-valid epileptic phenotypes: not only are they unambiguous, but they represent a direct and easily assayed readout for whether experimental treatment attempts have been effective in reducing seizure frequency or severity. Unfortunately, however, many genetic mouse models of epilepsy have seizure phenotypes that are not so conveniently assayed. In general, there are problems of two sorts: seizures that are difficult to measure and seizures that are overly severe and fatal.

#### Problems of the first sort: seizures that are difficult to measure

Researchers must reliably detect and score seizures in order to obtain an accurate baseline against which to compare animals receiving experimental treatments. However, many models have relatively rare seizures, making accurate quantification difficult without continuous, long-term EEG-video recording. For example, there are many genetic mouse models in which spontaneous seizures occur only once per week or less (Kash et al., 1997; Malas et al., 2003; McColl et al., 2006; Singh et al., 2008). In some models, seizures are spread unevenly over time. In the widely used A/J (The Jackson Laboratory) mouse strain, seizures occurred mostly during sleep (Strohl et al., 2007), in common with many epilepsy patients (Chokroverty and Nobili, 2017). Other models only have spontaneous seizures within certain age ranges. For example, *Tsc1*<sup>+/-</sup> mice develop frequent, spontaneous seizures at post-natal day (P)9 that resolve by 3 weeks of age (Gataullina et al., 2016; Lozovaya et al., 2014). By contrast, *Pum2*-deficient mice do not develop spontaneous seizures until 5 months of age (Follwaczny et al., 2017). The timeline for spontaneous seizure emergence can also differ substantially between patients and models. For example, mouse models of CDKL5 deficiency disorder have failed to exhibit the early-onset spontaneous seizures that occur in human patients (Amendola et al., 2014; Fehr et al., 2016; Okuda et al., 2017). Instead, spontaneous seizures in these models emerge well into adulthood at around 10 months of age (Mulcahey et al., 2020).

Aside from seizure rarity, many models exhibit non-convulsive electrographic seizures (Box 1) that may be difficult to detect or score. This is especially true for models with absence seizures (Chung et al., 2009; Jarre et al., 2017; Tan et al., 2007). The behavioural arrests typical of these seizures are often frequent but are inherently difficult to quantify without EEG recordings (Chung et al., 2009; Jarre et al., 2017). Other subtle seizures such as brief myoclonic jerks may also prove difficult to monitor. In one study of *Fosb*-null mice, sudden behavioural arrests and myoclonic jerks were simply not recorded owing to the inherent difficulty in quantifying them (Yutsudo et al., 2013).

#### Problems of the second sort: severe, fatal seizures

In contrast to models with rare or subtle seizures, many genetic epilepsy models suffer from severe but fatal seizures. Typically, such models show a sudden spike in mortality concomitant with the onset of spontaneous seizures in early life, resulting in a dramatically reduced life expectancy (Bunton-Stasyshyn et al., 2019; Chung et al., 2009; Kerjan et al., 2009; Meikle et al., 2007; Zhang et al., 2016). For example, *Dcx*; *Dclk2*-null mice show increased mortality after the onset of spontaneous seizures around P16, with over 90% of mice dying by 5 months of age (Kerjan et al., 2009). This limits the translational value of such genetic models as

longitudinal studies are not possible. It is also difficult to ethically justify the use of sudden death as an outcome measure for experimental treatments. Furthermore, as many of these models die after a limited number of seizures, some after a single seizure (Kerjan et al., 2009; Meikle et al., 2007), they are arguably less relevant for modelling epilepsy than as models for SUDEP (Moore et al., 2014; Wagnon et al., 2015).

#### Can we get around the seizure quantification challenges in genetic models?

For researchers who have developed genetic models but have failed to detect spontaneous seizures, the question is whether the model has problems of the first sort – seizures that are difficult to measure – or whether the model simply has no face-valid phenotype. Answering this question is of key translational importance. Face validity does not only mean that relevant readouts are available for preclinical studies; it ultimately reflects the construct validity of the model, which extends beyond whether an orthologous gene exists. For example, a study has recently shown that mice recapitulating the D252H missense mutation in neuronal translation-elongation factor eEF1A2, which is associated with neurodevelopmental disorders and late childhood epilepsy, do not show face validity for spontaneous seizures or neurodevelopmental deficits, despite the fact that human and murine eEF1A2 are almost identical (Davies et al., 2020). These mice were not studied beyond 1 year of age, and it is possible that spontaneous seizures may have developed later, in line with the late onset in children. Nevertheless, their apparent lack of face validity demonstrates how recapitulating clinically relevant mutations in orthologous genes is not always sufficient to generate a face-valid disease model. Only if the biochemical milieu of the gene products is highly conserved between mice and humans, and only if pathological changes occur within a homologous developmental and neurobiological context, will human epileptogenic mutations also be epileptogenic in mice (Belzung and Lemoine, 2011). The ability to conclusively test face validity in genetic models is therefore vital if we wish to exclude models that are unlikely to provide a window onto human pathology (Garner, 2014).

Where genetic models fail to exhibit detectable spontaneous seizures, one recourse is to induce seizures using chemoconvulsants or auditory stimuli. By varying the auditory stimulus or chemoconvulsant dose, researchers can assess whether genetic mutants have increased seizure susceptibility compared with controls (De Sarro et al., 2004; Musumeci et al., 2000; Okuda et al., 2017; Pacey et al., 2009). This approach seems to marry the precision of genetic models with the utility of induced models in terms of seizure measurement. However, the fact remains that these models do not have seizures without the application of proconvulsant stimuli.

As discussed above, it is clear that the clinical community requires new ASDs with novel targets and mechanisms of action to address drug resistance in epilepsy. There is also a pressing need to develop disease-modifying anti-epileptogenic therapies that can reverse epileptogenesis rather than only providing seizure control (Baulac et al., 2015; Bialer et al., 2018; Pitkänen et al., 2013). If researchers can find ways to validate clinically relevant genetic models of epilepsy, we will have succeeded in capturing the pathophysiology associated with diverse epilepsy aetiologies. These models could then be used for the discovery of novel anti-seizure or anti-epileptogenic drugs.

To improve assessments of face validity in genetic models of epilepsy, researchers have continued to develop video-EEG seizure monitoring and are generating alternatives to EEG-based seizure

detection. Continuous video-EEG monitoring is the gold-standard approach for characterising both genetic and induced rodent epilepsy models (Fig. 2), as it facilitates accurate and reliable seizure detection (Gu and Dalton, 2017). Over the past decade, there have been advances in the development of both the hardware and software used to capture and analyse rodent EEGs. Besides the open sharing of system designs and acquisition software, multi-channel electrophysiology amplifiers have decreased in price by orders of magnitude, enabling more research laboratories to rapidly and inexpensively implement recording systems (Hermiz et al., 2016; Siegle et al., 2017; Wasilczuk et al., 2016). Signals can be digitised directly on the mouse through advance head-stage amplifiers, thus negating artefacts caused by cable movement. Meanwhile, advances in microelectrode fabrication techniques allow high channel counts in a relatively small surface area, enabling the acquisition of EEGs with higher spatial resolution and brain coverage (Obien et al., 2014; Wasilczuk et al., 2016). Furthermore, multiple wireless recording systems are now available that allow long-term recordings without tethering mice, providing an opportunity for improved animal welfare (Chang et al., 2011; Jiang et al., 2017; Lidster et al., 2016).

As many epilepsy models have only rare seizures, researchers need to record and monitor animals for a period of weeks to months to establish an accurate seizure baseline (Gu and Dalton, 2017). To streamline the detection and quantification of EEG abnormalities over these timescales, numerous freely available open-source algorithms can automatically detect interictal (Box 1) spikes and/or seizures from rodent EEGs (Anjum et al., 2018; Bergstrom et al., 2013; Brown et al., 2018; Buteneers et al., 2011; Casillas-Espinosa et al., 2019; Colasante et al., 2020; Jang and Cho, 2019; Pfammatter et al., 2019; Tieng et al., 2016, 2017; Wykes et al., 2012), either offline or in real time. EEG traces typically contain artefacts caused by electromagnetic or biophysical interference (Kadam et al., 2017; Pfammatter et al., 2019), but many algorithms can automatically or semi-automatically filter these out (Anjum et al., 2018; Bergstrom et al., 2013; Buteneers et al., 2011; Casillas-Espinosa et al., 2019; Tieng et al., 2016). As a result, many of these systems report sensitivities and specificities approaching 100% for the detection of epileptiform EEG abnormalities (Anjum et al., 2018; Bergstrom et al., 2013; Buteneers et al., 2011; Casillas-Espinosa et al., 2019; Jang and Cho, 2019; Pfammatter et al., 2019; Tieng et al., 2016).

Automating EEG-based detection of seizures will allow researchers to overcome many of the challenges associated with validating genetic epilepsy models with problems of the first sort, including rare seizures or seizures that predominantly occur during certain stages of the sleep-wake or life cycles. Indeed, algorithms have successfully detected and tracked seizures occurring as rarely as 0.3 times per week (Anjum et al., 2018). Moreover, automated seizure classification could remove the subjectivity and human error inherent to manual EEG interpretation that often result in considerable variability (Abend et al., 2011; Duez et al., 2018; Halford et al., 2015).

Despite these technical advances, there remain issues relating to the use of EEG in rodents, especially long-term continuous EEG. The implantation of intracranial electrodes or installation of electrode arrays is an invasive and time-consuming surgical procedure, which itself could cause damage leading to epileptic activity (Burman and Parrish, 2018). Moreover, to prevent animal injury and damage to recording equipment, animals are often housed singly, both post-operatively and over the duration of continuous EEG recordings, which can last for months. Mice and rats are social animals and it is now well established that single housing causes stress (Ieraci et al., 2016; Lukkes et al., 2009;

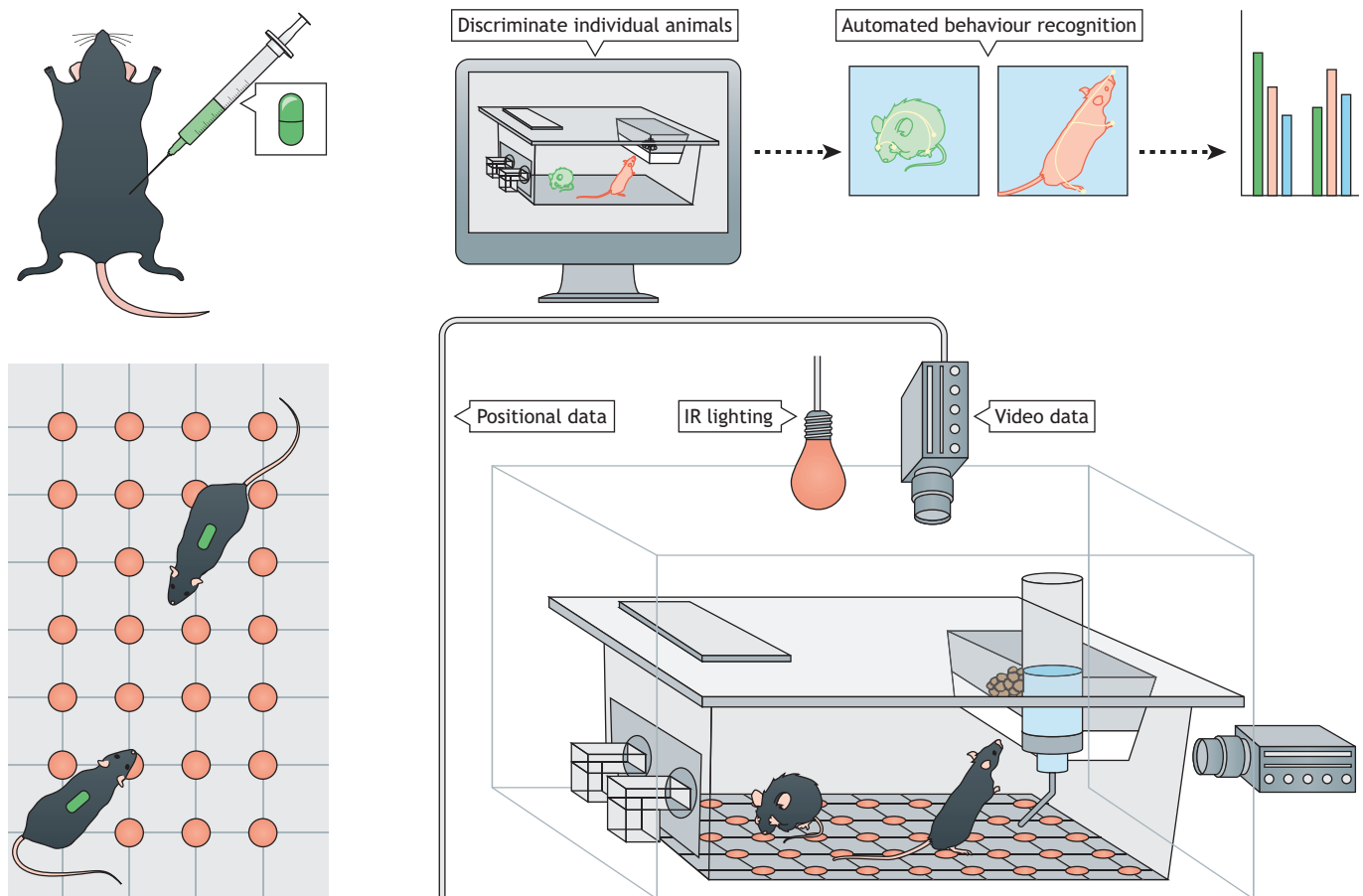
Manouze et al., 2019; Weintraub et al., 2010). Social isolation of young mice results not only in behavioural abnormalities but also increased seizure susceptibility in adulthood (Amiri et al., 2017). There is also evidence that social isolation can affect seizure phenotypes in adult male mice (Amiri et al., 2014; Matsumoto et al., 2003). Meanwhile, a recent study in rats showed that socially isolated animals had a 16-fold increase in spontaneous seizure frequency following treatment with the cholinergic agonist pilocarpine (Manouze et al., 2019).

Researchers need to develop accurate and reliable methods of seizure detection that are minimally invasive and that can be employed in group-housed rodents over extended time periods. In recent years, the most promising developments towards this goal have come from radio-frequency identification (RFID)-assisted in-cage monitoring systems (Fig. 3).

In-cage monitoring systems were developed to meet the need for continuous assessment of unforced behaviours in rodents. At present, the majority of these systems require single housing. However, a growing number of systems are capable of continuously monitoring individual animals within groups using subcutaneous RFID tags (Bains et al., 2016; Krackow et al., 2010; Peleh et al., 2019). Although there are currently no in-cage monitoring systems with validated seizure-detection capabilities, both continuous video capture and animal movement tracking present opportunities for non-invasive detection of overt seizures. In a recent study, Jankovic et al. (2019) employed a video-based movement tracking system called EthoVisionXT to continuously monitor animals following repeated injections of the convulsing agent pentylenetetrazole (Jankovic et al., 2019). The authors found that convulsive seizures (Box 1) were associated with brief spikes in whole-animal mobility and used these spikes to highlight sections of the recording to further screen for seizures. Although the study did not report the sensitivity and specificity of this approach, it established the potential for mobility-based seizure screening in rodents exhibiting the most overt seizures.

Aside from gross motion tracking, home-cage video monitoring could eventually enable the detection of behavioural seizures (Box 1) based on finer visual features. Machine-learning approaches have been used to generate video-based classifiers that can recognise and score a range of rodent behaviours in real time or offline. The repertoire of such detectable behaviours is constantly expanding and currently includes locomotion and climbing (Bains et al., 2018), eating and rearing (Aniszewska et al., 2014), and more subtle behaviours such as scratching (Park et al., 2019) and head bobbing (Baker, 2011). Video-based classifiers for seizures have not yet been developed, but many of the behaviours for which classifiers currently exist – such as rearing, scratching and head bobbing – are seen in rodent seizures (Kandratavicius et al., 2014) and could form the basis for future classifiers. The generation of video-based classifiers for overt seizures is likely to be labour intensive, requiring manual classification of many instances of a given seizure type (Sturman et al., 2020). However, once classifiers are developed for a given type of seizure, they could be used to characterise other models with similar seizure presentations.

Movement or video-based seizure detection would necessarily be limited to seizures with overt behavioural involvement. As discussed above, many rodent epilepsy models exhibit only electrographic or absence seizures, which will always require EEG for detection. Nevertheless, robust, non-invasive seizure monitoring would represent an important refinement for the subset of epilepsy models that exhibit overt seizures and that have already been characterised electrographically.



**Fig. 3. RFID-assisted in-cage monitoring system.** Standard rodent cages are placed within the in-cage monitoring system, where cameras positioned above or at the side of the cage allow continuous video monitoring. Infra-red (IR) cameras and illumination are preferred as they allow animals to be visualised during the dark phase of their 24-h light/dark cycle (Bains et al., 2016; Gu and Dalton, 2017). The majority of in-cage monitoring systems can only monitor single animals (Bains et al., 2018). Increasingly, subcutaneous radio-frequency identification (RFID) chips (depicted as green tags in the figure) are being used to discriminate individual animals within groups (Bains et al., 2016; Krackow et al., 2010; Peleh et al., 2019). The position of several RFID-tagged animals can be continuously tracked as they move over an RFID antenna array (red dots) beneath the home cage and/or near areas such as water bottles or food hoppers.

Even without seizure-detection capabilities, in-cage monitoring is a relevant approach in preclinical epilepsy research. There is a growing appreciation of epilepsy as a spectrum disorder including not only spontaneous and recurrent seizures, but also cognitive, social and behavioural deficits (Fisher et al., 2014; Greenberg and Subaran, 2011; Holmes and Noebels, 2016; Sirven, 2015). These deficits can be the sequelae of chronic seizures or epileptiform activity, i.e. epileptic encephalopathy, but can also arise in parallel with seizures as a result of genetic mutations. In-cage monitoring of group-housed animals offers the opportunity to study levels of activity and social interaction in an ethologically relevant context, unlocking new behavioural domains in which face-valid phenotypes might be present. This could enhance the translational value of genetic epilepsy models by allowing direct assessment of any reversal of social and behavioural deficits during preclinical trials.

### Conclusions

To make progress in finding new treatments for epilepsy, as with all disorders, researchers will need to develop a range of different model systems (Box 2) and use them in a rational, integrated way. Initial drug screening can be carried out cheaply and efficiently in model systems like zebrafish larvae, where specific genetic alterations can be induced using CRISPR gene editing.

Convulsive swimming movements can be captured with video monitoring and scored, with larvae arrayed in microtitre plates in which different wells can be exposed to different drugs. This system allows for initial high-throughput, relatively cheap screening that can then be followed up with electrophysiological confirmation (Griffin et al., 2016). Candidate drugs from such screens can then be directly tested in appropriate mammalian models; ultimately, rational drug design may allow direct mammalian testing approaches.

Novel therapies for epilepsies, even for those not caused by mutations in a single gene, may also emerge from the fields of gene therapy/gene targeting. Conventional gene therapy, in which loss of function of a specific gene is corrected by delivery of a viral vector encoding the missing product, is already being tested in monogenic epilepsy models (e.g. Niibori et al., 2020). Further developments include the use of antisense oligonucleotides to upregulate expression of the sodium channel  $Na_v1.1$ , leading to a reduction in seizure frequency and severity in a mouse model of Dravet syndrome (Han et al., 2020).

Additional novel approaches that target the underlying mechanisms rather than specific genes could allow wider populations to be treated. Recent striking examples include the testing of autoregulatory gene therapy, in which neurons are inhibited in response to rises in extracellular glutamate (Lieb et al.,

2018) and the use of CRISPRa (which modulates promoters) to upregulate expression of the potassium channel gene *Kcna1* in excitatory neurons, dampening neuronal excitability and reducing seizure frequency in a mouse model (Colasante et al., 2020).

Thus, the use of multi-pronged strategies may also allow us eventually to circle back from the initial blunt approach of finding drugs that treated seizures with no regard to underlying cause, to finding that therapies initially designed for monogenic epilepsies may, in fact, benefit much broader patient groups on the basis of their underlying genetic susceptibilities. Heritability estimates based on twin studies support a strong genetic component in epilepsy overall (Kjeldsen et al., 2001; Miller et al., 1998), and up to 80% of epilepsy cases are attributable to genetics (Koeleman, 2018), with many considered to have polygenic inheritance patterns (Hildebrand et al., 2013; Koeleman, 2018). Furthermore, many genes mutated in severe early-onset genetic epilepsies have also been implicated in other types of epilepsy, either as milder mutations (Kaiser et al., 2020), as genetic modifiers (Mirza et al., 2017), or on the basis of network analysis showing overlap between genetic causes and drug targets (Delahaye-Duriez et al., 2016). In addition, it is becoming clear that diverse neurodevelopmental disorders converge onto common molecular pathways (Auerbach et al., 2011; Barnes et al., 2015). It is therefore possible that animal models of monogenic epilepsies may yield therapies with broader treatment applications.

If genetic models can lead to the development and testing of specific therapies aimed at monogenic epilepsies, the same drugs can then be tested in induced seizure models on the basis that altering the expression or function of target genes may have wider applicability. This can, in turn, benefit much broader patient populations and thus help to alleviate problems associated with epilepsy and other neurodevelopmental disorders in large numbers of individuals and their families.

#### Competing interests

The authors declare no competing or financial interests.

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#### References

- Abend, N. S., Gutierrez-Colina, A., Zhao, H., Guo, R., Marsh, E., Clancy, R. R. and Dlugos, D. J. (2011). Interobserver reproducibility of electroencephalogram interpretation in critically ill children. *J. Clin. Neurophysiol.* **28**, 15-19. doi:10.1097/WNP.0b013e3182051123
- Accardi, M. V., Huang, H. and Authier, S. (2018). Seizure liability assessments using the hippocampal tissue slice: Comparison of non-clinical species. *J. Pharmacol. Toxicol. Methods* **93**, 59-68. doi:10.1016/j.vascn.2017.11.003
- Afrikanova, T., Serruys, A.-S. K., Buenafe, O. E. M., Clinckers, R., Smolders, I., de Witte, P. A. M., Crawford, A. D. and Esguerra, C. V. (2013). Validation of the zebrafish pentylenetetrazol seizure model: locomotor versus electrographic responses to antiepileptic drugs. *PLoS ONE* **8**, e54166. doi:10.1371/journal.pone.0054166
- Amador, A., Bostick, C. D., Olson, H., Peters, J., Camp, C. R., Krizay, D., Chen, W., Han, W., Tang, W., Kanber, A. et al. (2020). Modelling and treating GRIN2A developmental and epileptic encephalopathy in mice. *Brain* **143**, 2039-2057. doi:10.1093/brain/awaa147
- Amendola, E., Zhan, Y., Mattucci, C., Castroflorio, E., Calcagno, E., Fuchs, C., Lonetti, G., Siliardi, D., Vyssotski, A. L., Farley, D. et al. (2014). Mapping pathological phenotypes in a mouse model of CDKL5 disorder. *PLoS ONE* **9**, e91613. doi:10.1371/journal.pone.0091613
- Amiri, S., Shirzadian, A., Haj-Mirzaian, A., Imran-Khan, M., Rahimi Balaei, M., Kordjazy, N., Dehpour, A. R. and Mehr, S. E. (2014). Involvement of the nitergic system in the proconvulsant effect of social isolation stress in male mice. *Epilepsy Behav.* **41**, 158-163. doi:10.1016/j.yebeh.2014.09.080
- Amiri, S., Haj-Mirzaian, A., Amini-Khoei, H., Razmi, A., Shirzadian, A., Rahimi-Balaei, M., Olson, C. O., Mohsenzadeh, A., Rastegar, M., Zarrindast, M.-R. et al. (2017). Protective effects of gabapentin against the seizure susceptibility and comorbid behavioral abnormalities in the early socially isolated mice. *Eur. J. Pharmacol.* **797**, 106-114. doi:10.1016/j.ejphar.2017.01.024
- Aniszewska, A., Szymanski, J., Winnicka, M. and Turlejski, K. (2014). Interleukin 6 deficiency affects spontaneous activity of mice in age- and sex-dependent manner. *Acta Neurobiol. Exp. (Wars.)* **74**, 424-432.
- Anjum, S. M. M., Käufer, C., Hopfengärtner, R., Watti, I., Bröer, S. and Löscher, W. (2018). Automated quantification of EEG spikes and spike clusters as a new read out in Theiler's virus mouse model of encephalitis-induced epilepsy. *Epilepsy Behav.* **88**, 189-204. doi:10.1016/j.yebeh.2018.09.016
- Asinof, S., Mahaffey, C., Beyer, B., Frankel, W. N. and Boumil, R. (2016). Dynamin 1 isoform roles in a mouse model of severe childhood epileptic encephalopathy. *Neurobiol. Dis.* **95**, 1-11. doi:10.1016/j.nbd.2016.06.014
- Auerbach, B. D., Osterweil, E. K. and Bear, M. F. (2011). Mutations causing syndromic autism define an axis of synaptic pathophysiology. *Nature* **480**, 63-68. doi:10.1038/nature10658
- Avdesh, A., Chen, M., Martin-Iverson, M. T., Mondal, A., Ong, D., Rainey-Smith, S., Taddei, K., Lardelli, M., Groth, D. M., Verdile, G. et al. (2012). Regular care and maintenance of a zebrafish (*Danio rerio*) laboratory: an introduction. *J. Vis. Exp.*, e4196. doi:10.3791/4196
- Bains, R. S., Cater, H. L., Sillito, R. R., Chartsias, A., Sneddon, D., Concas, D., Keskkivali-Bond, P., Lukins, T. C., Wells, S., Acevedo Arozena, A. et al. (2016). Analysis of individual mouse activity in group housed animals of different inbred strains using a novel automated home cage analysis system. *Front. Behav. Neurosci.* **10**, 106. doi:10.3389/fnbeh.2016.00106
- Bains, R. S., Wells, S., Sillito, R. R., Armstrong, J. D., Cater, H. L., Banks, G. and Nolan, P. M. (2018). Assessing mouse behaviour throughout the light/dark cycle using automated in-cage analysis tools. *J. Neurosci. Methods* **300**, 37-47. doi:10.1016/j.jneumeth.2017.04.014
- Baker, M. (2011). Animal models: inside the minds of mice and men. *Nature* **475**, 123-128. doi:10.1038/475123a
- Baraban, S. C., Dinday, M. T. and Hortopan, G. A. (2013). Drug screening in Scn1a zebrafish mutant identifies clemizole as a potential Dravet syndrome treatment. *Nat. Commun.* **4**, 2410. doi:10.1038/ncomms3410
- Bargmann, C. I. (1998). Neurobiology of the *Caenorhabditis elegans* genome. *Science* **282**, 2028-2033. doi:10.1126/science.282.5396.2028
- Barnes, S. A., Wijetunge, L. S., Jackson, A. D., Katsanevaki, D., Osterweil, E. K., Komiya, N. H., Grant, S. G. N., Bear, M. F., Nägerl, U. V., Kind, P. C. et al. (2015). Convergence of hippocampal pathophysiology in Syngap+/- and Fmr1-/- mice. *J. Neurosci.* **35**, 15073-15081. doi:10.1523/JNEUROSCI.1087-15.2015
- Baulac, M., de Boer, H., Elger, C., Glynn, M., Kälviäinen, R., Little, A., Mifsud, J., Perucca, E., Pitkänen, A. and Ryvlin, P. (2015). Epilepsy priorities in Europe: a report of the ILAE-IBE epilepsy advocacy Europe Task Force. *Epilepsia* **56**, 1687-1695. doi:10.1111/epi.13201
- Beghi, E. and Giussani, G. (2018). Aging and the epidemiology of epilepsy. *Neuroepidemiology* **51**, 216-223. doi:10.1159/000493484
- Belzung, C. and Lemoine, M. (2011). Criteria of validity for animal models of psychiatric disorders: focus on anxiety disorders and depression. *Biol. Mood Anxiety Disord.* **1**, 9. doi:10.1186/2045-5380-1-9
- Bergstrom, R. A., Choi, J. H., Manduca, A., Shin, H.-S., Worrell, G. A. and Howe, C. L. (2013). Automated identification of multiple seizure-related and interictal epileptiform event types in the EEG of mice. *Sci. Rep.* **3**, 1483. doi:10.1038/srep01483
- Bertram, E. (2007). The relevance of kindling for human epilepsy. *Epilepsia* **48** Suppl. 2, 65-74. doi:10.1111/j.1528-1167.2007.01068.x
- Bialer, M., Johannessen, S. I., Levy, R. H., Perucca, E., Tomson, T. and White, H. S. (2013). Progress report on new antiepileptic drugs: a summary of the Eleventh Eilat Conference (EILAT XI). *Epilepsy Res.* **103**, 2-30. doi:10.1016/j.eplepsyres.2012.10.001
- Bialer, M., Johannessen, S. I., Levy, R. H., Perucca, E., Tomson, T. and White, H. S. (2015). Progress report on new antiepileptic drugs: a summary of the Twelfth Eilat Conference (EILAT XII). *Epilepsy Res.* **111**, 85-141. doi:10.1016/j.eplepsyres.2015.01.001
- Bialer, M., Johannessen, S. I., Levy, R. H., Perucca, E., Tomson, T. and White, H. S. (2017). Progress report on new antiepileptic drugs: a summary of the Thirteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIII). *Epilepsia* **58**, 181-221. doi:10.1111/epi.13634
- Bialer, M., Johannessen, S. I., Koepf, M. J., Levy, R. H., Perucca, E., Tomson, T. and White, H. S. (2018). Progress report on new antiepileptic drugs: a summary of the Fourteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIV). I. Drugs in preclinical and early clinical development. *Epilepsia* **59**, 1811-1841. doi:10.1111/epi.14557
- Bier, E. (2005). *Drosophila*, the golden bug, emerges as a tool for human genetics. *Nat. Rev. Genet.* **6**, 9-23. doi:10.1038/nrg1503
- Brown, R., Lam, A. D., Gonzalez-Sulser, A., Ying, A., Jones, M., Chou, R. C.-C., Tzioras, M., Jordan, C. Y., Jedrasiak-Cape, I., Hemonnot, A.-L. et al. (2018). Circadian and brain state modulation of network hyperexcitability in Alzheimer's disease. *ENEURO* **5**, ENEURO.0426-17. doi:10.1523/ENEURO.0426-17.2018
- Brusa, R., Zimmermann, F., Koh, D. S., Feldmeyer, D., Gass, P., Seeburg, P. H. and Sprengel, R. (1995). Early-onset epilepsy and postnatal lethality associated

- with an editing-deficient GluR-B allele in mice. *Science* **270**, 1677-1680. doi:10.1126/science.270.5242.1677
- Bunton-Stasyshyn, R. K. A., Wagnon, J. L., Wengert, E. R., Barker, B. S., Faulkner, A., Wagley, P. K., Bhatia, K., Jones, J. M., Maniaci, M. R., Parent, J. M. et al. (2019). Prominent role of forebrain excitatory neurons in SCN8A encephalopathy. *Brain* **142**, 362-375. doi:10.1093/brain/awy324
- Burman, R. J. and Parrish, R. R. (2018). The widespread network effects of focal epilepsy. *J. Neurosci.* **38**, 8107-8109. doi:10.1523/JNEUROSCI.1471-18.2018
- Burrows, D. R. W., Samarut, É., Liu, J., Baraban, S. C., Richardson, M. P., Meyer, M. P. and Rosch, R. E. (2020). Imaging epilepsy in larval zebrafish. *Eur. J. Paediatr. Neurol.* **24**, 70-80. doi:10.1016/j.ejpn.2020.01.006
- Buteneers, P., Verstraeten, D., van Mierlo, P., Wyckhuys, T., Strooband, D., Raedt, R., Hallez, H. and Schrauwen, B. (2011). Automatic detection of epileptic seizures on the intra-cranial electroencephalogram of rats using reservoir computing. *Artif. Intell. Med.* **53**, 215-223. doi:10.1016/j.artmed.2011.08.006
- Calhoun, J. D., Hawkins, N. A., Zachwieja, N. J. and Kearney, J. A. (2016). Cacna1g is a genetic modifier of epilepsy caused by mutation of voltage-gated sodium channel *Scn2a*. *Epilepsia* **57**, e103-e107. doi:10.1111/epi.13390
- Cao, F., Liu, J. J., Zhou, S., Cortez, M. A., Snead, O. C., Han, J. and Jia, Z. (2020). Neuroligin 2 regulates absence seizures and behavioral arrests through GABAergic transmission within the thalamocortical circuitry. *Nat. Commun.* **11**, 3744. doi:10.1038/s41467-020-17560-3
- Casillas-Espinosa, P. M., Sargsyan, A., Melkonian, D. and O'Brien, T. J. (2019). A universal automated tool for reliable detection of seizures in rodent models of acquired and genetic epilepsy. *Epilepsia* **60**, 783-791. doi:10.1111/epi.14691
- Cavalheiro, E. A. (1995). The pilocarpine model of epilepsy. *Ital. J. Neurol. Sci.* **16**, 33-37. doi:10.1007/BF02229072
- Chabrol, E., Navarro, V., Provenzano, G., Cohen, I., Dinocourt, C., Rivaud-Péchoix, S., Fricker, D., Baulac, M., Miles, R., Leguern, E. et al. (2010). Electroclinical characterization of epileptic seizures in leucine-rich, glioma-inactivated 1-deficient mice. *Brain* **133**, 2749-2762. doi:10.1093/brain/awq171
- Chang, P., Hashemi, K. S. and Walker, M. C. (2011). A novel telemetry system for recording EEG in small animals. *J. Neurosci. Methods* **201**, 106-115. doi:10.1016/j.jneumeth.2011.07.018
- Chao, H.-T., Chen, H., Samaco, R. C., Xue, M., Chahrour, M., Yoo, J., Neul, J. L., Gong, S., Lu, H.-C., Heintz, N. et al. (2010). Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. *Nature* **468**, 263-269. doi:10.1038/nature09582
- Chatterjee, N. and Sinha, S. (2007). Understanding the mind of a worm: hierarchical network structure underlying nervous system function in *C. elegans*. *Prog. Brain Res.* **168**, 145-153. doi:10.1016/S0079-6123(07)68012-1
- Chen, C., Westenbroek, R. E., Xu, X., Edwards, C. A., Sorenson, D. R., Chen, Y., McEwen, D. P., O'Malley, H. A., Bharucha, V., Meadows, L. S. et al. (2004). Mice lacking sodium channel  $\beta$ 1 subunits display defects in neuronal excitability, sodium channel expression, and nodal architecture. *J. Neurosci.* **24**, 4030-4042. doi:10.1523/JNEUROSCI.4139-03.2004
- Cho, S.-J., Byun, D., Nam, T.-S., Choi, S.-Y., Lee, B.-G., Kim, M.-K. and Kim, S. (2017). Zebrafish as an animal model in epilepsy studies with multichannel EEG recordings. *Sci. Rep.* **7**, 3099. doi:10.1038/s41598-017-03482-6
- Chokroverty, S. and Nobili, L. (2017). Sleep and epilepsy. In *Sleep Disorders Medicine* (ed. S. Chokroverty), pp. 915-961. New York, NY: Springer New York.
- Chung, W. K., Shin, M., Jaramillo, T. C., Leibel, R. L., LeDuc, C. A., Fischer, S. G., Tzilianos, E., Gheith, A. A., Lewis, A. S. and Chetkovich, D. M. (2009). Absence epilepsy in apathetic, a spontaneous mutant mouse lacking the h channel subunit, HCN2. *Neurobiol. Dis.* **33**, 499-508. doi:10.1016/j.nbd.2008.12.004
- Colasante, G., Qiu, Y., Massimino, L., Di Bernardino, C., Cornford, J. H., Snowball, A., Weston, M., Jones, S. P., Giannelli, S., Lieb, A. et al. (2020). In vivo CRISPRa decreases seizures and rescues cognitive deficits in a rodent model of epilepsy. *Brain* **143**, 891-905. doi:10.1093/brain/awaa045
- Creson, T. K., Rojas, C., Hwaun, E., Vaissiere, T., Kilinc, M., Jimenez-Gomez, A., Holder, J. L., Tang, J., Colgin, L. L., Miller, C. A. et al. (2019). Re-expression of SynGAP protein in adulthood improves translatable measures of brain function and behavior. *eLife* **8**, e46752. doi:10.7554/eLife.46752
- Danover, L., Deransart, C., Depaulis, A., Vergnes, M. and Marescaux, C. (1998). Pathophysiological mechanisms of genetic absence epilepsy in the rat. *Prog. Neurobiol.* **55**, 27-57. doi:10.1016/S0301-0082(97)00091-9
- Davies, F. C. J., Hope, J. E., McLachlan, F., Nunez, F., Doig, J., Bengani, H., Smith, C. and Abbott, C. M. (2017). Biallelic mutations in the gene encoding eEF1A2 cause seizures and sudden death in F0 mice. *Sci. Rep.* **7**, 46019. doi:10.1038/srep46019
- Davies, F. C. J., Hope, J. E., McLachlan, F., Marshall, G. F., Kaminioti-Dumont, L., Qarkaxhija, V., Nunez, F., Dando, O., Smith, C., Wood, E. et al. (2020). Recapitulation of the eEF1A2 D252H neurodevelopmental disorder-causing missense mutation in mice reveals a toxic gain of function. *Hum. Mol. Genet.* **29**, 1592-1606. doi:10.1093/hmg/ddaa042
- D'Cruz, J. A., Wu, C., Zahid, T., El-Hayek, Y., Zhang, L. and Eubanks, J. H. (2010). Alterations of cortical and hippocampal EEG activity in MeCP2-deficient mice. *Neurobiol. Dis.* **38**, 8-16. doi:10.1016/j.nbd.2009.12.018
- de Ligt, J., Willemsen, M. H., van Bon, B. W. M., Kleefstra, T., Yntema, H. G., Kroes, T., Vulto-van Silfhout, A. T., Koolen, D. A., de Vries, P., Gilissen, C. et al. (2012). Diagnostic exome sequencing in persons with severe intellectual disability. *N. Engl. J. Med.* **367**, 1921-1929. doi:10.1056/NEJMoa1206524
- De Sarro, G., Russo, E., Ferreri, G., Giuseppe, B., Flocco, M. A., Di Paola, E. D. and De Sarro, A. (2004). Seizure susceptibility to various convulsant stimuli of knockout interleukin-6 mice. *Pharmacol. Biochem. Behav.* **77**, 761-766. doi:10.1016/j.pbb.2004.01.012
- Delahaye-Duriez, A., Srivastava, P., Shkura, K., Langley, S. R., Laaniste, L., Moreno-Moral, A., Danis, B., Mazzuferi, M., Foerch, P., Gazina, E. V. et al. (2016). Rare and common epilepsies converge on a shared gene regulatory network providing opportunities for novel antiepileptic drug discovery. *Genome Biol.* **17**, 245. doi:10.1186/s13059-016-1097-7
- Dhindsa, R. S., Bradrick, S. S., Yao, X., Heinzen, E. L., Petrovski, S., Krueger, B. J., Johnson, M. R., Frankel, W. N., Petrou, S., Boumil, R. M. et al. (2015). Epileptic encephalopathy-causing mutations in DNMT1 impair synaptic vesicle endocytosis. *Neural. Genet.* **1**, e4. doi:10.1212/01.NXG.0000464295.65736.da
- Duez, C. H. V., Ebbesen, M. Q., Benedek, K., Fabricius, M., Atkins, M. D., Beniczky, S., Kjaer, T. W., Kirkegaard, H. and Johnsen, B. (2018). Large inter-rater variability on EEG-reactivity is improved by a novel quantitative method. *Clin. Neurophysiol.* **129**, 724-730. doi:10.1016/j.clinph.2018.01.054
- Dyhrfeld-Johnsen, J., Berdichevsky, Y., Swiercz, W., Sabolek, H. and Staley, J. (2010). Interictal spikes precede ictal discharges in an organotypic hippocampal slice culture model of epileptogenesis. *J. Clin. Neurophysiol.* **27**, 418-424. doi:10.1097/WNP.0b013e3181fe0709
- Eggenschwiler, R., Moslem, M., Fráguas, M. S., Galla, M., Papp, O., Naujock, M., Fonfara, I., Gensch, I., Wähner, A., Beh-Pajoo, A. et al. (2016). Improved bi-allelic modification of a transcriptionally silent locus in patient-derived iPSC by Cas9 nickase. *Sci. Rep.* **6**, 38198. doi:10.1038/srep38198
- Ellenbroek, B. and Youn, J. (2016). Rodent models in neuroscience research: is it a rat race? *Dis. Model. Mech.* **9**, 1079-1087. doi:10.1242/dmm.026120
- Everett, G. M. and Richards, R. K. (1945). Comparative Anticonvulsant Action of 3,5,5-trimethylloxazolidine-2,4-dione (Tridione), Dilantin and Phenobarbital. *Anesthesiology* **6**, 448. doi:10.1097/00000542-194507000-00047
- Fallah, M. S. and Eubanks, J. H. (2020). Seizures in mouse models of rare neurodevelopmental disorders. *Neuroscience* **445**, 50-68. doi:10.1016/j.neuroscience.2020.01.041
- Fehr, S., Wong, K., Chin, R., Williams, S., de Klerk, N., Forbes, D., Krishnaraj, R., Christodoulou, J., Downs, J. and Leonard, H. (2016). Seizure variables and their relationship to genotype and functional abilities in the CDKL5 disorder. *Neurology* **87**, 2206-2213. doi:10.1212/WNL.0000000000003352
- Feng, Y., Zhang, S., Zhang, Z., Guo, J., Tan, Z., Zhu, Y., Tao, J. and Ji, Y.-H. (2019). Understanding genotypes and phenotypes of the mutations in voltage-gated sodium channel  $\alpha$  subunits in epilepsy. *CNS Neurol. Disord. Drug Targets* **18**, 266-272. doi:10.2174/1871527317666181026164825
- Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., Engel, J., Forsgren, L., French, J. A., Glynn, M. et al. (2014). ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* **55**, 475-482. doi:10.1111/epi.12550
- Follwaczny, P., Schieweck, R., Riedemann, T., Demleitner, A., Straub, T., Klemm, A. H., Bilban, M., Sutor, B., Popper, B. and Kiebler, M. A. (2017). Pumlilio2-deficient mice show a predisposition for epilepsy. *Dis. Model. Mech.* **10**, 1333-1342. doi:10.1242/dmm.029678
- Fontana, B. D., Mezzomo, N. J., Kalueff, A. V. and Rosemberg, D. B. (2018). The developing utility of zebrafish models of neurological and neuropsychiatric disorders: a critical review. *Exp. Neurol.* **299**, 157-171. doi:10.1016/j.expneurol.2017.10.004
- Fujii, T., Ito, Y., Takahashi, S., Shimono, K., Natsume, J., Yanagihara, K. and Oguni, H. (2016). Outcome of ketogenic diets in GLUT1 deficiency syndrome in Japan: A nationwide survey. *Brain Dev.* **38**, 628-637. doi:10.1016/j.braindev.2016.01.002
- Ganesh, S., Delgado-Escueta, A. V., Sakamoto, T., Avila, M. R., Machado-Salas, J., Hoshii, Y., Akagi, T., Gomi, H., Suzuki, T., Amano, K. et al. (2002). Targeted disruption of the Epm2a gene causes formation of Lafora inclusion bodies, neurodegeneration, ataxia, myoclonus epilepsy and impaired behavioral response in mice. *Hum. Mol. Genet.* **11**, 1251-1262. doi:10.1093/hmg/11.11.1251
- Garner, J. P. (2014). The significance of meaning: why do over 90% of behavioral neuroscience results fail to translate to humans, and what can we do to fix it? *ILAR J.* **55**, 438-456. doi:10.1093/ilar/iltu047
- Gataullina, S., Lemaire, E., Wendling, F., Kaminska, A., Watrin, F., Riquet, A., Ville, D., Moutard, M.-L., de Saint Martin, A., Napuri, S. et al. (2016). Epilepsy in young Tsc1(+/-) mice exhibits age-dependent expression that mimics that of human tuberous sclerosis complex. *Epilepsia* **57**, 648-659. doi:10.1111/epi.13325
- Gez, J. and Thomas, P. Q. (2020). Disentangling the paradox of the PCDH19 clustering epilepsy, a disorder of cellular mosaics. *Curr. Opin. Genet. Dev.* **65**, 169-175. doi:10.1016/j.cde.2020.06.012
- Gonzalez-Sulser, A. (2020). Rodent genetic models of neurodevelopmental disorders and epilepsy. *Eur. J. Paediatr. Neurol.* **24**, 66-69. doi:10.1016/j.ejpn.2019.12.012

- Goodman, M. B., Lindsay, T. H., Lockery, S. R. and Richmond, J. E. (2012). Electrophysiological methods for *Caenorhabditis elegans* neurobiology. *Methods Cell Biol.* **107**, 409-436. doi:10.1016/B978-0-12-394620-1.00014-X
- Greenberg, D. A. and Subaran, R. (2011). Blinders, phenotype, and fashionable genetic analysis: a critical examination of the current state of epilepsy genetic studies. *Epilepsia* **52**, 1-9. doi:10.1111/j.1528-1167.2010.02734.x
- Griffin, A., Krasniak, C. and Baraban, S. C. (2016). Advancing epilepsy treatment through personalized genetic zebrafish models. *Prog. Brain Res.* **226**, 195-207. doi:10.1016/bs.pbr.2016.03.012
- Gu, B. and Dalton, K. A. (2017). Models and detection of spontaneous recurrent seizures in laboratory rodents. *Zool. Res.* **38**, 171-179. doi:10.24272/j.issn.2095-8137.2017.042
- Guan, Y., Shao, Y., Li, D. and Liu, M. (2014). Generation of site-specific mutations in the rat genome via CRISPR/Cas9. *Meth. Enzymol.* **546**, 297-317. doi:10.1016/B978-0-12-801185-0.00014-3
- Gurumurthy, C. B. and Lloyd, K. C. K. (2019). Generating mouse models for biomedical research: technological advances. *Dis. Model. Mech.* **12**, dmm029462. doi:10.1242/dmm.029462
- Guy, J., Gan, J., Selfridge, J., Cobb, S. and Bird, A. (2007). Reversal of neurological defects in a mouse model of Rett syndrome. *Science* **315**, 1143-1147. doi:10.1126/science.1138389
- Halford, J. J., Shiau, D., Desrochers, J. A., Kolls, B. J., Dean, B. C., Waters, C. G., Azar, N. J., Haas, K. F., Kutluay, E., Martz, G. U. et al. (2015). Inter-rater agreement on identification of electrographic seizures and periodic discharges in ICU EEG recordings. *Clin. Neurophysiol.* **126**, 1661-1669. doi:10.1016/j.clinph.2014.11.008
- Han, K., Holder, J. L., Schaaf, C. P., Lu, H., Chen, H., Kang, H., Tang, J., Wu, Z., Hao, S., Cheung, S. W. et al. (2013). SHANK3 overexpression causes manic-like behaviour with unique pharmacogenetic properties. *Nature* **503**, 72-77. doi:10.1038/nature12630
- Han, Z., Chen, C., Christiansen, A., Ji, S., Lin, Q., Anumonwo, C., Liu, C., Leiser, S. C., Meena, Aznarez, I. et al. (2020). Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome. *Sci. Transl. Med.* **12**, eaa26100. doi:10.1126/scitranslmed. aaz6100
- Heilbronner, S. R., Rodriguez-Romaguera, J., Quirk, G. J., Groenewegen, H. J. and Haber, S. N. (2016). Circuit-based corticostriatal homologies between rat and primate. *Biol. Psychiatry* **80**, 509-521. doi:10.1016/j.biopsych.2016.05.012
- Helbig, I. and Ellis, C. A. (2020). Personalized medicine in genetic epilepsies - possibilities, challenges, and new frontiers. *Neuropharmacology* **172**, 107970. doi:10.1016/j.neuropharm.2020.107970
- Hermiz, J., Rogers, N., Kaestner, E., Ganji, M., Cleary, D., Snider, J., Barba, D., Dayeh, S., Halgren, E., Gilja, V. et al. (2016). A clinic compatible, open source electrophysiology system. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2016**, 4511-4514. doi:10.1109/EMBC.2016.7591730
- Hildebrand, M. S., Dahl, H.-H. M., Damiano, J. A., Smith, R. J. H., Scheffer, I. E. and Berkovic, S. F. (2013). Recent advances in the molecular genetics of epilepsy. *J. Med. Genet.* **50**, 271-279. doi:10.1136/jmedgenet-2012-101448
- Hill, A. J., Jones, N. A., Williams, C. M., Stephens, G. J. and Whalley, B. J. (2010). Development of multi-electrode array screening for anticonvulsants in acute rat brain slices. *J. Neurosci. Methods* **185**, 246-256. doi:10.1016/j.jneumeth.2009.10.007
- Hodge, R. D., Bakken, T. E., Miller, J. A., Smith, K. A., Barkan, E. R., Graybuck, L. T., Close, J. L., Long, B., Johansen, N., Penn, O. et al. (2019). Conserved cell types with divergent features in human versus mouse cortex. *Nature* **573**, 61-68. doi:10.1038/s41586-019-1506-7
- Holmes, G. L. and Noebels, J. L. (2016). The epilepsy spectrum: targeting future research challenges. *Cold Spring Harb. Perspect. Med.* **6**, a028043. doi:10.1101/cshperspect.a028043
- Howe, K., Clark, M. D., Torroja, C. F., Torrance, J., Berthelot, C., Muffato, M., Collins, J. E., Humphray, S., McLaren, K., Matthews, L. et al. (2013). The zebrafish reference genome sequence and its relationship to the human genome. *Nature* **496**, 498-503. doi:10.1038/nature12111
- Huang, H., Winter, E. E., Wang, H., Weinstock, K. G., Xing, H., Goodstadt, L., Stenson, P. D., Cooper, D. N., Smith, D., Albà, M. M. et al. (2004). Evolutionary conservation and selection of human disease gene orthologs in the rat and mouse genomes. *Genome Biol.* **5**, R47. doi:10.1186/gb-2004-5-7-r47
- Ieraci, A., Mallei, A. and Popoli, M. (2016). Social isolation stress induces anxious-depressive-like behavior and alterations of neuroplasticity-related genes in adult male mice. *Neural Plast.* **2016**, 6212983. doi:10.1155/2016/6212983
- Izsak, J., Seth, H., Andersson, M., Vizlin-Hodzic, D., Theiss, S., Hanse, E., Ågren, H., Funa, K. and Illes, S. (2019). Robust generation of person-specific, synchronously active neuronal networks using purely isogenic human iPSC-3D neural aggregate cultures. *Front. Neurosci.* **13**, 351. doi:10.3389/fnins.2019.00351
- Jang, H.-J. and Cho, K.-O. (2019). Dual deep neural network-based classifiers to detect experimental seizures. *Korean J. Physiol. Pharmacol.* **23**, 131-139. doi:10.4196/kjpp.2019.23.2.131
- Jankovic, M. J., Kapadia, P. P. and Krishnan, V. (2019). Home-cage monitoring ascertains signatures of ictal and interictal behavior in mouse models of generalized seizures. *PLoS ONE* **14**, e0224856. doi:10.1371/journal.pone.0224856
- Jarre, G., Guillemain, I., Deransart, C. and Depaulis, A. (2017). Genetic models of absence epilepsy in rats and mice. In *Models of Seizures and Epilepsy* (ed. A. Pitkänen, P. Buckmaster, A. Galanopoulou, S. Moshé), pp. 455-471. Elsevier.
- Jiang, Y. H., Armstrong, D., Albrecht, U., Atkins, C. M., Noebels, J. L., Eichele, G., Sweatt, J. D. and Beaudet, A. L. (1998). Mutation of the Angelman ubiquitin ligase in mice causes increased cytoplasmic p53 and deficits of contextual learning and long-term potentiation. *Neuron* **21**, 799-811. doi:10.1016/S0896-6273(00)80596-6
- Jiang, Z., Huxter, J. R., Bowyer, S. A., Blockeel, A. J., Butler, J., Imtiaz, S. A., Wafford, K. A., Phillips, K. G., Tricklebank, M. D., Marston, H. M. et al. (2017). TaiNi: maximizing research output whilst improving animals' welfare in neurophysiology experiments. *Sci. Rep.* **7**, 8086. doi:10.1038/s41598-017-08078-8
- Jin, C., Zhang, Y., Kim, S., Kim, Y., Lee, Y. and Han, K. (2018). Spontaneous seizure and partial lethality of juvenile Shank3-overexpressing mice in C57BL/6 J background. *Mol. Brain* **11**, 57. doi:10.1186/s13041-018-0403-6
- Judson, M. C., Wallace, M. L., Sidorov, M. S., Burette, A. C., Gu, B., van Woerden, G. M., King, I. F., Han, J. E., Zylka, M. J., Elgersma, Y. et al. (2016). GABAergic neuron-specific loss of Ube3a causes Angelman syndrome-like EEG abnormalities and enhances seizure susceptibility. *Neuron* **90**, 56-69. doi:10.1016/j.neuron.2016.02.040
- Kadam, S. D., D'Ambrosio, R., Duveau, V., Roucard, C., Garcia-Cairasco, N., Ikeda, A., de Curtis, M., Galanopoulou, A. S. and Kelly, K. M. (2017). Methodological standards and interpretation of video-electroencephalography in adult control rodents. A TASK1-WG1 report of the AES/LAE Translational Task Force of the ILAE. *Epilepsia* **58** Suppl. 4, 10-27. doi:10.1111/epi.13903
- Kaletta, T. and Hengartner, M. O. (2006). Finding function in novel targets: *C. elegans* as a model organism. *Nat. Rev. Drug Discov.* **5**, 387-399. doi:10.1038/nrd2031
- Kandratavicius, L., Balista, P. A., Lopes-Aguiar, C., Ruggiero, R. N., Umeoka, E. H., Garcia-Cairasco, N., Bueno-Junior, L. S. and Leite, J. P. (2014). Animal models of epilepsy: use and limitations. *Neuropsychiatr. Dis. Treat.* **10**, 1693-1705. doi:10.2147/NDT.S50371
- Kang, J.-Q., Shen, W., Zhou, C., Xu, D. and Macdonald, R. L. (2015). The human epilepsy mutation GABRG2(Q390X) causes chronic subunit accumulation and neurodegeneration. *Nat. Neurosci.* **18**, 988-996. doi:10.1038/nn.4024
- Karler, R., Murphy, V., Calder, L. D. and Turkkanis, S. A. (1989). Pentylentetrazol kindling in mice. *Neuropharmacology* **28**, 775-780. doi:10.1016/0028-3908(89)90166-4
- Kash, S. F., Johnson, R. S., Tecott, L. H., Noebels, J. L., Mayfield, R. D., Hanahan, D. and Baekkeskov, S. (1997). Epilepsy in mice deficient in the 65-kDa isoform of glutamic acid decarboxylase. *Proc. Natl. Acad. Sci. USA* **94**, 14060-14065. doi:10.1073/pnas.94.25.14060
- Kerjan, G., Koizumi, H., Han, E. B., Dubé, C. M., Djakovic, S. N., Patrick, G. N., Baram, T. Z., Heinemann, S. F. and Gleeson, J. G. (2009). Mice lacking doublecortin and doublecortin-like kinase 2 display altered hippocampal neuronal maturation and spontaneous seizures. *Proc. Natl. Acad. Sci. USA* **106**, 6766-6771. doi:10.1073/pnas.0812687106
- Kjeldsen, M. J., Kyvik, K. O., Christensen, K. and Friis, M. L. (2001). Genetic and environmental factors in epilepsy: a population-based study of 11 900 Danish twin pairs. *Epilepsy Res.* **44**, 167-178. doi:10.1016/S0920-1211(01)00196-6
- Klaassen, A., Glykys, J., Maguire, J., Labarca, C., Mody, I. and Boulter, J. (2006). Seizures and enhanced cortical GABAergic inhibition in two mouse models of human autosomal dominant nocturnal frontal lobe epilepsy. *Proc. Natl. Acad. Sci. USA* **103**, 19152-19157. doi:10.1073/pnas.0608215103
- Klein, S., Bankstahl, M. and Löscher, W. (2015). Inter-individual variation in the effect of antiepileptic drugs in the intrahippocampal kainate model of mesial temporal lobe epilepsy in mice. *Neuropharmacology* **90**, 53-62. doi:10.1016/j.neuropharm.2014.11.008
- Koelmann, B. P. C. (2018). What do genetic studies tell us about the heritable basis of common epilepsy? Polygenic or complex epilepsy? *Neurosci. Lett.* **667**, 10-16. doi:10.1016/j.neulet.2017.03.042
- Kogut, I., McCarthy, S. M., Pavlova, M., Astling, D. P., Chen, X., Jakimenko, A., Jones, K. L., Getahun, A., Cambier, J. C., Pasmooij, A. M. G. et al. (2018). High-efficiency RNA-based reprogramming of human primary fibroblasts. *Nat. Commun.* **9**, 745. doi:10.1038/s41467-018-03190-3
- Kovacevic, J., Maroteaux, G., Schut, D., Loos, M., Dubey, M., Pitsch, J., Rimmelink, E., Koopmans, B., Crowley, J., Cornelisse, L. N. et al. (2018). Protein instability, haploinsufficiency, and cortical hyper-excitability underlie STXBP1 encephalopathy. *Brain* **141**, 1350-1374. doi:10.1093/brain/awy046
- Krackow, S., Vannoni, E., Codita, A., Mohammed, A. H., Cirulli, F., Branchi, I., Alleva, E., Reichelt, A., Willuweit, A., Voikar, V. et al. (2010). Consistent behavioral phenotype differences between inbred mouse strains in the IntelliCage. *Genes Brain Behav.* **9**, 722-731. doi:10.1111/j.1601-183X.2010.00606.x

- Kroll, J. R., Wong, K. G., Siddiqui, F. M. and Tanouye, M. A. (2015a). Disruption of endocytosis with the dynamin mutant shibirets1 suppresses seizures in *Drosophila*. *Genetics* **201**, 1087-1102. doi:10.1534/genetics.115.177600
- Kroll, J. R., Saras, A. and Tanouye, M. A. (2015b). *Drosophila* sodium channel mutations: Contributions to seizure-susceptibility. *Exp. Neurol.* **274**, 80-87. doi:10.1016/j.expneurol.2015.06.018
- Kuijlaars, J., Oyelami, T., Diels, A., Rohrbacher, J., Versweyveld, S., Meneghello, G., Tuefferd, M., Verstraelen, P., Detrez, J. R., Verschuuren, M. et al. (2016). Sustained synchronized neuronal network activity in a human astrocyte co-culture system. *Sci. Rep.* **6**, 36529. doi:10.1038/srep36529
- Kwan, P., Arzimanoglou, A., Berg, A. T., Brodie, M. J., Allen Hauser, W., Mathern, G., Moshé, S. L., Perucca, E., Wiebe, S. and French, J. (2010). Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* **51**, 1069-1077. doi:10.1111/j.1528-1167.2009.02397.x
- Kyttälä, A., Moraghebi, R., Valensisi, C., Kettunen, J., Andrus, C., Pasumarthy, K. K., Nakanishi, M., Nishimura, K., Ohtaka, M., Weltner, J. et al. (2016). Genetic variability overrides the impact of parental cell type and determines iPSC differentiation potential. *Stem Cell Rep.* **6**, 200-212. doi:10.1016/j.stemcr.2015.12.009
- Lai, C. H., Chou, C. Y., Ch'ang, L. Y., Liu, C. S. and Lin, W. (2000). Identification of novel human genes evolutionarily conserved in *Caenorhabditis elegans* by comparative proteomics. *Genome Res.* **10**, 703-713. doi:10.1101/gr.10.5.703
- Lam, W. W. K., Millichap, J. J., Soares, D. C., Chin, R., McLellan, A., FitzPatrick, D. R., Elmslie, F., Lees, M. M., Schaefer, G. B., DDD study et al. (2016). Novel de novo EEF1A2 missense mutations causing epilepsy and intellectual disability. *Mol. Genet. Genomic Med.* **4**, 465-474. doi:10.1002/mgg3.219
- Lee, Y., Seo, H. W., Lee, K. J., Jang, J.-W. and Kim, S. (2020). A microfluidic system for stable and continuous EEG monitoring from multiple larval zebrafish. *Sensors (Basel)* **20**, 5903. doi:10.3390/s20205903
- Leech, C. K. and McIntyre, D. C. (1976). Kindling rates in inbred mice: an analog to learning? *Behav. Biol.* **16**, 439-452. doi:10.1016/S0091-6773(76)91603-5
- Lévesque, M. and Avoli, M. (2013). The kainic acid model of temporal lobe epilepsy. *Neurosci. Biobehav. Rev.* **37**, 2887-2899. doi:10.1016/j.neubiorev.2013.10.011
- Lidster, K., Jefferys, J. G., Blümcke, I., Crunelli, V., Flecknell, P., Freguelli, B. G., Gray, W. P., Kaminski, R., Pitkänen, A., Ragan, I. et al. (2016). Opportunities for improving animal welfare in rodent models of epilepsy and seizures. *J. Neurosci. Methods* **260**, 2-25. doi:10.1016/j.jneumeth.2015.09.007
- Lieb, A., Qiu, Y., Dixon, C. L., Heller, J. P., Walker, M. C., Schorge, S. and Kullmann, D. M. (2018). Biochemical autoregulatory gene therapy for focal epilepsy. *Nat. Med.* **24**, 1324-1329. doi:10.1038/s41591-018-0103-x
- Liu, S., Yu, W. and Lü, Y. (2016). The causes of new-onset epilepsy and seizures in the elderly. *Neuropsychiatr. Dis. Treat.* **12**, 1425-1434. doi:10.2147/NDT.S107905
- Löscher, W. (2011). Critical review of current animal models of seizures and epilepsy used in the discovery and development of new antiepileptic drugs. *Seizure* **20**, 359-368. doi:10.1016/j.seizure.2011.01.003
- Löscher, W. (2017). Animal models of seizures and epilepsy: past, present, and future role for the discovery of antiseizure drugs. *Neurochem. Res.* **42**, 1873-1888. doi:10.1007/s11064-017-2222-z
- Lozovaya, N., Gataullina, S., Tsintsadze, T., Tsintsadze, V., Pallesi-Pocachard, E., Minlebaev, M., Goriounova, N. A., Buhler, E., Watrin, F., Shityakov, S. et al. (2014). Selective suppression of excessive GluN2C expression rescues early epilepsy in a tuberous sclerosis murine model. *Nat. Commun.* **5**, 4563. doi:10.1038/ncomms5563
- Lu, H., Zou, Q., Gu, H., Raichle, M. E., Stein, E. A. and Yang, Y. (2012). Rat brains also have a default mode network. *Proc. Natl. Acad. Sci. USA* **109**, 3979-3984. doi:10.1073/pnas.1200506109
- Lukkes, J. L., Mokin, M. V., Scholl, J. L. and Forster, G. L. (2009). Adult rats exposed to early-life social isolation exhibit increased anxiety and conditioned fear behavior, and altered hormonal stress responses. *Horm. Behav.* **55**, 248-256. doi:10.1016/j.yhbeh.2008.10.014
- Malas, S., Postlethwaite, M., Ekonomou, A., Whalley, B., Nishiguchi, S., Wood, H., Meldrum, B., Constanti, A. and Episkopou, V. (2003). Sox1-deficient mice suffer from epilepsy associated with abnormal ventral forebrain development and olfactory cortex hyperexcitability. *Neuroscience* **119**, 421-432. doi:10.1016/S0306-4522(03)00158-1
- Manouze, H., Ghestem, A., Poillerat, V., Bennis, M., Ba-M'hamed, S., Benoliel, J. J., Becker, C. and Bernard, C. (2019). Effects of single cage housing on stress, cognitive, and seizure parameters in the rat and mouse pilocarpine models of epilepsy. *ENEURO* **6**, ENEURO.0179-18.2019. doi:10.1523/ENEURO.0179-18.2019
- Martin, M. S., Dutt, K., Papale, L. A., Dubé, C. M., Dutton, S. B., de Haan, G., Shankar, A., Tufik, S., Meisler, M. H., Baram, T. Z. et al. (2010). Altered function of the SCN1A voltage-gated sodium channel leads to gamma-aminobutyric acid-ergic (GABAergic) interneuron abnormalities. *J. Biol. Chem.* **285**, 9823-9834. doi:10.1074/jbc.M109.078568
- Matsumoto, K., Nomura, H., Murakami, Y., Taki, K., Takahata, H. and Watanabe, H. (2003). Long-term social isolation enhances picrotoxin seizure susceptibility in mice: up-regulatory role of endogenous brain allopregnanolone in GABAergic systems. *Pharmacol. Biochem. Behav.* **75**, 831-835. doi:10.1016/S0091-3057(03)00169-2
- McColl, C. D., Jacoby, A. S., Shine, J., Iismaa, T. P. and Bekkers, J. M. (2006). Galanin receptor-1 knockout mice exhibit spontaneous epilepsy, abnormal EEGs and altered inhibition in the hippocampus. *Neuropharmacology* **50**, 209-218. doi:10.1016/j.neuropharm.2005.09.001
- McGuire, M. J., Gertz, S. M., McCutcheon, J. D., Richardson, C. R. and Poulsen, D. J. (2019). Use of a wireless video-EEG system to monitor epileptiform discharges following lateral fluid-percussion induced traumatic brain injury. *J. Vis. Exp.* doi:10.3791/59637
- McTague, A., Howell, K. B., Cross, J. H., Kurian, M. A. and Scheffer, I. E. (2016). The genetic landscape of the epileptic encephalopathies of infancy and childhood. *Lancet Neurol.* **15**, 304-316. doi:10.1016/S1474-4422(15)00250-1
- Medlej, Y., Asdikar, R., Wadi, L., Salah, H., Dosh, L., Hashash, R., Karnib, N., Medlej, M., Darwish, H., Kobeissy, F. et al. (2019). Enhanced setup for wired continuous long-term EEG monitoring in juvenile and adult rats: application for epilepsy and other disorders. *BMC Neurosci.* **20**, 8. doi:10.1186/s12868-019-0490-z
- Meikle, L., Talos, D. M., Onda, H., Pollizzi, K., Rotenberg, A., Sahin, M., Jensen, F. E. and Kwiatkowski, D. J. (2007). A mouse model of tuberous sclerosis: neuronal loss of Tsc1 causes dysplastic and ectopic neurons, reduced myelination, seizure activity, and limited survival. *J. Neurosci.* **27**, 5546-5558. doi:10.1523/JNEUROSCI.5540-06.2007
- Meisler, M. H. (2019). SCN8A encephalopathy: mechanisms and models. *Epilepsia* **60** Suppl. 3, S86-S91. doi:10.1111/epi.14703
- Miller, L. L., Pellock, J. M., DeLorenzo, R. J., Meyer, J. M. and Corey, L. A. (1998). Univariate genetic analyses of epilepsy and seizures in a population-based twin study: the Virginia twin registry. *Genet. Epidemiol.* **15**, 33-49. doi:10.1002/(SICI)1098-2272(1998)15:1<33::AID-GEPI3>3.0.CO;2-5
- Mirza, N., Appleton, R., Burn, S., du Plessis, D., Duncan, R., Farah, J. O., Feenstra, B., Hviid, A., Josan, V., Mohanraj, R. et al. (2017). Genetic regulation of gene expression in the epileptic human hippocampus. *Hum. Mol. Genet.* **26**, 1759-1769. doi:10.1093/hmg/ddx061
- Miyamoto, H., Tatsukawa, T., Shimohata, A., Yamagata, T., Suzuki, T., Amano, K., Mazaki, E., Raveau, M., Ogiwara, I., Oba-Asaka, A. et al. (2019). Impaired cortico-striatal excitatory transmission triggers epilepsy. *Nat. Commun.* **10**, 1917. doi:10.1038/s41467-019-09954-9
- Moore, B. M., Jerry Jou, C., Tatalovic, M., Kaufman, E. S., Kline, D. D. and Kunze, D. L. (2014). The Kv1.1 null mouse, a model of sudden unexpected death in epilepsy (SUDEP). *Epilepsia* **55**, 1808-1816. doi:10.1111/epi.12793
- Mouse Genome Sequencing Consortium, Waterston, R. H., Lindblad-Toh, K., Birney, E., Rogers, J., Abril, J. F., Agarwal, P., Agarwala, R., Ainscough, R., Alexandersson, M. et al. (2002). Initial sequencing and comparative analysis of the mouse genome. *Nature* **420**, 520-562. doi:10.1038/nature01262
- Moyer, J. T., Gnatkovsky, V., Ono, T., Otáhal, J., Wagenaar, J., Stacey, W. C., Noebels, J., Ikeda, A., Staley, K., de Curtis, M. et al. (2017). Standards for data acquisition and software-based analysis of in vivo electroencephalography recordings from animals. A TASK1-WG5 report of the AES/ILAE Translational Task Force of the ILAE. *Epilepsia* **58** Suppl. 4, 53-67. doi:10.1111/epi.13909
- Mulcahey, P. J., Tang, S., Takano, H., White, A., Davila Portillo, D. R., Kane, O. M., Marsh, E. D., Zhou, Z. and Coulter, D. A. (2020). Aged heterozygous Cdk5 mutant mice exhibit spontaneous epileptic spasms. *Exp. Neurol.* **332**, 113388. doi:10.1016/j.expneurol.2020.113388
- Musumeci, S. A., Bosco, P., Calabrese, G., Bakker, C., De Sarro, G. B., Elia, M., Ferri, R. and Oostra, B. A. (2000). Audiogenic seizures susceptibility in transgenic mice with fragile X syndrome. *Epilepsia* **41**, 19-23. doi:10.1111/j.1528-1157.2000.tb01499.x
- Nicholas, C. R., Chen, J., Tang, Y., Southwell, D. G., Chalmers, N., Vogt, D., Arnold, C. M., Chen, Y.-J. J., Stanley, E. G., Elefanty, A. G. et al. (2013). Functional maturation of hPSC-derived forebrain interneurons requires an extended timeline and mimics human neural development. *Cell Stem Cell* **12**, 573-586. doi:10.1016/j.stem.2013.04.005
- Niibori, Y., Lee, S. J., Minassian, B. A. and Hampson, D. R. (2020). Sexually divergent mortality and partial phenotypic rescue after gene therapy in a mouse model of dravet syndrome. *Hum. Gene Ther.* **31**, 339-351. doi:10.1089/hum.2019.225
- Obien, M. E. J., Deligkaris, K., Bullmann, T., Bakkum, D. J. and Frey, U. (2014). Revealing neuronal function through microelectrode array recordings. *Front. Neurosci.* **8**, 423. doi:10.3389/fnins.2014.00423
- Ogiwara, I., Miyamoto, H., Morita, N., Atapour, N., Mazaki, E., Inoue, I., Takeuchi, T., Itoharu, S., Yanagawa, Y., Obata, K. et al. (2007). Nav1.1 localizes to axons of parvalbumin-positive inhibitory interneurons: a circuit basis for epileptic seizures in mice carrying an Scn1a gene mutation. *J. Neurosci.* **27**, 5903-5914. doi:10.1523/JNEUROSCI.5270-06.2007
- Ohmori, I., Kobayashi, K. and Ouchida, M. (2020). Scn1a and Cacna1a mutations mutually alter their original phenotypes in rats. *Neurochem. Int.* **141**, 104859. doi:10.1016/j.neuint.2020.104859
- Okuda, K., Kobayashi, S., Fukaya, M., Watanabe, A., Murakami, T., Hagiwara, M., Sato, T., Ueno, H., Ogonuki, N., Komano-Inoue, S. et al. (2017). CDKL5

- controls postsynaptic localization of GluN2B-containing NMDA receptors in the hippocampus and regulates seizure susceptibility. *Neurobiol. Dis.* **106**, 158-170. doi:10.1016/j.nbd.2017.07.002
- O'Malley, H. A., Hull, J. M., Clawson, B. C., Chen, C., Owens-Fiestan, G., Jameson, M. B., Aton, S. J., Parent, J. M. and Isom, L. L. (2019). Scn1b deletion in adult mice results in seizures and SUDEP. *Ann Clin Transl Neurol* **6**, 1121-1126. doi:10.1002/actn3.785
- Otto, J. F., Singh, N. A., Dahle, E. J., Leppert, M. F., Pappas, C. M., Pruess, T. H., Wilcox, K. S. and White, H. S. (2009). Electroconvulsive seizure thresholds and kindling acquisition rates are altered in mouse models of human KCNQ2 and KCNQ3 mutations for benign familial neonatal convulsions. *Epilepsia* **50**, 1752-1759. doi:10.1111/j.1528-1167.2009.02100.x
- Ozkan, E. D., Creson, T. K., Kramár, E. A., Rojas, C., Seese, R. R., Babyan, A. H., Shi, Y., Lucero, R., Xu, X., Noebels, J. L. et al. (2014). Reduced cognition in Syngap1 mutants is caused by isolated damage within developing forebrain excitatory neurons. *Neuron* **82**, 1317-1333. doi:10.1016/j.neuron.2014.05.015
- Pacey, L. K. K., Heximer, S. P. and Hampson, D. R. (2009). Increased GABA(B) receptor-mediated signaling reduces the susceptibility of fragile X knockout mice to audiogenic seizures. *Mol. Pharmacol.* **76**, 18-24. doi:10.1124/mol.109.056127
- Pandey, U. B. and Nichols, C. D. (2011). Human disease models in *Drosophila melanogaster* and the role of the fly in therapeutic drug discovery. *Pharmacol. Rev.* **63**, 411-436. doi:10.1124/pr.110.003293
- Pandey, R., Gupta, S., Tandon, S., Wolkenhauer, O., Vera, J. and Gupta, S. K. (2010). Baccoside A suppresses epileptic-like seizure/convulsion in *Caenorhabditis elegans*. *Seizure* **19**, 439-442. doi:10.1016/j.seizure.2010.06.005
- Papale, L. A., Beyer, B., Jones, J. M., Sharkey, L. M., Tufik, S., Epstein, M., Letts, V. A., Meisler, M. H., Frankel, W. N. and Escayg, A. (2009). Heterozygous mutations of the voltage-gated sodium channel SCN8A are associated with spike-wave discharges and absence epilepsy in mice. *Hum. Mol. Genet.* **18**, 1633-1641. doi:10.1093/hmg/ddp081
- Park, I., Lee, K., Bishayee, K., Jeon, H. J., Lee, H. and Lee, U. (2019). Machine-learning based automatic and real-time detection of mouse scratching behaviors. *Exp. Neurobiol.* **28**, 54-61. doi:10.5607/en.2019.28.1.54
- Parker, L., Howlett, I. C., Rusan, Z. M. and Tanouye, M. A. (2011a). Seizure and epilepsy: studies of seizure disorders in *Drosophila*. *Int. Rev. Neurobiol.* **99**, 1-21. doi:10.1016/B978-0-12-387003-2.00001-X
- Parker, L., Padilla, M., Du, Y., Dong, K. and Tanouye, M. A. (2011b). *Drosophila* as a model for epilepsy: bss is a gain-of-function mutation in the para sodium channel gene that leads to seizures. *Genetics* **187**, 523-534. doi:10.1534/genetics.110.123299
- Patino, G. A., Claes, L. R. F., Lopez-Santiago, L. F., Slat, E. A., Dondeti, R. S. R., Chen, C., O'Malley, H. A., Gray, C. B. B., Miyazaki, H., Nukina, N. et al. (2009). A functional null mutation of SCN1B in a patient with Dravet syndrome. *J. Neurosci.* **29**, 10764-10778. doi:10.1523/JNEUROSCI.2475-09.2009
- Peleh, T., Bai, X., Kas, M. J. H. and Hengerer, B. (2019). RFID-supported video tracking for automated analysis of social behaviour in groups of mice. *J. Neurosci. Methods* **325**, 108323. doi:10.1016/j.jneumeth.2019.108323
- Peñagarikano, O., Abrahams, B. S., Herman, E. I., Winden, K. D., Gdalyahu, A., Dong, H., Sonnenblick, L. I., Gruver, R., Almajano, J., Bragin, A. et al. (2011). Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. *Cell* **147**, 235-246. doi:10.1016/j.cell.2011.08.040
- Pfammatter, J. A., Maganti, R. K. and Jones, M. V. (2019). An automated, machine learning-based detection algorithm for spike-wave discharges (SWDs) in a mouse model of absence epilepsy. *Epilepsia Open* **4**, 110-122. doi:10.1002/epi4.12303
- Pitkänen, A., Nehlig, A., Brooks-Kayal, A. R., Dudek, F. E., Friedman, D., Galanopoulou, A. S., Jensen, F. E., Kaminski, R. M., Kapur, J., Klitgaard, H. et al. (2013). Issues related to development of antiepileptogenic therapies. *Epilepsia* **54** Suppl. 4, 35-43. doi:10.1111/epi.12297
- Prè, D., Nestor, M. W., Sproul, A. A., Jacob, S., Koppensteiner, P., Chinchalongporn, V., Zimmer, M., Yamamoto, A., Noggle, S. A. and Arancio, O. (2014). A time course analysis of the electrophysiological properties of neurons differentiated from human induced pluripotent stem cells (iPSCs). *PLoS ONE* **9**, e103418. doi:10.1371/journal.pone.0103418
- Qaiser, F., Yuen, R. K. C. and Andrade, D. M. (2020). Genetics of epileptic networks: from focal to generalized genetic epilepsies. *Curr. Neurol. Neurosci. Rep.* **20**, 46. doi:10.1007/s11910-020-01059-x
- Qu, S., Catron, M., Zhou, C., Janve, V., Shen, W., Howe, R. K. and Macdonald, R. L. (2020). GABA $\alpha$  receptor  $\beta$ 3 subunit mutation D120N causes Lennox-Gastaut syndrome in knock-in mice. *Brain Commun.* **2**, fcaa028. doi:10.1093/braincoms/fcaa028
- Quraishi, I. H., Mercier, M. R., McClure, H., Couture, R. L., Schwartz, M. L., Lukowski, R., Ruth, P. and Kaczmarek, L. K. (2020). Impaired motor skill learning and altered seizure susceptibility in mice with loss or gain of function of the Kcnt1 gene encoding Slack (KNa1.1) Na $^{+}$ -activated K $^{+}$  channels. *Sci. Rep.* **10**, 3213. doi:10.1038/s41598-020-60028-z
- Racine, R. J. (1972). Modification of seizure activity by electrical stimulation. II. Motor seizure. *Electroencephalogr. Clin. Neurophysiol.* **32**, 281-294. doi:10.1016/0013-4694(72)90177-0
- Radlicz, C., Chambers, A., Olis, E. and Kuebler, D. (2019). The addition of a lipid-rich dietary supplement eliminates seizure-like activity and paralysis in the *Drosophila* bang sensitive mutants. *Epilepsy Res.* **155**, 106153. doi:10.1016/j.epilepsyres.2019.106153
- Ramos-Lizana, J., Rodriguez-Lucenilla, M. I., Aguilera-López, P., Aguirre-Rodríguez, J. and Cassinello-García, E. (2012). A study of drug-resistant childhood epilepsy testing the new ILAE criteria. *Seizure* **21**, 266-272. doi:10.1016/j.seizure.2012.01.009
- Reynolds, E. R., Stauffer, E. A., Feeney, L., Rojahn, E., Jacobs, B. and McKeever, C. (2004). Treatment with the antiepileptic drugs phenytoin and gabapentin ameliorates seizure and paralysis of *Drosophila* bang-sensitive mutants. *J. Neurobiol.* **58**, 503-513. doi:10.1002/neu.10297
- Riban, V., Boullieret, V., Pham-Lê, B. T., Fritschy, J. M., Marescaux, C. and Depaulis, A. (2002). Evolution of hippocampal epileptic activity during the development of hippocampal sclerosis in a mouse model of temporal lobe epilepsy. *Neuroscience* **112**, 101-111. doi:10.1016/S0306-4522(02)00064-7
- Risley, M. G., Kelly, S. P., Jia, K., Grill, B. and Dawson-Scully, K. (2016). Modulating behavior in *C. elegans* using electroshock and antiepileptic drugs. *PLoS ONE* **11**, e0163786. doi:10.1371/journal.pone.0163786
- Rotaru, D. C., Mientjes, E. J. and Elgersma, Y. (2020). Angelman syndrome: from mouse models to therapy. *Neuroscience* **445**, 172-189. doi:10.1016/j.neuroscience.2020.02.017
- Sah, M., Shore, A. N., Petri, S., Kanber, A., Yang, M., Weston, M. C. and Frankel, W. N. (2020). Altered excitatory transmission onto hippocampal interneurons in the IQSEC2 mouse model of X-linked neurodevelopmental disease. *Neurobiol. Dis.* **137**, 104758. doi:10.1016/j.nbd.2020.104758
- Saras, A. and Tanouye, M. A. (2016). Mutations of the calcium channel gene cacophony suppress seizures in *Drosophila*. *PLoS Genet.* **12**, e1005784. doi:10.1371/journal.pgen.1005784
- Schmidt, J. (1987). Changes in seizure susceptibility in rats following chronic administration of pentylenetetrazol. *Biomed. Biochim. Acta* **46**, 267-270.
- Seidner, G., Alvarez, M. G., Yeh, J. I., O'Driscoll, K. R., Klepper, J., Stump, T. S., Wang, D., Spinner, N. B., Birnbaum, M. J. and De Vivo, D. C. (1998). GLUT-1 deficiency syndrome caused by haploinsufficiency of the blood-brain barrier hexose carrier. *Nat. Genet.* **18**, 188-191. doi:10.1038/ng0298-188
- Siegle, J. H., López, A. C., Patel, Y. A., Abramov, K., Ohayon, S. and Voigts, J. (2017). Open Ephys: an open-source, plugin-based platform for multichannel electrophysiology. *J. Neural Eng.* **14**, 045003. doi:10.1088/1741-2552/aa5eea
- Siehr, M. S., Massey, C. A. and Noebels, J. L. (2020). Arx expansion mutation perturbs cortical development by augmenting apoptosis without activating innate immunity in a mouse model of X-linked infantile spasms syndrome. *Dis. Model. Mech.* **13**, dmm042515. doi:10.1242/dmm.042515
- Singh, N. A., Otto, J. F., Dahle, E. J., Pappas, C., Leslie, J. D., Vilaythong, A., Noebels, J. L., White, H. S., Wilcox, K. S. and Leppert, M. F. (2008). Mouse models of human KCNQ2 and KCNQ3 mutations for benign familial neonatal convulsions show seizures and neuronal plasticity without synaptic reorganization. *J. Physiol. (Lond.)* **586**, 3405-3423. doi:10.1113/jphysiol.2008.154971
- Sirven, J. I. (2015). Epilepsy: a spectrum disorder. *Cold Spring Harb. Perspect. Med.* **5**, a022848. doi:10.1101/cshperspect.a022848
- Stawicki, T. M., Takayanagi-Kiya, S., Zhou, K. and Jin, Y. (2013). Neuropeptides function in a homeostatic manner to modulate excitation-inhibition imbalance in *C. elegans*. *PLoS Genet.* **9**, e1003472. doi:10.1371/journal.pgen.1003472
- Strand, A. D., Aragaki, A. K., Baquet, Z. C., Hodges, A., Cunningham, P., Holmans, P., Jones, K. R., Jones, L., Kooperberg, C. and Olson, J. M. (2007). Conservation of regional gene expression in mouse and human brain. *PLoS Genet.* **3**, e59. doi:10.1371/journal.pgen.0030059
- Strohl, K. P., Gallagher, L., Lynn, A., Friedman, L., Hill, A., Singer, J. B., Lander, E. S. and Nadeau, J. (2007). Sleep-related epilepsy in the *A/J* mouse. *Sleep* **30**, 169-176. doi:10.1093/sleep/30.2.169
- Sturman, O., von Ziegler, L., Schläppi, C., Akyol, F., Privitera, M., Slominski, D., Grimm, C., Thieren, L., Zerbi, V., Grewe, B. et al. (2020). Deep learning-based behavioral analysis reaches human accuracy and is capable of outperforming commercial solutions. *Neuropsychopharmacology* **45**, 1942-1952. doi:10.1038/s41386-020-0776-y
- Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K. and Yamanaka, S. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* **131**, 861-872. doi:10.1016/j.cell.2007.11.019
- Tan, H. O., Reid, C. A., Single, F. N., Davies, P. J., Chiu, C., Murphy, S., Clarke, A. L., Dibbens, L., Krestel, H., Mulley, J. C. et al. (2007). Reduced cortical inhibition in a mouse model of familial childhood absence epilepsy. *Proc. Natl. Acad. Sci. USA* **104**, 17536-17541. doi:10.1073/pnas.0708440104
- Téllez-Zenteno, J. F., Hernández-Ronquillo, L., Buckley, S., Zahagun, R. and Rizvi, S. (2014). A validation of the new definition of drug-resistant epilepsy by the International League Against Epilepsy. *Epilepsia* **55**, 829-834. doi:10.1111/epi.12633
- Teoh, J., Subramanian, N., Pero, M. E., Bartolini, F., Amador, A., Kanber, A., Williams, D., Petri, S., Yang, M., Allen, A. S. et al. (2020). Argef1 haploinsufficiency in mice alters neuronal endosome composition and



- decreases membrane surface postsynaptic GABAA receptors. *Neurobiol. Dis.* **134**, 104632. doi:10.1016/j.nbd.2019.104632
- Tidball, A. M. and Parent, J. M.** (2016). Concise review: exciting cells: modeling genetic epilepsies with patient-derived induced pluripotent stem cells. *Stem Cells* **34**, 27-33. doi:10.1002/stem.2203
- Tieng, Q. M., Kharatishvili, I., Chen, M. and Reutens, D. C.** (2016). Mouse EEG spike detection based on the adapted continuous wavelet transform. *J. Neural Eng.* **13**, 026018. doi:10.1088/1741-2560/13/2/026018
- Tieng, Q. M., Anbazhagan, A., Chen, M. and Reutens, D. C.** (2017). Mouse epileptic seizure detection with multiple EEG features and simple thresholding technique. *J. Neural Eng.* **14**, 066006. doi:10.1088/1741-2552/aa8069
- Toman, J. E. P., Swinyard, E. A. and Goodman, L. S.** (1946). Properties of maximal seizures, and their alteration by anticonvulsant drugs and other agents. *J. Neurophysiol.* **9**, 231-239. doi:10.1152/jn.1946.9.3.231
- Trujillo, C. A., Gao, R., Negraes, P. D., Gu, J., Buchanan, J., Preissl, S., Wang, A., Wu, W., Haddad, G. G., Chaim, I. A. et al.** (2019). Complex oscillatory waves emerging from cortical organoids model early human brain network development. *Cell Stem Cell* **25**, 558-569.e7. doi:10.1016/j.stem.2019.08.002
- Ugur, B., Chen, K. and Bellen, H. J.** (2016). Drosophila tools and assays for the study of human diseases. *Dis. Model. Mech.* **9**, 235-244. doi:10.1242/dmm.023762
- Vicini, S., Ferguson, C., Prybylowski, K., Kralic, J., Morrow, A. L. and Homanics, G. E.** (2001). GABA(A) receptor  $\alpha 1$  subunit deletion prevents developmental changes of inhibitory synaptic currents in cerebellar neurons. *J. Neurosci.* **21**, 3009-3016. doi:10.1523/JNEUROSCI.21-09-03009.2001
- Wagnon, J. L., Korn, M. J., Parent, R., Tarpey, T. A., Jones, J. M., Hammer, M. F., Murphy, G. G., Parent, J. M. and Meisler, M. H.** (2015). Convulsive seizures and SUDEP in a mouse model of SCN8A epileptic encephalopathy. *Hum. Mol. Genet.* **24**, 506-515. doi:10.1093/hmg/ddu470
- Warner, T. A., Shen, W., Huang, X., Liu, Z., Macdonald, R. L. and Kang, J.-Q.** (2016). Differential molecular and behavioural alterations in mouse models of GABRG2 haploinsufficiency versus dominant negative mutations associated with human epilepsy. *Hum. Mol. Genet.* **25**, 3192-3207. doi:10.1093/hmg/ddw168
- Wasilczuk, A. Z., Proekt, A., Kelz, M. B. and McKinstry-Wu, A. R.** (2016). High-density electroencephalographic acquisition in a rodent model using low-cost and open-source resources. *J. Vis. Exp.* doi:10.3791/54908
- Weintraub, A., Singaravelu, J. and Bhatnagar, S.** (2010). Enduring and sex-specific effects of adolescent social isolation in rats on adult stress reactivity. *Brain Res.* **1343**, 83-92. doi:10.1016/j.brainres.2010.04.068
- Wiegand, C. and Banerjee, I.** (2019). Recent advances in the applications of iPSC technology. *Curr. Opin. Biotechnol.* **60**, 250-258. doi:10.1016/j.copbio.2019.05.011
- Williams, S. N., Locke, C. J., Braden, A. L., Caldwell, K. A. and Caldwell, G. A.** (2004). Epileptic-like convulsions associated with LIS-1 in the cytoskeletal control of neurotransmitter signaling in *Caenorhabditis elegans*. *Hum. Mol. Genet.* **13**, 2043-2059. doi:10.1093/hmg/ddh209
- Willner, P.** (1984). The validity of animal models of depression. *Psychopharmacology* **83**, 1-16. doi:10.1007/BF00427414
- Wirrell, E. C., Grossardt, B. R., Wong-Kissel, L. C. L. and Nickels, K. C.** (2011). Incidence and classification of new-onset epilepsy and epilepsy syndromes in children in Olmsted County, Minnesota from 1980 to 2004: a population-based study. *Epilepsy Res.* **95**, 110-118. doi:10.1016/j.eplesyres.2011.03.009
- Wolff, M., Johannesen, K. M., Hedrich, U. B. S., Masnada, S., Rubboli, G., Gardella, E., Lesca, G., Ville, D., Milh, M., Villard, L. et al.** (2017). Genetic and phenotypic heterogeneity suggest therapeutic implications in SCN2A-related disorders. *Brain* **140**, 1316-1336. doi:10.1093/brain/awx054
- Wong, S. Q., Jones, A., Dodd, S., Grimes, D., Barclay, J. W., Marson, A. G., Cunliffe, V. T., Burgoyne, R. D., Sills, G. J. and Morgan, A.** (2018). A *Caenorhabditis elegans* assay of seizure-like activity optimised for identifying antiepileptic drugs and their mechanisms of action. *J. Neurosci. Methods* **309**, 132-142. doi:10.1016/j.jneumeth.2018.09.004
- Wu, W., Li, Y., Wei, Y., Bosco, D. B., Xie, M., Zhao, M.-G., Richardson, J. R. and Wu, L.-J.** (2020). Microglial depletion aggravates the severity of acute and chronic seizures in mice. *Brain Behav. Immun.* **89**, 245-255. doi:10.1016/j.bbi.2020.06.028
- Wykes, R. C., Heeroma, J. H., Mantoan, L., Zheng, K., MacDonald, D. C., Deisseroth, K., Hashemi, K. S., Walker, M. C., Schorge, S. and Kullmann, D. M.** (2012). Optogenetic and potassium channel gene therapy in a rodent model of focal neocortical epilepsy. *Sci. Transl. Med.* **4**, 161ra152. doi:10.1126/scitranslmed.3004190
- Yu, F. H., Mantegazza, M., Westenbroek, R. E., Robbins, C. A., Kalume, F., Burton, K. A., Spain, W. J., McKnight, G. S., Scheuer, T. and Catterall, W. A.** (2006). Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. *Nat. Neurosci.* **9**, 1142-1149. doi:10.1038/nn1754
- Yu, W., Hill, S. F., Xenakis, J. G., Pardo-Manuel de Villena, F., Wagnon, J. L. and Meisler, M. H.** (2020). *Gabra2* is a genetic modifier of *Scn8a* encephalopathy in the mouse. *Epilepsia* **61**, 2847-2856. doi:10.1111/epi.16741
- Yutsudo, N., Kamada, T., Kajitani, K., Nomaru, H., Katogi, A., Ohnishi, Y. H., Ohnishi, Y. N., Takase, K., Sakumi, K., Shigeto, H. et al.** (2013). *fosB*-null mice display impaired adult hippocampal neurogenesis and spontaneous epilepsy with depressive behavior. *Neuropsychopharmacology* **38**, 895-906. doi:10.1038/npp.2012.260
- Zafeiriou, M.-P., Bao, G., Hudson, J., Halder, R., Blenkle, A., Schreiber, M.-K., Fischer, A., Schild, D. and Zimmermann, W.-H.** (2020). Developmental GABA polarity switch and neuronal plasticity in Bioengineered Neuronal Organoids. *Nat. Commun.* **11**, 3791. doi:10.1038/s41467-020-17521-w
- Zeng, L.-H., Rensing, N. R., Zhang, B., Gutmann, D. H., Gambello, M. J. and Wong, M.** (2011). *Tsc2* gene inactivation causes a more severe epilepsy phenotype than *Tsc1* inactivation in a mouse model of tuberous sclerosis complex. *Hum. Mol. Genet.* **20**, 445-454. doi:10.1093/hmg/ddq491
- Zhang, B., Zou, J., Han, L., Rensing, N. and Wong, M.** (2016). Microglial activation during epileptogenesis in a mouse model of tuberous sclerosis complex. *Epilepsia* **57**, 1317-1325. doi:10.1111/epi.13429
- Zhang, D., Liu, X. and Deng, X.** (2017). Genetic basis of pediatric epilepsy syndromes. *Exp. Ther. Med.* **13**, 2129-2133. doi:10.3892/etm.2017.4267