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Edging toward breakthroughs in epilepsy diagnostics and care

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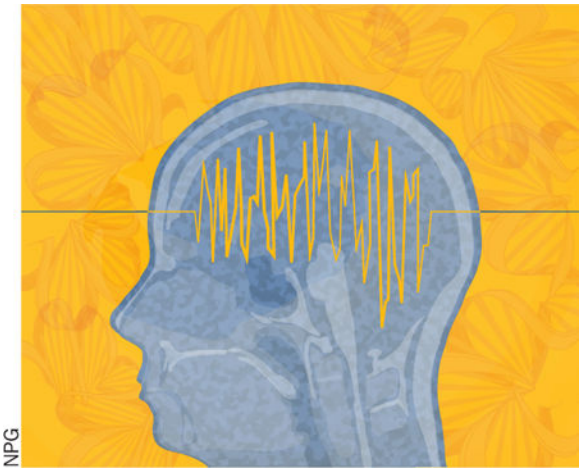
Abstract

The past decade has yielded a host of important conceptual advances in epilepsy, along with some promising findings related to diagnostics and therapeutics. We are on an upswing where precise identification of the cause of a patient's seizure disorder can be matched to therapy that has a high likelihood of success.

Graphical Abstract



Epilepsy is a disease characterized by recurrent seizures, which are transient signs or symptoms of abnormal, excessive or synchronous neuronal activity in the brain. Although the pace of translational discoveries in epilepsy has not yet matched some of the dramatic achievements seen in fields such as oncology and infectious disease, a number of important advances have been made in the past decade. These advances have revised our thinking about some core concepts related to the pathophysiological mechanisms of epilepsy. Genetic diagnoses are increasingly available and provide an opportunity for patient- tailored treatment. Moreover, on-demand neurostimulation devices have become available for patients, and other promising novel treatment strategies are on the horizon.

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Competing interests

The author declares no competing interests.

The conceptual advances cover the gamut from the literal definition of epilepsy and the range of symptoms associated with the disorder, to the fundamental characteristics of neuronal network dysfunction that constitute a seizure. Prompted by the problems created by the prevailing notion that the diagnosis of epilepsy requires the patient to have at least two unprovoked seizures, a task force of the International League Against Epilepsy recently proposed that the diagnosis can also be established when a patient has one seizure in the setting of other factors that make recurrence likely, such as a family history of epilepsy, or epileptiform abnormalities seen on EEG.[1] This modification to the diagnostic criteria of epilepsy will have a major impact on direct patient care in terms of making diagnostic and treatment decisions, as well as on clinical research, including epidemiological studies.

Another profound recent innovation in thinking about epilepsy relates to the range of behavioural and pathophysiological abnormalities associated with the disorder.[2] By far the dominant conceptualization of epilepsy has been that it is a brain disease characterized by recurrent seizures. However, this view fails to recognize the existence of numerous comorbidities in many patients, including problems in cognition (such as memory loss, cognitive slowing and autism) and psychiatric diseases (such as depression, anxiety and certain personality disorders). Thus, it seems highly likely that many forms of epilepsy are complex neuronal network abnormalities that vary in their timescale and triggers, with seizures being but one of a variety of behavioural disturbances.

Our understanding of the basic electro-physiological properties of a seizure has also evolved in recent years. Until recently, the canonical view was that a seizure arose from the hyperexcitability and hypersynchronization of a small network of neurons, with gradual spread depending on the degree to which surround inhibition is maintained. However, recent studies using single microelectrodes demonstrated that a seizure begins with ‘micro-seizures’ emanating asynchronously from small neuronal clusters, which then coalesce and constitute the macroscale hypersynchronization that characterizes most seizures.[3] These findings have important implications regarding our understanding of the stochastic processes that seem to govern the transition of a cortical region from the interictal to the ictal state and, thus, our ability to predict the occurrence of a seizure.

The past 5–6 years have seen some clear breakthroughs in our understanding of the genetic basis of epilepsy. These advances follow something of a ‘dark age’ between 2001 and 2009, when some epilepsy-related genes were discovered among families with rare epilepsy syndromes that followed a Mendelian inheritance pattern, but over 100 genome-wide association studies largely produced negative or non-reproducible results. Arguably the most important discovery, based on the global collaboration of several research groups, was the recognition that *de novo* mutations are the explanation for a substantial proportion of patients with so-called ‘epileptic encephalopathies’—severe forms of treatment-resistant epilepsy that arise early in life and are often associated with profound developmental delay.[4] These findings have led to expanded use of clinical genetic testing in the routine evaluation of patients with these syndromes and, as a consequence, a marked improvement in the ability to establish a definitive diagnosis and provide accurate genetic counselling.

The causes of the most common forms of epilepsy—generalized epilepsy and nonlesional focal epilepsy, both of which are thought to have a strong genetic component—continue for the most part to elude us despite intensive research (although major improvements in brain imaging have reduced the number of patients previously diagnosed as 'non-lesional'). However, two areas of study have shed light on the genetic architecture in this group of patients. First, copy number variants, which have been identified as the basis for a variety of rare epilepsy syndromes, were shown to account for at least a few percent of the common epilepsies.[5] Second, a recent large meta-analysis of genome-wide association studies of this patient population found only three loci that reached genome-wide significance, providing further evidence that the common epilepsies are likely to be explained by the combined influence of numerous common variants of small effect, or multiple rare variants.[6] To adequately assess both possibilities, further progress will require the application of next-generation sequencing to the analysis of genomes from tens of thousands of patients.

Another major diagnostic advance has been the recognition that a paraneoplastic syndrome could be the basis of epilepsy of particularly explosive and malignant onset in patients who were previously healthy.[7] Interestingly, in some cases, antibodies are generated against targets that are also implicated in genetic epilepsies. Thus, evaluation in patients with this presentation increasingly relies on assays for autoantibodies directed against CNS autoantigens such as potassium channels or glutamate receptors, as well as a search for an underlying cancer.

Despite the introduction of well over a dozen new antiepileptic drugs (AEDs) since 1970, there is little evidence that therapeutic efficacy has changed. AEDs continue to fail in approximately 30% of patients, although some of the new medications arguably offer better options in terms of ease of use and adverse effect profile. The past 10 years have, however, seen a definite improvement in understanding the management of epilepsy in women, as important studies have demonstrated the effects of specific AEDs on pregnancy outcome, safety of breast milk, and the development of osteoporosis.

The past decade has also seen the introduction of new and promising alternatives to the traditional medical and surgical approaches for treating epilepsy. Novel proof-of-principle experiments using animal models have shown that closed-loop systems incorporating EEG detection and optogenetic control of neuronal activity can rapidly abort seizures at onset, and implantation of inhibitory neuron precursors can reverse the process of epileptogenesis, even in the adult animal.[8,9] Pivotal clinical trials have recently led to the approval of new neurostimulation devices for patients, including a closed-loop system that detects incipient seizure activity with intracranial electrodes, which then deliver focal stimulation to terminate the seizures.

Finally, the genetic diagnoses described previously are beginning to provide guidance for treatment decisions. Although the findings should be considered preliminary, there are now examples of patients with defined, causative mutations who respond to specific drugs prescribed on the basis of *in vitro* assays of pharmacoresponsiveness. This step towards individualized treatment together with the recognition that some of the underlying mechanisms of epileptogenesis can be mapped onto distinct cellular pathways (such as

mTOR, and pathways related to synaptic machinery), has led to the suggestion that we are at the dawn of precision medicine in epilepsy.[10]

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