# *Epilepsy research: a window onto function and dysfunction of the human brain*

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*As one of the most common neurological disorders, epilepsy has devastating behavioral, social, and occupational consequences and is associated with accumulating brain damage and neurological deficits. Epilepsy comprises a large number of syndromes, which vary greatly with respect to their etiology and clinical features, but share the characteristic clinical hallmark of epilepsy—recurrent spontaneous seizures. Research aimed at understanding the genetic, molecular, and cellular basis of epilepsy has to integrate various research approaches and techniques ranging from clinical expertise, functional analyses of the system and cellular levels, both in human subjects and rodent models of epilepsy, to human and mouse genetics. This knowledge may then be developed into novel treatment options with better control of seizures and/or fewer side effects. In addition, the study of epilepsy has frequently shed light on basic mechanisms underlying the function and dysfunction of the human brain.*



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Epilepsy is one of the most common neurological disorders (~8 000 000 patients in the European Union). It has devastating behavioral, social, and occupational consequences, and is associated with accumulating brain damage and neurological deficits. Epilepsy comprises a large number of syndromes, which vary greatly with respect to their clinical features, treatment, and prognosis. However, all of these syndromes share the characteristic clinical hallmark of epilepsy—recurrent spontaneous seizures.

Even though the key manifestation of all epilepsies is recurrent seizures, the etiologies that can give rise to an increased propensity of the human brain to generate synchronized neuronal activity and seizures are diverse. Epileptic seizures are associated with overt causes, such as certain central nervous system (CNS) tumors or neurodevelopmental abnormalities, CNS trauma, or inflammation (symptomatic epilepsies). In a small number of epilepsy patients, a mutation in a single gene suffices to cause chronic seizures. Additionally, a large group of epilepsies has a yet-unknown etiology (idiopathic epilepsies). Studies of the genetic or molecular and cellular causes of epilepsy have to take account of the fact that epilepsy is not a uniform disorder, but a mixture of many different entities. A precise analysis of the clinical, neurophysiological, and neuropathological phenotype of human epilepsies with a definition of homogenous subgroups/syndromes is a prerequisite not only for genetic studies, but also for the development of appropriate animal models to study the cellular basis of seizures and epilepsy. Because of the etiological diversity of epilepsy, modern approaches to epilepsy

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## Selected abbreviations and acronyms

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| ***AED*** | *antiepileptic drug* |
| ***AHS*** | *Ammon's horn sclerosis* |
| ***CNS*** | *central nervous system* |
| ***fMRI*** | *functional magnetic resonance imaging* |
| ***SE*** | *status epilepticus* |
| ***TLE*** | *temporal lobe epilepsy* |

research involve many different fields. These include clinical fields such as clinical epileptology and neurosurgery, neurology, psychiatry, and neuropathology, but also basic research areas such as human genetics, neuropsychology, immunology, neurophysiology, neurophysics, molecular biology and transgenics, developmental neurobiology, and neuropharmacology.

The ultimate goal of studies into the molecular and cellular mechanisms of epilepsy is to develop novel, and more effective, therapies. This may be approached in several ways. Firstly, a better understanding of the underlying disease mechanisms may in some instances lead to the identification of novel treatment options. Secondly, it is important to understand why currently available therapies do not help certain patients, while they are very effective in others. Finally, another goal of epilepsy research is to identify mechanisms underlying side effects of drug therapy, because these often limit drug therapy.

In addition to the intrinsic value of studying disease processes in one of the most common neurological disorders, epilepsy research is an excellent model for understanding basic mechanisms of CNS function and plasticity, in particular in the human brain, for several reasons. Firstly, seizures are known to initiate a large number of plastic changes on a molecular and cellular level in the brain. Many of these plasticity mechanisms have been recognized as key components of normal brain function (ie, brain development or learning and memory) or in other neurological disorders. Secondly, understanding the cellular basis of aberrant synchronized discharges of neurons during epileptic seizures also yields insights into the mechanisms of normal synchronization in the brain. Finally, the necessity to perform invasive electrode (depth and subdural) recordings in patients with epilepsy results in unique opportunities to study human cognitive processes at extremely high time resolution by recording field or even single unit potentials during cognitive tasks. This technique can be combined with different functional imaging techniques, which ideally complement invasive recordings from the human brain by providing excellent spatial resolution.

## Research into the basic mechanisms of epilepsy

### The study of idiopathic genetic epilepsies: how do single gene mutations cause epilepsy?

Genetic factors are the major determinants in at least 40% of all epilepsies; these are designated as "idiopathic epilepsies." Only about 2% of these idiopathic epilepsies are inherited as monogenic disorders, in which one gene conveys the major heritable impact, while environment and lifestyle play a limited role. Genetic studies have allowed identification of the first disease genes that define monogenic idiopathic epilepsies.[1,2] In these cases, genetic studies have identified causal gene variants, many of them neuronal ion channels, receptors, or associated proteins. Subsequently, the function of these variants was examined carefully in expression systems, and specific functional changes were found. These analyses, while compelling in implicating specific genes in idiopathic epilepsies, are not the last word in understanding how a gene mutation leads to a behavioral and clinical phenotype. We are beginning to obtain such an understanding in some instances from transgenic mouse models that carry disease-associated gene variants.[3] The advantage of such models is that they harbor human disease-associated gene variants, and can be examined at various points during the development of epilepsy with in vitro and molecular techniques. The limitation of such models is that the mechanisms of epileptogenesis may not be the same in mice and humans, and that disease-associated human gene variants are expressed on a background of mouse genes that may interact in unexpected ways with the human ortholog. Nevertheless, such studies are increasingly part of an integrated strategy to understand the mechanisms of monogenic epilepsies involving both human genetics and physiological, and molecular studies in transgenic mouse models.

### The study of focal epilepsy

*What are the mechanisms of seizures?*

By far most types of epilepsies, however, are not monogenic. Rather, they most probably involve both the effects of various combinations of gene variants, environmental factors, and precipitating injuries early during development. The relative importance of these fac-

tors in common focal epilepsies such as temporal lobe epilepsy (TLE) is unknown. For obvious reasons, it is difficult to investigate how these epilepsies develop over time prior to the first clinical manifestation. This is probably why research in the field has focused more on identifying key mechanisms that govern abnormal excitability and synchronization in chronic epilepsy, in particular those which might be potential targets for therapeutic manipulation. Animal models generated for this goal have been selected with the rationale that they should reproduce the neuropathological, clinical, and physiological features of the chronic stage of epilepsy. This has been achieved to some extent for temporal lobe epilepsy. Models of temporal lobe epilepsy (TLE) include the kainate model,[4] the pilocarpine model,[5] and the self-sustaining limbic status model.[6] All rely on the induction of status epilepticus (SE) either pharmacologically (with the ionotropic glutamate receptor agonist kainate or the muscarinic agonist pilocarpine), or via electrical stimulation (self-sustaining limbic status model). After a period of a few weeks, animals that have experienced SE exhibit several hallmarks of temporal lobe epilepsy, including (i) spontaneous seizures; (ii) a pattern of neuropathological damage similar to a subset of temporal lobe epilepsy patients with segmental hippocampal cell loss, gliosis and axonal reorganization; and (iii) dispersion of granule cells. In TLE, we have the unique possibility of validating such animal models because tissue from TLE patients is available from epilepsy surgery. From comparative neuropathological studies, we know that the pattern of damage in the abovementioned models is surprisingly close to that seen in a subgroup of TLE patients with so-called Ammon's horn sclerosis (AHS). Patients with AHS also display severe segmental neuron loss, axonal reorganization, and gliosis, along with dispersion of granule neurons.[7-9] It should be noted that in other instances, these epilepsy models differ from the human condition. For instance, damage in the pilocarpine model is not restricted to the hippocampus, involving instead many other brain regions. Nevertheless, these and similar models have been used extensively to study cellular and molecular changes in chronic epilepsy, and how these might lead to seizure generation. These changes have in some cases been compared with data obtained from human neurons obtained from epilepsy surgical specimens.[10]

A further group of TLE patients does not display the neuropathological features of AHS, even though they experience seizures originating from the mesial temporal lobe.[7-9] In this group of TLE patients, epilepsy is often a consequence of a mesial temporal lobe tumor or developmental malformation. An animal model that is thought to replicate some features of these human patients is the kindling model. In this model, repeated application of subthreshold electrical stimulation to limbic structures results in the expression of permanent limbic hyperexcitability. In this model, significant neuropathological damage is largely absent. In comparison with studies on human and experimental TLE, work on models of epilepsies with neocortical seizure foci has been relatively scarce, even though such models can also be validated in human in vitro studies.

Models of TLE have proven useful as a complementary strategy to investigations on human epileptic brain tissue. In experiments on human tissue, a fundamental problem is the lack of living control tissue. Very rarely, nonepileptic human control tissue is available from the penumbra of tumor resections in the temporal lobe. Other than this rare commodity, experimenters are left with the option of comparing epileptic tissue with autopsy control tissue, which is impossible for physiological and some molecular biological approaches. A further, commonly used approach is to compare tissue from patients with AHS vs lesion-associated epilepsy. This strategy has allowed the investigation of the expression of candidate molecules associated with changes present only in one of these patient groups. For instance, molecules important in synaptic reorganization would be expected to be present in specific areas in AHS, but not in lesion-associated epilepsy. Studies in animal models, on the other hand, always require validation with studies on human tissue to demonstrate their relevance to the human disorder unequivocally.[11] However, animal models do complement human studies in important ways. Firstly, animal models allow molecular and functional changes to be studied in detail without the constraints imposed by the lack of control material in experiments with human tissue. Further, having identified clear molecular changes, animal models allow us to determine the importance of such changes for hyperexcitability and epileptogenesis. This question is important because a large number of regulated candidate molecules have been identified, all of which may be potentially important in the development of epilepsy. A major challenge will be to determine which of these manifold changes are functionally important in common forms of epilepsy. To decipher the causal role of candi-

date genes, it has become increasingly accepted that it is necessary to generate cell-specific and inducible gain- as well as loss-of-function models on a more systematic scale than previously attempted. Such approaches may be realized using viral transfer of small interfering RNAs (siRNAs), or transgenic models that allow cell-specific and inducible genetic modifications. Finally, animal models allow to study some aspects of epileptogenesis, which is virtually impossible in human tissue, because specimens are only obtained late during the disease course.

*What are the mechanisms of epileptogenesis?*

Broadly speaking, epileptogenesis can be defined as a plastic process leading from a normal to a chronically epileptic brain. Precipitating brain insults (ie, febrile seizures, local infections, SE, ischemia, or trauma) in concert with genetic susceptibility factors are thought to trigger such persistent changes. As explained above, to directly address this issue in human subjects is extremely difficult. In recent years, investigators have therefore increasingly turned to animal models for this purpose. In the case of TLE, most investigators have studied epileptogenesis after an initial SE. It is important to realize that TLE models replicate the chronic features of TLE reasonably well. It is however not clear how much the mechanisms underlying SE-induced epileptogenesis overlap with the mechanisms underlying epileptogenesis in TLE patients, in whom this process is likely multifactorial and not triggered by SE. Nevertheless, studies of epileptogenesis in SE models have been worthwhile because they have resulted in an increased understanding of the basic mechanisms underlying key features of AHS, such as sprouting, cell death, and gliosis.

It may seem easier to establish models of epileptogenesis in symptomatic epilepsies, for instance epilepsy associated with CNS tumors, developmental malformations, or CNS trauma, for the simple reason that the initial precipitating injury is known, and can be replicated quite well in many cases. However, developing such models has proven surprisingly elusive. Models for tumor-associated epilepsy are scarce, and have relied on the injection of rapidly proliferating tumor cell lines into the brain of rodents.[12] While potentially valuable to assess the consequences of a rapidly growing malignancy in the CNS, these models are probably not that informative on mechanisms of epileptogenesis and seizure generation involved in human epilepsy patients. This is mainly because the tumors that are likely to cause epilepsy are mostly low-grade tumors with slow proliferation. The reasons for this association are unknown. It will be necessary to create additional models aimed at replicating features of these tumors. Regarding developmental malformations, there are several models in which the proper formation of cortical structures has been disrupted. These include models in which drugs are applied during cortical development that arrest neuronal migration, or in which lesions are applied to the cortex during cortex formation, which also lead to formation of a cortex with a disturbed laminar organization.[13] In trauma models, fluid percussion injury results in a circumscribed traumatic cortical injury zone.[14] These models have been informative because they have revealed manifold changes in excitability in and surrounding the abnormal cortical areas, and address the underlying mechanisms. However, it is not yet clear if these models lead to symptomatic epilepsy. More recently, genetic models of cortical malformations have been introduced. These models rely on the temporally selective and cell-type specific disruption of genes important in neuronal differentiation and migration. A further intriguing model that may address a common mechanism in many epilepsies is disruption of the blood-brain barrier. It has been recently shown that focal disruption of the blood-brain barrier results in development of a hyperexcitable focus.[15,16] Since blood-brain barrier disruption is a common feature of status epilepticus, ischemia, trauma, and CNS tumors, it may be that this is a common mechanism for hyperexcitability in these models. The proliferation of these and other models has led to an intense discussion in the field regarding the validity of such models for the human condition. A worthwhile aspect of this discussion is that it has led to an awareness that animal models only replicate specific aspects of any human condition, and it is paramount to be aware of the areas where a specific model is informative versus the ones where it is not.

What are the key questions that have been addressed in studies of epileptogenesis? Firstly, experiments primarily in post-status models of epileptogenesis have addressed the role of changes in voltage- and transmitter-operated ion channels in epileptogenesis. Generally, activity-dependent changes in neuronal function can be subdivided into changes in synaptic communication between neurons (termed synaptic plasticity), and changes in intrinsic membrane properties of neurons (termed intrinsic plasticity) that govern how synaptic

input is integrated. Work on *synaptic plasticity* has focused on changes in the expression and function of neurotransmitter receptors at synapses, as well as changed properties of presynaptic neurotransmitter release. Research on *intrinsic plasticity* has addressed changes in voltage-gated ion channels in the somatic, dendritic, and axonal membrane of neurons.[17] There have been multiple such changes described convincingly in the literature. A crucial question is how to evaluate the role of individual molecular changes seen in animal models in the development of epilepsy. There are several strategies that could be used to this end. Perhaps the most straightforward of these is to specifically interfere genetically or pharmacologically with ion channel regulation. Due to the novel genetic tools available in recent years, this is becoming more and more feasible. To transfer these types of studies to the human is more difficult. As stated above, human tissue obtained from epilepsy patients reflects the end stage of chronic epilepsy in most cases. It is therefore doubtful that human tissue can serve as a useful control for animal models at an early stage of epileptogenesis. One avenue which may provide a useful link between animal models and human epilepsy, however, is the use of genetic techniques to address whether polymorphisms in ion channel genes, associated proteins, or relevant transcription factors are associated with an increased propensity to develop epilepsy.

What causes changes in ion-channel function? The underlying molecular mechanisms are just beginning to be unraveled. One feature of epileptogenesis is the selective and coordinated regulation of transcription. This regulation affects mRNA levels encoding for groups of ion channels. The mechanisms that drive altered transcription have been identified in only few cases. Identification of the responsible transcription factors is one possible avenue to inhibit specific features of epileptogenesis. Persistent changes in transcription, however, are not only determined by a persistent activation of transcription factors, but can also be caused by changes in the chromatin state or autoregulatory feedback loops involving key transcription factors. Following transcription, alterations at the post-transcriptional level may be caused by changes in translational regulation. Finally, trafficking of ion-channel subunit proteins, as well as post-translational modifications, are important determinants of function that may be altered in chronic epilepsy. Understanding changes in intrinsic neuronal properties and synaptic function are also relevant for understanding mechanisms of drug actions, as well as why resistance to these drugs occurs. A large number of voltage-gated ion channels and some presynaptic proteins are targets for antiepileptic drugs, and changes in these targets may cause reduced drug sensitivity (explained in more detail below).

In addition to changes in membrane-bound ion channels, epileptogenesis is associated with large changes in mitochondrial function, including mitochondrial DNA depletion, failure of energy supply, and production of reactive oxygen species.[18,19] Such changes play a large role in the initiation of cell death cascades. Studies on mitochondrial function have been conducted in chronic experimental and human epilepsy. As above, studies on the mechanisms underlying the development of mitochondrial dysfunction are difficult in human tissue obtained at chronic stages. Here also, genetic studies provide an important link to epileptogenesis. An increasing number of studies have addressed whether genetic variability in genes encoding mitochondrial proteins confers susceptibility to epileptogenesis.[20]

An intriguing novel facet of epileptogenesis, that will likely necessitate the development of new model systems, is the involvement of immune cells in the development of epilepsy. Immune cells profoundly influence processes in the normal brain, such as neurogenesis or synaptic plasticity. The link between neuroimmunological processes and epilepsy is highlighted by inflammatory/autoinflammatory epileptic syndromes (eg, Rasmussen encephalitis or limbic encephalitis). Innate immune cells may not only play a role in the pathogenesis of these relatively rare epileptic syndromes, but also in the process of epileptogenesis in common chronic epilepsies which were not previously considered to have "encephalitic" components.[21-23]

## How does epilepsy research lead to improved therapies?

In many patients with epilepsy, seizures are well-controlled with currently available antiepileptic drugs. However, seizures persist in a considerable proportion of these patients.[24] The exact fraction of epilepsy patients that are considered refractory varies in the literature, mostly because the criteria for classification as pharmacoresistant have varied. Nevertheless, a substantial fraction (~30%) of epilepsy patients does not respond to any of two to three first-line antiepileptic drugs (AEDs), despite administration in an optimally monitored regi-

men.[25] Despite the clinical relevance of this phenomenon, the cellular basis of pharmacoresistance has remained elusive. However, integrated strategies integrating clinical, genetic, and molecular physiological techniques are providing some insight into possible mechanisms. What are the key strategies that can be used to unravel mechanisms of pharmacoresistance?

The first approach is pharmacogenomic. The ultimate goal of pharmacogenomics is to define the contributions of genetic differences in drug response.[26] The variability of an individual's response to a given drug can be considerable, and identifying causal genetic factors is expected to lead to improved safety and efficacy of drug therapy through use of genetically guided, individualized treatment. Pharmacogenomic approaches require both substantial clinical and genetic expertise. Following delineation of pharmacoresistant and pharmacoresponsive patient groups, powerful tools for disease gene mapping and identification afforded by the human genome project can be exploited. These tools, which include a large number of catalogued sequence variants, permit genome-wide studies for the identification of genetic loci underlying diseases and related phenotypes, including the response to drug treatment. These studies may allow identification of novel gene variations conferring risk for the development of epilepsy and pharmacoresistance. While this approach sounds straightforward, it is far from simple in practice. This is also clear from the large number of polymorphisms found in such association studies which could not be reproduced in replication studies. Major problems that still have to be overcome are firstly, that pharmacoresponse may not be determined by a single gene polymorphisms, rather, it may be the result of a combination of polymorphisms. Accordingly, the impact of single genes may be rather small, requiring large patient cohorts. In addition, gathering large patient cohorts prospectively, which are carefully matched according to their drug response, is extremely difficult and requires collaboration between epilepsy centers. Finally, it will be necessary to address experimentally in those cases in which polymorphisms are found in association studies whether they have biologically plausible effects that may result in pharmacoresistance. It is clearly worthwhile to exploit such strategies to the utmost, because genetic approaches can nowadays provide a genome-wide analysis at comparatively low cost. Thus, we are not limited by our preconceptions regarding the specific molecules important in pharmacoresistance.

An alternate approach to the problem of pharmacoresistance has been to examine directly the response of drug targets in epileptic tissue. This work has focused on targets such as voltage-gated sodium channels, for which AED responsiveness is well established.[27] Subsequently, the response of channels to AEDs was investigated in both animal models of TLE and human epilepsy.[10] In some cases, as for voltage-gated sodium channels, a loss of sensitivity of the channel complex to AEDs was found, both in experimental and human epilepsy. Importantly, such in-vitro data can be correlated with the clinical phenotype. Indeed, in the case of carbamazepine, pharmacoresistance observed clinically was found to correlate with a loss of carbamazepine sensitivity of voltage-gated sodium channels. This strategy may be integrated with genetic approaches to provide a potentially very informative approach to pharmacoresistance. The increasing availability of genetic information also on epilepsy patients who undergo epilepsy surgery opens the possibility to perform genetic analyses on key molecules implicated in the response to AEDs (ie, ion channels, presynaptic proteins, or drug transporters). Subsequent to the epilepsy surgery, a number of experiments can be done on human tissue from these patients. Firstly, ion channel or drug transporter function can be assessed directly. Secondly, seizure activity can be elicited in human brain slices, and the pharmacoresponse of this activity can be quantitatively determined. In both cases, a correlation with genetic information can provide useful information on the functional relevance of genetic variability.

The analyses in human tissue—while potentially very useful—are hampered by the fact that human tissue is only available from a subgroup of epilepsy patients. This has sparked a quest for other suitable human model systems. One possibility is to use cells generated from human embryonic stem cells and differentiated into either neurons or glial cells in vitro. This approach would permit to test the effects of antiepileptic drugs in a cell model with a human background. Alternatively, it may be possible to isolate adult human stem cells from epilepsy surgical specimens, amplify them and generate appropriate neural populations. The latter approach has the advantage that the genetic phenotype of the patient is available for individual interpretation of differential drug responses. In addition to experiments aimed at understanding mechanisms of drug resistance, and the development of new drugs, other avenues for treatment

of epilepsy have been explored. One of these avenues is the transplantation of defined neuronal populations into either the epileptic focus itself or into sites that contribute to seizure generalization. It has been shown that such approaches can ameliorate seizure activity.[28] An alternate approach is to predict and prevent seizures with invasive recording and stimulation techniques.[29] Seizure prediction is a field of great interest in the clinical and basic neuroscience communities. This is not only because of its potential clinical application in warning and therapeutic antiepileptic devices, but also for its promise of increasing our understanding of the mechanisms underlying epilepsy and seizure generation.

## Mechanisms of cognitive deficits associated with epilepsy

Epilepsy is frequently associated with cognitive deficits that may be due to an a-priori brain pathology, plastic changes induced by the epilepsy, adverse effects of drug treatment, or epilepsy surgery. The prevalence and clinical importance of cognitive deficits has triggered intense research activity in this field, in particular concerning pre- and postsurgical memory and language impairments. However, epilepsy and the employed invasive diagnostic and therapeutic procedures also provide neuroscientists with a unique and unprecedented opportunity to study the neurophysiological basis of cognition and emotions in vivo. The specific techniques that can be used for such clinical and cognitive analyses are, for instance, recordings from implanted depth electrodes, which provide a high temporal resolution of activity in the cortex or deeper brain structures, in particular the hippocampus.[30-32] In addition to recording activity from collective neuronal behavior, single unit activity from temporal lobe neurons can be analyzed, thereby enabling the analysis of cognitive functions at the single cell level.[33] Complementing these techniques, functional imaging techniques offer high spatial resolution but less precise temporal information about neuronal activity. They also permit functional analysis of areas in which electrode placement is clinically unnecessary, and allow the analysis of structural and functional changes of connectivity. The combination of these techniques is of considerable interest, primarily because they are complementary with regard to spatial and temporal resolution. It will therefore constitute a fundamental advance to acquire combined (ie, simultaneous) intracranial electroencephalogram (EEG)/single unit and functional magnetic resonance imaging (fMRI) data during cognitive tasks. While this will also contribute significantly to resolving the current debate about the neuronal correlate of fMRI signals in humans, combining these technologies will enable the investigation of the "brain at work" at an unprecedented degree of accuracy. A clinical demand also exists for such combined recordings (ie, the detection of seizure foci with spike-triggered fMRI). A simultaneous recording of intracranial EEG/single units and fMRI is in principle possible. Several companies are currently performing safety evaluations with pending applications for approval of their intracranial electrodes for use within fMRI scanners.

So far, analyses utilizing intracranial EEG recordings have allowed important insights into the function of mesial temporal lobe structures in the human, and have allowed to directly study mechanisms underlying episodic memory processes and their plasticity due to hippocampal dysfunction in the human. They have also resulted in an increased understanding of the perception and production of language, and declarative memory functions related to language. Interesting areas that can be studied using such techniques are also those aimed at understanding how the human amygdala and hippocampus process fear and emotional stimuli. Interaction with researchers of other disciplines, such as economy and social sciences, may permit the investigation of human problem-solving mechanisms employing realistic paradigms. A further interesting avenue is to conduct pharmacological in-vivo studies, in which pharmacological manipulations are performed in healthy subjects and epilepsy patients (ie, N-methyl-D-aspartate [NMDA] receptor antagonists), both during invasive depth electrode recordings and fMRI experiments.[34] These approaches have proven important to dissect out the contribution of specific neurotransmitter systems to cognitive functions. They also potentially provide an endophenotype that may predict drug efficacy or side effects.

Apart from functional imaging techniques, modern imaging technologies provide an unprecendented look at structural changes in the human brain associated with epilepsy. It has become increasingly clear that both functional (ie, an hyperexcitable focus) or structural lesions can lead to shifts in the local representation of function in the brain, and to substantial changes in functional and structural connectivity between brain areas. Using modern structural and functional MRI techniques, such as diffusion tensor imaging or dynamic causal modeling, allows analysis of

such changes in human subjects with excellent spatial resolution, with respect to the functions described above. Such experiments will reveal the properties and time course of structural and functional disease associated plasticity, as well as which aspects of this plasticity can be influenced (ie, by seizure suppression or epilepsy surgery).

## Relationship of epilepsy to other neurological disorders

It is becoming increasingly clear that key molecules and mechanisms responsible for the development of epilepsy may also be pivotal in other neurological disorders. For instance, evidence from animal studies suggests that mechanisms of neuronal degeneration may be very similar in models of epilepsy, trauma, ischemia, and perhaps other chronic neurodegenerative disorders. Furthermore, the conversion of glial cells to a reactive phenotype occurs not only in epilepsy, but also in a wide range of neurological disorders. There are numerous other examples for stereotypical, disease-associated plastic changes in neurons in different neurological disorders. In addition to these similarities, genetic studies also suggest shared susceptibility factors. These shared molecular mechanisms are thought to underlie the phenomenon of comorbidity (ie, an epidemiological association of epilepsy with other disorders). Since it is likely that comorbidity results from a shared genetic susceptibility, genetic approaches are well-suited for identifying these common pathways. An important further aspect is the availability of human brain tissue in the context of an epilepsy surgical center for cellular and molecular analyses, as well as in-vitro physiology and pharmacology experiments. These human brain materials represent a unique resource for the assessment of specific pathophysiological hypotheses, especially in combination with tissues from appropriate animal models. Furthermore, frequent comorbid disorders, such as depression, occur often enough within epilepsy patient collectives to allow relevant numbers of experiments using a combination of in-vivo physiology and fMRI, on matched groups of epilepsy patients with and without comorbid disorders. In contrast to electrophysiological recordings, which can only be done on epilepsy patients, fMRI studies can be performed on both epilepsy patients, nonepileptic patients with comorbidity (ie, depression or migraine), and control subjects. These experiments will yield unique insights as to the relationship between epilepsy, comorbid disorders, and cognitive processes. They will also allow us to examine the effects of drugs used in other CNS disorders on cognitive processes with high resolution.

## Conclusion

In summary, the study of the neurobiological basis of epilepsy using approaches that integrate genetic, human functional and behavioral studies, and work on animal models, is important for developing novel therapeutic strategies. It is also one of the few existing research approaches that can be utilized to examine the function of the human brain at high temporal, spatial, and cellular resolution. ❑

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## *Investigación en epilepsia: una ventana hacia la función y disfunción del cerebro humano*

*La epilepsia es uno de los trastornos neurológicos más comunes y tiene consecuencias conductuales, sociales y ocupacionales devastadoras, y se asocia con daño cerebral acumulativo y déficit neurológicos. La epilepsia incluye un gran número de síndromes, que varían ampliamente en relación con la etiología y los aspectos clínicos, pero que comparten el sello clínico característico de la epilepsia: las crisis espontáneas recurrentes. La investigación orientada a la comprensión de las bases genéticas, moleculares y celulares de la epilepsia ha integrado varias aproximaciones y técnicas de investigación que van desde la habilidad clínica, los análisis funcionales de los sistemas y el nivel celular, tanto en modelos de epilepsia en humanos como en roedores, hasta la genética en ratones. Este conocimiento entonces puede dar origen a nuevas opciones terapéuticas con mejor control de las convulsiones y/o menores efectos secundarios. Además, el estudio de la epilepsia frecuentemente ha dado luces acerca de los mecanismos básicos que subyacen a la función y disfunción del cerebro humano.*

## *Recherche sur l'épilepsie : une fenêtre sur le fonctionnement et le dysfonctionnement du cerveau humain*

*Les conséquences comportementales, sociales et professionnelles de l'épilepsie, l'un des troubles neurologiques les plus courants, sont dévastatrices. L'épilepsie est associée à une accumulation d'altérations cérébrales et de déficits neurologiques. Ses syndromes sont nombreux et varient beaucoup selon leur étiologie et leurs particularités cliniques, mais partagent l'aspect clinique caractéristique de l'épilepsie : les crises spontanées récidivantes. La recherche s'est efforcée de comprendre les bases génétiques, moléculaires et cellulaires de l'épilepsie en intégrant diverses approches et techniques allant de l'expertise clinique, de l'analyse fonctionnelle des systèmes à un niveau cellulaire, à la fois chez les humains et dans des modèles murins d'épilepsie, jusqu'à la génétique humaine et la génétique murine. Grâce à cette connaissance, de nouveaux traitements pourraient être développés, les crises mieux contrôlées et/ou les effets indésirables plus restreints. L'étude de l'épilepsie a, en outre, fréquemment permis d'éclairer les mécanismes de base du fonctionnement et du dysfonctionnement du cerveau humain.*



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