

Basic Mechanisms Underlying Seizures and Epilepsy

I. Introduction

A. Definitions

A seizure (from the Latin *sacire*—to take possession of) is the clinical manifestation of an abnormal, excessive, hypersynchronous discharge of a population of cortical neurons. Epilepsy is a disorder of the central nervous system characterized by recurrent seizures unprovoked by an acute systemic or neurologic insult. Epileptogenesis is the sequence of events that turns a normal neuronal network into a hyperexcitable network. (Slide 2)

Slide 2: Basic Mechanisms Underlying Seizures and Epilepsy

- ♦ Seizure: the clinical manifestation of an abnormal and excessive excitation and synchronization of a population of cortical neurons
- ♦ Epilepsy: a tendency toward recurrent seizures unprovoked by any systemic or acute neurologic insults
- ♦ Epileptogenesis: sequence of events that converts a normal neuronal network into a hyperexcitable network

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Recognizing the distinction between seizures and epilepsy is essential. Epilepsy may require chronic treatment (with antiepileptic medication and, in some cases, surgery) whereas therapy for an isolated seizure is directed toward the underlying cause and may not require antiepileptic drugs (AEDs). Furthermore, epilepsy often has profound psychosocial ramifications for the patient, and is thus a diagnosis to be assigned with care.

B. Overview

In order to understand the concepts of seizures, epilepsy and epileptogenesis, we will first consider some of the basic anatomic and electrophysiologic properties of the cerebral cortex, and the factors that determine the level of neural activity at the cellular and cell network level. We will then discuss the physiologic basis of the elec-

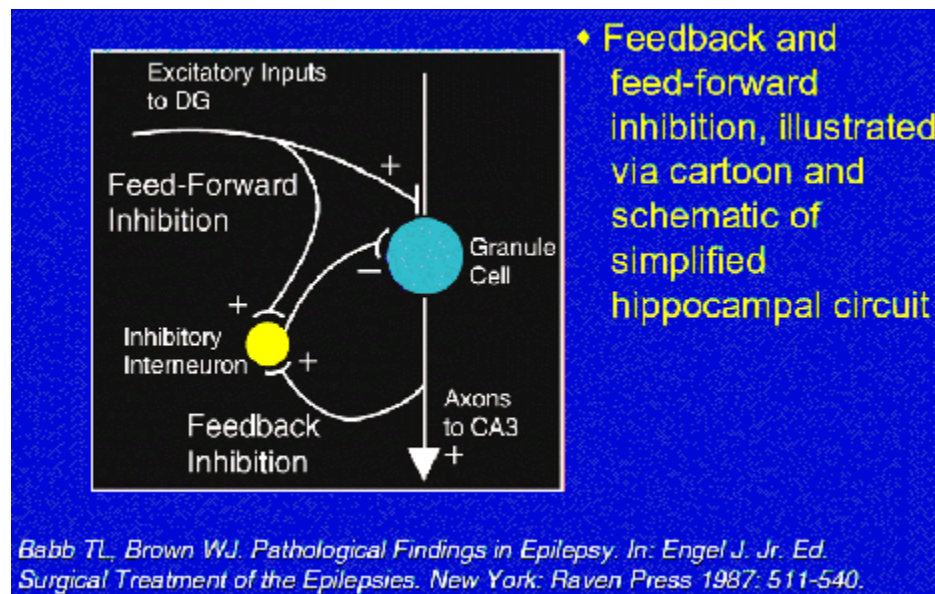
encephalogram (EEG), routinely used in assessing patients with seizures and other neurological disorders. Finally, we will address some of the main features of the abnormal physiological activity that occurs within a seizure focus, and present a few of the proposed mechanisms that may underlie certain seizure types.

II. Neurophysiology of the Cerebral Cortex

A. Basic Anatomy of Cortex

The human cerebral cortex consists of 3 to 6 layers of neurons. The phylogenetically oldest part of the cortex (archipallium) has 3 distinct neuronal layers, and is exemplified by the hippocampus, which is found in the medial temporal lobe. The majority of the cortex (neocortex or neopallium) has 6 distinct cell layers and covers most of the surface of the cerebral hemispheres. A particularly important cortical structure in the pathophysiology of one of the more common epilepsy syndromes is the hippocampus. This structure illustrated in Slide 3 is common in temporal lobe epilepsy. As seen in the slide, the hippocampus consists of three major regions: subiculum, hippocampus proper (Ammon's horn) and dentate gyrus. The hippocampus and dentate gyrus have a three layered cortex. The subiculum is the transition zone from the three to the six layered cortex. Important regions of the hippocampus proper include CA1, CA 2, CA3.

Slide 3: Basic Mechanisms Underlying Seizures and Epilepsy

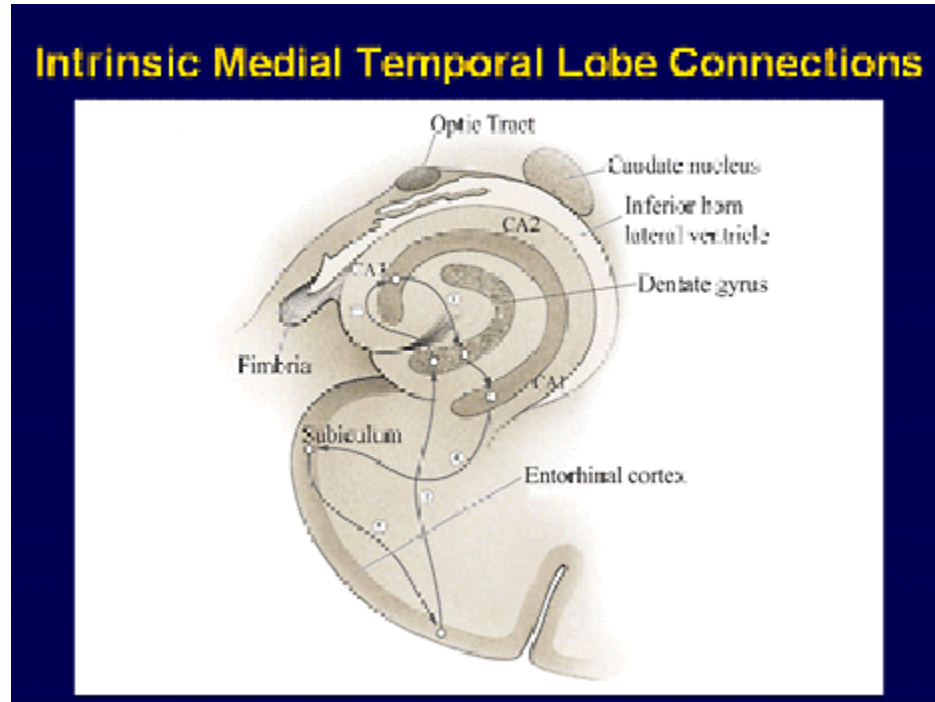


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The cortex includes two general classes of neurons. The projection, or principal, neurons (e.g., pyramidal neurons) are cells that "project" or send information to neurons located in distant areas of the brain. Interneurons (e.g., basket cells) are generally considered to be local-circuit cells which influence the activity of nearby neurons. Most principal neurons form excitatory synapses on post-synaptic neurons, while most interneurons form inhibitory synapses on principal cells or other inhibitory neurons. Recurrent inhibition can occur when a

principal neuron forms synapses on an inhibitory neuron, which in turn forms synapses back on the principal cells to achieve a negative feedback loop. (Slide 4 illustrates an example of a type of interneuron-granule cell and its role in a negative feedback loop in the hippocampus.)

Slide 4: Basic Mechanisms Underlying Seizures and Epilepsy



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Recent work suggests that some interneurons appear to have rather extensive axonal projections, rather than the local, confined axonal structures previously suggested. In some cases, such interneurons may provide a very strong synchronization or pacer activity to large groups of neurons.

B. Basic Neurophysiology and Neurochemistry Governing Excitability

Given that the basic mechanism of neuronal excitability is the action potential, a hyperexcitable state can result from increased excitatory synaptic neurotransmission, decreased inhibitory neurotransmission, an alteration in voltage-gated ion channels, or an alteration of intra- or extra-cellular ion concentrations in favor of membrane depolarization. A hyperexcitable state can also result when several synchronous subthreshold excitatory stimuli occur, allowing their temporal summation in the post synaptic neurons.

Action potentials occur due to depolarization of the neuronal membrane, with membrane depolarization propagating down the axon to induce neurotransmitter release at the axon terminal. The action potential occurs in an all-or-none fashion as a result of local changes in membrane potential brought about by net positive inward ion fluxes. Membrane potential thus varies with activation of ligand-gated channels, whose conductance is affected by binding to neurotransmitters; or with activation of voltage-gated channels, whose conductance is affected by changes in transmembrane potential; or with changes in intracellular ion compartmentalization.

Neurotransmitters are substances that are released by the presynaptic nerve terminal at a synapse and subsequently bind to specific postsynaptic receptors for that ligand. Ligand binding results in channel activation and passage of ions into or out of the cells. The major neurotransmitters in the brain are glutamate, gamma-aminobutyric acid (GABA), acetylcholine (ACh), norepinephrine, dopamine, serotonin, and histamine. Other molecules, such as neuropeptides and hormones, play modulatory roles that modify neurotransmission over longer time periods.

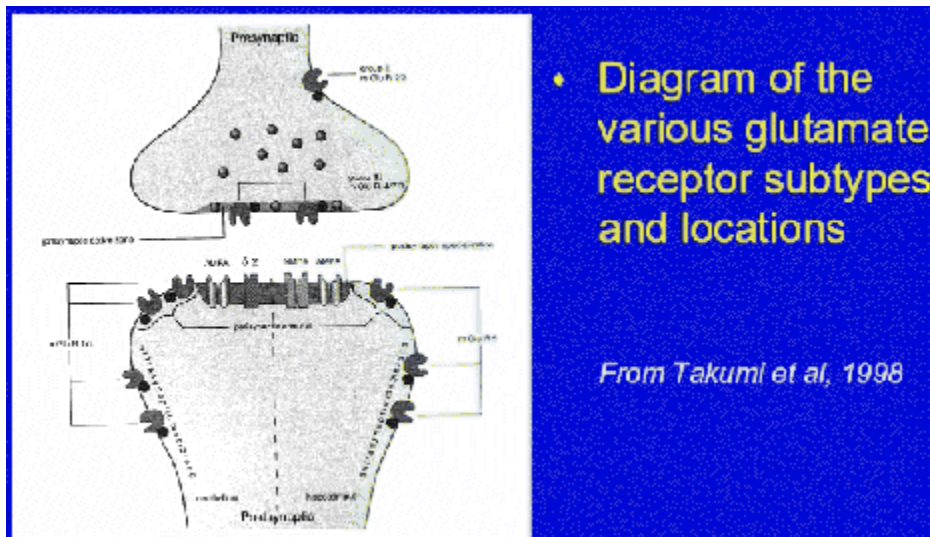
The major excitatory neurotransmitter is the amino acid glutamate. There are several subtypes of glutamate receptors. Glutamate receptors can be found postsynaptically on excitatory principal cells as well as on inhibitory interneurons, and have been demonstrated on certain types of glial cells. The ionotropic subclasses are the alpha-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA), kainate receptors, and N-methyl-D-aspartate (NMDA); these allow ion influx upon activation by glutamate (Appendix A, Table 1). They are differentiated from one another by cation permeability as well as differential sensitivity to pharmacological agonists/antagonists. All ionotropic glutamate receptors are permeable to Na^+ and K^+ , and it is the influx of Na^+ and outflow of K^+ through these channels that contribute to membrane depolarization and generation of the action potential. The NMDA receptor also has a Ca^{++} channel that is blocked by Mg^{++} ions in the resting state, but under conditions of local membrane depolarization, Mg^{++} is displaced and the channel becomes permeable to Ca^{++} ; influx of Ca^{++} tends to further depolarize the cell, and is thought also to contribute to Ca^{++} mediated neuronal injury under conditions of excessive neuronal activation (such as status epilepticus and ischemia), potentially leading to cell death, a process termed excitotoxicity. The other major type of glutamate receptor is the metabotropic receptor, which functions by means of receptor-activated signal transduction involving membrane-associated G-proteins (Appendix A, Table 2). There are at least 3 subtypes of metabotropic receptors, based on differential agonist potency, mechanism of signal transduction, and pre- versus post-synaptic localization. (Slides 5 & 6)

Slide 5: Epilepsy—Glutamate

- ♦ The brain's major excitatory neurotransmitter
- ♦ Two groups of glutamate receptors
 - Ionotropic—fast synaptic transmission
 - NMDA, AMPA, kainate
 - Gated Ca^{++} and Gated Na^+ channels
 - Metabotropic—slow synaptic transmission
 - Quisqualate
 - Regulation of second messengers (cAMP and Inositol)
 - Modulation of synaptic activity
- ♦ Modulation of glutamate receptors
 - Glycine, polyamine sites, Zinc, redox site

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Slide 6: Epilepsy—Glutamate



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Experimental studies using animal epilepsy models have shown that NMDA, AMPA and kainate agonists induce seizure activity, whereas their antagonists suppress seizure activity. Metabotropic agonists appear to have variable effects likely dependent upon their different location and mechanisms of signal transduction.

The major inhibitory neurotransmitter, GABA, interacts with 2 major subtypes of receptor: GABA_A and GABA_B receptors. GABA_A receptors are found postsynaptically, while GABA_B receptors are found presynaptically, and can thereby modulate synaptic release. In the adult brain, GABA_A receptors are permeable to Cl^- ions; upon activation Cl^- influx hyperpolarizes the membrane and inhibits action potentials. Therefore, sub-

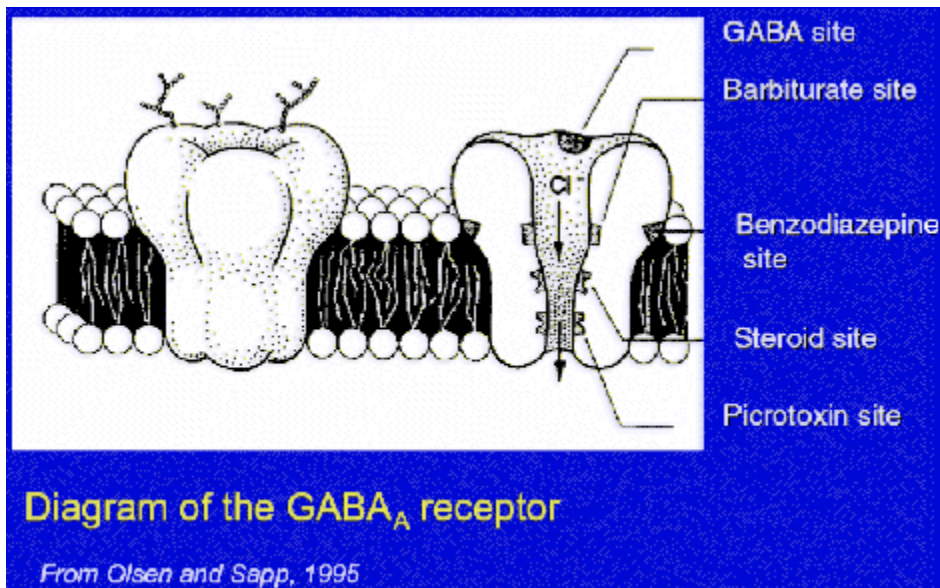
stances which are GABA_A receptor agonists, such as barbiturates and benzodiazepines, are well known to suppress seizure activity. GABA_B receptors are associated with second messenger systems rather than Cl⁻ channels, and lead to attenuation of transmitter release due to their presynaptic location. The second messenger systems often result in opening of K⁺ channels, leading to a hyperpolarizing current. Certain GABA_B agonists, such as baclofen, have been reported to exacerbate hyperexcitability and seizures. (Slides 7 & 8)

Slide 7: Epilepsy—GABA

- ♦ Major inhibitory neurotransmitter in the CNS
- ♦ Two types of receptors
 - GABA_A—post-synaptic, specific recognition sites, linked to Cl⁻ channel
 - GABA_B—presynaptic autoreceptors, mediated by K⁺ currents

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Slide 8: Epilepsy—GABA



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Relevant to epilepsy, glutamate and GABA both require active reuptake to be cleared from the synaptic cleft. Transporters for both glutamate and GABA exist on both neurons and glia (primarily astrocytes). Interference with transporter function has also been shown to activate or suppress epileptiform activity in animal models, depending on which transporter is being blocked.

C. Factors Governing Excitability of Individual Neurons

The complexity of neuronal activity is partly due to various mechanisms controlling the level of electrical activation in one or more cellular regions. These mechanisms may act inside the neuron or in the cellular environment, including other cells (e.g., neighboring neurons, glia, and vascular endothelial cells) as well as the extracellular space, to modify neuronal excitability. The former may be termed "neuronal" or "intrinsic," and the latter "extra-neuronal" or "extrinsic." (Slide 9)

Slide 9: Cellular Mechanisms of Seizure Generation

- ◆ **Excitation (too much)**
 - Ionic—inward Na^+ , Ca^{++} currents
 - Neurotransmitter—glutamate, aspartate
- ◆ **Inhibition (too little)**
 - Ionic—inward Cl^- , outward K^+ currents
 - Neurotransmitter—GABA

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1. Examples of neuronal (intrinsic) factors include: (Slide 10)

Slide 10: Neuronal (Intrinsic) Factors Modifying Neuronal Excitability

- ♦ Ion channel type, number, and distribution
- ♦ Biochemical modification of receptors
- ♦ Activation of second-messenger systems
- ♦ Modulation of gene expression (e.g., for receptor proteins)



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- *The type, number and distribution of voltage- and ligand-gated channels.* Such channels determine the direction, degree, and rate of changes in the transmembrane potential, which in turn determine whether an action potential occurs. Voltage-gated sodium channels, for example, form the basis of the rapid depolarization constituting the action potential. Among ligand-gated channels, the GABA receptor complex mediates inflow of chloride ions which hyperpolarize the cell, forming the basis of neuronal inhibition, as described previously.
- *Biochemical modification of receptors.* For example, phosphorylation of the NMDA receptor increases permeability to Ca^{++} , resulting in increased excitability.
- *Activation of second-messenger systems.* Binding of norepinephrine to its alpha receptor, for example, activates cyclic GMP, in turn activating G-proteins which open K^{+} channels, thereby decreasing excitability.
- *Modulating gene expression, as by RNA editing.* For example, editing a single base pair of mRNA encoding a specific glutamate receptor subunit can change the ion selectivity of the assembled channel.

2. Examples of extra-neuronal (extrinsic) factors include: (Slide 11)

Slide 11: Extra-Neuronal (Extrinsic) Factors Modifying Neuronal Excitability

- Changes in extracellular ion concentration
- Remodeling of synapse location or configuration by afferent input
- Modulation of transmitter metabolism or uptake by glial cells



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- *Changes in extracellular ion concentration due to variations in the volume of the extracellular space.* For example, decreased extracellular volume leads to increased extracellular K^+ concentration, resisting the outward movement of K^+ ions needed to repolarize the cell, thereby effectively increasing excitability.
- *Remodeling of synaptic contacts.* For example, movement of an afferent axon terminal closer to the target cell body increases the likelihood that inward ionic currents at the synapse will bring the target neuron to threshold. The coupling between the pre- and post-synaptic elements can be made more efficient by shortening of the spine neck. In addition, previous synaptic experience such as a brief burst of high frequency stimulation (e.g., long-term potentiation-LTP) also increases the efficacy of such synapses, increasing their excitability.
- *Modulating transmitter metabolism by glial cells.* Excitability increases, for example, if glial metabolism or uptake of excitatory transmitters such as glutamate or ACh decreases.

D. How Network Organization Influences Neuronal Excitability

Neurons are connected together in elaborate arrays that provide additional levels of control of neuronal excitability. An example of a very basic neuronal network is the well-studied dentate gyrus and hippocampus, as shown in Slide 12. In the dentate gyrus, afferent connections to the network can directly activate the projection cell (e.g., granule cells). The input can also directly activate local interneurons (bipolar and basket cells), and these may inhibit projection cells in the vicinity (feed-forward inhibition). Also, the projection neuron may in turn activate the interneurons which in turn act on the projection neurons (feedback inhibition). Thus, changes in the function of one or more cells within a circuit can significantly affect both neighboring and distant neurons. (Slide 13). For example, sprouting of excitatory axons to make more numerous connections can increase excitability of the network of connected neurons. Alternatively, loss of inhibitory neurons will also increase the excitability of the network. Inhibitory function can also be reduced by a loss of excitatory neurons that activate or "drive" the inhibitory neurons.

Slide 12: Mechanisms of Generating Hyperexcitable Networks

- ◆ Excitatory axonal “sprouting”
- ◆ Loss of inhibitory neurons
- ◆ Loss of excitatory neurons “driving” inhibitory neurons

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Slide 13: Electroencephalogram (EEG)

- ◆ Graphical depiction of cortical electrical activity, usually recorded from the scalp.
- ◆ Advantage of high temporal resolution but poor spatial resolution of cortical disorders.
- ◆ EEG is the most important neurophysiological study for the diagnosis, prognosis, and treatment of epilepsy.

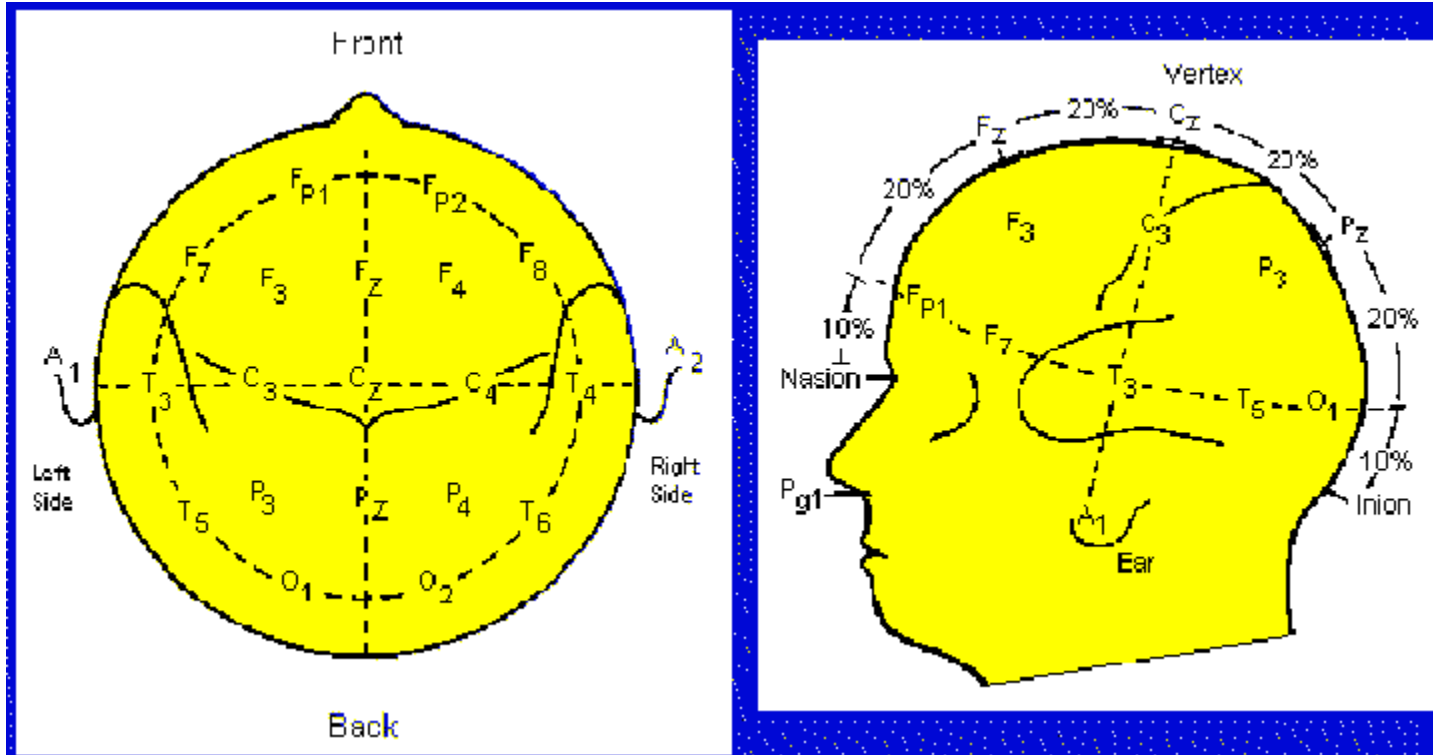
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III. Physiological Basis of the EEG

The electroencephalogram (EEG) is a recording of the electrical activity of the cerebral cortex, through electrodes placed on the scalp. (Slide 14) The EEG measures the electrical potentials of cortical neuronal dendrites near the brain's surface. Consider the electrical activity of a single pyramidal cell activated by an afferent pathway. The incoming excitatory signal at the synapse gives rise to a post-synaptic potential resulting from positively charged ions rushing into the cell. This leaves a relatively negative charge in the extracellular space in the vicinity of the synapse. The inward current at the synapse (referred to as the "sink") flows down the dendrite and ultimately moves outward across the cell membrane at sites distant from the synapse (referred to as the "source"). The outward flow of positive charge leaves a relatively positive charge in the extracellular space. At this instant

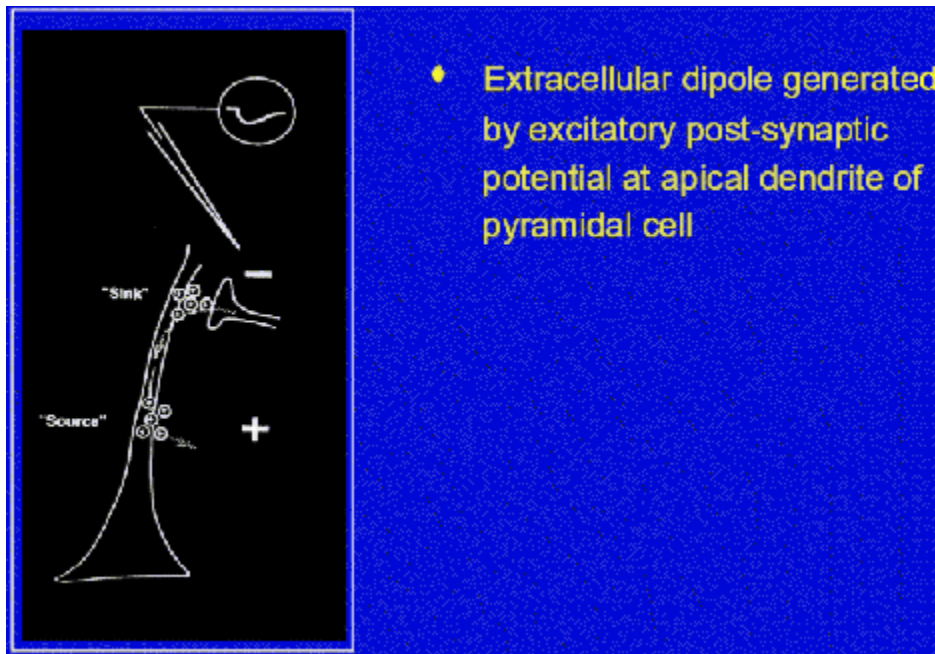
there is a dipole outside the dendrite, with a relatively negative charge at the distal part of the dendrite and a positive charge closer to the cell body. Thus, an extracellular electrode placed near the end of the dendrite detects a negative potential. (Slide 15)

Slide 14: 10/20 System of EEG Electrode Placement



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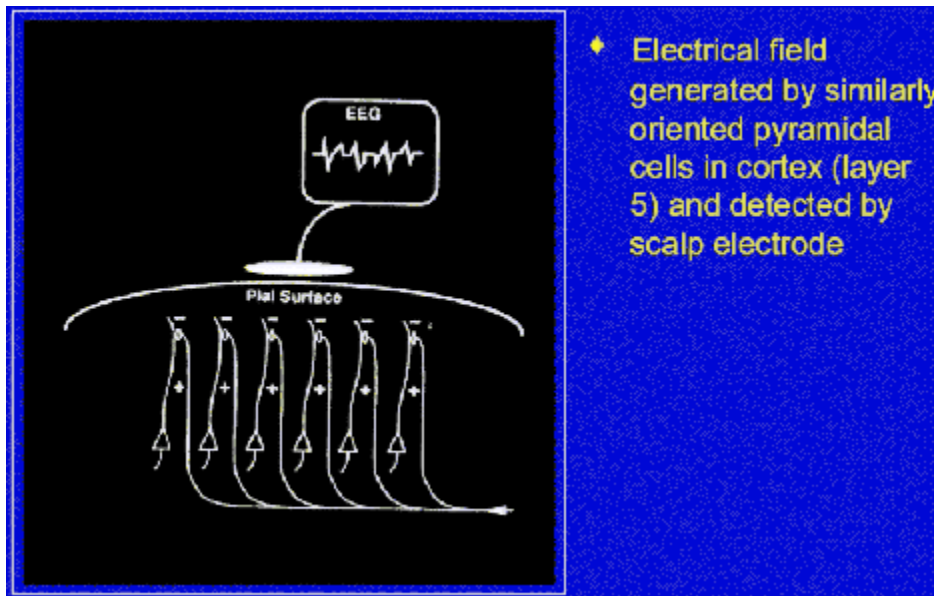
Slide 15: Physiological Basis of the EEG



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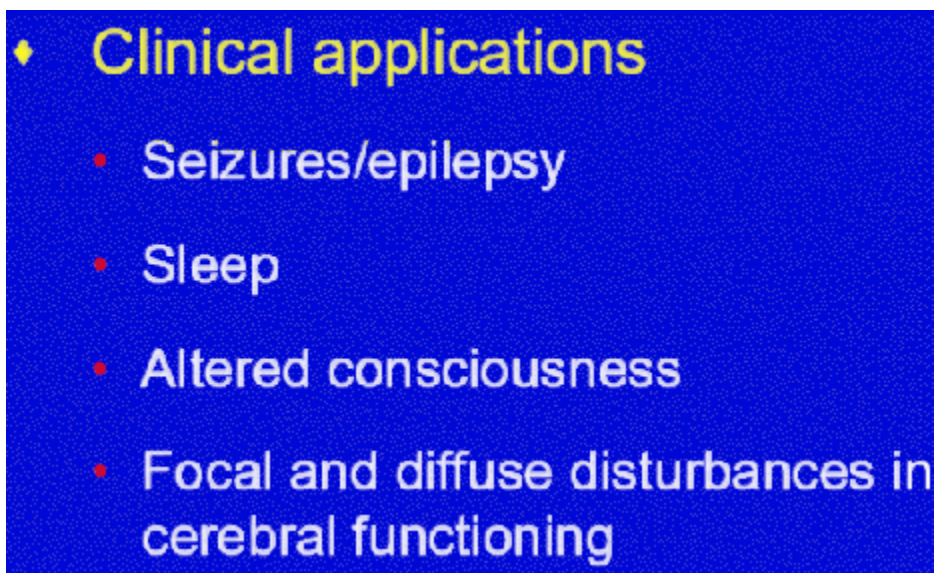
An electrode placed at the scalp cannot detect these electrical changes in a single neuron because: 1) the potentials are small in magnitude (due to the low extracellular resistance), and 2) there is considerable distance from the cell to the scalp surface. However, two cortical properties permit us to record the brain's electrical potential. First, pyramidal cells all have the same relative orientation and polarity. Second, many cells are synchronously activated. Slide 16 shows the changes in potentials generated by a layer of cortical neurons activated at the same time. The summation of the dipoles created at each of thousands of neurons creates an electrical potential detectable at the scalp. In practice, 20 or more scalp electrodes are placed at specific locations on the head to allow the simultaneous recording from the cortical regions of both hemispheres; each electrode can detect synchronous activity generated by approximately 6 sq. cm. of cortex, generally that found at gyral surfaces. The cortex that faces the cortical sulci generally does not contribute to the EEG potentials because the cortical dipoles generated in this location cancel each other. In clinical medicine the EEG is an important diagnostic test in the evaluation of patients with seizure disorders, sleep disorders, and altered levels of consciousness (e.g., coma), and can help localize and diagnose certain infections and focal processes within the central nervous system (CNS). (Slide 17)

Slide 16: Physiological Basis of the EEG



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Slide 17: Electroencephalogram (EEG)



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The EEG waveforms are divided into four major frequency bands: delta (0–3+ Hz), theta (4–7+ Hz), alpha (8–13+ Hz), and beta (>14 Hz) (Slides 18 & 19). At first glance, the normal spontaneous electrical activity detected by the EEG appears somewhat chaotic. However, there is a certain organization and rhythmicity of the activity that depends on the level of alertness or sleep and the age of the subject. The physiological basis of at least some of these rhythms seems to arise from intrinsic pacemaker cells in the cortex and thalamus. Several EEG rhythms can be characterized on the basis of the location, frequency and reactivity of the activity and the clinical state of the patient. For example, a symmetrical rhythm is observed over the posterior head regions

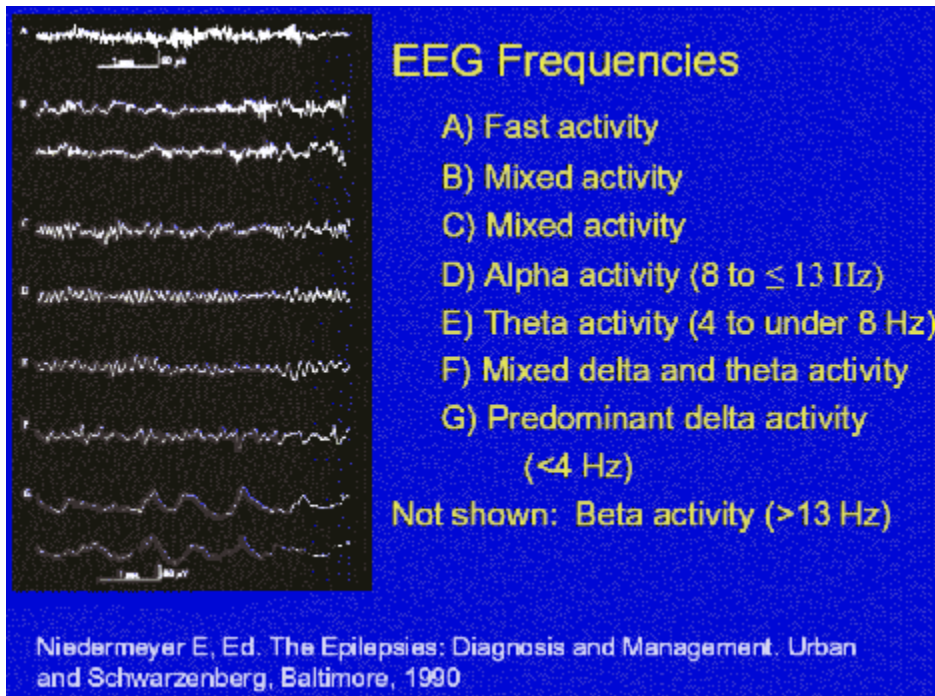
during relaxed wakefulness with eyes closed, that undergoes amplitude attenuation with eye opening or mental alerting activities. It is called the posterior dominant rhythm or alpha rhythm, because in adults it has a frequency of 8–13 Hz (slide 20); however, its frequency in children may be in the theta range.

Slide 18: EEG Frequencies

- ◆ Alpha: 8 to \leq 13 Hz
- ◆ Beta: $>$ 13 Hz
- ◆ Theta: 4 to under 8 Hz
- ◆ Delta: $<$ 4 Hz

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Slide 19: EEG Frequencies



EEG Frequencies

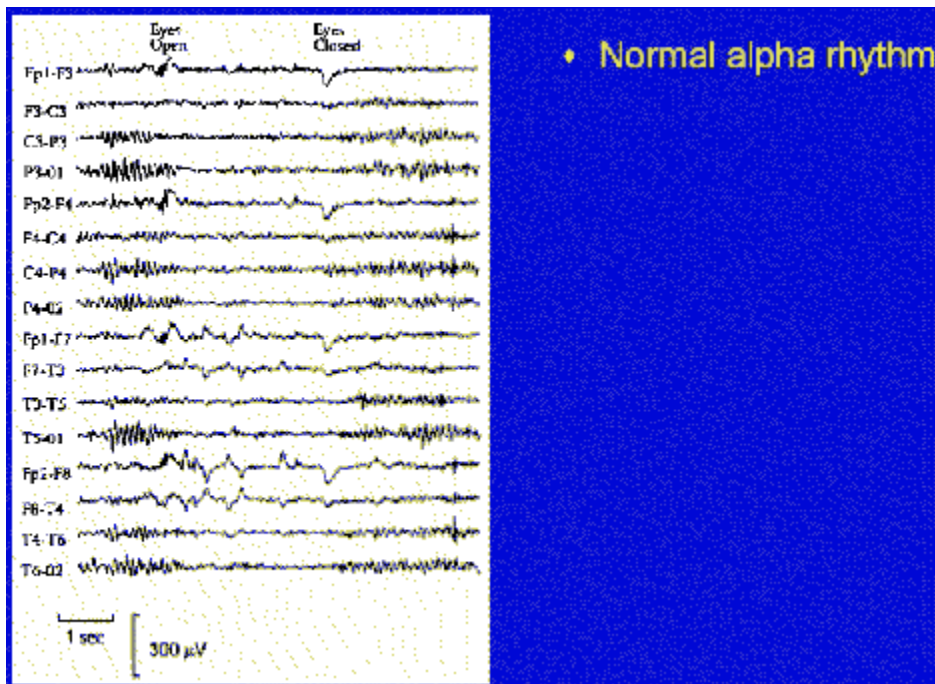
- A) Fast activity
- B) Mixed activity
- C) Mixed activity
- D) Alpha activity (8 to ≤ 13 Hz)
- E) Theta activity (4 to under 8 Hz)
- F) Mixed delta and theta activity
- G) Predominant delta activity (<4 Hz)

Not shown: Beta activity (>13 Hz)

Niedermeyer E, Ed. The Epilepsies: Diagnosis and Management. Urban and Schwarzenberg, Baltimore, 1990

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Slide 20: Normal Adult EEG



Normal alpha rhythm

EEG traces showing various channels (Fp1-F3, F3-C3, C3-P3, P3-O1, Fp2-F4, F4-C4, C4-P4, O4-O2, Fp1-T7, F7-T3, T3-T5, T5-O1, Fp2-F8, F8-T4, T4-T6, T6-O2) under 'Eyes Open' and 'Eyes Closed' conditions. Scale bars indicate 1 sec and 300 μ V.

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Alterations of brain function often result in abnormally slow frequency activity in the EEG. Pathologic slowing, when localized, often correlates with focal brain lesions; when diffuse, slow activity often signifies an encephalopathy. Epileptiform activity characteristic of people with epilepsy includes abnormalities such as spikes, sharp waves and spike-wave complexes, (slides 21 & 22).

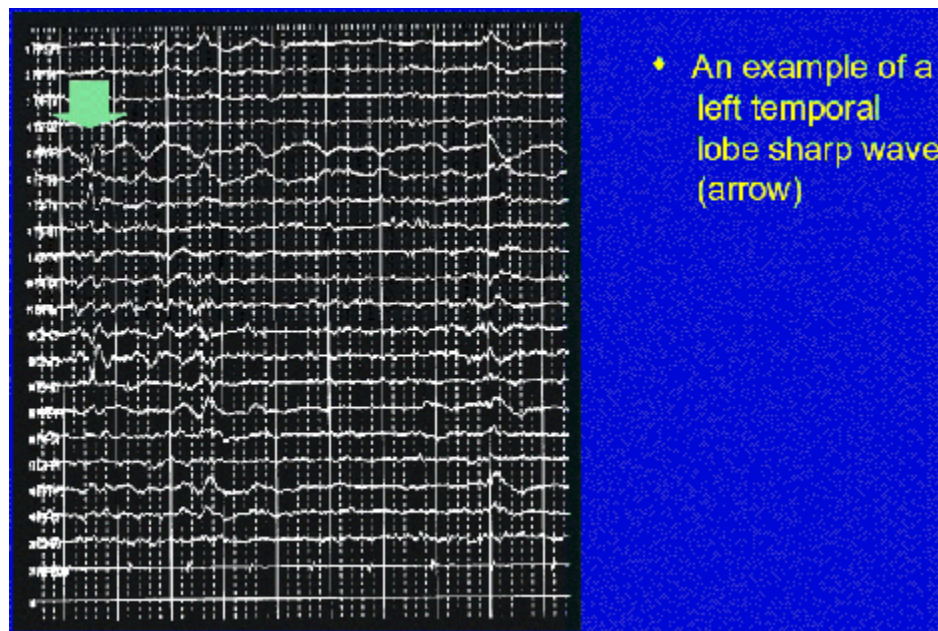
Slide 21: EEG Abnormalities

- **Background activity abnormalities**
 - Slowing not consistent with behavioral state
 - May be focal, lateralized, or generalized
 - Significant asymmetry
- **Transient abnormalities / Discharges**
 - Spikes
 - Sharp waves
 - Spike and slow wave complexes
 - May be focal, lateralized, or generalized



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Slide 22: Sharp Waves



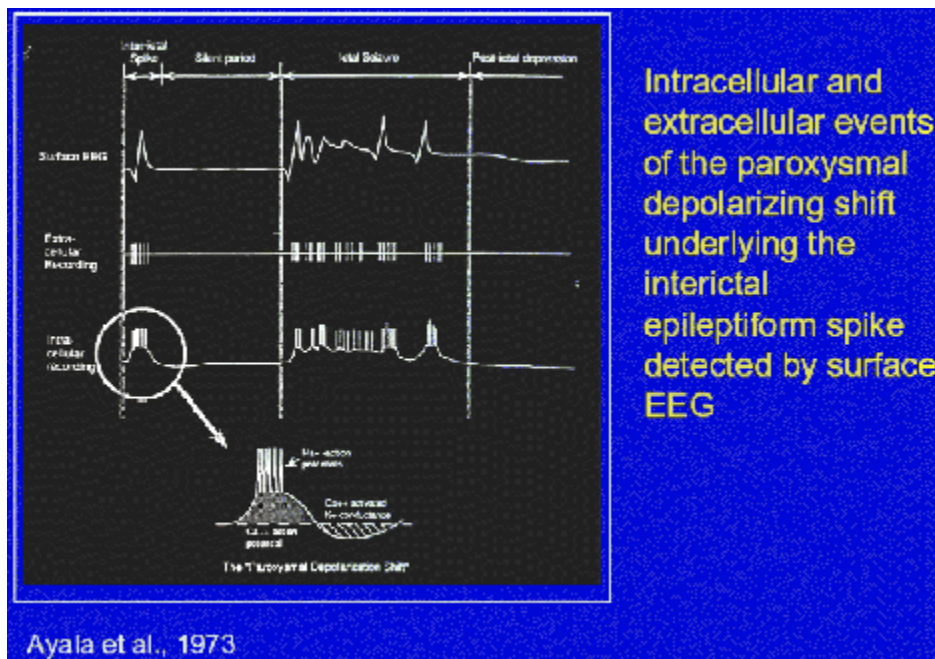
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IV. Pathophysiology of Seizures: An Alteration in the Normal Balance of Inhibition and Excitation

A. Basic Mechanisms of Focal Seizure Initiation and Propagation

The hypersynchronous discharges that occur during a seizure may begin in a very discrete region of cortex and then spread to neighboring regions. Seizure initiation is characterized by two concurrent events: 1) high-frequency bursts of action potentials, and 2) hypersynchronization of a neuronal population. The synchronized bursts from a sufficient number of neurons result in a so-called spike discharge on the EEG. At the level of single neurons, epileptiform activity consists of sustained neuronal depolarization resulting in a burst of action potentials, a plateau-like depolarization associated with completion of the action potential burst, and then a rapid repolarization followed by hyperpolarization. This sequence is called the paroxysmal depolarizing shift. (Slide 23) The bursting activity resulting from the relatively prolonged depolarization of the neuronal membrane is due to influx of extracellular Ca^{++} , which leads to the opening of voltage-dependent Na^+ channels, influx of Na^+ , and generation of repetitive action potentials. The subsequent hyperpolarizing afterpotential is mediated by GABA receptors and Cl^- influx, or by K^+ efflux, depending on the cell type.

Slide 23: The "Interictal Spike and Paroxysmal Depolarization Shift"



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Seizure propagation, the process by which a partial seizure spreads within the brain, occurs when there is sufficient activation to recruit surrounding neurons. This leads to a loss of surround inhibition and spread of seizure activity into contiguous areas via local cortical connections, and to more distant areas via long association pathways such as the corpus callosum.

The propagation of bursting activity is normally prevented by intact hyperpolarization and a region of surrounding inhibition created by inhibitory neurons. With sufficient activation there is a recruitment of surrounding neurons via a number of mechanisms. Repetitive discharges lead to: 1) an increase in extracellular K^+ , which blunts the extent of hyperpolarizing outward K^+ currents, tending to depolarize neighboring neurons; 2) accumulation of Ca^{++} in presynaptic terminals, leading to enhanced neurotransmitter release; and 3) depolarization-induced activation of the NMDA subtype of the excitatory amino acid receptor, which causes more Ca^{++} influx and neuronal activation. Of equal interest, but less well understood, is the process by which seizures typically end, usually after seconds or minutes, and what underlies the failure of this spontaneous seizure termination in the life-threatening condition known as status epilepticus (see Clinical Epilepsy syllabus).

B. Current Theories as to How Inhibition and Excitation Can Be Altered at the Network Level

Our understanding of the CNS abnormalities causing patients to have recurrent seizures remains limited. It is important to understand that seizures and epilepsy can result from many different pathologic processes that upset the balance between excitation and inhibition. Epilepsy can result from processes which disturb extracellular ion homeostasis, alter energy metabolism, change receptor function, or alter transmitter uptake. Despite major differences in etiology, the outcome of synchronous bursting of cortical neurons may superficially appear to have a similar phenotype. Seizure phenotype may be modified more by the location and function of the neuronal network recruited into the synchronous bursting than by the underlying pathophysiology.

Because of the well organized and relatively simple circuits within the entorhinal-dentate-hippocampal loop, the limbic system has been intensively studied in experimental models of epilepsy. These investigations have led to two theories regarding the cellular network changes which cause the hippocampus, among the most common sites of origin of partial seizures, to become hyperexcitable. The first proposes that a selective loss of interneurons decreases the normal feed-forward and feedback inhibition of the dentate granule cells, an important group of principal neurons. The other theory suggests that synaptic reorganization follows injury and creates recurrent excitatory connections, via axonal "sprouting," between neighboring dentate granule cells. More recently, it has been proposed that the loss, rather than being of GABAergic inhibitory neurons, is actually of excitatory neurons which normally stimulate the inhibitory interneurons to, in turn, inhibit the dentate granule cells. These mechanisms of hyperexcitability of the neuronal network are not mutually exclusive, could act synergistically, and may coexist in the human epileptic brain.

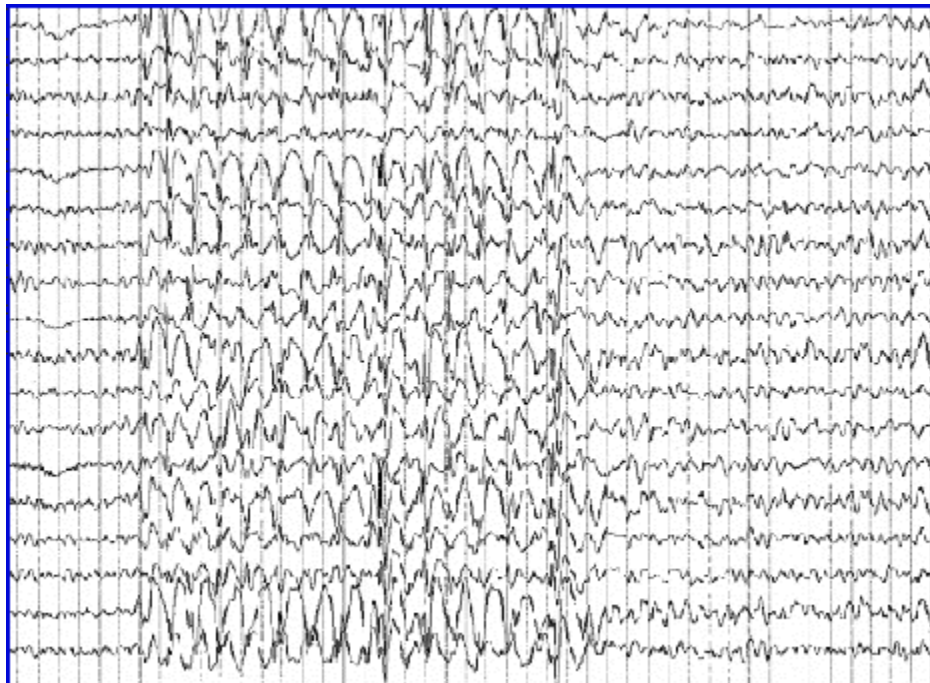
Seizures may also appear to arise from widespread cortical areas virtually simultaneously. The mechanisms underlying such generalized seizures (Slide 24) are uncertain. One type of generalized seizure, the absence seizure, (also called petit mal) is a generalized seizure consisting clinically of a brief staring spell in conjunction with a characteristic burst of spike-wave complexes on the EEG (Slide 25). Generalized spike-wave discharges in absence seizures may result from aberrations of oscillatory rhythms that are normally generated during sleep by circuits connecting the cortex and thalamus. This oscillatory behavior involves an interaction between $GABA_B$ receptors, Ca^{++} channels and K^+ channels located within the thalamus. Pharmacologic modulation of these receptors and channels can induce absence seizures, and there is speculation that genetic forms of absence epilepsy may be associated with mutations of components of this system.

Slide 24: Generalize Spike Wave Discharge



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Slide 25: EEG: Absence Seizure



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C. Epileptogenesis: The Transformation of a Normal Network Into a Hyperexcitable Network

Clinical observations suggest that certain forms of epilepsy are caused by particular events. For example, approximately 50% of patients who suffer a severe head injury will develop a seizure disorder. However, in a significant number of these patients, the seizures will not become clinically evident for months or years. This "silent period" after the initial injury indicates that in some cases the epileptogenic process involves a gradual transformation of the neural network over time. Changes occurring during this period could include delayed necrosis of inhibitory interneurons (or the excitatory interneurons driving them), or sprouting of axonal collaterals leading to reverberating, or self-reinforcing, circuits. In the future, patients at risk for developing epilepsy due to an acquired lesion may benefit from treatment with "anti-epileptogenic" compounds that could prevent these network changes.

An important experimental model of epileptogenesis is kindling, discovered by Goddard and coworkers in the 1960s. Daily, subconvulsive stimulation (electrical or chemical) of certain brain regions such as the hippocampus or amygdala result in electrical afterdischarges, eventually leading to stimulation-induced clinical seizures, and in some instances, spontaneous seizures. This change in excitability is permanent and presumably involves long-lasting biochemical and/or structural changes in the CNS. A variety of changes have been measured in kindling models, including alterations in glutamate channel properties, selective loss of neurons, and axonal reorganization. However, the exact mechanisms underlying kindling, and its applicability to human epileptogenesis, remain unknown. (Slide 26)

Slide 26: Possible Mechanism of Delayed Epileptogenesis

◆ Kindling model: repeated subconvulsive stimuli resulting in electrical afterdischarges

- Eventually lead to stimulation-induced clinical seizures
- In some cases, lead to spontaneous seizures (epilepsy)
- Applicability to human epilepsy uncertain

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Appendix A

Table 1. Ionotropic Glutamate Receptor Pharmacology

	NMDA¹	AMPA²	Kainate
Ion permeability	Na ⁺ , K ⁺ , Ca ⁺⁺	Na ⁺ , K ⁺ (Ca ⁺⁺ if GluR2 subunit absent)	Na ⁺ , K ⁺
Receptor subunits	NR1 (multiple isoforms) NR2A, NR2B, NR2C, NR2D	GluR1, GluR2, GluR3, GluR4	GluR5, GluR6 KA1, KA2
Agonists	NMDA site: NMDA glycine site: glycine	AMPA, quisqualate	Kainate domoate
Antagonists	<u>competitive</u> : D-AP5 ³ , CGS-19755, CGP-37849, CPP ⁴ <u>glycine site</u> : felbamate, 7-chlorokynurenate <u>channel blockers</u> : MK-801 ⁵ , memantine, PCP ⁶ <u>redox site</u> : PQQ ⁷	NBQX ⁸ , GYKI ⁹	GAMS ¹⁰

1. NMDA: n-methyl-d-aspartate

2. AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

3. AP-5: DL -2-amino-5-phosphonopentanoic acid
4. CPP-3: (2-carbonypiperazine-4-yl) propyl-1-phosphonic acid
5. Merck-801
6. Phencyclidine
7. Pyrroloquinoline quinone
8. NBQX: 1,2,3,4-tetrahydro-6-nitro-2,3-dioxobenzoquinoxaline-7-sufonamide
9. GYKI 52466: 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-[5H-2,3]-benzodiazepine
10. γ -d-glutamylaminomethylsulfonic acid

Table 2. Metabotropic Glutamate Receptors

	Group I	Group II	Group III
Location	postsynaptic	presynaptic	presynaptic
Subunits	mGluR1, mGluR5	mGluR2, mGluR3	mGluR4, mGluR6 mGluR7, mGluR8
Signalling mechanism	PI ¹ hydrolysis	inhibits adenyly cyclase (\downarrow cAMP ²)	inhibits adenyly cyclase (\downarrow cAMP ²)
Agonists (in order of potency)	quisqualate > L- glutamate \geq ibotenate > ACPD ³	L- glutamate > 3,5 dihydroxyphenylglycine > ACPD ³	L-AP4 ⁴ > L- glutamate
Antagonists	4-CPG ⁵ , MCPG ⁶	MSOPPE ⁷ , EGLU ⁸ , MCPG ⁹ 6	MSPG ⁹

1. PI-phosphatidylinositol
2. cAMP: cyclic adenosine monophosphate
3. ACPD: 1-amino-cyclopentane-1,3-dicarboxylic acid
4. L-AP4: L-2-amino-4-phosphonobutanoic acid
5. 4-CPG: 4-cyclopropylglutamic acid
6. MCPG: α -methyl-4-carboxyphenyl glycine
7. MSOPPE: (RS)- α -methylserine-o-phosphate monophenyl ester
8. EGLU: [2s]-ethylglutamic acid
9. MSPG- α -methyl-(4-sulfonophenyl) glycine

Appendix B

Early Development of the Cerebral Cortex

Developmental lesions, occurring as a result of widespread or localized cortical malformations, have been increasingly recognized as a cause of epilepsy. Understanding their formation depends upon recognition of normal cerebral development.

The formation of the cerebral cortex begins as the neural folds begin to close, forming the neural tube by the 22nd gestational day. The prosencephalon, the most rostral portion of the neural tube, is then poised to bud off into the lateral cerebral hemispheres, olfactory bulbs and diencephalon. Both cerebral vesicles begin to bulge from the neural tube by the end of the fifth week of gestation. By 6 to 8 weeks of gestation, the lamina reunions, an area of densely packed, rapidly proliferating neurons, forms between the two expanding hemispheres. After the first 6 weeks of gestation, the hemispheres expand by increasing the number of neurons and glia and then

by the growth of existing neuronal and glial cell processes. By 3 months of gestation, the nervous system has its full adult complement of neurons, but these must functionally mature and evolve. Glial proliferation continues throughout life. (Slide 27)

Slide 27: Cortical Development

- ◆ Neural tube
- ◆ Cerebral vesicles
- ◆ Germinal matrix
- ◆ Neuronal migration and differentiation
- ◆ "Pruning" of neurons and neuronal connections
- ◆ Myelination



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The cells from which the embryonic cerebral cortex originates reside as stem cells in the walls of the early neural tube, a germinal matrix. Following later mitoses, the stem cells transform into neurons and associate themselves with radially oriented glial cells that act as guide wires, directing the migrating neurons from the ventricular zone to the newly forming cortex. Most cortex forms its deeper layers first, with later arriving, migrating neurons occupying more superficial cortical positions. The process of guiding young neurons to their proper location within the cortex involves a columnar organization of functionally and clonally related cells.

Neuronal differentiation follows immediately after the cells are formed and migration initiated. As many young neurons migrate, one advancing edge of the neuron forms a growth cone that leads a primitive axon, through chemical and perhaps electrical gradients, to migrate under the influence of substances such as fibronectin and laminin. The growth cone "follows" these gradients, bringing the emerging axon into contiguity with its intended target position. Likewise, neurons begin sprouting dendrites as soon as they reach their final destiny in the developing cerebral cortex. Much of hemispheric growth, following the completion of neuronal proliferation and migration in the 5th fetal month, results from elaboration of axonal and dendritic processes and their accompanying glial support cells.

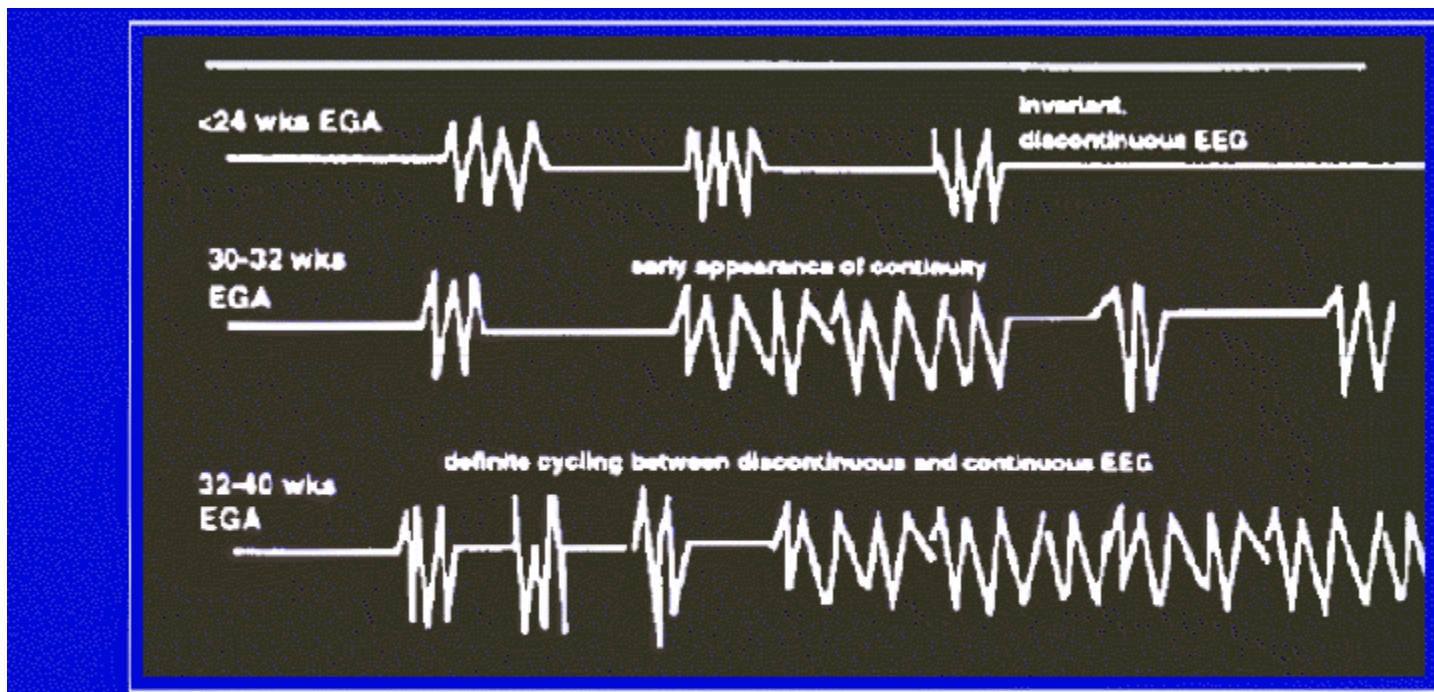
The final anatomic form of the cerebral cortices results from remodeling of the neurons and their processes. Just as sculptors chisel the final form of their creations from an excess of clay, the central nervous system removes unnecessary neurons and synapses. To survive, neurons must compete for a limited supply of vital substances at their target sites, such as nerve growth factors. Synaptic connections are also subject to remodeling, after an initial overgrowth of processes. The biochemistry underlying this pruning process is under intense scrutiny and may partly involve excitatory amino acid neurotransmitters.

The biochemistry of neural transmission in the immature cortex parallels anatomic development. Synapse formation begins in some brain regions as early as the 3rd month of gestation. Following synapse formation, action potentials may develop, at a time when the nervous system is just beginning the myelination process. Myelination proceeds in a site-specific fashion: some brain regions myelinate much earlier than others. For example, early myelination is robust in regions such as the motor and sensory nerve roots and in vital brainstem areas. In contrast, myelination in prefrontal cortex appears much later, and continues for years after birth, reflecting the relative unimportance of this higher cortical area to prenatal or neonatal function. Myelination also depends upon the type of interneuronal connections: cortico-cortical connections are among the last to myelinate, a finding that influences the characteristics, geographic spread, and electroclinical manifestations of seizures in the most immature brains.

Although animal studies show that neurotransmitter expression is highly developmentally regulated, little is known about the specific patterns of neurotransmitter development in different human brain regions. In the rodent hippocampus and neocortex, for example, the maturation of the excitatory receptor system generally precedes the development of inhibitory neurotransmission. In fact, during critical windows of development characterized by rapid brain growth and plasticity, certain classes of glutamate receptors (NMDA and AMPA) actually undergo an overshoot in density compared with later adult values. Receptor subunit composition also is developmentally regulated. For instance, NMDA receptor subunits associated with enhanced NMDA currents are expressed at higher levels in the developing brain than in the adult brain. Subunit combinations underlying Ca^{++} permeability at the AMPA receptor are also present at higher levels and on many more cell types in the immature brain than in the adult brain. During the period of development characterized by an enhancement of excitation, the GABAergic system is relatively underdeveloped. GABA levels, receptor density, and synthetic enzymes are all at lower levels in the developing brain than in the adult brain. In this way, the immature brain is relatively hyperexcitable compared to the adult brain. This has been presumed to explain, at least in part, the enhanced plasticity and synaptogenesis (activity-mediated growth) present in the immature brain. However, it is this same enhancement of excitability which may make the immature brain more susceptible to seizures than is the adult brain.

In parallel with the marked changes taking place in neuronal migration and connectivity, the EEG undergoes rapid changes during development. (Slides 28, 29 & 30) The first EEG activity present at the cortical surface appears just after the 8th gestational week. By the 20th week of gestation, the EEG is an invariant, discontinuous signal that does not cycle through any obvious biobehavioral states. By 24 weeks of gestation, there are emerging suggestions of state differentiation characterized by: 1) a continuous EEG signal accompanied by greater fetal motor activity, and 2) periods of more discontinuous EEG in which the fetus "quietly" sleeps and displays less motoric activity. Definite electrographic seizures have been recorded from premature babies as early as the 24th week after conception. The location of onset, anatomical spread, and electroclinical correlations of these seizures depend on the maturationally determined anatomical-functional status of the immature cerebral cortex when the causative insult occurred.

Slide 28: Behavioral Cycling and EEG Changes During Development



EGA = embryonic gestational age

Kellway P and Crawley JW. A primer of Electroencephalography of Infants, Section I and II: Methodology and Criteria of Normality. Baylor University College of Medicine, Houston, Texas 1964.

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Slide 29: EEG Change During Development

EEG Evolution and Early Cortical Development

Estimated Gestational Age, in Weeks	EEG Evolution
8	First appearance of EEG signal across cortex
<24	Discontinuous EEG; no state cycling
24	Some continuous EEG; mostly discontinuous EEG; early state cycling
30-32	Definite state cycling
32-34	Consolidation of behavioral states

Kellway P and Crawley JW. A primer of Electroencephalography of Infants, Section I and II: Methodology and Criteria of Normality. Baylor University College of Medicine, Houston, Texas 1964.

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Slide 30: EEG Change During Development

EEG Evolution and Early Cortical Development

Estimated Gestational Age, in Weeks	EEG Evolution
40	Predictable cycles of "active" and "quiet" sleep
44 - 46	First appearance of sleep spindles during quiet sleep
4 Months Post-Term	Sleep onset quiet sleep and emergence of mature sleep architecture

Kellway P and Crawley JW. A primer of Electroencephalography of Infants, Section I and II: Methodology and Criteria of Normality. Baylor University College of Medicine, Houston, Texas 1964.

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