Chapter 1

Brain Circuits Responsible for Seizure Generation, Propagation, and Control: Insights from Preclinical Research

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1. Introduction

In the early 1870s, John Hughlings Jackson, the father of modern epileptology wrote, that a seizure is "a symptom, and implies only that there is an occasional, an excessive, and a disorderly discharge of nerve tissue" [1]. When one considers that he wrote this more than 50 years before the first human electroencephalographic recordings [2], his level of insight is quite remarkable. Indeed, his later definition of epilepsy as "the name for occasional, sudden, excessive, rapid, and local discharge of grey matter" [3] could be used without alteration today.

There is a key difference between Jackson's two definitions: his later definition no longer included the concept of seizures as "disorderly". While seizures are a symptom of a disorder, the temporal pattern of signs and symptoms of seizures are far from disorderly or disorganized; this was evident to Jackson in the march of seizure activity through somatosensory cortex [1,4]. Today, relying not only on seizure semiology, but also electroencephalographic, neuroimaging, and animal models, we can without hesitation state that seizure activity does not spread randomly through the brain, but moves through anatomically constrained pathways and networks.

These pathways are the focus of this chapter; we will discuss specific brain networks that are capable of seizure generation, seizure propagation, and seizure suppression. From the perspective of preclinical research, we will emphasize several points:

1. How do we identify seizure circuits?
2. What is the importance of animal models for understanding seizures (with an emphasis on circuit-level manipulations and species-specific features)?

3. How do emerging technologies enable translation of network-level manipulations to the clinic?

2. Identifying seizure circuits

Seizure semiology can provide insight into the brain networks impacted for a given seizure type: for example, the "fencing posture" seen in patients with frontal lobe seizures involving pre-motor cortex can be recapitulated by selective stimulation of pre-motor cortex [5,6]. Similarly, sensory-specific auras e.g., odors in temporal lobe epilepsy can be localized to piriform cortex, [7,8], complex visual hallucinations in anteromedial temporal lobe, occipito-temporal and occipital epilepsy [9]. These symptoms provide an index of regions impacted by seizures, and the temporal order of the occurrence of these symptoms can provide a measure of seizure spread. However, working backwards from these symptoms to identify the path and origin of seizure propagation is a near impossible challenge.

Take, for example, electrical wiring in a house as an anology: a surge of power may cause the lights to flicker in the living room, but that does not necessitate (or even indicate) that the surge started in the living room. Indeed, we know that both parallel and serial wires exist in the house, connecting power sources to fuse boxes to distribution nodes. Various signs and symptoms (burnt wiring, a tripped circuit breaker, etc.) may represent primary causes or secondary effects. Troubleshooting a circuit problem in the house, as complex as it may be, is feasible because there are wiring diagrams to guide you. Without these wiring diagrams tracing a problem would be much more complicated.

At the present, we are working, at best, with very incomplete wiring diagrams for the brain. Thus, we assert that understanding how seizure networks are wired in the "normal" brain is essential to determine how faults in this wiring leads to chronic seizures.

A variety of "mapping" approaches have been employed to identify brain regions engaged by seizures, including electrographic, metabolic (e.g., 2-deoxyglucose), immediate early gene (e.g., fos, zif), and functional magnetic resonance imaging [10–19]. While informative, these approaches, in isolation, only identify areas activated by seizures. Mapping approaches alone cannot determine the role of a region in initiation, propagation, or seizure suppression; these determinations can only be made on the basis of circuit manipulations. The need for circuit-level manipulations is one of several reasons that animal models are vital for deciphering seizure circuitry.

3. Importance of preclinical research using animal models

Studies in human patients have provided many valuable insights into the networks supporting seizures, but the conclusions that can be drawn from these studies are limited by the following:

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1. Changes observed in association with repeated or recurrent seizures cannot be readily identified as cause, effect, or compensation.

2. The great deal of variability across patients and studies with respect to diagnosis, etiology, and treatment.

3. The inability to use matched controls for invasive procedures.

Animal models overcome these limitations. For example, it is only by directly manipulating a brain pathway or region that one can determine whether the structure is necessary for seizure initiation, amplification, distribution, or inhibitory (feedback) control. These direct manipulations include circumscribed lesions, electrical stimulation, pharmacological inactivation/silencing, and optogenetic approaches.

When these techniques are applied to intact, normal animals, their impact on the circuitry can be evaluated uncompromised by preexisting pathologies. Moreover, the effect of the manipulation can be studied in both animals with a seizure profile and in control animals that are seizure naïve, allowing one to determine how pathology changes circuit function.

Four major types of animal models have been used in epilepsy research: genetic (naturally-occurring and engineered), evoked epileptogenesis, and evoked seizures. Entire texts have been written on this subject (see for example, [20]), so our discussion below is by no means intended to be comprehensive.

Naturally-occurring and inbred models are seen in a variety of species, ranging from mouse (e.g., the El mouse [21–24]; and others [25]), rats (e.g., GEPR rats [26–28]; Wistar Audiogenic Rats [29,30]), gerbils [31], dogs [32], and non-human primates (e.g., baboons [33]). The truly spontaneous seizures that occur in these cases suggest that the circuitry that produces epilepsy has been highly conserved over phylogeny.

Transgenic models of epilepsy are of increasing importance as new mutations for inherited epilepsies are discovered. These models have been used to identify abnormalities at the microcircuit level (e.g., interneurons in the SCN1A knockout mice [34]), but abnormalities at the macrocircuit level still require investigation for most of these models.

Models that evoke epileptogenesis are vital when the goal is to identify what neuroplastic changes, if any, lead to epilepsy. However, if the goal is to delineate networks through which seizures preferentially propagate, then the use of an acute or subacute seizure model is most appropriate, especially a model that does not cause brain injury. It may be worthwhile to compare the pattern of seizure propagation in an injured vs uninjured brain, but for this purpose, the injury should be highly controlled and reproducible. Unfortunately, models such as status-epilepticus (SE) induced spontaneous seizures suffer from some of the one of the same drawbacks associated with studies in patient populations, e.g., heterogeneity of injury. Moreover, SE can cause severe and widespread damage that often exceeds the level of damage seen clinically [35]. The need for highly reproducible and focal epileptogenic insults may potentially be filled by controlled models of traumatic brain injury, which provide greater control over the location and extent of damage [36-38].

4. Types of models and manifestations: what is seizure-related and what is due to compensatory mechanisms?

Determining how seizure networks are changed by epileptogenesis is a necessary step in understanding epilepsy, however, this can only be understood in the context of a comparison between the "normal" and "disease" state. The need to examine seizure propagation in a "normal" network is one of several reasons that evoked seizure models are a powerful tool in modern preclinical epileptology. In addition to this utility, evoked seizure models may be preferable for examining network mechanisms because they offer experimental control of seizure timing, severity, etc. This contrasts with most models of epileptogenesis, in which seizures occur spontaneously and unpredictably.

5. Seizure models evoked by pharmacological agents

In rats and mice, systemic administration of GABA-A receptor antagonists (bicuculline, pentylenetetrazole, picrotoxin, beta-carbolines) trigger, in a dose-dependent manner, myoclonic, clonic (complex partial/limbic-motor), and tonic-clonic seizures (for a review see: [39]). These compounds have been used to screen virtually every anticonvulsant drug currently available for clinical use. At least one of these compounds (pentylenetetrazole, Metrazol) has been used to trigger tonic-clonic seizures in human patients. In the non-human primate, most of these compounds trigger generalized tonic-clonic response at the lowest effective dose; this may reflect higher sensitivity of hindbrain seizure networks as compared to limbic forebrain networks in the monkey (discussed below).

Other chemoconvulsants (e.g., pilocarpine, kainate) have been widely used for modeling epileptogenesis, and have also been used to examine seizure circuitry [40,41]. Non-convulsant seizure triggering agents (e.g., gammabutyrolactone) have been used to evaluate circuitry underlying thalamocortical spike-and-wave seizures [42].

Focal application of drugs or electrical stimulation of discrete brain nuclei allows for highly controlled and reproducibly evoked seizures of focal or partial onset. This approach also allows for multiple sites within a network to be manipulated. An example of an especially sensitive and circumscribed site in the forebrain effective for triggering complex partial seizures is "Area Tempestas". This functionally defined region is located in the anterior deep piriform cortex and has been identified in rodents and non-human primates [43–48]. Interestingly, fMRI and PET data suggest that an anatomically homologous area exists in human patients with epilepsy [49]. Moreover, unruptured aneurysms of the middle cerebral artery, located in close proximity to piriform cortex, have been associated with unilateral olfactory auras and complex partial seizures (e.g., [7,8]).

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6. Multiple seizure networks

While a seizure can appear to "progress" on a continuum from complex partial to generalized tonic-clonic, the progression actually results from successive engagement of independent and dissociable seizure networks: one network supporting complex partial seizures and another supporting tonic-clonic seizures [50–52].

For example, complex partial seizures can be evoked by stimulation of the piriform cortex [43], while activation of the inferior colliculus [53] and/or reticular nuclei [54] triggers tonic-clonic seizures. While it is striking that such focal manipulations can trigger these seizures, the independence of these seizure networks is even more impressive. In both the cat and rat, disconnection of the forebrain from the hindbrain via precollicular transections does not impede the ability of the forebrain to show characteristic EEG seizure responses to focal or systemic chemoconvulsant treatment [50,52,55]. Thus, communication with the hindbrain is not necessary for forebrain seizures. Moreover, these animals are still capable of demonstrating normal tonic-clonic and running/bouncing clonus. Thus, communication with the forebrain is not necessary for hindbrain seizures. These data provide a compelling argument for the independence of these seizure networks, an observation that has been supported by localization of focal trigger zones and circuits for these various seizure types. This leads us to the question, are these seizure "trigger zones" necessarily the same as a "seizure focus"?

7. Insights into seizure foci from animal models

It is often assumed that the first site to show ictal activity is the site of seizure initiation. By focally evoking seizures from piriform cortex in the rat, we have found that this is not necessarily the case. Shortly after bicuculline microinjection, piriform cortex displays an interictal like pattern, while ictal activity can be seen in other limbic brain regions. Thus the first ictal activity can appear in a site distal to the site that triggers a seizure.

Clinically, sites of histopathology are often examined as presumptive seizure foci. While in some cases the site(s) of pathology may indeed be the site(s) of seizure onset, animal models have demonstrated that this is not true in all cases. For example, in the tish rat (a model of cortical heterotopia), the *normotopic* neurons, not the heterotopic neurons, are more likely to display epileptiform activity [56]. Moreover, suppression of activity within the heterotopias reduces epileptiform activity *only within the heterotopia* and not within normotopic cortex; conversely, suppression of activity within normotopic cortex suppresses epileptiform activity in both normotopic and heterotopic cortex.

Indeed, even in a highly controlled animal model (e.g., electrically-induced self-sustained status epilepticus), the site within the limbic network showing earliest ictal electrographic activity can vary both between and within subjects [57]. Together, these findings suggest that pathology is not by necessity a clear indicator of the site of seizure initiation. While this does not preclude the possibility that a seizure *can* begin at the site of pathology, it underscores that this is not necessarily the case.

8. Translating semiology and terminology across species

Much of the terminology that is used to describe seizures in animal models has been borrowed from the clinic. However, because seizure semiology differs across species, accurate mapping of terms presents a challenge.

For example, there are behavioral differences in seizures evoked from area tempestas in the monkey as compared to rodents. In the monkey, these seizures are characterized by facial automatisms and arm posturing – behaviors that are strikingly similar to those seen during complex partial seizures in humans. These seizures have high face validity. AT-evoked seizures in the rat are typical limbic-motor seizures, similar to those seen after low doses of systemically-administered bicuculline, pentylenetetrazole, kainate, or after electrical kindling [43,58]. These seizures are characterized by facial clonus (perhaps akin to lip smacking seen in patients and monkeys), forelimb clonus (perhaps akin to arm posturing), and rearing with loss of balance. The rearing and loss of balance seen in rats is strikingly different than the behaviors observed in primate species.

Thus, by examining AT-evoked seizures across species, it has become clear that complex partial seizures have species-specific behavioral manifestations but share the qualities of focal automatisms and engage the same brain network.

9. Species specific nature of seizure spread: What is a generalized seizure?

In human patients, complex partial seizures that secondarily generalize have two characteristic features: 1) involvement of the whole brain when the seizure generalizes and 2) tonic-clonic manifestations when the seizure generalizes (as compared to automatisms prior to generalization).

In the monkey, AT-evoked seizures can secondarily generalize showing bilaterally asynchronous tonic-clonic and electrographic features. This pattern fits both the electrographic and behavioral definitions used for secondary generalization in humans. In contrast, in the rat, AT-evoked seizures do not show tonic-clonic (brainstem) manifestations, but rapidly show bilateral synchronization of the limbic/cortical EEG and associated motor automatisms with rearing and loss of balance. Thus, in the rat, it appears that the "path of least resistance" for seizure propagation is transcallosal or commissural (hence bilaterally synchronized limbic motor and electrographic manifestations) whereas in the primate it appears to be down the neuraxis (hence the involvement of brainstem seizure networks).

Can, then, the limbic motor seizure with rearing and loss of balance in the rat (i.e., a Racine Stage 5 seizure) be considered a secondarily generalized tonic-clonic seizure? Some have suggested that because these seizures engage basal ganglia, they should be considered generalized [59,60]. However, seizure activity in limbic-evoked motor seizures (i.e., Stage 5 amygdala kindled) engages basal ganglia substrates (substantia nigra pars reticulata) even before other limbic structures (such as hippocampus) [61–63]. Moreover, because these

seizures lack the prominent tonic-extensor phase (which requires brainstem engagement) seen in secondarily generalized seizures in monkeys and humans, we suggest that the repeated clonus and rearing/loss of balance that is characteristic of these seizures should not be considered tonic-clonic. On this basis, we suggest that focal limbic seizures (e.g., seizures early in kindling that do not engage the basal ganglia) are akin to simple partial seizures, seizures that spread to the basal ganglia are akin to complex partial seizures (as they are still confined to the forebrain), and only when hindbrain circuits are engaged should these seizures be considered truly generalized.

10. Manipulating circuits with focal stimulation as a therapeutic intervention

With the success of deep brain stimulation trials in epilepsy (e.g., stimulation of the anterior nucleus of the thalamus), focal manipulation of circuitry for the control of epilepsy has become a reality. However, identifying the best locations for targeting is a work-in-progress. Continued circuit analysis in animals is essential, not only for identifying targets, but also for examining newer approaches (e.g., optogenetics, chemical-genetics) that offer exciting levels of specificity in cell-type and pathway-specific targeting [64-70].

One approach that remains underexplored clinically is enhancing the function of seizure-suppressive network nodes that have been identified in animal models. One such node is the substantia nigra pars reticulata [71–76]. Suppression of activity within this region is potently anticonvulsant in a variety of seizure models, and across several species. This structure is particularly compelling for further investigation because it is positioned at the interface of two different seizure networks (i.e., the forebrain network, with heavy interconnections to limbic structures, and the hindbrain network, projections to colliculus and brainstem targets). This anatomical position may underlie the anticonvulsant effects that this region exerts across seizure types: it decreases the duration of tonic hindlimb extension triggered by maximal electroshock and it decreases seizures focally evoked from piriform cortex. As we continue to refine our circuit maps, we open the door to therapeutic approaches such as suppressing activity in seizure "distribution" nodes or activation of endogenous "surge suppressors". These possibilities that can only be realized through the use of appropriate animal models.

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