Epilepsy and Schizophrenia

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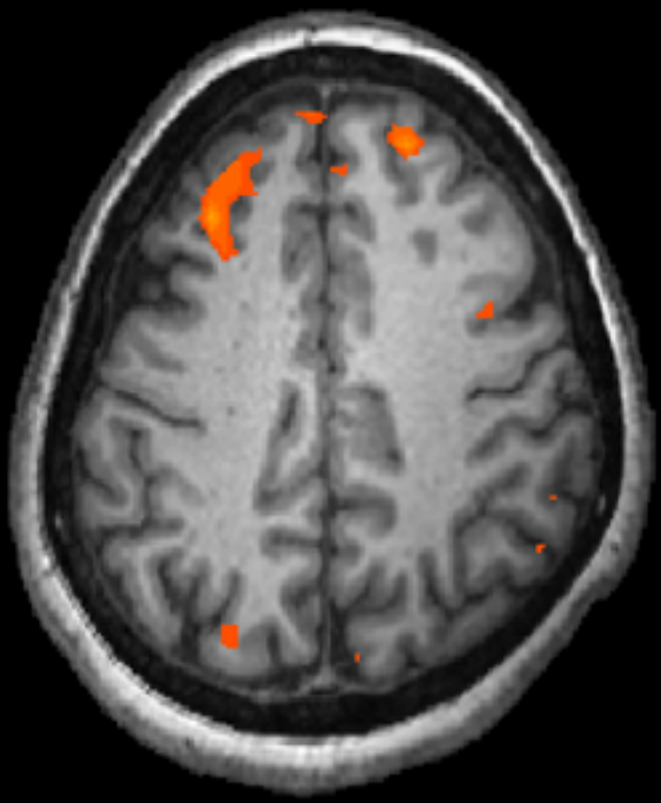

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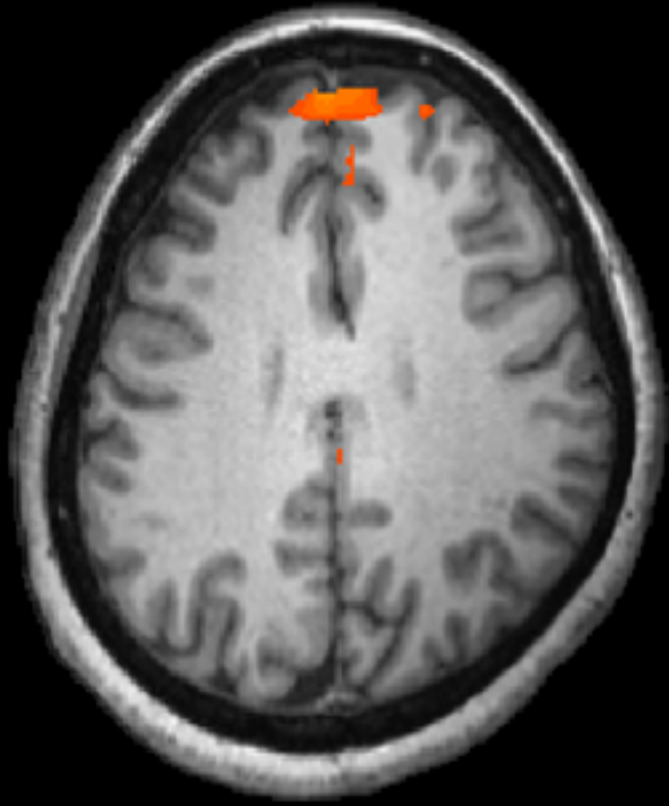

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Epilepsy

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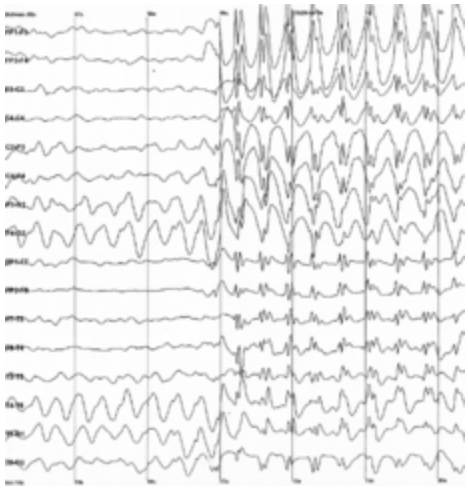

Generalized 3 Hz spike and wave discharges in EEG

ICD-10	G40.-G41.
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Epilepsy (from the Ancient Greek ἐπιληψία (*epilēpsía*) — "to seize") is a common chronic neurological disorder characterized by seizures. These seizures are transient signs and/or symptoms of abnormal, excessive or synchronous neuronal activity in the brain. About 50 million people worldwide have epilepsy, and nearly two out of every three new cases are discovered in developing countries. Epilepsy is more likely to occur in young children, or people over the age of 65 years; however, it can occur at any time. As a consequence of brain surgery, epileptic seizures may occur in recovering patients.

Epilepsy is usually controlled, but cannot be cured with medication, although surgery may be considered in difficult cases. However, over 30% of people with epilepsy do not have seizure control even with the best available medications. Not all epilepsy syndromes are lifelong – some forms are confined to particular stages of childhood. Epilepsy should not be understood as a single disorder, but rather as syndromic with vastly divergent symptoms but all involving episodic abnormal electrical activity in the brain.

Classification

Epilepsies are classified in five ways:

1. By their first cause (or etiology).
2. By the observable manifestations of the seizures, known as semiology.
3. By the location in the brain where the seizures originate.
4. As a part of discrete, identifiable medical syndromes.
5. By the event that triggers the seizures, as in primary reading epilepsy or musicogenic epilepsy.

In 1981, the International League Against Epilepsy (ILAE) proposed a classification scheme for individual seizures that remains in common use. This classification is based on observation (clinical and EEG) rather than the underlying pathophysiology or anatomy and is outlined later here. In 1989, the ILAE proposed a classification scheme for epilepsies and epileptic syndromes. This can be broadly described as a two-axis scheme having the cause on one axis and the extent of localization within the brain on the other. Since 1997, the ILAE have been working on a new scheme that has five axes:

1. ictal phenomenon, (pertaining to an epileptic seizure)

2. seizure type,

3. syndrome,

4. etiology,

5. impairment.

Seizure types

Seizure types are organized firstly according to whether the source of the seizure within the brain is localized (*partial* or *focal* onset seizures) or distributed (*generalized* seizures). Partial seizures are further divided on the extent to which consciousness is affected. If it is unaffected, then it is a *simple partial* seizure; otherwise it is a *complex partial* (psychomotor) seizure. A partial seizure may spread within the brain - a process known as *secondary generalization*. Generalized seizures are divided according to the effect on the body but all involve loss of consciousness. These include absence (petit mal), myoclonic, clonic, tonic, tonic-clonic (grand mal), and atonic seizures.

Children may exhibit behaviors that are easily mistaken for epileptic seizures but are not caused by epilepsy. These include:

- Inattentive staring
- Benign shudders (among children younger than age 2, usually when they are tired or excited)
- Self-gratification behaviors (nodding, rocking, head banging)
- Conversion disorder (flailing and jerking of the head, often in response to severe personal stress such as physical abuse)

Conversion disorder can be distinguished from epilepsy because the episodes never occur during sleep and do not involve incontinence or self-injury.

Epilepsy syndromes

There are over 40 different types of epilepsy, including: Absence seizures, atonic seizures, benign Rolandic epilepsy, childhood absence, clonic seizures, complex partial seizures, frontal lobe epilepsy, febrile seizures, infantile spasms, juvenile myoclonic epilepsy, juvenile absence epilepsy, hot water epilepsy, Lennox-Gastaut syndrome, Landau-Kleffner syndrome , myoclonic seizures, mitochondrial disorders, progressive myoclonic epilepsy, psychogenic seizures, reflex epilepsy, Rasmussen's syndrome, simple partial seizures, secondarily generalized seizures, temporal lobe epilepsy, tonic-clonic seizures, tonic seizures, psychomotor seizures, limbic epilepsy, partial-onset seizures, Rett syndrome, generalized-onset seizures, status epilepticus, abdominal epilepsy, akinetic seizures, autonomic seizures, massive bilateral myoclonus, catamenial epilepsy, drop seizures, emotional seizures, focal seizures, gelastic seizures, Jacksonian seizure disorder, Lafora disease, motor seizures, multifocal seizures, neonatal seizures, nocturnal seizures, photosensitive epilepsy, pseudoseizures, sensory seizures, subtle seizures, Sylvan seizures, withdrawal seizures and visual reflex seizures, among others.

Each type of epilepsy presents with its own unique combination of seizure type, typical age of onset, EEG findings, treatment, and prognosis. The most widespread classification of the epilepsies divides epilepsy syndromes by location or distribution of seizures (as revealed by the appearance of the seizures and by EEG) and by cause. Syndromes are divided into localization-related epilepsies, generalized epilepsies, or epilepsies of unknown localization.

Localization-related epilepsies, sometimes termed partial or focal epilepsies, arise from an epileptic focus, a small portion of the brain that serves as the irritant driving the epileptic response. Generalized epilepsies, in contrast, arise from many independent foci (multifocal epilepsies) or from epileptic circuits that involve the whole brain. Epilepsies of unknown localization remain unclear as to whether they arise from a portion of the brain or from more widespread circuits.

Epilepsy syndromes are further divided by presumptive cause: idiopathic, symptomatic, and cryptogenic. In general, idiopathic epilepsies are thought to arise from genetic

abnormalities that lead to alteration of basic neuronal regulation. Symptomatic epilepsies arise from the effects of an epileptic lesion, whether that lesion is focal, such as a tumor, or a defect in metabolism causing widespread injury to the brain. Cryptogenic epilepsies involve a presumptive lesion that is otherwise difficult or impossible to uncover during evaluation.

The genetic component to epilepsy is receiving particular interest from the scientific community. Conditions such as ring chromosome 20 syndrome (r(20)) are gaining acknowledgment, and although only 60 cases have been reported in the literature since 1976, "more widespread cytogenetic chromosomal karyotyping in nonetiological cases of epilepsy" is likely.

Some epileptic syndromes are difficult to fit within this classification scheme and fall in the unknown localization/etiology category. People having had only a single seizure, or those with seizures that occur only after specific precipitants ("provoked seizures"), have "epilepsies" that fall into this category. Febrile convulsions are an example of seizures bound to a particular precipitant. Landau-Kleffner syndrome is another epilepsy that, because of its variety of EEG distributions, falls uneasily in clear categories. What can be even more confusing is that certain syndromes, such as West syndrome, featuring seizures such as infantile spasms, can be classified as idiopathic, syndromic, or cryptogenic depending on cause and can arise from both focal or generalized epileptic lesions.

Below are some common seizure syndromes:

- **Autosomal dominant nocturnal frontal lobe epilepsy** (ADNFLE) is an idiopathic localization-related epilepsy that is an inherited epileptic disorder that causes seizures during sleep. Onset is usually in childhood. These seizures arise from the frontal lobes and consist of complex motor movements, such as hand clenching, arm raising/lowering, and knee bending. Vocalizations such as shouting, moaning, or crying are also common. ADNFLE is often misdiagnosed as nightmares. ADNFLE has a genetic basis. These genes encode various nicotinic acetylcholine receptors.

- **Benign centrotemporal lobe epilepsy of childhood** or benign Rolandic epilepsy is an idiopathic localization-related epilepsy that occurs in children between the ages of 3 and 13 years, with peak onset in prepubertal late childhood. Apart from their seizure disorder, these patients are otherwise normal. This syndrome features simple partial seizures that involve facial muscles and frequently cause drooling. Although most episodes are brief, seizures sometimes spread and generalize. Seizures are typically nocturnal and confined to sleep. The EEG may demonstrate spike discharges that occur over the centrotemporal scalp over the central sulcus of the brain (the Rolandic sulcus) that are predisposed to occur during drowsiness or light sleep. Seizures cease near puberty. Seizures may require anticonvulsant treatment, but sometimes are infrequent enough to allow physicians to defer treatment.

- **Benign occipital epilepsy of childhood** (BOEC) is an idiopathic localization-related epilepsy and consists of an evolving group of syndromes. Most authorities include two subtypes, an early subtype with onset between three and five years, and a late onset between seven and 10 years. Seizures in BOEC usually feature visual symptoms such as scotoma or fortifications (brightly colored spots or lines) or amaurosis (blindness or impairment of vision). Convulsions involving one half the body, hemiconvulsions, or forced eye deviation or head turning are common. Younger patients typically experience symptoms similar to migraine with nausea and headache, and older patients typically complain of more visual symptoms. The EEG in BOEC shows spikes recorded from the occipital (back of head) regions. The EEG and genetic pattern suggest an autosomal dominant transmission as described by Ruben Kuzniecky, et al. Lately, a group of epilepsies termed Panayiotopoulos syndrome that share some clinical features of BOEC but have a wider variety of EEG findings are classified by some as BOEC.

- **Catamenial epilepsy** (CE) is when seizures cluster around certain phases of a woman's menstrual cycle.

- **Childhood absence epilepsy** (CAE) is an idiopathic generalized epilepsy that affects children between the ages of four and 12 years of age, although peak onset is around five to six years old. These patients have recurrent absence seizures, brief episodes of unresponsive staring, sometimes with minor motor features such as eye blinking or subtle chewing. The EEG finding in CAE is generalized 3 Hz spike and wave discharges. Some go on to develop generalized tonic-clonic seizures. This condition carries a good prognosis because children do not usually show cognitive decline or neurological deficits, and the seizures in the majority cease spontaneously with onging maturation.

- **Dravet's syndrome**, previously known as severe myoclonic epilepsy of infancy (SMEI), is a neurodevelopmental disorder beginning in infancy and characterized by severe epilepsy that does not respond well to treatment. This syndrome was described by Charlotte Dravet, French psychiatrist and epileptologist (born July 14, 1936). Dravet described this syndrome while working at the Centre Saint Paul at the University of Marseille. At Centre Saint Paul, one of her supervisors was Henri Gastaut, who described the Lennox-Gastaut syndrome. She described this condition in 1978 Estimates of the prevalence of this rare disorder have ranged from 1:20,000 to 1:40,000 births, though the incidence may be found to be greater as the syndrome becomes better recognized and new genetic evidence is discovered. It is thought to occur with similar frequency in both genders, and knows no geographic or ethnic boundaries.

  The course of Dravet syndrome is highly variable from person to person. Seizures begin during the first year of life and development is normal prior to their onset. In most cases, the first seizures occur with fever and are generalized tonic-clonic (grand mal) or unilateral (one-sided) convulsions. These seizures are often prolonged, and may lead to status epilepticus, a medical emergency. In time,

seizures increase in frequency and begin to occur without fever. Additional seizure types appear, most often these are myoclonic, atypical absence, and complex-partial seizures.
Additional features that are seen in significant numbers of patients with Dravet syndrome may include sensory integration disorders and other autism spectrum characteristics, orthopedic or movement disorders, frequent or chronic upper respiratory and ear infections, sleep disturbance, dysautonomia, and problems with growth and nutrition.

- **Frontal lobe epilepsy**, usually a symptomatic or cryptogenic localization-related epilepsy, arises from lesions causing seizures that occur in the frontal lobes of the brain. These epilepsies can be difficult to diagnose because the symptoms of seizures can easily be confused with nonepileptic spells and, because of limitations of the EEG, be difficult to "see" with standard scalp EEG.

- **Juvenile absence epilepsy** is an idiopathic generalized epilepsy with later onset than CAE, typically in prepubertal adolescence, with the most frequent seizure type being absence seizures. Generalized tonic-clonic seizures can occur. Often, 3 Hz spike-wave or multiple spike discharges can be seen on EEG. The prognosis is mixed, with some patients going on to a syndrome that is poorly distinguishable from JME.

- **Juvenile myoclonic epilepsy** (JME) is an idiopathic generalized epilepsy that occurs in patients aged 8 to 20 years. Patients have normal cognition and are otherwise neurologically intact. The most common seizures are myoclonic jerks, although generalized tonic-clonic seizures and absence seizures may occur as well. Myoclonic jerks usually cluster in the early morning after awakening. The EEG reveals generalized 4–6 Hz spike wave discharges or multiple spike discharges. Interestingly, these patients are often first diagnosed when they have their first generalized tonic-clonic seizure later in life, when they experience sleep deprivation (e.g., freshman year in college after staying up late to study for exams). Alcohol withdrawal can also be a major contributing factor in breakthrough seizures, as well. The risk of the tendency to have seizures is lifelong; however, the majority have well-controlled seizures with anticonvulsant medication and avoidance of seizure precipitants.

- **Lennox-Gastaut syndrome** (LGS) is a generalized epilepsy that consists of a triad of developmental delay or childhood dementia, mixed generalized seizures, and EEG demonstrating a pattern of approximately 2 Hz "slow" spike-waves. Onset occurs between two and 18 years. As in West syndrome, LGS result from idiopathic, symptomatic, or cryptogenic causes, and many patients first have West syndrome. Authorities emphasize different seizure types as important in LGS, but most have astatic seizures (drop attacks), tonic seizures, tonic-clonic seizures, atypical absence seizures, and sometimes, complex partial seizures. Anticonvulsants are usually only partially successful in treatment.

- **Ohtahara syndrome** is a rare, but severe epilepsy syndrome usually starting in the first few days or weeks of life. The seizures are often in the form of stiffening spasms but other seizures including unilateral ones may be seen. The electroencephalogram (EEG) is characteristic. The prognosis is poor with about half of the infants dying in the first year of life; most if not all surviving infants are severely intellectually disabled and many have cerebral palsy. There is no effective treatment. A number of children have underlying structural brain abnormalities.
- **Primary reading epilepsy** is a reflex epilepsy classified as an idiopathic localization-related epilepsy. Reading in susceptible individuals triggers characteristic seizures.

- **Progressive myoclonic epilepsies** define a group of symptomatic generalized epilepsies characterized by progressive dementia and myoclonic seizures. Tonic-clonic seizures may occur as well. Diseases usually classified in this group are Unverricht-Lundborg disease, myoclonus epilepsy with ragged red fibers (MERRF syndrome), Lafora disease, neuronal ceroid lipofucinosis, and sialdosis.

- **Rasmussen's encephalitis** is a symptomatic localization-related epilepsy that is a progressive, inflammatory lesion affecting children with onset before the age of 10. Seizures start as separate simple partial or complex partial seizures and may progress to epilepsia partialis continua (simple partial status epilepticus). Neuroimaging shows inflammatory encephalitis on one side of the brain that may spread if not treated. Dementia and hemiparesis are other problems. The cause is hypothesized to involve an immulogical attack against glutamate receptors, a common neurotransmitter in the brain.

- **Symptomatic localization-related epilepsies** are divided by the location in the brain of the epileptic lesion, since the symptoms of the seizures are more closely tied to the brain location rather than the cause of the lesion. Tumors, atriovenous malformations, cavernous malformations, trauma, and cerebral infarcts can all be causes of epileptic foci in different brain regions.

- **Temporal lobe epilepsy** (TLE), a symptomatic localization-related epilepsy, is the most common epilepsy of adults who experience seizures poorly controlled with anticonvulsant medications. In most cases, the epileptogenic region is found in the midline (mesial) temporal structures (e.g., the hippocampus, amygdala, and parahippocampal gyrus). Seizures begin in late childhood and adolescence. Most of these patients have complex partial seizures sometimes preceded by an aura, and some TLE patients also suffer from secondary generalized tonic-clonic seizures. If the patient does not respond sufficiently to medical treatment, epilepsy surgery may be considered.

- **Tuberous Sclerosis** (TSC) is a genetic disorder that causes tumors to form in many different organs, primarily in the brain, eyes, heart, kidney, skin and lungs.

Several types of brain lesions can occur in individuals with TSC and 60% - 90% of people with TSC develop epilepsy.

- **West syndrome** is a triad of developmental delay, seizures termed infantile spasms, and EEG demonstrating a pattern termed hypsarrhythmia. Onset occurs between three months and two years, with peak onset between eight and 9 months. West syndrome may arise from idiopathic, symptomatic, or cryptogenic causes. The most common cause is tuberous sclerosis. The prognosis varies with the underlying cause. In general, most surviving patients remain with significant cognitive impairment and continuing seizures and may evolve to another eponymic syndrome, Lennox-Gastaut syndrome.

Causes

The diagnosis of epilepsy usually requires that the seizures occur spontaneously. Nevertheless, certain epilepsy syndromes require particular precipitants or triggers for seizures to occur. These are termed reflex epilepsy. For example, patients with primary reading epilepsy have seizures triggered by reading. Photosensitive epilepsy can be limited to seizures triggered by flashing lights. Other precipitants can trigger an epileptic seizure in patients who otherwise would be susceptible to spontaneous seizures. For example, children with childhood absence epilepsy may be susceptible to hyperventilation. In fact, flashing lights and hyperventilation are activating procedures used in clinical EEG to help trigger seizures to aid diagnosis. Finally, other precipitants can facilitate, rather than obligately trigger, seizures in susceptible individuals. Emotional stress, sleep deprivation, sleep itself, heat stress, alcohol and febrile illness are examples of precipitants cited by patients with epilepsy. Notably, the influence of various precipitants varies with the epilepsy syndrome. Likewise, the menstrual cycle in women with epilepsy can influence patterns of seizure recurrence. Catamenial epilepsy is the term denoting seizures linked to the menstrual cycle.

There are different causes of epilepsy that are common in certain age groups.

- During the neonatal period and early infancy the most common causes include hypoxic-ischemic encephalopathy, CNS infections, trauma, congenital CNS abnormalities, and metabolic disorders.
- During late infancy and early childhood, febrile seizures are fairly common. These may be caused by many different things, some thought to be things such as CNS infections and trauma.
- During childhood, well-defined epilepsy syndromes are generally seen.
- During adolescence and adulthood, the causes are more likely to be secondary to any CNS lesion. Further, idiopathic epilepsy is less common. Other causes associated with these age groups are stress, trauma, CNS infections, brain tumors, illicit drug use and alcohol withdrawal.
- In older adults, cerebrovascular disease is a very common cause. Other causes are CNS tumors, head trauma, and other degenerative diseases that are common in the older age group, such as dementia.

Pathophysiology

Mutations in several genes have been linked to some types of epilepsy. Several genes that code for protein subunits of voltage-gated and ligand-gated ion channels have been associated with forms of generalized epilepsy and infantile seizure syndromes. Several ligand-gated ion channels have been linked to some types of frontal and generalized epilepsies. One speculated mechanism for some forms of inherited epilepsy are mutations of the genes that code for sodium channel proteins; these defective sodium channels stay open for too long, thus making the neuron hyper-excitable. Glutamate, an excitatory neurotransmitter, may, therefore, be released from these neurons in large amounts, which — by binding with nearby glutamatergic neurons — triggers excessive calcium (Ca^{2+}) release in these post-synaptic cells. Such excessive calcium release can be neurotoxic to the affected cell. The hippocampus, which contains a large volume of just such glutamanergic neurons (and NMDA receptors, which are permeable to Ca^{2+} entry after binding of both sodium and glutamate), is especially vulnerable to epileptic seizure, subsequent spread of excitation, and possible neuronal death. Another possible mechanism involves mutations leading to ineffective GABA (the brain's most common inhibitory neurotransmitter) action. Epilepsy-related mutations in some non-ion channel genes have also been identified.

Epileptogenesis is the process by which a normal brain develops epilepsy after trauma, such as a lesion on the brain. One interesting finding in animals is that repeated low-level electrical stimulation to some brain sites can lead to permanent increases in seizure susceptibility: in other words, a permanent decrease in seizure "threshold." This phenomenon, known as kindling (by analogy with the use of burning twigs to start a larger fire) was discovered by Dr. Graham Goddard in 1967. It is important to note that these "kindled" animals do not experience spontaneous seizures. Chemical stimulation can also induce seizures; repeated exposures to some pesticides have been shown to induce seizures in both humans and animals. One mechanism proposed for this is called excitotoxicity. The roles of kindling and excitotoxicity, if any, in human epilepsy are currently hotly debated.

Other causes of epilepsy are brain lesions, where there is scar tissue or another abnormal mass of tissue in an area of the brain.

The complexity of understanding what seizures are have led to considerable efforts to use computational models of epilepsy to both interpret experimental and clinical data, as well as guide strategies for therapy.

Management

Epilepsy is usually treated with medication prescribed by a physician; primary caregivers, neurologists, and neurosurgeons all frequently care for people with epilepsy. However, it has been stressed that accurate differentiation between generalized and partial seizures is especially important in determining the appropriate treatment. In some cases the implantation of a stimulator of the vagus nerve, or a special diet can be helpful.

Neurosurgical operations for epilepsy can be palliative, reducing the frequency or severity of seizures; or, in some patients, an operation can be curative.

The proper initial response to a generalized tonic-clonic epileptic seizure is to prevent the person from self-injury by moving them away from sharp edges, placing something soft beneath the head, and rolling the person into the recovery position. Should the person regurgitate, this should be allowed to drip out the side of the person's mouth. If a seizure lasts longer than 5 minutes, or if more than one seizure occurs without regaining consciousness emergency medical services should be contacted.

Medications

The mainstay of treatment of epilepsy is anticonvulsant medications. Often, anticonvulsant medication treatment will be lifelong and can have major effects on quality of life. The choice among anticonvulsants and their effectiveness differs by epilepsy syndrome. Mechanisms, effectiveness for particular epilepsy syndromes, and side-effects differ among the individual anticonvulsant medications. Some general findings about the use of anticonvulsants are outlined below.

Availability - Currently there are 20 medications approved by the Food and Drug Administration for the use of treatment of epileptic seizures in the US: carbamazepine (common US brand name Tegretol), clorazepate (Tranxene), clonazepam (Klonopin), ethosuximide (Zarontin), felbamate (Felbatol), fosphenytoin (Cerebyx), gabapentin (Neurontin), lacosamide (Vimpat), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), phenobarbital (Luminal), phenytoin (Dilantin), pregabalin (Lyrica), primidone (Mysoline), tiagabine (Gabitril), topiramate (Topamax), valproate semisodium (Depakote), valproic acid (Depakene), and zonisamide (Zonegran). Most of these appeared after 1990.

Medications commonly available outside the US but still labelled as "investigational" within the US are clobazam (Frisium) and vigabatrin (Sabril). Medications currently under clinical trial under the supervision of the FDA include retigabine, brivaracetam, and seletracetam.

Other drugs are commonly used to abort an active seizure or interrupt a seizure flurry; these include diazepam (Valium, Diastat) and lorazepam (Ativan). Drugs used only in the treatment of refractory status epilepticus include paraldehyde (Paral), midazolam (Versed), and pentobarbital (Nembutal).

Some anticonvulsant medications do not have primary FDA-approved uses in epilepsy but are used in limited trials, remain in rare use in difficult cases, have limited "grandfather" status, are bound to particular severe epilepsies, or are under current investigation. These include acetazolamide (Diamox), progesterone, adrenocorticotropic hormone (ACTH, Acthar), various corticotropic steroid hormones (prednisone), or bromide.

Effectiveness - The definition of "effective" varies. FDA approval usually requires that 50% of the patient treatment group had at least a 50% improvement in the rate of epileptic seizures. About 20% of patients with epilepsy continue to have breakthrough epileptic seizures despite best anticonvulsant treatment.

Safety and Side Effects - 88% of patients with epilepsy, in a European survey, reported at least one anticonvulsant related side-effect. Most side effects are mild and "dose-related" and can often be avoided or minimized by the use of the smallest effective amount. Some examples include mood changes, sleepiness, or unsteadiness in gait. Some anticonvulsant medications have "idiosyncratic" side effects that can not be predicted by dose. Some examples include drug rashes, liver toxicity (hepatitis), or aplastic anemia. Safety includes the consideration of teratogenicity (the effects of medications on fetal development) when women with epilepsy become pregnant.

Principles of Anticonvulsant Use and Management - The goal for individual patients is no seizures and minimal side-effects, and the job of the physician is to aid the patient to find the best balance between the two during the prescribing of anticonvulsants. Most patients can achieve this balance best with *monotherapy*, the use of a single anticonvulsant medication. Some patients, however, require *polypharmacy*, the use of two or more anticonvulsants.

Serum levels of AEDs can be checked to determine medication compliance, to assess the effects of new drug-drug interactions upon previous stable medication levels, or to help establish if particular symptoms such as instability or sleepiness can be considered a drug side effect or are due to different causes. Children or impaired adults who may not be able to communicate side-effects may benefit from routine screening of drug levels. Beyond baseline screening, however, trials of recurrent, routine blood or urine monitoring show no proven benefits and may lead to unnecessary medication adjustments in most older children and adults using routine anticonvulsants.

If a person's epilepsy cannot be brought under control after adequate trials of two or three (experts vary here) different drugs, that person's epilepsy is generally said to be *medically refractory*. A study of patients with previously untreated epilepsy demonstrated that 47% achieved control of seizures with the use of their first single drug. 14% became seizure free during treatment with a second or third drug. An additional 3% became seizure-free with the use of two drugs simultaneously. Other treatments, in addition to or instead of, anticonvulsant medications may be considered by those people with continuing seizures.

Surgery

Epilepsy surgery is an option for patients whose seizures remain resistant to treatment with anticonvulsant medications who also have symptomatic localization-related epilepsy; a focal abnormality that can be located and therefore removed. The goal for these procedures is total control of epileptic seizures, although anticonvulsant medications may still be required.

The evaluation for epilepsy surgery is designed to locate the "epileptic focus" (the location of the epileptic abnormality) and to determine if resective surgery will affect normal brain function. Physicians will also confirm the diagnosis of epilepsy to make sure that spells arise from epilepsy (as opposed to non-epileptic seizures). The evaluation typically includes neurological examination, routine EEG, Long-term video-EEG monitoring, neuropsychological evaluation, and neuroimaging such as MRI, Single photon emission computed tomography (SPECT), positron emission tomography (PET). Some epilepsy centers use intracarotid sodium amobarbital test (Wada test), functional MRI or Magnetoencephalography (MEG) as supplementary tests.

Certain lesions require Long-term video-EEG monitoring with the use of intracranial electrodes if noninvasive testing was inadequate to identify the epileptic focus or distinguish the surgical target from normal brain tissue and function. Brain mapping by the technique of cortical electrical stimulation or Electrocorticography are other procedures used in the process of invasive testing in some patients.

The most common surgeries are the resection of lesions like tumors or arteriovenous malformations, which, in the process of treating the underlying lesion, often result in control of epileptic seizures caused by these lesions.

Other lesions are more subtle and feature epilepsy as the main or sole symptom. The most common form of intractable epilepsy in these disorders in adults is temporal lobe epilepsy with hippocampal sclerosis, and the most common type of epilepsy surgery is the anterior temporal lobectomy, or the removal of the front portion of the temporal lobe including the amygdala and hippocampus. Some neurosurgeons recommend selective amygdalahippocampectomy because of possible benefits in postoperative memory or language function. Surgery for temporal lobe epilepsy is effective, durable, and results in decreased health care costs. Despite the efficacy of epilepsy surgery, some patients decide not to undergo surgery owing to fear or the uncertainty of having a brain operation.

Palliative surgery for epilepsy is intended to reduce the frequency or severity of seizures. Examples are callosotomy or commissurotomy to prevent seizures from generalizing (spreading to involve the entire brain), which results in a loss of consciousness. This procedure can therefore prevent injury due to the person falling to the ground after losing consciousness. It is performed only when the seizures cannot be controlled by other means. Multiple subpial transection can also be used to decrease the spread of seizures across the cortex especially when the epileptic focus is located near important functional areas of the cortex. Resective surgery can be considered palliative if it is undertaken with the expectation that it will reduce but not eliminate seizures.

Hemispherectomy involves removal or a functional disconnection of most or all of one half of the cerebrum. It is reserved for people suffering from the most catastrophic epilepsies, such as those due to Rasmussen syndrome. If the surgery is performed on very young patients (2–5 years old), the remaining hemisphere may acquire some rudimentary motor control of the ipsilateral body; in older patients, paralysis results on the side of the

body opposite to the part of the brain that was removed. Because of these and other side-effects, it is usually reserved for patients having exhausted other treatment options.

Other

A **ketogenic diet** (high-fat, low-carbohydrate) was developed in the 1920s, and was largely forgotten with the advent of effective anticonvulsants, but was resurrected in the 1990s. The mechanism of action is unknown. It is used mainly in the treatment of children with severe, medically intractable epilepsies, and the New York Times reported that use is supported by peer-reviewed research that found that the diet reduced seizures among drug-resistant epileptics by >50% in 38% of patients and by >90% in 7% of patients.

While far from a cure, operant-based **biofeedback** based on conditioning of EEG waves has some experimental support. Overall, the support is based on a handful of studies reviewed by Barry Sterman. These studies report a 30% reduction in weekly seizures.

Electrical stimulation methods of anticonvulsant treatment are both currently approved for treatment and investigational uses. A currently approved device is vagus nerve stimulation (VNS). Investigational devices include the responsive neurostimulation system (RNS) and deep brain stimulation (DBS).

- **Vagus nerve stimulation** (US manufacturer Cyberonics) consists of a computerized electrical device similar in size, shape and implant location to a heart pacemaker that connects to the vagus nerve in the neck. The device stimulates the vagus nerve at preset intervals and intensities of current. Efficacy has been tested in patients with localization-related epilepsies, demonstrating 50% of patients experience a 50% improvement in seizure rate. Case series have demonstrated similar efficacies in certain generalized epilepsies, such as Lennox-Gastaut syndrome. Although success rates are not usually equal to that of epilepsy surgery, it is a reasonable alternative when the patient is reluctant to proceed with any required invasive monitoring, when appropriate presurgical evaluation fails to uncover the location of epileptic foci, or when there are multiple epileptic foci.

- **Responsive neurostimulator system** (US manufacturer Neuropace) consists of a computerized electrical device implanted in the skull, with electrodes implanted in presumed epileptic foci within the brain. The brain electrodes send EEG signals to the device which contains seizure-detection software. When certain EEG seizure criteria are met, the device delivers a small electrical charge to other electrodes near the epileptic focus, which disrupt the seizure. The efficacy of the RNS is under current investigation with the goal of FDA approval.

- **Deep brain stimulation** (US manufacturer Medtronic) consists of a computerized electrical device implanted in the chest in a manner similar to the VNS, but electrical stimulation is delivered to deep brain structures through depth electrodes implanted through the skull. In epilepsy, the electrode target is the

anterior nucleus of the thalamus. The efficacy of the DBS in localization-related epilepsies is currently under investigation.

Noninvasive surgery using the gamma knife or other devices used in radiosurgery is currently being investigated as analternative to traditional open surgery in patients who would otherwise qualify for anterior temporal lobectomy.

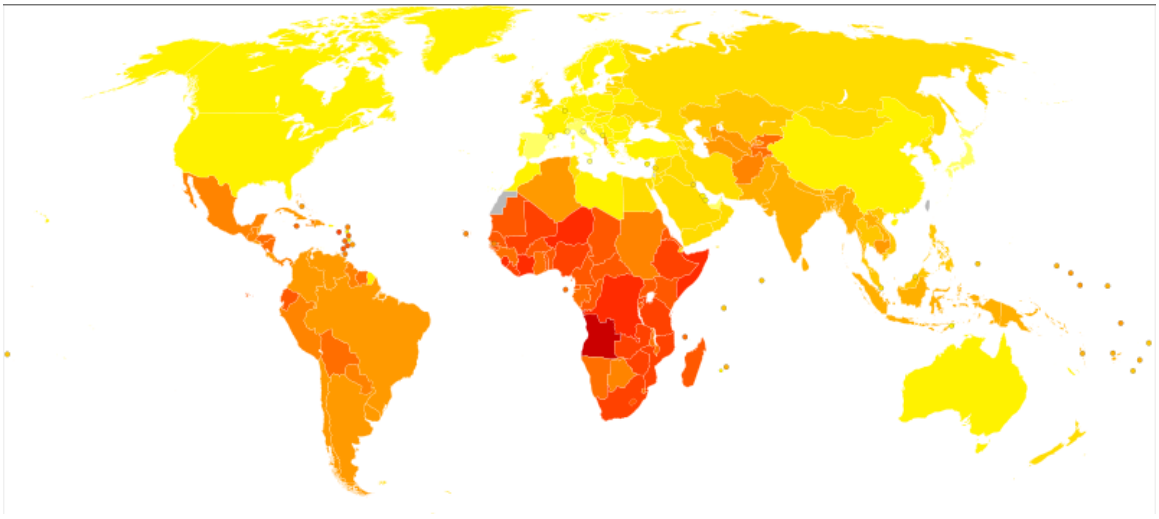
Avoidance therapy consists of minimizing or eliminating triggers in patients whose seizures are particularly susceptible to seizure precipitants. For example, sunglasses that counter exposure to particular light wavelengths can improve seizure control in certain photosensitive epilepsies.

Canine warning system is where a seizure response dog, a form of service dog, is trained to summon help or ensure personal safety when a seizure occurs. These are not suitable for everybody, and not all dogs can be so trained. Rarely, a dog may develop the ability to sense a seizure before it occurs. Development of electronic forms of seizure detection systems are currently under investigation.

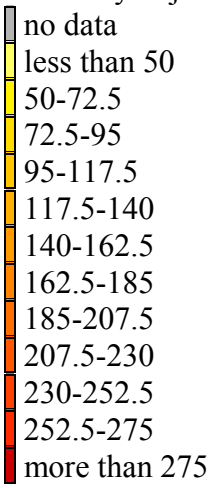
Seizure prediction-based devices using long-term EEG recordings is presently being evaluated as a new way to stop epileptic seizures before they appear clinically.

Alternative or complementary medicine, including acupuncture, psychological interventions, vitamins and yoga, was evaluated in a number of systematic reviews by the Cochrane Collaboration into treatments for epilepsy, and found there is no reliable evidence to support the use of these as treatments for epilepsy. Exercise or other physical activity have also been proposed as efficacious strategies for preventing or treating epilepsy. The Memorial Sloan-Kettering Cancer Center says dimethylglycine dietary supplement (DMG) will "enhance oxygen utilization during hypoxia, reduce lactic acid build-up in the blood during stressful events," and reduce the number of seizures experienced in epilepsy.

Epidemiology



Disability-adjusted life year for epilepsy per 100,000 inhabitants in 2002.



Epilepsy is one of the most common of the serious neurological disorders. Genetic, congenital, and developmental conditions are mostly associated with it among younger patients; tumors are more likely over age 40; head trauma and central nervous system infections may occur at any age. The prevalence of active epilepsy is roughly in the range 5–10 per 1000 people. Up to 5% of people experience non febrile seizures at some point in life; epilepsy's lifetime prevalence is relatively high because most patients either stop having seizures or (less commonly) die of it. Epilepsy's approximate annual incidence rate is 40–70 per 100,000 in industrialized countries and 100–190 per 100,000 in resource-poor countries; socioeconomically deprived people are at higher risk. In industrialized countries the incidence rate decreased in children but increased among the elderly during the three decades prior to 2003, for reasons not fully understood.

Beyond symptoms of the underlying diseases that can be a part of certain epilepsies, people with epilepsy are at risk for death from four main problems: status epilepticus (most often associated with anticonvulsant noncompliance), suicide associated with depression, trauma from seizures, and sudden unexpected death in epilepsy (SUDEP) Those at highest risk for epilepsy-related deaths usually have underlying neurological impairment or poorly controlled seizures; those with more benign epilepsy syndromes have little risk for epilepsy-related death.

The NICE National Sentinel Audit of Epilepsy-Related Deaths, led by "Epilepsy Bereaved" drew attention to this important problem. The Audit revealed; "1,000 deaths occur every year in the UK as a result of epilepsy" and most of them are associated with seizures and 42% of deaths were potentially avoidable".

Certain diseases also seem to occur in higher than expected rates in people with epilepsy, and the risk of these "comorbidities" often varies with the epilepsy syndrome. These diseases include depression and anxiety disorders, migraine and other headaches, infertility and low sexual libido. Attention-deficit/hyperactivity disorder (ADHD) affects

three to five times more children with epilepsy than children in the general population. Epilepsy is prevalent in autism.

History

The word *epilepsy* is derived from the Ancient Greek ἐπιληψία *epilēpsía*, which was from ἐπιλαμβάνειν *epilambánein* "to take hold of", which in turn was combined from ἐπί *epí* "upon" and λαμβάνειν *lambánein* "to take". In the past, epilepsy was associated with religious experiences and even demonic possession. In ancient times, epilepsy was known as the "Sacred Disease" because people thought that epileptic seizures were a form of attack by demons, or that the visions experienced by persons with epilepsy were sent by the gods. Among animist Hmong families, for example, epilepsy was understood as an attack by an evil spirit, but the affected person could become revered as a shaman through these otherworldly experiences.

However, in most cultures, persons with epilepsy have been stigmatized, shunned, or even imprisoned; in the Salpêtrière, the birthplace of modern neurology, Jean-Martin Charcot found people with epilepsy side-by-side with the mentally retarded, those with chronic syphilis, and the criminally insane. In Tanzania to this day, as with other parts of Africa, epilepsy is associated with possession by evil spirits, witchcraft, or poisoning and is believed by many to be contagious. In ancient Rome, epilepsy was known as the *Morbus Comitialis* ('disease of the assembly hall') and was seen as a curse from the gods.

Stigma continues to this day, in both the public and private spheres, but polls suggest it is generally decreasing with time, at least in the developed world; Hippocrates remarked that epilepsy would cease to be considered divine the day it was understood.

Chapter 2

Epileptic Seizure

Seizure	
ICD-10	G40., P90., R56.
ICD-9	345.9, 780.3
DiseasesDB	19011
eMedicine	neuro/694 neuro/415
MeSH	D012640

An **epileptic seizure**, occasionally referred to as a **fit**, is defined as a transient symptom of "abnormal excessive or synchronous neuronal activity in the brain". The outward effect can be as dramatic as a wild thrashing movement (tonic-clonic seizure) or as mild as a brief loss of awareness. It can manifest as an alteration in mental state, tonic or clonic movements, convulsions, and various other psychic symptoms (such as déjà vu or jamais vu). Sometimes it is not accompanied by convulsions but a full body "slump", where the person simply will lose control of their body and slump to the ground. The medical syndrome of recurrent, unprovoked seizures is termed epilepsy, but seizures can occur in people who do not have epilepsy.

About 4% of people will have an unprovoked seizure by the age of 80 and the chance of experiencing a second seizure is between 30% and 50%. Treatment may reduce the chance of a second one by as much as half. Most single episode seizures are managed by primary care physicians (emergency or general practitioners), whereas investigation and management of ongoing epilepsy is usually by neurologists. Difficult-to-manage epilepsy may require consultation with an epileptologist, a neurologist with an interest in epilepsy.

Classification

Seizure types are organized according to whether the source of the seizure within the brain is localized (*partial* or *focal* onset seizures) or distributed (*generalized* seizures). Partial seizures are further divided on the extent to which consciousness is affected (simple partial seizures and complex partial seizures). If consciousness is unaffected, then

it is a *simple partial* seizure; otherwise it is a *complex partial* seizure. A partial seizure may spread within the brain—a process known as *secondary generalization*. Generalized seizures are divided according to the effect on the body, but all involve loss of consciousness. These include absence, myoclonic, clonic, tonic, tonic–clonic, and atonic seizures. A *mixed seizure* is defined as the existence of both generalized and partial seizures in the same patient.

Following standardization proposals published in 1970, out-dated terms such as "petit mal", "grand mal", "Jacksonian", "psychomotor", and "temporal-lobe seizure" have fallen into disuse.

Signs and symptoms

Seizures may cause involuntary changes in body movement or function, sensation, awareness, or behavior. Seizures are often associated with a sudden and involuntary contraction of a group of muscles and loss of consciousness. However, a seizure can also be as subtle as a fleeting numbness of a part of the body, a brief or long term loss of memory, visual changes, sensing/discharging of an unpleasant odor, a strange epigastric sensation, or a sensation of fear and total state of confusion. A seizure can last from a few seconds to status epilepticus, a continuous group of seizures that is often life-threatening without immediate intervention. Therefore seizures are typically classified as motor, sensory, autonomic, emotional or cognitive. After a seizure, while the brain is recovering, there can be a transient loss of memory; usually the short term memory.

In some cases, the full onset of a seizure event is preceded by some of the sensations described above, called Vertiginous epilepsy. These sensations can serve as a warning to the sufferer that a generalized tonic–clonic seizure is about to occur. These "warning sensations" are cumulatively called an *aura*. Also, it is commonly believed among healthcare providers that many seizures, especially those in children, are preceded by tachycardia that frequently persists throughout the seizure. This early increase in heart rate may supplement an aura as a physiological warning sign of an imminent seizure.

Some patients are able to tell when a seizure is about to happen. Some symptoms experienced by the person before a seizure may include dizziness, lightheadedness, tightening of the chest, and some experience things in slow-motion just prior to the seizure. Symptoms experienced by a person during a seizure depend on where in the brain the disturbance in electrical activity occurs. Partial and frontal seizures and focal epileptic discharges tend to happen more during sleep than during wakefulness. In contrast, psychogenic nonepileptic seizures are rare between midnight and 6 a m. and never occur during sleep. Generalized epilepsy but not focal epilepsy is higher in the morning probably reflecting a diurnal variation in cortical excitability. A person having a tonic–clonic seizure may cry out, lose consciousness and fall to the ground, and convulse, often violently. A person having a complex partial seizure may appear confused or dazed and will not be able to respond to questions or direction. Some people have seizures that are not noticeable to others. Sometimes, the only clue that a person is having an absence seizure is rapid blinking, extreme confusion for a few seconds or sometimes into hours.

Causes

Unprovoked seizures are often associated with epilepsy and related seizure disorders.

Causes of *provoked* seizures include:

- sleep deprivation
- cavernoma or cavernous malformation is a treatable medical condition that can cause seizures, headaches, and brain hemorrhages. An MRI can quickly confirm or reject this as a cause.
- arteriovenous malformation (AVM) is a treatable medical condition that can cause seizures, headaches, and brain hemorrhages. An MRI can quickly confirm or reject this as a cause.
- head injury may cause non-epileptic post-traumatic seizures or post-traumatic epilepsy, in which the seizures chronically recur.
- intoxication with drugs, for example aminophylline or local anaesthetics
- normal doses of certain drugs that lower the seizure threshold, such as tricyclic antidepressants
- infection, such as encephalitis or meningitis
- fever leading to febrile convulsions
- metabolic disturbances, such as hypoglycaemia, hyponatremia or hypoxia
- withdrawal from drugs (anticonvulsants, antidepressants, and sedatives such as alcohol, barbiturates, and benzodiazepines,)
- space-occupying lesions in the brain (abscesses, tumors)
- seizures during (or shortly after) pregnancy can be a sign of eclampsia.
- seizures in a person with hydrocephalus may indicate severe shunt failure.
- binaural beat brainwave entrainment may trigger seizures in both epileptics and non-epileptics
- haemorrhagic stroke can occasionally present with seizures, embolic strokes generally do not (though epilepsy is a common later complication); cerebral venous sinus thrombosis, a rare type of stroke, is more likely to be accompanied by seizures than other types of stroke
- multiple sclerosis sufferers may rarely experience seizures

Some medications produce an increased risk of seizures and electroconvulsive therapy (ECT) deliberately sets out to induce a seizure for the treatment of major depression. Many seizures have unknown causes.

Seizures which are provoked are not associated with epilepsy, and people who experience such seizures are normally not diagnosed with epilepsy. However, the seizures described above resemble those of epilepsy both outwardly, and on EEG testing.

Seizures can occur after a subject witnesses a traumatic event. This type of seizure is known as a psychogenic non-epileptic seizure and is related to posttraumatic stress disorder.

Diagnosis

Only about 25 percent of people who have a seizure or develop status epilepticus have epilepsy. It is important to distinguish primary epileptic seizures from secondary causes. Blood tests, lumbar puncture or toxicology screening can be helpful in specific circumstances suggestive of an underlying cause like alcohol or benzodiazepine withdrawal, meningitis or drug overdose, but there is insufficient evidence to support their routine use in the work-up of an adult with an apparently unprovoked first seizure. A 2007 evidence-based review from the American Academy of Neurology and the American Epilepsy Society recommends an electroencephalogram (EEG, brain wave activity) and brain imaging with CT scan or MRI scan in the work-up. MRI is more sensitive in a first apparently unprovoked seizure.

Differentiating an epileptic seizure from other conditions such as syncope can be difficult. A reliable description of a witnessed seizure is the most important factor in determining whether a seizure has occurred.

Physical examination

Most patients are in a postictal state following a seizure. In this state they are drowsy and often confused. There may be signs of other injuries. A small study found that finding a bite to the side of the tongue was very helpful when present: while only a quarter of those with seizures had such a bite (sensitivity of 24%), the finding was very specific for seizures, with only 1% due to other causes (specificity of 99%).

Serum prolactin level

Two meta-analyses have quantified the role of an elevated serum prolactin. The first meta-analysis found that: "If a serum prolactin concentration is greater than three times the baseline when taken within one hour of syncope, then in the absence of test "modifiers":

1. the patient is nine times more likely to have suffered a GTCS as compared with a pseudoseizure positive LR = 8.92 (95% CI (1.31 to 60.91)), SN = 0.62 (95% CI (0.40 to 0.83)), SP = 0.89 (95% CI (0.60 to 0.98))
2. five times more likely to have suffered a GTCS as compared with non-convulsive syncope positive LR 4.60 (95% CI (1.25 to 16.90)), SN = 0.71 (95% CI (0.49 to 0.87)), SP = 0.85 (95% CI (0.55 to 0.98)). "

The second meta-analysis found:

1. "Elevated serum prolactin assay, when measured in the appropriate clinical setting at 10 to 20 minutes after a suspected event, is a useful adjunct for the differentiation of generalized tonic-clonic or complex partial seizure from psychogenic nonepileptic seizure among adults and older children (Level B)."

2. "Serum prolactin assay does not distinguish epileptic seizures from syncope (Level B).
3. "The use of serum PRL assay has not been established in the evaluation of status" epilepticus, repetitive seizures, and neonatal seizures (Level U)."

The serum prolactin level is less sensitive for detecting partial seizures.

EEG

An isolated abnormal electrical activity recorded by an electroencephalography examination without a clinical presentation is called subclinical seizure. They can identify background epileptogenic activity, as well as help identify causes of seizures.

Investigation of underlying cause

Additional diagnostic methods include CT Scanning and MRI imaging or angiography. These may show structural lesions within the brain and heart, but the majority of those with epilepsy show nothing unusual.

As seizures have a differential diagnosis, it is common for patients to be simultaneously investigated for cardiac and endocrine causes. Checking glucose levels, for example, is a mandatory action in the management of seizures as hypoglycemia may cause seizures, and failure to administer glucose would be harmful to the patient. Other causes typically considered are syncope and cardiac arrhythmias, and occasionally panic attacks and cataplexy. In addition, 5% of patients with a positive tilt table test may have seizure-like activity that seems to be due to cerebral hypoxia.

Management

The first aid for a seizure depends on the type of seizure occurring. Generalized seizures will cause the person to fall, which may result in injury. A tonic–clonic seizure results in violent movements that cannot and should not be suppressed. The person should never be restrained, nor should there be any attempt to put something in the mouth. Potentially sharp or dangerous objects should also be moved from the vicinity, so that the individual is not hurt. After the seizure if the person is not fully conscious and alert, they should be placed in the recovery position. Bystanders should remain calm and avoid crowding the person.

It is not necessary to call an ambulance if the person is known to have epilepsy, if the seizure is shorter than five minutes and is typical for them, if it is not immediately followed by another seizure, and if the person is uninjured. Otherwise, or if in any doubt, medical assistance should be sought.

A seizure longer than five minutes is a medical emergency. Relatives and other caregivers of those known to have epilepsy often carry medicine such as rectal diazepam or buccal midazolam in order to rapidly end the seizure.

Safety

A sudden fall can lead to broken bones and other injuries. Children who are affected by frequent drop seizures may wear helmets to protect the head during a fall.

The unusual behavior resulting from the chaotic brain activity of a seizure can be misinterpreted as an aggressive act. This may invoke a hostile response or police involvement, where there was no intention to cause harm or trouble.

A seizure response dog can be trained to summon help or ensure personal safety when a seizure occurs. These are not suitable for everybody. Rarely, a dog may develop the ability to sense a seizure before it occurs.

Prognosis

In adults, after 6 months seizure free, after a first seizure the risk of a subsequent seizure in the next year is less than 20% regardless of treatment.

Chapter 3

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is a rare epileptic disorder that causes frequent violent seizures during sleep. These seizures often involve complex motor movements, such as hand clenching, arm raising/lowering, and knee bending. Vocalizations such as shouting, moaning, or crying are also common. ADNFLE is often misdiagnosed as nightmares. Attacks often occur in clusters and typically first manifest in childhood. There are four known loci for ADNFLE, three with known causative genes. These genes encode various nicotinic acetylcholine receptor α and β subunits CHRNA4, CHRNB2, and CHRNA2.

Autosomal dominant nocturnal frontal lobe epilepsy

OMIM 600513 603204 605375 610353

Signs and symptoms

ADNFLE is a partial epilepsy disorder characterized by brief violent seizures during sleep. Seizures are complex, consisting of arm and leg movements, fist clenching, and vocalizations such as yelling and moaning. These seizures often occur in clusters and can first manifest in childhood. Diagnosis is often initially incorrectly made as nightmares, night terrors, parasomnias and various psychiatric disorders.

Causes

While not well understood, it is believed that malfunction in thalamocortical loops plays a vital role in ADNFLE. The reasons for this belief are threefold. Firstly, thalamocortical loops are important in sleep and the frontal cortex is the origin of ADNFLE seizures. Secondly, both the thalamus and cortex receive cholinergic inputs and acetylcholine receptor subunits comprise the three known causative genes for ADNFLE. Thirdly, K-complex are almost invariably present at the start of seizures.

Pathophysiology

CHRNA4

The first mutation associated with ADNFLE is a serine to phenylalanine transition at position 248 (S248F) according to the Pacific electric ray *Torpedo californica* protein numbering, located in the second transmembrane spanning region of the gene encoding a nicotinic acetylcholine receptor α subunit. Using the numbering based on the human CHRNA4 protein, this mutation is called S280F. Receptors containing this mutant subunit are functional, but desensitize at a much faster pace compared to wild-type only receptors. These mutant containing receptors also recover from desensitization at a much slower rate than wild-type only receptors. Interestingly, these mutant receptors also have a decreased single channel conductance than wild-type and have a lower affinity for acetylcholine. Also importantly, this mutation along with the others in CHRNA4 produce receptors less sensitive to calcium.

The second discovered ADNFLE mutation was also in CHRNA4. This mutation, L259_I260insL, is caused by the insertion of three nucleotides (GCT) between a stretch of leucine amino acids and an isoleucine. As with the S248F mutation, the L259_I260insL mutation is located in the second transmembrane spanning region. Electrophysiological experiments have shown that this mutant is tenfold more sensitive to acetylcholine than wild-type. Calcium permeability, however is notably decreased in mutant compared to wild-type containing receptors. Furthermore, this mutant shows slowed desensitization compared to both wild-type and S248F mutant receptors.

Also located in the second transmembrane spanning region, the S252L mutation has also been associated with ADNFLE. This mutant displays increased affinity for acetylcholine faster desensitization compared to wild-type receptors.

The most recently discovered mutation in CHRNA4 associated with ADNFLE is T265M, again located in the second transmembrane spanning segment. This mutation has been little studied and all that is known is that it produces receptors with increased sensitivity to acetylcholine and has a low penetrance.

15q24

Some families have been shown to not have mutations in CHRNA4 and, furthermore, to show no linkage around it. Instead some of these families show strong linkage on chromosome 15 (15q24) near CHRNA3, CHRNA5, and CHRNB4. Causative genes in this area are still unknown.

CHRNB2

Three mutations have been found in the gene CHRNB2, which encodes an acetylcholine receptor β subunit. Two of these mutations, V287L and V287M, occur at the same amino acid, again in the second transmembrane spanning region. The V287L mutation results in

receptors that desensitize at a much slower rate compared to wild-type. The V287M mutant displays a higher affinity for acetylcholine when compared to wild-type receptors. As with the mutations in CHRNA4, these mutants lead to receptors less sensitive to calcium.

The other known mutation in CHRNB2 is I312M, located in the third membrane-spanning region. Receptors containing these mutant subunits display much larger currents and a higher sensitivity to acetylcholine than wild-type receptors.

CHRNA2

Recently, the I279N mutation has been discovered in the first transmembrane spanning segment of CHRNA2, which encodes a nicotinic acetylcholine receptor α subunit similar to that encoded by CHRNA4. This mutant shows a higher sensitivity to acetylcholine and unchanged desensitization compared to wild-type.

Diagnosis

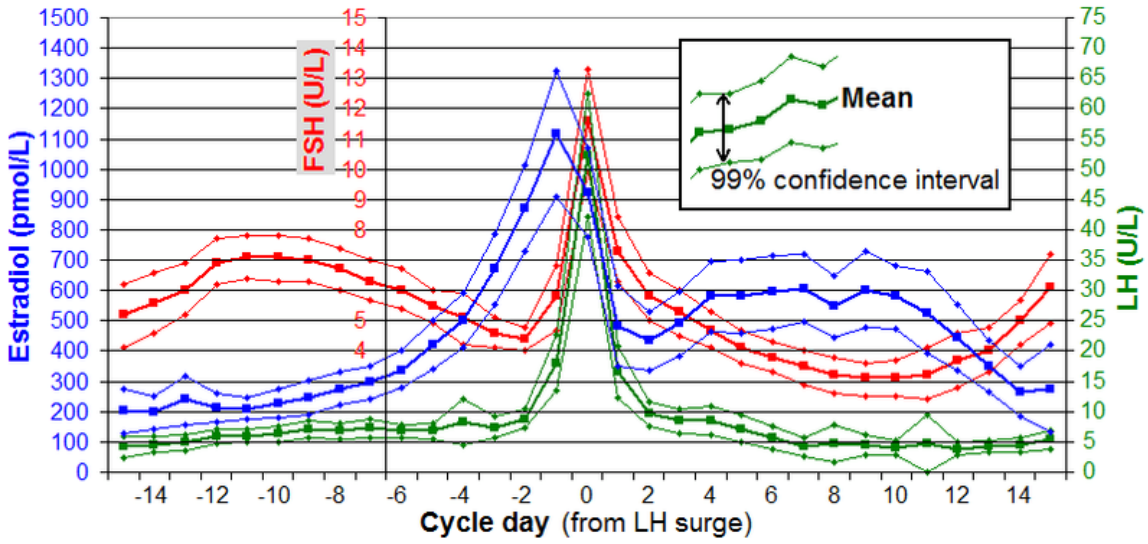
Diagnosis is typically made upon patient history, although EEG recordings can be confirmatory if they occur during attacks.

Treatment/Management

Anti-epileptic drugs are normally used to combat ADNFLE.

Chapter 4

Catamenial Epilepsy

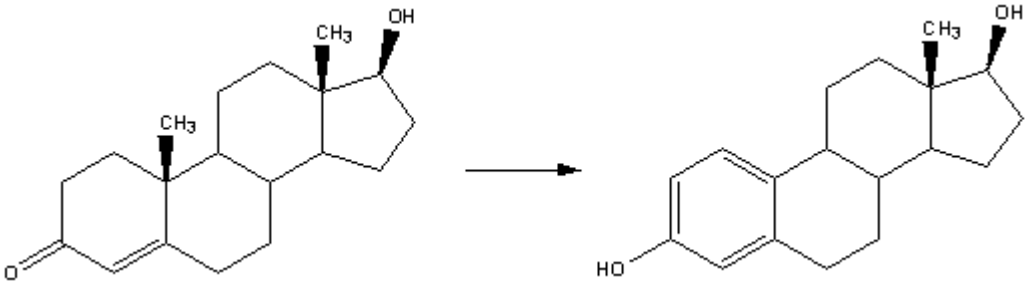


Sex hormones in menstrual cycle

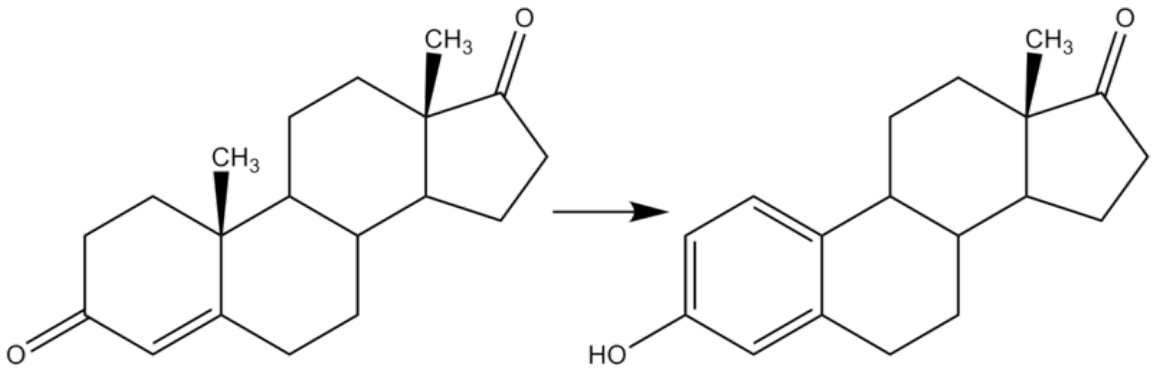
Catamenial epilepsy is a subtype of epilepsy, which is a chronic neurological condition characterized by recurrent seizures. Catamenial epilepsy is a subset of this population, which includes women of whom their seizure exacerbation is aligned with their menstrual cycle. Women with catamenial epilepsy are unusually sensitive to endogenous hormonal changes. This seizure exacerbation has a statistically significant positive correlation to serum estradiol/estrogen levels and ratios.

Since at least the Greek times, there has been documented study of women with epilepsy and its correlation to the menstrual cycle. These patterns can easily be seen by charting out menses against seizure occurrence and type.

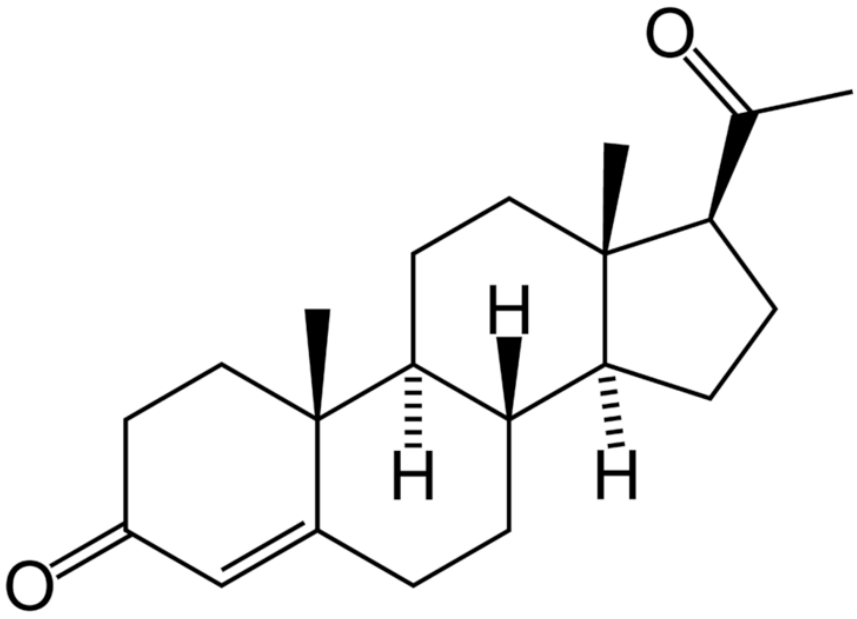
Pathophysiology



Conversion of testosterone to estradiol



Aromatase converts androstenedione to estrone



Progesterone

Our understanding of the major gonadal hormones, estrogen, progesterone, and testosterone, has significantly increased in the last century. These hormones are synthesized in various locations in the body, including the ovaries, adrenal gland, liver, subcutaneous fat, and brain. There is considerable research showing that these steroidal hormones take part in an important role in the pathophysiology of epilepsy. Broadly defined, estrogen and its many forms are thought to be "proconvulsant," whereas progesterone is thought to be "anticonvulsant."

Estrogen (Estradiol, Estrone, Estriol)

Estrogen can be found in the female body in various forms, all of which affect women with catamenial epilepsy. Estrone (E1), estradiol (E2), and estriol (E3) are the three principal circulating estrogens in the body. These three forms influence neuronal excitability, but very little is known about their inter-hormone interactions, the relative concentrations and ratios of E1/E2/E3 and how that may influence the seizure frequency behavior in women with epilepsy. In normally menstruating women, serum estradiol levels are typically present by day 10 of the menstrual cycle, and persist until ovulation.

- *Estrone*'s main source is adipose tissue (subcutaneous fat), where it is formed by aromatization of androstenedione. Estrone is the major estrogen after menopause, and this hormone may be very influential in seizure control of the catamenial woman if she is severely overweight or obese.

- *Estradiol* represents the most prolific estrogen ligand receptor in the female body, particularly in non-pregnant females, and is a more effective activator of estrogen receptor function than estrone or estriol. Estradiol directly increases NMDA mediated receptors of glutamate activity at the neuronal membrane. Through this mechanism hippocampal pyramidal neurons CA1 are excited, and a repetitive firing response is induced. Dendritic spine density on CA1 hippocampal pyramidal cells is dependent upon estradiol levels, showing a direct correlation during normal fluctuations during the menstrual cycle. Estradiol has been shown to apply its affects on dendritic spine density of hippocampal cells by using a mechanism that requires activation of NMDA receptors. Furthermore, Herzog postulates that, "estradiol may thus further increase excitatory input to the CA1 neurons." Through many animal models, as well as human-use of estrogen-based hormone replacement therapy, estrogens have been seen to increase the excitability of neurons, leading to a decreased seizure threshold. In female adult rat experimental trials, the limbic seizure threshold fluctuates inversely to estradiol levels during the estrous cycle.

- *Estriol* is known to inhibit GABA and to promote kindling and epileptiform discharges. Estriol is only produced in significant quantities during pregnancy via placental aromatization of fetal androgen, however it can also be synthesized in smaller quantities (non-pregnancy) in the liver by hydroxylation of estrone.

Progesterone

Similar to estrogen, progesterone receptors bind several molecules other than only progesterone. Progestagens are group of natural non-synthetic hormones, including progesterone, which binds to progesterone receptors. Other than progesterone, progestagens have several neuroactive metabolites, most notably allopregnanolone. Progesterone has been shown to lower the number of estrogen receptors, and thus act as an antagonist to estrogen actions. In trials, both progesterone and allopregnanolone administration have shown a neuroprotective effect on hippocampal neurons in seizure models induced by kainic acid.

Classification

The proper classification for catamenial epilepsy has been debatable for several decades. Researchers have defined catamenial epilepsy from the broadest definition of a "greater than" approach indicating an increase in seizure frequency or severity during any specific phase of the menstrual cycle, to a "sixfold increase" in average daily seizure frequency during specific times in the cycle. In recent years, Herzog's 1997 proposal of an admittedly arbitrary "twofold" increase has generally been accepted: Perimenstrual (C1), Periovulatory (C2), and Luteal (C3). These three classifications are based upon serum estradiol:progesterone ratio, and a 24-34 day menstrual cycle in which menses begins on day 1, and ovulation occurs 14 days prior to menstruation. By this measure, approximately one third of women with epilepsy would be classified under the designation of catamenial epilepsy.

Perimenstrual "C1"

Perimenstrual classification (in normal cycles, days -3 to 3 of menstruation) is associated with a twofold or greater increase in average daily seizure occurrence during the menstrual phase (M) compared to the follicular (F) and luteal (L) phases. The menstrual phase is characterized by drastic decreases in progesterone and estrogen levels. The estradiol:progesterone ratio is highest during the days before menstruation (C1) and ovulation (C2). Perimenstrual seizure exacerbation has been recognized as the withdrawal of the protective effects of progesterone. In a 2009 study, it was found that patients with C1 pattern of catamenial epilepsy had overall lower progesterone levels than healthy controls during the M phase.

Periovulatory "C2"

Periovulatory classification (in normal cycles, days 10 to -13) is associated with a twofold or greater increase in average daily seizure occurrence during the O phase compared to the F and L phases. The ovulatory phase is characterized by a surge of estrogen before ovulation, while an associated progesterone surge does not occur until ovulation actually occurs. This estrogen effect, without a corresponding progesterone surge of protection, intensifies seizure events.

Luteal “C3”

Luteal classification (abnormal or inadequate luteal phase cycles, days 10 to 3) is associated with a twofold or greater increase in average daily seizure occurrence during the O, L and M phases. Anovulatory females do not typically have a midcycle surge of progesterone, but still experience a surge in estrogen. These women have abnormally low progesterone levels during the O, L and M, regardless of whether ovulation occurs. In study by El-Khayat et al., it was found that patients with C3 pattern of catamenial epilepsy had overall lower progesterone levels than healthy controls during the L phase of the menstrual cycle.

Menopause

During menopause, there are drastic changes in the production of gonadal hormones. Most of the reproductive hormones, including the estrogens, progesterone and testosterone, diminish initially (perimenopause), becoming irregular, often showing wide and unpredictable fluctuations. As menopause progresses, there is cessation of estrogen production by the ovaries. Rosciszewska was one of the first researchers to report an increased risk of seizures during perimenopause, but found a marked decreased risk of seizures during menopause if there was a catamenial relationship. This difference may be associated with the radical fluctuations of estradiol and progesterone during the perimenopausal period than what is experienced during the menopausal period and menstrual cycles of reproductive years. Recall that estrone is the predominant estrogen present during menopause (from subcutaneous fat), and little is known about the effect of estrone specifically on epilepsy. Women with epilepsy who do not follow a catamenial pattern may have an unpredictable increase or decrease in seizure activity in perimenopause and menopause, but women with catamenial epilepsy typically follow a more predictable pattern.

Hormone replacement therapy

The use of hormone replacement therapy (HRT), such as Premarin, has shown severe negative effects on the seizure patterns of women with catamenial epilepsy. During perimenopause, women with catamenial epilepsy generally experience an increase in seizure frequency, and HRT use does not change this likelihood. However HRT use after perimenopause has been significantly associated with an increase in seizure frequency and severity. Women progressing through peri- and post-menopause using HRT may be in greater need of anticonvulsant medication monitoring to maintain or reduce seizure occurrence. These same results have not been seen in laboratory counterparts. Adult female rats that have been ovariectomized, a parallel state to menopause, show increased seizure frequency overall. There are, however, several factors that could explain this difference, including ovariectomized rats do not have the analogous brain hormones milieu as menopausal women. Several studies following HRT use in women with catamenial epilepsy have demonstrated more influencable data than animal models, in this case.

Treatment Methods

Several treatment methods have been determined exclusively for women with catamenial epilepsy. A great majority of these therapies include progestagens (naturally occurring) or progestins (synthetic progestagen). Drug interactions are an important factor when using progesterone therapy, as many antiseizure medications augment hepatic metabolism of gonadal steroids, and increase serum protein binding to hormones. There are many unfortunate side effects frequently seen in progesterone therapy usage, including vaginal dryness, dyspareunia, osteoporosis, and cardiovascular disease.

- *Cyclic progesterone therapy* supplements the patient with natural progesterone during the luteal phase when progesterone is normally low, and gradually reduces the supplementation premenstrually.

- *Suppressive progestin therapy* intends to suppress the menstrual cycle entirely by using injectable progestins or gonadotropin-releasing hormones (GnRH). GnRH basically mimics an ovary-free environment in the female, which is characteristic of the lack of menstrual cycle during menopause.

Chapter 5

Generalized Epilepsy with Febrile Seizures Plus

Generalized epilepsy with febrile seizures plus (GEFS+) is a syndromic autosomal dominant disorder where afflicted individuals can exhibit numerous epilepsy phenotypes. GEFS+ can persist beyond early childhood (i.e., 6 years of age). GEFS+ is also now believed to encompass three other epilepsy disorders: severe myoclonic epilepsy of infancy (SMEI), which is also known as Dravet's syndrome, borderline SMEI (SMEB), and intractable epilepsy of childhood (IEC). There are at least five types of GEFS+, delineated by their causative gene. Known causative genes are the sodium channel α subunit genes SCN1A and SCN2A, an associated β subunit SCN1B, and a $GABA_A$ receptor γ subunit gene, GABRG2. Penetrance for this disorder is estimated at approximately 60%.

GEFS+	
ICD-10	G40.3
OMIM	604233 609800 607208

Symptoms and signs

Individuals with GEFS+ present with a range of epilepsy phenotypes. These include febrile seizures that end by age 6 (FS), such seizures extending beyond age 6 that may include afebrile tonic-clonic, myoclonic, absence, atonic seizures and myoclonic-astatic epilepsy. Individuals may also present with SMEI, which is characterized by generally tonic-clonic seizures, impaired psychomotor development, myoclonic seizures, ataxia, and poor response to many epileptic drugs.

Diagnosis

Pathophysiology

Type 1

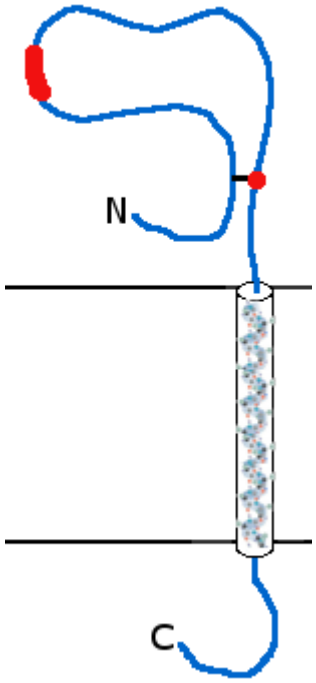


Figure 1. Schematic structure of SCN1B with GEFS+ type 1 mutations shown in red. The single red spot is the C121W mutant at the disulfide bond (black) and the stretch of red the I70_E74del mutation.

GEFS+ type 1 is a subtype of GEFS+ in which there are mutations in SCN1B, a gene encoding a sodium channel β subunit. The β subunit is required for proper channel inactivation. There are two known mutations in SCN1B that lead to GEFS+ (Figure 1). The first and best characterized of these mutations is C121W. This mutation alters a cysteine involved in a disulfide bond in the extracellular N-terminus of the protein. This extracellular region is similar to the cell adhesion molecule contactin and other cell adhesion molecules. It is believed that the disulfide bond disrupted by the C121W mutation is required for the proper folding of this N-terminus motif. Coexpression of SCN1B with sodium channel α subunits in oocytes and other cells results in channels that inactivate more slowly. Expression of C121W mutant along with wild-type α subunits produces current indistinguishable from that through α subunits alone. Further investigation of this mutation has indicated that it results in decreased frequency dependent rundown and, thus, likely hyperexcitability when compared to cells expressing the wild-type subunit. Interestingly, this mutation also disrupts the subunit's ability to induce cellular aggregation. The importance of this last fact is unclear, though it is presumed that proper channel aggregation within cells and cell-cell contact are required for normal neuronal function.

A second mutation has been found in one kindred with GEFS+ type 1. This mutation is in a splice acceptor site of exon 3. The loss of this acceptor site reveals a downstream cryptic acceptor site and a protein missing 5 amino acids in the N-terminus (I70_E74del). This mutation has not been further characterized.

Type 2

A second subtype of GEFS+, type 2, is the result of mutations in SCN1A, a gene encoding a sodium channel α subunit. There are currently almost 90 known mutations in the SCN1A gene throughout the entirety of the channel (see table 1). These mutations result in almost any imaginable mutation type in the gene, short of duplications. The results of these mutations are highly variable, some producing functional channels while others result in non-functional channels. Some functional channels result in membrane hyperexcitability while others result in hypoexcitability. Most of the functional mutant channels result in hyperexcitability due to decreased frequency dependent rundown. An example of this is the D188V mutation. A 10 Hz stimulation of wild-type channels causes current to decrease to approximately 70% of maximum whereas the same stimulation of mutant channels results in rundown to 90% of maximum. This is causes by an expedited recovery from inactivation for mutant channels versus wild-type. The D188V mutant, for example, recovers to 90% maximal current in 200ms while wild-type channels are unable to recover to this degree in >1000ms. Some other functional mutations that lead to hyperexcitability due so by other means, such as decreasing the rate of entrance into the slow inactivated state.

Some of the other functional mutations are believed to result in hypoexcitability. The R859C mutation, for example, has a more depolarized voltage dependence of activation, meaning that the membrane must be more depolarized for the channel to open. This mutant also recovers more slowly from inactivation. The nonfunctional channels are believed to produce similar changes in cell excitability. Likewise, many of the nonsense mutations likely result in nonfunctional channels and hypoexcitability, though this has yet to be tested. It is also unclear how this membrane hypoexcitability leads to the GEFS+ phenotype.

Table 1. Summary of mutations found in patients diagnosed with GEFS+ type 2

Mutation	Region	Functional?	Excitability Prediction	References
R101Q	N-Terminus			
S103G	N-Terminus			
T112I	N-Terminus			
V144fsX148	D1S1			
G177fsX180	D1S2-S3			
D188V	D1S2-S3	Yes	Hyperexcitable	
F190R	D1S3			
S219fsX275	D1S4			
R222X	D1S4			

G265W	D1S5		
G343E	D1S5-S6		
E435X	D1-2		
R613X	D1-2		
R701X	D1-2		
P707fsX715	D1-2		
R712X	D1-2		
Q732fsX749	D1-2		
Y779C	D2S1		
T808S	D2S2	Yes	Hyperexcitable
R859C	D2S4	Yes	Hypoexcitability
T875M	D2S4	Yes	Hyperexcitable*
F902C	D2S5	No	Hypoexcitable
S914fsX934	D2S5-6		
M924I	D2S5-6		
V934A	D2S5-6		
R936C	D2S5-6		
R936H	D2S5-6		
W942X	D2S5-6		
R946fsX953	D2S5-6		
W952X	D2S5-6		
D958fsX973	D2S5-6		
M960V	D2S5-6		
G979R	D2S6	No	Hypoexcitable
V983A	D2S6	Yes	Hyperexcitable
N985I	D2S6		
L986F	D2S6	No	Hypoexcitable
N1011I	D2-3	Yes	Hyperexcitable
K1100fsX1107	D2-3		
L1156fsX1172	D2-3		
W1204R	D2-3	Yes	Hyperexcitable
W1204X	D2-3		
R1213X	D2-3		
S1231R	D3S1		
S1231T	D3S1		
F1263L	D3S2		
W1284X	D3S3		
L1345P	D3S5		

V1353L	D3S5	No	Hypoexcitable
Splice	Exon 4		
R1397X	D3S5-6		
R1407X	D3S5-6		
W1408X	D3S5-6		
V1428A	D3S6		
S1516X	D3-4		
R1525X	D3-4		
M1549del	D4S1		
V1611F	D4S3	Yes	Hyperexcitable
P1632S	D4S3	Yes	Hyperexcitable
R1635X	D4S4		
R1648C	D4S4	Yes	Hyperexcitable
R1648H	D4S4	Yes	Hyperexcitable
I1656M	D4S4	Yes	
R1657C	D4S4	Yes	Hypoexcitable
F1661S	D4S4	Yes	Hyperexcitable
L1670fsX1678	D4S4-5		
G1674R	D4S4-5	No	Hypoexcitable
F1682S	D4S5		
Y1684C	D4S5		
A1685V	D4S5	No	Hypoexcitable
A1685D	D4S5		
T1709I	D4S5-6	No	Hypoexcitable
D1742G	D4S5-6		
G1749E	D4S6	Yes	Hypoexcitable
F1756del	D4S6		
F1765fsX1794	D4S6		
Y1771C	D4S6		
1807delMFYE	C-Terminus		
F1808L	C-Terminus	Yes	Hyperexcitable
W1812G	C-Terminus		
F1831S	C-Terminus		
M1841T	C-Terminus		
S1846fsX1856	C-Terminus		
R1882X	C-Terminus		
D1886Y	C-Terminus	Yes	Hyperexcitable
R1892X	C-Terminus		

R1902X	C-Terminus
Q1904fsX1945	C-Terminus

* Results are dependent on experimental paradigm

Type 3

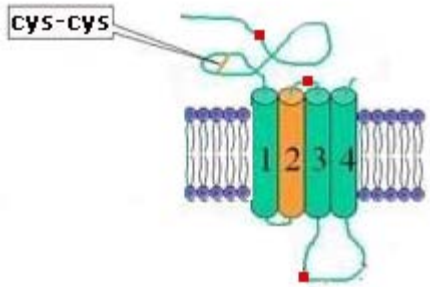


Figure 2. Schematic structure of GABRG2 with the GEFS+ type 3 mutations noted in red.

Patients with GEFS+ type 3 have mutations in the GABRG2 gene, which encodes the $GABA_A$ γ2 subunit (figure 2). The first mutation discovered in GABRG2 was K289M, in the extracellular region linking membrane-spanning domains M2 and M3. Oocytes injected with α1, β2, and γ2 subunits produce large GABA inducible currents whereas those injected with K289M mutant instead of wild-type subunits produce currents much smaller (about 10% of wild-type). This abnormal current is not the result of non-incorporation of mutant subunits since mutant containing receptors are still sensitive to benzodiazepines, a property for which functional γ subunits are required. Because of these results, it is believed that the GEFS+ phenotype in these individuals is a result of hyperexcitability.

Concurrent with the previous mutation, a second group found a second mutation in GABRG2 associated with GEFS+. This mutation, R43Q, is located in the one of two benzodiazepine binding-sites located in the extracellular N-terminus. Benzodiazepines, such as Diazepam, potentiate GABA induced current. This potentiation is abolished in cells expressing the R43Q mutant subunit instead of the wild-type γ subunit. This mutation does not affect the subunit's ability to coassemble into function receptors as it still confers resistance to GABA current blockade by zinc. As with the previous mutation, this mutation is expected to result in neuronal hyperexcitability.

The final known GEFS+ type 3 mutation is a nonsense mutation, Q351X, located in the intracellular region linking the third and fourth membrane spanning segments. When this mutant subunit is expressed in cells with wild-type α and β subunits it produces non-functional receptors. Since wild-type α and β subunits expressed alone are able to produce GABA inducible current this indicates that the mutation either prevents both coassembly of the mutant and wild-type subunits but also coassembly of the wild-type α

and β subunits or prevents proper trafficking of the formed receptor to the membrane. Fusion of GFP onto this mutated subunit has indicated that it is localized to the endoplasmic reticulum instead of the cell membrane. As with other known GEFS+ type 3 mutation, Q351X likely results in neuronal hyperexcitability.

SCN2A mutations

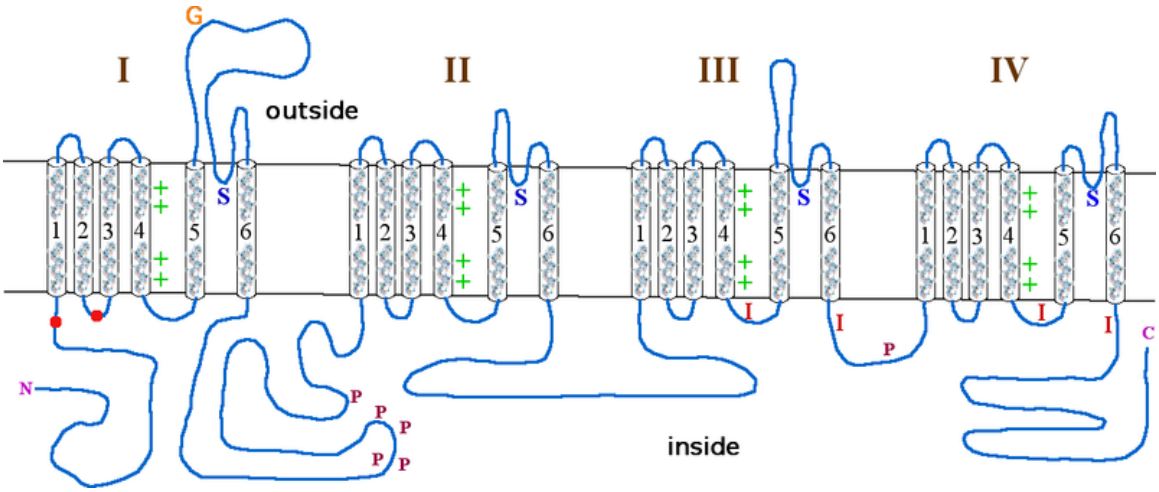


Figure 3. Schematic structure of SCN2A with GEFS+ associated mutation positions indicated by red dots.

The final type of GEFS+ is caused by mutations in the SCN2A gene, which encodes a sodium channel α subunit. The first associated mutation in this gene is R187W, located on the intracellular region linking membrane spanning units two and three in the first domain (D1S2-S3, figure 3). Patients with this mutation have both febrile and afebrile seizures. Electrophysiological examination of this mutant revealed that it increases the time constant for inactivation, presumably increasing sodium current and leading to hyperexcitability. However, this mutation also yields channels that inactivate at more hyperpolarized potentials relative to wild-type channels, indicative of hypoexcitability. Whether the end result on membrane excitability of this mutation is hyperexcitability or hypoexcitability is, as yet, unclear.

The second known mutation in SCN2A associated with GEFS+ is R102X. This mutation is located in the intracellular N-terminus (figure 3) and results in SMEI in patients. The result of this mutation is completely non-functional channels and membrane hypoexcitability. Interestingly, the truncated mutant protein also seems to cause wild-type channels to inactivate at more hyperpolarized potentials, indicating that it also acts in a dominant negative manner.

Treatment/Management

Children and Adults with Dravet syndrome experience multiple seizure types that are resistant to most anti-epileptic medications. Currently, the evidence supports the use of

"rational polytherapy" which consists of a step-wise introduction of medications that have been shown to improve seizure control in patients with Dravet syndrome until the patient either responds favorably or experiences unacceptable side effects. It must be emphasized that significant differences exist between countries with regard to drug dose preferences and availability of anti-epileptic medications.

The following medications have been shown to benefit patients with Dravet syndrome:

- divalproex sodium and derivatives (Depakote, Depakene,Epilim, Epival, Micropakine)
- topiramate (Topamax)
- stiripentol (Diacomit)
- clobazam (Frisium, Urbanyl)
- clonazepam (Klonipin, Rivotril)
- levetiracetam (Keppra)
- bromides

The following medications may aggravate seizures in Dravet syndrome:

- lamotrigine (Lamictal)
- phenytoin (Dilantin, Epanutin)
- fosphenytoin (Cerebyx, Prodilantin)
- carbamazepine (Tegretol, Calepsin, Cargagen, Barbatrol, Epitol, Finlepsin, Sirtal, Stazepine)
- oxcarbazepine (Trileptal)
- vigabatrin (Sabril, Sabrilan, Sabrilex)

Non-pharmacologic therapy with the ketogenic diet has been shown to improve seizure control in a significant percentage of children with Dravet syndrome.

Focal resective surgery is usually not helpful as SMEI is a systemic disorder without identifiable focal pathology.

Epidemiology

Febrile seizures affect approximately 6% of the population.

Chapter 6

Frontal Lobe Epilepsy

Frontal lobe epilepsy, or FLE, is a neurological disorder that is characterized by brief, recurring seizures that arise in the frontal lobes of the brain, often while the patient is sleeping. It is the second most common type of epilepsy after temporal lobe epilepsy (TLE), and is related to the temporal form by the fact that both forms are characterized by the occurrence of partial (focal) seizures. Partial seizures occurring in the frontal lobes can occur in one of two different forms: either simple partial seizures (that do not affect awareness or memory) or complex partial seizures (that affect awareness or memory either before, during or after a seizure). The symptoms and clinical manifestations of frontal lobe epilepsy can differ depending on which specific area of the frontal lobe is affected.

The onset of a seizure may be hard to detect since the frontal lobes contain and regulate many structures and functions about which relatively little is known. Due to the lack of knowledge surrounding the functions associated with the frontal lobes, seizures occurring in these regions of the brain may produce unusual symptoms which can often be misdiagnosed as a psychiatric disorder, non-epileptic seizure or a sleep disorder.

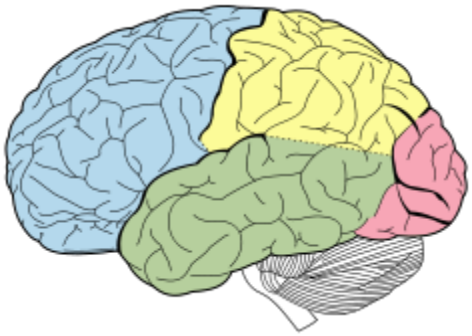
During the onset of a seizure, the patient may exhibit abnormal body posturing, sensorimotor tics, or other abnormalities in motor skills. In rare cases, uncontrollable laughing or crying may occur during a seizure. Afflicted persons may or may not be aware that they are behaving in an abnormal manner, depending on the patient and type of seizure. A brief period of confusion known as a postictal state may sometimes follow a seizure occurring in the frontal lobes. However, these postictal states are oftentimes undetectable and generally do not last as long as the periods of confusion following seizures that occur in the temporal lobes.

There are a variety of different causes of frontal lobe epilepsy ranging from genetics to head trauma that result in lesions in the frontal lobes. Although frontal lobe epilepsy is often misdiagnosed, tests such as prolonged EEG monitoring and/or a MRI scan of the frontal lobes can be administered in order to reveal the presence of a tumor or vascular malformation. Unlike most epileptic EEGs, the abnormalities in FLE EEGs precede the physical onset of the seizure and aid in localization of the seizure's origin. Medications such as anticonvulsants can typically control the onset of seizures, however, if medications are ineffective the patient may undergo surgery to have focal areas of the frontal lobe removed.

Anatomy of Frontal Lobe Cortex

Due to the difference in brain processing and function as well as various surface anatomy landmarks, the frontal lobes have traditionally been divided into two major areas known as the precentral cortex and prefrontal cortex.

Brain: Frontal lobe



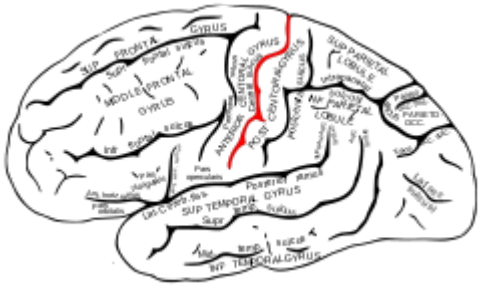
Frontal lobe

Temporal lobe

Parietal lobe

Occipital lobe

Principal fissures and lobes of the cerebrum viewed laterally. (Frontal lobe is blue.)



Lateral surface of left cerebral hemisphere, viewed from the side. Red line indicates the central sulcus.

Latin	*lobus frontalis*
Gray's	*subject #189 821*
NeuroNames	*hier-29*

NeuroLex ID *birnlex_4035*

Precentral Cortex

The precentral cortex is an area of the frontal cortex that is located directly anterior to the central sulcus and includes both the primary motor cortex and the supplementary motor area. Inputs that project to both of these areas arise from a variety of locations in the brain that integrate sensory stimuli including the primary motor cortex, the thalamus and corticospinal projections. These two areas along with several other main functional areas control both the preparation of motor movement as well as the execution of movements. These main functional areas are crucial to the development of the motor related symptoms associated with frontal lobe epilepsy focally when seizures are located within these defined areas. The major functional areas include:

- **Primary Motor Cortex**
  - Contains large neurons that project axons down to the spinal cord where they synapse onto alpha motor neurons. These neurons are involved in the planning of motor movements and the refining of motor movements based on sensory inputs that are received from the cerebellum.

- **Supplementary motor area**
  - Area anterior to the primary motor cortex that is involved in planning complex motor movements and coordinating movements along both hands. The main inputs for this area are received from the thalamus.

- **Frontal eye field**
  - The frontal eye field is a posterior part of the middle frontal gyrus and is involved in the control of saccadic, contralateral and conjugate eye movement. This area receives its main inputs from both the occipital cortex and dorsal thalamus.

- **Broca's Area**
  - Controls the motor movements of both the tongue and larynx that enables speech formation. This area receives direct inputs from the primary motor area as well as Wernicke's area located in the temporal lobe.

Prefrontal Cortex

The prefrontal cortex, the most anterior region of the brain, comprises several key areas that are particularly important for higher mental functions that control various aspects of human personality including anticipation and planning, initiative/judgement, memory and the control of decision making. Damage or lesions to this region of the brain can result in major changes in personality. A classic example is Phineas Gage, who exhibited a change in behavior after one or both frontal lobes were destroyed by a large iron bar accidentally driven through his head (though Gage did not exhibit the aggression, antiosocial behavior, or loss of impulse control sometimes reported in patients with similar injuries).

There are two main regions of the prefrontal cortex that each control various aspects of behavior and personality:

- **Dorsolateral Prefrontal Cortex**
  - This area is associated with the impairment of the cognitive abilities that control and regulate behavior and long term memory formation (especially relating to procedural sequence memory) when either brain damage or a lesion is present.

- **Orbitofrontal Cortex**
  - The orbitofrontal cortex has similar functions as the dorsolateral prefrontal cortex but is thought to be mainly responsible for the ability to make choices and determine right from wrong.

Symptoms

Epileptic symptoms are frequently the product of the spread of overactivation occurring within one central foci that travels to lateral brain regions thereby causing an array of symptoms. Due to the massive amount of diversity in both the cognitive and motor functions that occur within the frontal lobes, there is an immense variety in the types of symptoms that can arise from epileptic seizures based on the side and topography of the focal origin. In general these symptoms can range anywhere from asymmetric and abnormal body positionsing to repetitive vocal outburts and repetitive jerking movements. The symptoms typically come in short bursts that last less than a minute and often occur while a patient is sleeping. In most cases, a patient will experience a physical or emotional Aura of tingling, numbness or tension prior to a seizure occurring. Fear is associated with temporal and frontal lobe epilepsies, but in FLE the fear is predominantly expressed on the person's face whereas in TLE the fear is subjective and internal, not perceptible to the observer.

Tonic posture and clonic movements are common symptoms among most of the areas of the frontal lobe, therefore the type of seizures associated with frontal lobe epilepsy are commonly called tonic-clonic seizures. Dystonic motor movements are common to both TLE and FLE, but are usually the first symptom in FLE episodes where they are quite brief and do not affect consciousness. The seizures are complex partial, simple partial, secondarily generalized or a combination of the three. These partial seizures are often misdiagnosed as psychogenic seizures. A wide range of more specific symptoms arise when different parts of the frontal cortex are affected.

- **Supplementary motor area (SMA)**
  - The onset and relief of the seizure are quite abrupt.
  - The tonic posturing in this area is unilateral or asymmetric between the left and right hemispheres. A somatosensory aura frequently precedes many large motor and vocal symptoms and most often the afflicted person is responsive.

- *Motor symptoms*: Facial grimacing and complex automatisms like kicking and pelvic thrusting
- *Vocal symptoms*: Laughing, yelling, or speech arrest.

- **Primary motor cortex**
  - The primary motor cortex has jacksonian seizures that spread to adjacent areas of the lobe which often trigger a second round of seizures originating in another cortical area. The seizures are much simpler than those that originate in the SMA and are usually clonic or myoclonic movements with speech arrest. Some dystonic or contralateral adversive posturing may also be present.

- **Medial frontal, cingulate gyrus, orbitofrontal, or frontopolar regions**
  - Motor symptoms of seizures in this area are accompanied by emotional feelings and viscerosensory symptoms. Motor and vocal agitation are similar to that of the SMA with short repetitive thrashing, pedaling, thrusting, laughing, screaming and/or crying.
  - This is some of what can cause the misdiagnosis of a psychological disorder.

- **Dorsolateral cortex**
  - This area does not seem to have many motor symptoms beyond tonic posturing or clonic movements. Contralateral or less commonly ipsilateral head turn and eye deviation are commonly associated with this area as well.

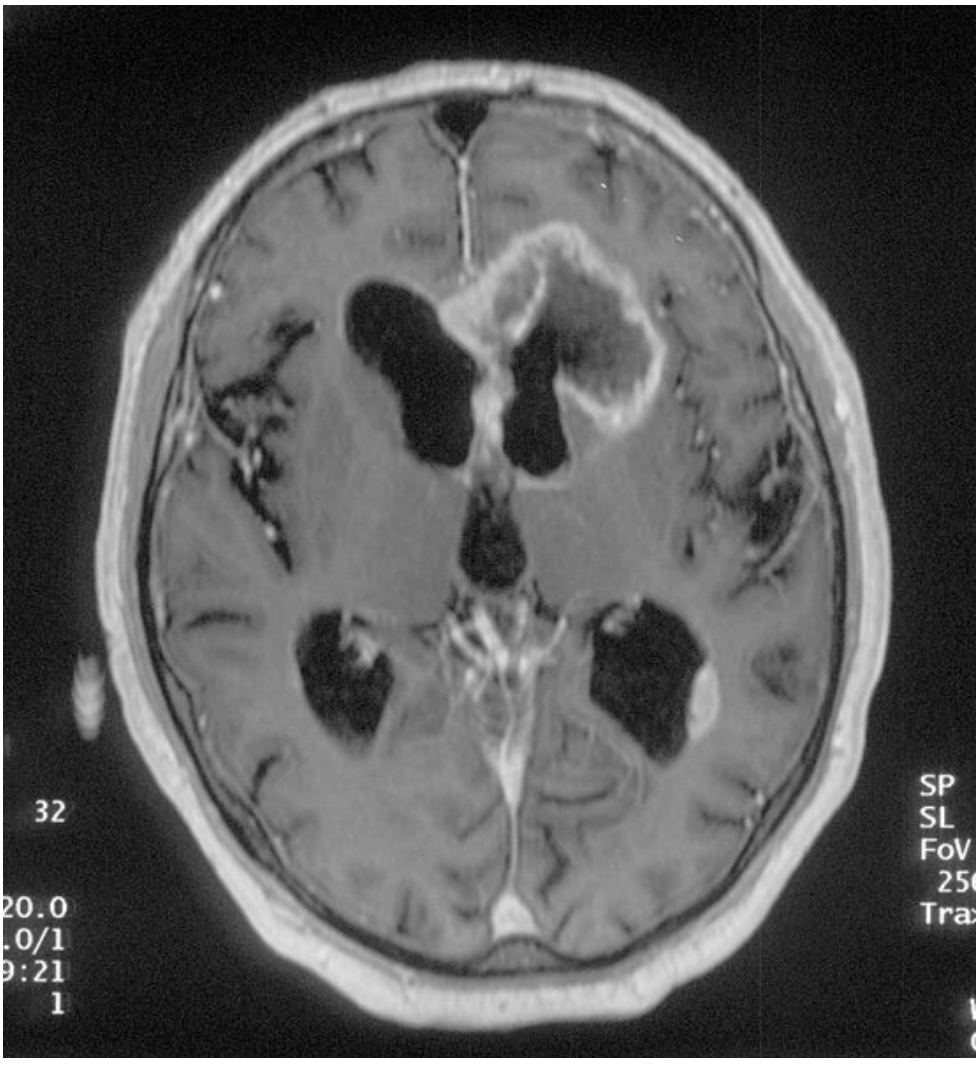
- **Operculum**
  - Many of the symptoms associated with this area involve the head and digestive tract: swallowing, salivation, mastication and possibly gustatory hallucinations. Preceding the seizure the person is fearful and often has an epigastric aura. There is not much physical movement except clonic facial movements. Speech is often arrested.

Common Misdiagnoses

Episodes that include complex hyperactivity of the proximal portions of the limbs that lead to increased overall motor activity are called hypermotor seizures. When associated with bizarre movements and vocalizations these seizures are often misdiagnosed as pseudoseizures or other episodic movement disorders such as psychogenic movement disorders, familial paroxysmal dystonic choreoathetosis, paroxysmal kinesogenic choreoathetosis, or episodic ataxia type 1. Hypermotor seizure in children are often confused with pavor nocturnus (night terrors). Paroxysmal nocturnal dystonia or hypnogenic paroxysmal dystonia are other names given to describe FLE symptoms but are simply just FLE.

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE) is the best understood form of frontal lobe epilepsy but is often misdiagnosed as sleep apnea. Both disorders are characterized by awakening during the night which leads to daytime sleepiness. Some symptoms of sleep apnea overlap with those of ADNFLE, such as sudden awakening accompanied by a feeling of choking and on occasion motor activity which makes diagnosis difficult based on symptoms alone. Video surveillance as well as EEG is occasionally needed to differentiate between the two disorders. It has been reported that sleep apnea might be associated with epilepsy which would account for some of the misdiagnoses.

Causes



An MRI image of a brain with an invasive, multilocular tumor in the left Frontal lobe of the brain.

The origins of frontal lobe seizures range from tumors to head trauma to genetics. Tumors account for about one third of all frontal lobe epilepsy cases. Low-grade tumors

such as gangliogliomas, low-grade gliomas, and epidermoid tumors are most common, but many high-grade tumors were most likely once involved with seizures. Other lesions on the frontal lobe such as hamartomas and nodular heterotopias can cause frontal lobe symptoms as well. Birth defects such as vascular malformation are known to cause seizures, especially arteriovenous malformations and cavernous angiomas. Head trauma frequently causes damage to the frontal lobe and can cause seizures directly or indirectly through gliosis. Seizures originating directly from head trauma usually occur within a few months, but occasionally they can take years to manifest. On occasion encephalitis can cause frontal lobe seizures but it is most often associated with temporal lobe affliction. The main genetic cause of frontal lobe epilepsy is an autosomal dominant disease called Autosomal Dominant Nocturnal Frontal Lobe Epilepsy, which involves mutations in 2 nicotinic acetylcholine receptor genes. A genetic mutation on chromosome 22 has also been associated with another genetic form of the disorder.

Frequency

Epilepsy is a relatively common disorder, affecting between 0.5-1% of the population, and frontal lobe epilepsy accounts for about 1-2% of all epilepsies. The most common subdivision of epilepsy is symptomatic partial epilepsy, which causes simple partial seizures, and can be further divided into temporal and frontal lobe epilepsy. Although the exact number of cases of frontal lobe epilepsy is not currently known, it is known that FLE is the less common type of partial epilepsy, accounting for 20-30% of operative procedures involving intractable epilepsy. The disorder also has no gender or age bias, affecting males and females of all ages. In a recent study, the mean subject age with frontal lobe epilepsy was 28.5 years old, and the average age of epilepsy onset for left frontal epilepsy was 9.3 years old whereas for right frontal epilepsy it was 11.1 years old.

Social Impacts and Quality of Life

Epilepsy has a substantial impact on the quality of life of the individuals that are afflicted with it. Physicians and researchers are coming to understand that the impact on the quality of life of the patient is as important as the effects of the seizures. Quality of life questionnaires and other assessment tools have been created to help quantify quality of life for individual patients. They consider such factors as physical health (including numbers and severity of seizures, medication side effects etc.), mental health, social relationships, lifestyle, role activities and life fulfillment. A Center for Disease Control study reported that seizure sufferers were more likely to have lower education levels, higher unemployment, higher levels of pain, hypersomnia/insomnia, increased psychological distress and social isolation/connection issues. Some of the issues which impact quality of life for epileptics are: ability to drive and travel, the ability to date, marry and have children, the ability to have a job and independence, the ability to have an education and learn, and the ability to have good health and mental functioning. Future research is needed to find ways to not only control frontal lobe seizures, but to also address the specific quality of life issues that plague those with frontal lobe epilepsy.

- **Driving and Transportation Restrictions**
  - Driving and travel restrictions are one of the greatest limitations that epileptic patients experience. Laws restricting driving privileges vary greatly in the United States as well as across the world. In the United States, 28 states require a patient to be seizure free for fixed periods of time ranging from 3–12 months. However, research done by Johns Hopkins University showed that there was no difference in seizure related fatal crash rates in states with 3 month restrictions versus states with 6-12 month seizure free restrictions. In 23 states, the restrictions and seizure free periods vary depending on the type of epilepsy and the individual case and in 13 states physicians were responsible for determining whether their patients should be allowed to drive. In 6 of those 13 states physicians could be held legally liable for their decisions regarding their epileptic patients' driving capabilities. In many states, patients can also be legally liable for accidents, injury, damage and death caused by seizure related accidents.
  - One of the major arguments in favor of restricting the licensing of epileptic drivers is the concern for public safety. However, the Johns Hopkins study showed that in a particular 2 year timeframe only .2% of fatal crashes occurred as a result of seizures. Alcohol related crash fatalities caused 156 times more driver deaths than seizure related crashes and young drivers between the ages of 16 and 24 were 123 times more likely to die in a fatal crash caused by their inexperience than an epileptic driver was to die in a crash that resulted from a seizure.
  - Frontal lobe epileptic seizures unlike other epileptic seizures create symptoms that are as dangerous as loss of consciousness and much more difficult to discern from other problems such as drug and alcohol abuse, psychiatric disorders and disobedience. Jerking movements/lack of motor control, pedaling, pelvic thrusting, lapses in cognitive functioning and other hallmark symptoms of frontal lobe epileptic seizures all create dangerous behavior behind the wheel. Studies have not been done to date to determine the differential risk posed by drivers with frontal lobe epilepsy relative to the general epileptic population.

- **Hormones & Pregnancy Issues**
  - Hormonal changes and pregnancy can shift seizure activity and the use of antiepileptic drugs can alter the efficacy of hormones as well as cause congenital malformations in fetuses. Seizure control in pregnant women is very important to the welfare of both the developing fetus and the mother. Hormonal shifts at puberty, with birth control and at menopause can also cause changes in the frequency and severity of seizures and must be closely monitored. Increased seizure activity is reported by 50% of women during the course of the pregnancy due to changing levels of hormones, fluids, salts and absorption and elimination of medications.

- **Employment**
  - A report by the Epilepsy Foundation noted that the unemployment rate amongst epileptics is 25% and in patients whose seizures are poorly controlled the rate jumps to 50%. Even though epileptics are protected under The Americans with Disabilities Act, employment discrimination and high rates of unemployment due to employer attitudes still exist. A study in the UK showed that 16% of employers surveyed felt there were no jobs in their company suitable for epileptics and that 21% felt that employing an epileptic would be a "major issue". Fifty percent of the employers said they had a high concern regarding employing epileptics with most citing safety concerns/workplace accidents as their major issue. Patients with frontal lobe epilepsy may be particularly prone to being discriminated against in employment and subject to higher rates of termination due to the unusual motor symptoms, speech, vocal outbursts and cognitive/judgment symptoms displayed during frontal lobe seizures. Frontal lobe seizures also tend to come on suddenly and progress rapidly making it difficult for an employer to control the exposure of the seizure to others.

- **Education/Learning & Cognitive Function**
  - Patients with frontal lobe epilepsy will likely also experience issues with learning and education. Many factors contribute to these issues including the impact of anticonvulsant medications. Anticonvulsant medications cause patients to feel "foggy" and sluggish. Drugs such as Topiramate cause problems such as mental blunting, word retrieval difficulties and irritability. Phenobarbital, Primidone and Vigabatrin can cause depression and suicidal tendencies. Stress and lack of sleep during exam periods can trigger seizures and many school sports teams restrict or ban epileptics from sports for safety and liability reasons. Frontal lobe epilepsy sufferers also exhibit dysfunctional cognitive skills and memory issues which can make learning challenging. Research has shown that frontal lobe epilepsy has a greater negative impact than other forms of epilepsy on cognitive functioning. Frontal lobe epileptics show decreased cognitive capabilities in the following areas: humor appreciation, recognition of emotional expressions, response selection/initiation and inhibition, hyperactivity, conscientiousness, obsession, addictive behavior, motor coordination and planning, attention span, performance speed, continuous performance without intrusion and interference errors, copying and recall, concept formation, anticipatory behavior, memory span, working memory, executive planning, visuo-spatial organization, mental flexibility, conceptual shift, problem solving, programming of complex motor sequences, impulse control, judgment and forecasting of consequences.

- **Physical Health & Risk Of Other Conditions**
  - Patients with epilepsy face a greater risk of accidents, injury and other medical conditions than the general population. A European study showed

that epileptics were at greater risk for accidental injuries related to seizures such as concussions, abrasions and wounds and reported more hospitalizations and medical action than the general population. Other studies have shown that epileptics are at a greater risk of seizure related drowning, suffocation, broken bones and burns and more likely to die in a fatal automobile crash.
    - Epilepsy Ontario reports that epileptics are also more likely to have other conditions than the general population such as: 30% of autistic children have epilepsy, 33% of cerebral palsy patients have epilepsy, 15-20% of fragile X syndrome patients have epilepsy, 50% of children with learning disabilities will have some form of epilepsy, 3-10% of patients with Lennox-Gastaut syndrome will have epilepsy, 80% of children with Rett syndrome will have epilepsy and 80% of patients with Tuberous Sclerosis will have epilepsy.

- **Mental/Emotional Health**
    - Epileptic patients are more prone to suffer psychological and social dysfunction than individuals that do not have epilepsy. They report higher levels of anxiety and stress due to social isolation, discrimination, the unpredictability of their seizures and people's reactions to them as well as fear of injury, death and brain damage from their seizures. Anticonvulsants can also result in lower functioning, depression, sluggishness and suicidal thoughts. Approximately 20% of epileptics are depressed and the rate of suicide amongst epileptics is 5 times the rate in the general population.
    - Frontal lobe epileptics experience more significant social effects because the manifested symptoms are more unusual. Symptoms such as screaming, bicycling limbs, pelvic thrusting, inhibition control and other outbursts can be particularly embarrassing and isolating for the patient.

Treatments

There are several different ways to treat frontal lobe epileptic seizures, however, the most common form of treatment is through the use of anticonvulsant medications that help to prevent seizures from occurring. In some cases, however, when medications are ineffective, a neurologist may choose to operate on the patient in order to remove the focal area of the brain in which the seizures are occurring. Other treatments that can be administered to aid in reducing the occurrence of seizures include the implementation of a specific, regimented diet and/or the implantation of a **vagus nerve stimulator**.

Medications

Anticonvulsants are the most successful medication in reducing and preventing seizures from reoccurring. The goal of these medications in being able to reduce the reoccurrence of seizures is to be able to limit the amount of rapid and extensive firing of neurons so that a focal region of neurons cannot become over-activated thereby initiating a seizure.

Although anticonvulsants are able to reduce the amount of seizures that occur in the brain, no medication has been discovered to date that is able to prevent the development of epilepsy following a head injury. There are a wide range of anticonvulsants that have both different modes of action and different abilities in preventing certain types of seizures. Some of the anticonvulsants that are prescribed to patients today include: Carbamazepine (Tegretol), Phenytoin (Dilantin Kapseals), Gabapentin (Neurontin), Levetiracetam (Keppra), Lamotrigine (Lamictal), Topiramate (Topamax), Tiagabine (Gabitril), Zonisamide (Zonegran) and Pregabalin (Lyrica).

Chemical Pathways for Anticonvulsants

Anticonvulsant medications can affect one or more ion channel pathways depending on the type of seizure. They typically affect GABA, sodium channels, calcium channels, glutamate, or a combination of these. One mechanism involves the increased release of GABA or the inhibition of its metabolism so that it is present in the synapse for longer periods of time. This is effective for generalized or focal seizures, and is the mechanism of medications such as valproate and gabapentin. Sodium channels are typically targeted for the prevention of focal seizures. This is accomplished by lengthening the refractory period, during which the channels are inactive, and as such eliminating the ability of the neuron to fire rapidly in succession. Medications that affect this pathway include Carbamazepine and Lamotrigine. Calcium channels can be blocked according to their subunits, specifically targeting T-calcium channels. Ethosuximide works in this manner, and it is effective against absence seizures. The final pathway involves blocking excitatory glutamate receptor, namely AMPA and NMDA. This effectively decreases the probability that a presynaptic action potential will produce an action potential in the postsynaptic neuron. Drugs utilizing this mechanism are effective, but no drug currently in use acts solely on this pathway. Some examples include diazepam and valproate.

Surgical Treatment

When both the amount and severity of seizures becomes uncontrollable and seizures remain resistant to the various anticonvulsants, a patient most likely will be considered for a **frontal lobectomy**. This procedure involves the removal of focal regions of the frontal lobes that have been identified as being problematic for the patient. It has been found that around 30% to 50% of patients that undergo a frontal lobectomy will forever be free from seizures that cause a loss of consciousness or cause abnormal movements.

If on the other hand, the seizures occur in an area that is too vital to remove (such as areas that control motor, sensory or language functions), then the surgeon will perform a procedure known as a **multiple subpial transection**. This procedure involves making a series of cuts that surround the focal region where the seizures have originated. By making cuts surrounding the focal region, the surgeon is able to isolate that specific section of the brain and prevent electrical impulses from being able to travel horizontally to other areas of the brain.

The last surgical procedure that can be done to help prevent the reoccurrence of seizures in the frontal lobes is to implant a stimulator on the vagus nerve. This device is a self-activating device that is inserted directly under the skin and can be controlled directly by the patient. When a patient is feeling the onset of an aura, he/she can activate the stimulator which in turn will provide stimulation to the left vagus nerve (the left vagus nerve is used because the right nerve plays a role in cardiac function). Although little is understood about the exact mechanism for vagal nerve stimulation, it has been proven to be a successful treatment that can often terminate seizures before they begin.

Diet

The use of a regimented diet is an approach that has been found to help control seizures in children with severe, medically-intractable frontal lobe epilepsy. Although the use of dieting to prevent seizures from occurring is a lost treatment that has been replaced by the use of new types of anticonvulsants, it is still recommended to patients to this day. A ketogenic diet is a high-fat, low-carbohydrate based diet that patients are typically asked to follow in conjunction with their anticonvulsant medications. This diet was designed in order to mimic many of the effects that starvation has on the metabolic functioning of the body. By limiting the amount of carbohydrates and increasing the amount of exogenous fats available to the metabolism, the body will create an excess of water-soluble compounds known as ketone bodies. Although the mechanism of action is still unknown, it is believed that these excessive amounts of ketone bodies become the brain's main source of energy and in turn are able to suppress the frequencty of seizure occurrence.

Importance of Neuroimaging

Once anticonvulsant medications prove to be no longer effective and a patient is selected to undergo resective epilepsy surgery, the doctors must begin the surgical process by first identifying the epileptogenic zone. The removal of the epileptogenic zone, the area of brain tissue that is responsible for the generation of seizures, can lead to a reduction or freedom in the amount of seizures. One of the major concerns for surgeons before they operate on patients that have intractable epilepsis is to not only be able to pinpoint the epileptogenic zone that is to be removed but to also map out the localized regions surrounding the focal area that are associated with somatosensory, cognitive and motor functions. Through the use of neuroimaging devices such as fMRIs, PET scans and SPECT scans doctors are now able to identify the exact positions of the lesions causing the seizures and can map out the sensorimotor, language, visual and memory functional locations in the frontal lobes of the brain prior to the resective surgery. Therefore structural and functional neuroimaging techniques help to fulfill two major goals: localiztion of the epileptogenic zone and the determination of the etiology producing the seizure. Prior to the invention of neuroimaging techniques, surgeries to eliminate frontal lobe seizures from occurring were very rare and not very successful. However the ability to localize the epiletogenic zone and the specific etiology for the seizures has made frontal lobe resective surgery just as successful as that for temporal lobe resective surgery.

Resective Surgery using Gamma-Knife Radiosurgery

Over the past decade or so, researchers have been attempting to discover less invasive, safer and more efficient technologies that enable surgeons to remove epileptogenic focal zones without causing any damage to neighboring cortical areas. One such technology that has emerged and has great promise, is the use of gamma knife radiosurgery to either excise a brain tumor or repair a vascular malformation.

In Gamma Knife radiosurgery, intersecting gamma radiation beams are applied directly to the tumor site or vascular malformation site that had been established using neuroimaging. Although each beam itself is not strong enough to damage brain tissue, when the beams interesect they are strong enough to destroy the specific brain tissue that is to be excised. This process is extremely efficient and entirely non-invasive and is therefore much safer than actual neurosurgery itself.

Recently researchers and surgeons alike have begun to use Gamma Knife radiosurgery to treat cases of epilepsy by removing tumors responsible for causing the seizures. The early success rates in being able to alleviate seizures seem to be similar to those of temporal resective surgery however Gamma Knife radiosurgery has less associated risk factors. Current research on this topic is aimed at improving the technique in order to increase success rates as well as developing non-invasive forms of physiologic monitoring in order to determine the epileptogenic focus conclusively.

Chapter 7

Juvenile Myoclonic Epilepsy

Juvenile myoclonic epilepsy	
ICD-10	G40.3
ICD-9	345.1
OMIM	606904 254770 604827 608816
DiseasesDB	32202
eMedicine	neuro/416
MeSH	D020190

Juvenile myoclonic epilepsy (JME), also known as Janz syndrome, is a fairly common form of idiopathic generalized epilepsy, representing 5-10% of all epilepsies. This disorder typically first manifests itself between the ages of 12 and 18 with myoclonus occurring early in the morning. Most patients also have tonic-clonic seizures and many also have absence seizures. Linkage studies have demonstrated at least 6 loci for JME, 4 with known causative genes. Most of these genes are ion channels with the one non-ion channel gene having been shown to affect ion channel currents.

Signs and symptoms

Signs of JME are myoclonus occurring early in the morning. This rarely results in patients falling, but rather dropping objects. Attacks of myoclonia are more common in the arms than the legs. Other seizure types such as generalized tonic-clonic and absence seizures can also occur. Myoclonic seizures can also occur in the later part of the day, and are not limited to the arms and hands. They can also occur in your lower legs, causing you to trip over your own feet. Clusters of myoclonics can led to absence seizures, and clusters of absence seizures can lead to generalized tonic-clonic seizures. Expression can occur as young as 18 months of age. Males in some families do not survive the crisis point at 24 months of age.

Pathophysiology

CACNB4

CACNB4 encodes a calcium channel β subunit. β subunits are important regulators of calcium channel current amplitude, voltage dependence, and also regulate channel trafficking. The β_4 isoform encoded by CACNB4 is most prevalent in the cerebellum. In mice, a naturally occurring null mutation leads to the "lethargic" phenotype, which is similar to JME. There are at least two mutations in the β_4 subunit associated with JME, C104F and R482X. When wild-type α_{1A} and β_4 subunits are expressed in oocytes they produce large Ba^{2+} currents that inactivate slowly. Incorporation of either of the mutant β_4 subunit into channels instead of wild-type subunits produces currents that are larger by 30-40%. The R482X mutation also increases the rate of fast inactivation of the channel. Since these effects are subtle, it is believed that they are contributory rather than completely causative for JME.

GABRA1

GABRA1 encodes an α subunit of the GABA A receptor, which encodes one of the major inhibitory neurotransmitter receptors. There is one known mutation in this gene that is associated with JME, A322D, which is located in the third segment of the protein. Expression of the $\alpha_1\beta_2\gamma_2$ combination of subunits in HEK 293 cells produces 6-fold greater current than similar subunits compositions containing mutant α_1 subunits. The mutation also results in greatly decreased sensitivity in the receptor for activation by GABA. This combination of mutant containing receptors also activates far more slowly than wild-type containing receptors. Although originally not reported to result in altered protein trafficking, more recent study has indicated that the A322D mutation reduced α_1 subunit trafficking to the membrane by >90%. Heterozygous expression of wild-type and mutant subunits produces current approximately 50% the size of wild-type due to this altered trafficking.

CLCN2

The CLCN2 gene encodes a chloride channel that is heavily expressed in brain regions inhibited by GABA. It is believed to be important in maintaining a proper chloride reversal potential needed in inhibitory neurotransmission by GABA. There are three known mutations in CLCN2 associated with JME, M200fsX231, 74_117del, and G715E. Neither the M200fsX231 nor the 74_117del mutation yield current when expressed in cells. Since these channels are responsible for the removal of intracellular chloride, these mutations are expected to lead to increased chloride concentrations and, thus, altered chloride reversal potential (E_{Cl}). As chloride is conducted through the normally inhibitory GABA receptors, this alteration in E_{Cl} may lead to either decreased GABAergic currents or GABAergic currents that are actually excitatory. The G715E mutation, on the other hand, produces normal sized currents but has altered voltage dependent activation. For this mutant, activation occurs at more positive potentials compared to wild-type channels. This may cause increased neuronal excitability.

GABRD

GABRD encodes the δ subunit of the GABA receptor, which is a subunit yielding receptors which do not desensitize and are localized outside of the synapse. There are three mutations in this gene associated with JME, E177A, R220C, and R220H, all located in the N-terminus of the protein. The last of these mutations is also present in normal controls. Receptors containing the E177A mutation have greatly decreased current compared to wild-type. This is not the case for the R220C mutation but is similar to the R220H mutation, though to a lesser extent than the E177A mutation. More recent study has found that the E177A mutant also has greatly decreased desensitization compared to wild-type receptors. Receptors containing only E177A or R220H mutants, versus heterozygotes, had significantly decreased surface expression compared to wild-type or heterozygotic receptors. These mutants also have decreased single-channel open times compared to wild-type. It should be noted, however, that these mutations are very rare as causes of JME.

EFHC1

The final known associated gene is EFHC1, which is poorly understood. EFHC1 has three DM10 domains (themselves of unknown function) and an EF hand motif, which is known to bind intracellular calcium. EFHC1 is expressed in many tissues, including the brain, where it is localized to the soma and dendrites of neurons, particularly the hippocampal CA1 region, pyramidal neurons in the cerebral cortex, and Purkinje cells in the cerebellum. There are 5 mutations in EFHC1 associated with JME; D210N, F229L, D253Y, P77T and R221H. The last two mutations were originally detected as a pair in the same individual. EFHC1 seems to be involved in programmed cell death as EFHC1 transfected cells have a higher rate of apoptosis. This rate is decreased by the double mutations P77T + R221H. Wild-type EFHC1 increased the R-type calcium channel currents in transfected cells. This stimulation is decreased by JME associated mutations. Because of this, programmed cell death is decreased and the pruning of unwanted neurons may be hampered. As with some other loci, mutations in EFHC1 is not a common loci for JME. More recently, R221H has been found without P77T in one JME kindred.

Other loci

There is also evidence linking a gene or genes on chromosome 15 (15q14) as well as the BRD2 gene on chromosome 6 (6p21) to JME. Causative genes in this region, however, have not been shown.

Relation to other rare disorders: genetic ciliopathy

Until recently, the medical literature did not indicate a connection among many genetic disorders, both genetic syndromes and genetic diseases, that are now being found to be related. As a result of new genetic research, some of these are, in fact, highly related in their root cause despite the widely-varying set of medical symptoms that are clinically

visible in the disorders. This emerging class of diseases are called cilopathies. The underlying cause may be a dysfunctional molecular mechanism in the primary cilia structures of the cell, organelles which are present in many cellular types throughout the human body. The cilia defects adversely affect "numerous critical developmental signaling pathways" essential to cellular development and thus offer a plausible hypothesis for the often multi-symptom nature of a large set of syndromes and diseases. Known ciliopathies include primary ciliary dyskinesia, Bardet-Biedl syndrome, polycystic kidney and liver disease, nephronophthisis, Alstrom syndrome, Meckel-Gruber syndrome and some forms of retinal degeneration. It has been suggested that juvenile myoclonic epilepsy may be a ciliopathy.

Diagnosis

Diagnosis is typically made based on patient history. EEG recordings are also sometimes used as confirmation.

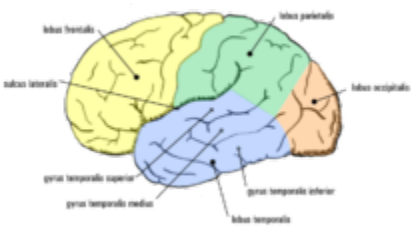
Treatment/Management

Before giving Carbamazepine do ask for history of early morning seizures and or jerks/twitches especially in a young person. Carbamazepine aggravates these.

Chapter 8

Temporal Lobe Epilepsy

Temporal lobe epilepsy



Lobe of the brain

ICD-10	G40.1.-G40.2.
ICD-9	345.4
DiseasesDB	29433
MedlinePlus	001399
eMedicine	neuro/365
MeSH	D004833

Temporal lobe epilepsy a.k.a. Psychomotor epilepsy, is a form of focal epilepsy, a chronic neurological condition characterized by recurrent seizures. Over 40 types of epilepsies are known. They fall into two main categories: partial-onset (focal or localization-related) epilepsies and generalized-onset epilepsies. Partial-onset epilepsies account for about 60% of all adult epilepsy cases, and temporal lobe epilepsy (TLE) is the most common single form causing refractory epilepsy.

Temporal lobe epilepsies are a group of medical disorders in which humans and animals experience recurrent epileptic seizures arising from one or both temporal lobes of the brain. Two main types are internationally recognized according to the International League Against Epilepsy.

- **Medial temporal lobe epilepsy (MTLE)** arises in the hippocampus, parahippocampal gyrus and amygdala which are located in the inner aspect of the temporal lobe.
- **Lateral temporal lobe epilepsy (LTLE)** arises in the neocortex on the outer surface of the temporal lobe of the brain.

Because of strong interconnections, seizures beginning in either the medial or lateral temporal areas often spread to involve both areas and also to neighboring areas on the same side of the brain as well as the temporal lobe on the opposite side of the brain. The causes or etiology of different temporal lobe epilepsies vary and are discussed below.

Syndrome of Temporal Lobe Epilepsy (TLE)

The classical syndrome of TLE may begin when there is a very early insult to the left or right hippocampus that causes neuron death. Infants may develop lung or skin infections resulting in a fever. Babies have an immature thermoregulation system, and the fever causes the baby's core body temperature to increase more drastically than in adults. In some children, elevated body temperature can cause febrile seizures. Febrile seizures are relatively normal as they occur in 2-5% of children under age 5 years. They typically last only a few minutes or even a matter of seconds, but are neither severe motor convulsions nor followed by weakness on one side of the body. In a small number of babies, these convulsions can last for over an hour and involve repeated convulsive episodes. These are known as complex febrile seizures and may be causatively associated with TLE. As discussed below in the section on causes, it remains controversial whether complex febrile seizures actually cause TLE, or whether they are simply the earliest manifestation of the TLE condition.

Causes

A link between febrile seizures (seizures coinciding with episodes of fever in young children) and subsequent temporal lobe epilepsy has been suggested, but the exact role remains unclear. Some studies have shown abnormalities of the hippocampus on magnetic resonance imaging (MRI) in status epilepticus, which supports the theory that prolonged seizures damage the brain. Interestingly, some cases of MTLE present without the typical changes of mesial temporal sclerosis or other abnormalities on MRI scans. This has been termed paradoxical mesial temporal lobe epilepsy. The epilepsy in these patients tends to occur at a later age, which might suggest that an early event leads to hippocampal damage causing MTLE. Although this theory needs confirmation, some studies have pointed to human herpesvirus 6 (HHV-6) as a possible link between febrile convulsions and later MTLE. Firstly, several studies suggest that HHV-6 infection occurs commonly prior to the occurrence of febrile seizures. However, only a minority of primary HHV-6 infections may be associated with febrile seizures. Secondly, other studies found HHV-6 DNA in brain tissue removed during surgery for MTLE.

Rarely, MTLE can be hereditary or related to brain tumors, spinal meningitis, encephalitis, head injury or blood vessel malformations. MTLE can occur in association with other brain malformations. Most often, a cause cannot be determined with certainty.

LTLE is less common. It can be hereditary, as in Autosomal Dominant Lateral Temporal Lobe Epilepsy (ADLTLE) with auditory or visual features, but can also be associated with tumors, meningitis, encephalitis, trauma, vascular malformations or congenital brain malformations. Again, in many affected persons it is common that no cause can be identified.

Dispersion of granule cell layer in the hippocampal dentate gyrus is occasionally seen in temporal lobe epilepsy and has been linked to the downregulation of reelin, a protein that normally keeps the layer compact by containing the neuronal migration. It is unknown whether changes in reelin expression play a role in epilepsy.

Symptoms

The symptoms felt by the person, and the signs observable by others, during seizures which begin in the temporal lobe depend upon the specific regions of the temporal lobe and neighboring brain areas affected by the seizure. The International Classification of Epileptic Seizures published in 1981 by the International League Against Epilepsy (ILAE) recognizes three types of seizures which persons with TLE may experience.

1. Simple Partial Seizures (SPS) involve small areas of the temporal lobe such as the amygdala or the hippocampus. The term "simple" means that consciousness is not altered. In temporal lobe epilepsy SPS usually only cause sensations. These sensations may be mnestic such as déjà vu (a feeling of familiarity), jamais vu (a feeling of unfamiliarity), a specific single or set of memories, or amnesia. The sensations may be auditory such as a sound or tune, gustatory such as a taste, or olfactory such as a smell that is not physically present. Sensations can also be visual, involve feelings on the skin or in the internal organs. The latter feelings may seem to move over the body. Psychic sensations can occur such as an out-of-body feeling. Dysphoric or euphoric feelings, fear, anger, and other sensations can also occur during SPS. Often, it is hard for persons with SPS of TLE to describe the feeling. SPS are often called "auras" by lay persons who mistake them for a warning sign of a subsequent seizure. In fact, they are indeed seizures. Persons experiencing only SPS may not recognize what they are or seek medical advice about them. SPS may or may not progress to the seizure types listed below.
2. Complex Partial Seizures (CPS) by definition are seizures which impair consciousness to some extent. This is to say that they alter the person's ability to interact with his or her environment. They usually begin with an SPS, but then the seizure spreads to a larger portion of the temporal lobe resulting in impaired consciousness. Signs may include motionless staring, automatic movements of the hands or mouth, altered ability to respond to others, unusual speech, or unusual behaviors.

3. Seizures which begin in the temporal lobe but then spread to the whole brain are known as Secondarily Generalized Tonic-Clonic Seizures (SGTCS). These begin with an SPS or CPS phase initially, but then the arms, trunk and legs stiffen (tonic) in either a flexed or extended position and then clonic jerking of the limbs often occurs. GTCS are often known in the vernacular as convulsions or "grand mal" (cf. French, grand maladie) seizures.

Following each of these seizures, there is some period of recovery in which neurological function is altered. This is called the postictal state. The degree and length of the impairment directly correlates with the severity of the 3 seizure types listed above. SPS often last less than 60 seconds, CPS often last less than 2 minutes, and SGTCS usually last less than 3 minutes. The postictal state in the case of CPS and GTCS often lasts much longer than the seizure ictus itself. Because a major function of the temporal lobe is short-term memory, CPS and GTCS cause amnesia for the seizure. As a result, many persons with temporal lobe CPS and GTCS will not remember having had a seizure.

Local and national laws exist regarding the operation of vehicles, aircraft and vessels by patients with epilepsy. Most licensing departments do not allow driving of vehicles by persons with CPS or GTCS until they have been seizure-free for a specified period of time. The laws are complex and varied; affected persons must check with the appropriate licensing authority. In a few locations, health care providers are legally-required to report patients with epilepsy (and other medical conditions which cause episodes of altered consciousness) to their local department of motor vehicles.

Treatments

There are many oral medications available for the management of epileptic seizures. They were previously called anticonvulsants but this term is misleading owing to the fact that most seizures are not convulsions. The modern term is antiepileptic drugs or AEDs, for short. In TLE, the most commonly used older AEDs are phenytoin, carbamazepine, primidone, valproate and phenobarbital. Newer drugs, such as gabapentin, topiramate, levetiracetam, lamotrigine, pregabalin, tiagabine, lacosamide, and zonisamide promise similar effectiveness, possibly with fewer side-effects. Felbamate and vigabatrin are newer AEDs, but can have serious adverse effects so they are not considered first-line AEDs. Nearly all AEDs function by decreasing the excitation of neurons (e.g., by blocking fast or slow sodium channels or modulating calcium channels) or by enhancing the inhibition of neurons (e.g., by potentiating the effects of inhibitory neurotransmitters like GABA). Unfortunately, many patients with mesial temporal lobe epilepsy (up to one-third) will not experience adequate seizure control with medication.

For patients with mesial TLE whose seizures remain uncontrolled after trials of several AEDs (intractable), resective surgery should be considered. Epilepsy surgery has been performed since the 1860s and physicians and surgeons had observed for decades that it was highly effective in producing seizure freedom. However, it was not until 2001 that a scientifically sound study was performed on the effectiveness of temporal lobectomy. This study proved that after the failure of several AEDs to control seizures in TLE

temporal lobe surgery is far more effective in producing seizure freedom than is additional medication trials. The unanswered question that remains is how many medications a person must fail before considering surgery. A United States sponsored research study called ERSET was begun to answer the question of whether surgery can successfully be performed early in the course of TLE. Although the study ended earlier than anticipated, limited results are expected soon.

In preparation for these surgeries, patients are monitored by various methods to determine the focus of their seizures (that is, the region of the brain where seizures tend to arise before spreading). This can be done with video-EEG monitoring, intracranial EEG (where electrodes are placed beneath the skull, either within or resting just outside the brain), or SPECT imaging. MRI studies may additionally be used to seek evidence of hippocampal sclerosis. Once the epileptic focus has been determined, it can be excised, which usually involves removing part of the hippocampus and often the amygdala. To avoid removing areas of the brain responsible for speech (so-called "eloquent" areas), the surgical team will conduct a Wada test pre-operatively, wherein amobarbital is injected in the left or right carotid artery to temporarily quiet one half of the brain. If the patient performs poorly on neuropsychological testing during the intracarotid amobarbital (Wada) test, the surgical team may advise the patient against surgery or may offer a more limited operation.

If a person is not an optimal candidate for epilepsy surgery, then AEDs not previously tried, the vagus nerve stimulator, or AEDs in clinical research trials might be alternative treatments.For children, the ketogenic diet may also be tried.Other possible future therapies such as brain cortex responsive neural stimulators, deep brain stimulation, and stereotactic radiosurgery (such as gamma knife) are undergoing research studies for treatment of TLE and other forms of epilepsy.

Social and artistic influence

Temporal Lobe Epilepsy and the Arts

As Eve LaPlante discusses in her book, *Seized*, the intense emotions, sensory experience including vibrancy of colors, and particular mental state provoked by temporal lobe abnormalities may have contributed to the creation of significant works of art. A number of well-known writers and artists are known, or in many cases suspected to have had temporal lobe epilepsy, aggravated, in some cases, by alcoholism. They include Charles Dodgson (a.k.a. Lewis Carroll), Edgar Allan Poe, Fyodor Dostoevsky (whose novel *The Idiot* features a protagonist with epilepsy, Prince Myshkin), Gustave Flaubert, Philip K. Dick, Sylvia Plath and contemporary author Thom Jones. Peter O'Leary has also discussed this in his "Gnostic Contagion: Robert Duncan and the Poetry of Illness". Sadi Ranson-Polizzotti has discussed the significance of Lewis Carroll's epilepsy online and in a forthcoming book on the subject.

Temporal Lobe Epilepsy, Neurotheology and Paranormal Experience

The first researcher to note and catalog the abnormal experiences associated with TLE was neurologist Norman Geschwind, who noted a constellation of symptoms, including hypergraphia, hyperreligiosity, fainting spells, and pedantism, often collectively ascribed to a condition known as Geschwind syndrome.

Vilayanur S. Ramachandran explored the neural basis of the hyperreligiosity seen in TLE using galvanic skin response (which correlates with emotional arousal) to determine whether the hyperreligiosity seen in TLE was due to an overall heightened emotional state or was specific to religious stimuli (Ramachandran and Blakeslee, 1998). By presenting subjects with neutral, sexually arousing and religious words while measuring GSR, Ramachandran was able to show that patients with TLE showed enhanced emotional responses to the religious words, diminished responses to the sexually charged words, and normal responses to the neutral words. These results suggest that the medial temporal lobe is specifically involved in generating some of the emotional reactions associated with religious words, images and symbols.

Cognitive neuroscience researcher Michael Persinger asserts that stimulating the temporal lobe electromagnetically can cause TLE and trigger hallucinations of apparent paranormal phenomena such as ghosts and UFOs. Persinger has even created a "God helmet" which purportedly can evoke altered states of consciousness through stimulation of the parietal and temporal lobes. Neurotheologians speculate that individuals with temporal lobe epilepsy, having a natural tendency to experience states of consciousness such as euphoria or *samādhi*, have functioned in human history as religious figures or shamans.

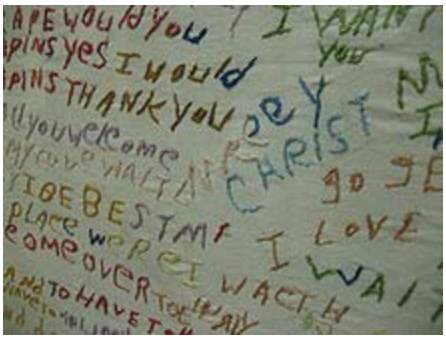
Temporal lobe epilepsy and hormones

Sex hormones can influence the timing and frequency of seizure activity. Estrogen is pro-epileptic and progesterone is anti-epileptic. These counterbalancing effects may account for "catamenial epilepsy" i.e. epilepsy preceding or made more severe prior to menstruation or during peri-ovulation. Gender may differentially influence neocortical pathologies in patients with refractory temporal lobe epilepsy.

Chapter 9

Introduction to Schizophrenia

Schizophrenia



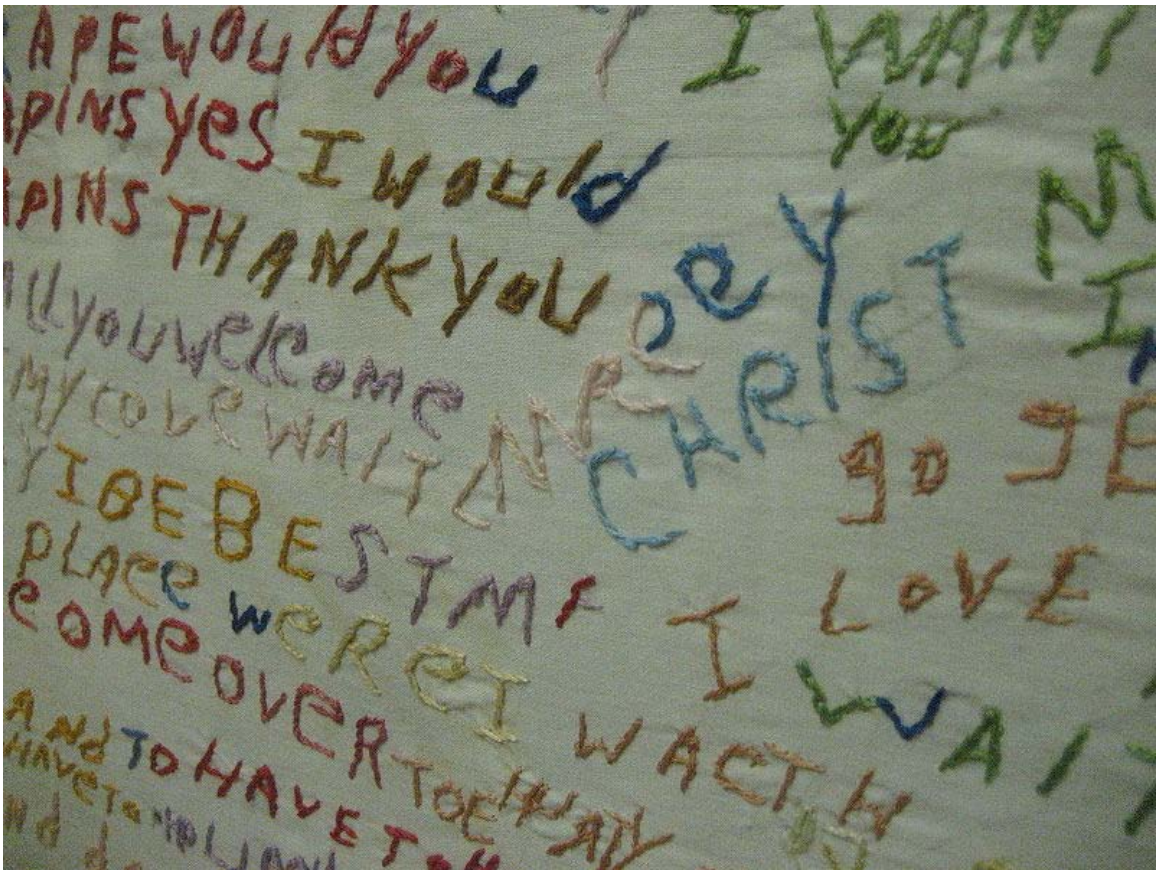
Cloth embroidered by a schizophrenia patient.

ICD-10	F20.
ICD-9	295
OMIM	181500
DiseasesDB	11890
MedlinePlus	000928
eMedicine	med/2072 emerg/520
MeSH	*F03.700.750*

Schizophrenia is a mental disorder characterized by a disintegration of the process of thinking and of emotional responsiveness. It most commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking, and it is accompanied by significant social or occupational dysfunction. The onset of symptoms typically occurs in young adulthood, with a global lifetime prevalence of around 1.5%. Diagnosis is based on the patient's self-reported experiences and observed behavior.

Schizophrenia has increasingly been recognized as a collection of neurodevelopmental disorders that involve alterations in brain circuits. Genetics, early environment, neurobiology, psychological and social processes appear to be important contributory

factors; some recreational and prescription drugs appear to cause or worsen symptoms. Current psychiatric research is focused on the role of neurobiology, but this inquiry has not isolated a single organic cause. As a result of the many possible combinations of symptoms, there is debate about whether the diagnosis represents a single disorder or a number of discrete syndromes. Despite the etymology of the term from the Greek roots *skhizein* (*σχίζειν*, "to split") and *phrēn, phren-* (*φρήν, φρεν-*; "mind"), schizophrenia does not imply a "split mind" and it is not the same as dissociative identity disorder—also known as "multiple personality disorder" or "split personality"—a condition with which it is often confused in public perception.



Unusually high dopamine activity in the mesolimbic pathway of the brain has been found in people with schizophrenia. The mainstay of treatment is antipsychotic medication; this type of drug primarily works by suppressing dopamine activity. Dosages of antipsychotics are generally lower than in the early decades of their use. Psychotherapy, and vocational and social rehabilitation, are also important. In more serious cases—where there is risk to self and others—involuntary hospitalization may be necessary, although hospital stays are shorter and less frequent than they were in previous times.

The disorder is thought mainly to affect cognition, but it also usually contributes to chronic problems with behavior and emotion. People with schizophrenia are likely to have additional (comorbid) conditions, including major depression and anxiety disorders; the lifetime occurrence of substance abuse is around 40%. Social problems, such as long-

term unemployment, poverty and homelessness, are common. Furthermore, the average life expectancy of people with the disorder is 10 to 12 years less than those without, due to increased physical health problems and a higher suicide rate (about 5%).

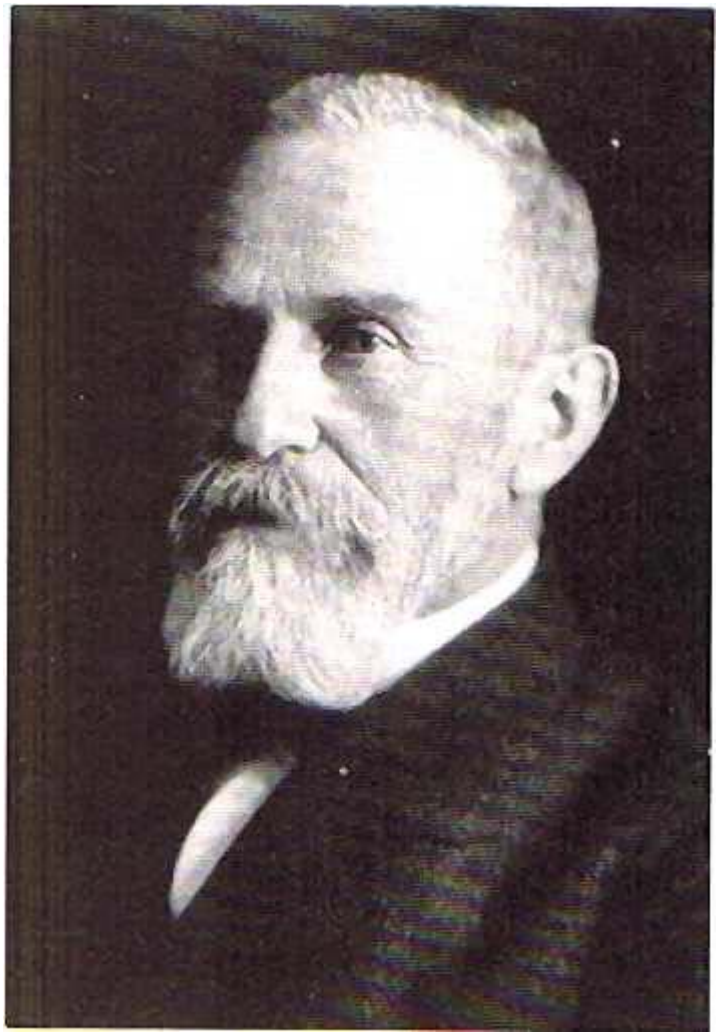
Schizophrenia has increasingly gained attention among the general public and the scientific community. Indeed, the November 11, 2010 issue of *Nature* was devoted to the theme of schizophrenia.

Signs and symptoms

A person diagnosed with schizophrenia may experience hallucinations (most commonly hearing voices), delusions (often bizarre or persecutory in nature), and disorganized thinking and speech. The latter may range from loss of train of thought, to sentences only loosely connected in meaning, to incoherence known as word salad in severe cases. There is often an observable pattern of emotional difficulty, for example lack of responsiveness or motivation. Impairment in social cognition is associated with schizophrenia, as are symptoms of paranoia, and social isolation commonly occurs. In one uncommon subtype, the person may be largely mute, remain motionless in bizarre postures, or exhibit purposeless agitation; these are signs of catatonia.

Late adolescence and early adulthood are peak years for the onset of schizophrenia. In 40% of men and 23% of women diagnosed with schizophrenia, the condition arose before the age of 19. These are critical periods in a young adult's social and vocational development. To minimize the developmental disruption associated with schizophrenia, much work has recently been done to identify and treat the prodromal (pre-onset) phase of the illness, which has been detected up to 30 months before the onset of symptoms, but may be present longer. Those who go on to develop schizophrenia may experience the non-specific symptoms of social withdrawal, irritability and dysphoria in the prodromal period, and transient or self-limiting psychotic symptoms in the prodromal phase before psychosis becomes apparent.

Schneiderian classification



The term Schizophrenia was coined by Eugen Bleuler

The psychiatrist Kurt Schneider (1887–1967) listed the forms of psychotic symptoms that he thought distinguished schizophrenia from other psychotic disorders. These are called *first-rank symptoms* or Schneider's first-rank symptoms, and they include delusions of being controlled by an external force; the belief that thoughts are being inserted into or withdrawn from one's conscious mind; the belief that one's thoughts are being broadcast to other people; and hearing hallucinatory voices that comment on one's thoughts or actions or that have a conversation with other hallucinated voices. Although they have significantly contributed to the current diagnostic criteria, the specificity of first-rank symptoms has been questioned. A review of the diagnostic studies conducted between 1970 and 2005 found that these studies allow neither a reconfirmation nor a rejection of Schneider's claims, and suggested that first-rank symptoms be de-emphasized in future revisions of diagnostic systems.

Positive and negative symptoms

Schizophrenia is often described in terms of *positive* and *negative* (or deficit) symptoms. The term *positive symptoms* refers to symptoms that most individuals do not normally experience but are present in schizophrenia. They include delusions, auditory hallucinations, and thought disorder, and are typically regarded as manifestations of psychosis. *Negative symptoms* are things that are not present in schizophrenic persons but are normally found in healthy persons, that is, symptoms that reflect the loss or absence of normal traits or abilities. Common negative symptoms include flat or blunted affect and emotion, poverty of speech (alogia), inability to experience pleasure (anhedonia), lack of desire to form relationships (asociality), and lack of motivation (avolition). Research suggests that negative symptoms contribute more to poor quality of life, functional disability, and the burden on others than do positive symptoms.

Diagnosis

Diagnosis is based on the self-reported experiences of the person, and abnormalities in behavior reported by family members, friends or co-workers, followed by a clinical assessment by a psychiatrist, social worker, clinical psychologist, mental health nurse or other mental health professional. Psychiatric assessment includes a psychiatric history and some form of mental status examination.

Standardized criteria

The most widely used standardized criteria for diagnosing schizophrenia come from the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, version DSM-IV-TR, and the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, the ICD-10. The latter criteria are typically used in European countries, while the DSM criteria are used in the United States and the rest of the world, as well as prevailing in research studies. The ICD-10 criteria put more emphasis on Schneiderian first-rank symptoms, although, in practice, agreement between the two systems is high.

According to the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), to be diagnosed with schizophrenia, three diagnostic criteria must be met:

1. **Characteristic symptoms**: Two or more of the following, each present for much of the time during a one-month period (or less, if symptoms remitted with treatment).
    - Delusions
    - Hallucinations
    - Disorganized speech, which is a manifestation of formal thought disorder
    - Grossly disorganized behavior (e.g. dressing inappropriately, crying frequently) or catatonic behavior

- Negative symptoms: Blunted affect (lack or decline in emotional response), alogia (lack or decline in speech), or avolition (lack or decline in motivation)

If the delusions are judged to be bizarre, or hallucinations consist of hearing one voice participating in a running commentary of the patient's actions or of hearing two or more voices conversing with each other, only that symptom is required above. The speech disorganization criterion is only met if it is severe enough to substantially impair communication.

2. **Social/occupational dysfunction**: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care, are markedly below the level achieved prior to the onset.
3. **Duration**: Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms (or less, if symptoms remitted with treatment).

If signs of disturbance are present for more than a month but less than six months, the diagnosis of schizophreniform disorder is applied. Psychotic symptoms lasting less than a month may be diagnosed as brief psychotic disorder, and various conditions may be classed as psychotic disorder not otherwise specified. Schizophrenia cannot be diagnosed if symptoms of mood disorder are substantially present (although schizoaffective disorder could be diagnosed), or if symptoms of pervasive developmental disorder are present unless prominent delusions or hallucinations are also present, or if the symptoms are the direct physiological result of a general medical condition or a substance, such as abuse of a drug or medication.

Confusion with other conditions

Psychotic symptoms may be present in several other mental disorders, including bipolar disorder, borderline personality disorder, drug intoxication and drug-induced psychosis. Delusions ("non-bizarre") are also present in delusional disorder, and social withdrawal in social anxiety disorder, avoidant personality disorder and schizotypal personality disorder. Schizophrenia is complicated with obsessive-compulsive disorder (OCD) considerably more often than could be explained by pure chance, although it can be difficult to distinguish obsessions that occur in OCD from the delusions of schizophrenia.

A more general medical and neurological examination may be needed to rule out medical illnesses which may rarely produce psychotic schizophrenia-like symptoms, such as metabolic disturbance, systemic infection, syphilis, HIV infection, epilepsy, and brain lesions. It may be necessary to rule out a delirium, which can be distinguished by visual hallucinations, acute onset and fluctuating level of consciousness, and indicates an underlying medical illness. Investigations are not generally repeated for relapse unless there is a specific *medical* indication or possible adverse effects from antipsychotic medication.

"Schizophrenia" does ***not*** mean dissociative identity disorder—formerly and still widely known as "multiple personalities"—despite the etymology of the word (Greek σχίζω = "I split").

Subtypes

The DSM-IV-TR contains five sub-classifications of schizophrenia, although the developers of DSM-5 are recommending they be dropped from the new classification:

- **Paranoid type**: Where delusions and hallucinations are present but thought disorder, disorganized behavior, and affective flattening are absent. (DSM code 295.3/ICD code F20.0)

Paranoid schizophrenia	
ICD-10	F20.0
ICD-9	295.3
MeSH	D012563

Paranoid schizophrenia is a sub-type of schizophrenia as defined in the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV code 295.30.

It is the most common type of schizophrenia. The clinical picture is dominated by relatively stable, often paranoid, delusions, usually accompanied by hallucinations, particularly of the auditory variety (hearing voices), and perceptual disturbances. Disturbances of affect, volition, and speech, and catatonic symptoms, are not prominent.

- **Disorganized type**: Named *hebephrenic schizophrenia* in the ICD. Where thought disorder and flat affect are present together. (DSM code 295.1/ICD code F20.1)

Hebephrenic schizophrenia	
ICD-10	F20.1
ICD-9	295.1
MeSH	D012562

Disorganized schizophrenia, also known as **foldermenia** is a subtype of schizophrenia as defined in the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV code 295.10.

Disorganized schizophrenia is thought to be an extreme expression of the 'disorganization syndrome' that has been hypothesised to be one aspect of a three-factor model of symptoms in schizophrenia The other factors being 'reality distortion' (involving delusions and hallucinations) and 'psychomotor poverty' (poverty of speech, lack of spontaneous movement and various aspects of blunting of emotion).

Presentation

This type is characterized by prominent disorganized behavior and speech including schizophasia, and flat or inappropriate emotion and affect. The criteria for the catatonic subtype of schizophrenia must not have been met as well. This type of schizophrenia is also known as hebephrenia, and is named after the Greek goddess of youth, Hebe, in reference to the typical age of onset in puberty.

Unlike the paranoid subtype of schizophrenia, delusions and hallucinations are not the most prominent feature, although fragmentary delusions and hallucinations may be present.

The emotional responses of people diagnosed with this subtype can often seem strange or inappropriate to the situation. Inappropriate facial responses may be common and behavior is sometimes described as 'silly', such as inappropriate laughter. Complete lack of expressed emotion is sometimes seen, as is an apparent indifference, anhedonia (the lack of pleasure), and avolition (a lack of motivation). Some of these features are also present in other types of schizophrenia, but they are most prominent in Disorganized Schizophrenia.

Treatment

This form of schizophrenia is typically associated with early onset (often between the ages of 15 and 25 years) and is thought to have a poor prognosis because of the rapid development of 'negative' symptoms and decline in social functioning.

Use of electroconvulsive therapy has been proposed.

- **Catatonic type**: The subject may be almost immobile or exhibit agitated, purposeless movement. Symptoms can include catatonic stupor and waxy flexibility. (DSM code 295.2/ICD code F20.2)

Catatonic schizophrenia	
ICD-10	F20.2
ICD-9	295.2
MeSH	D002389

Catatonia is a syndrome of psychological and motorological disturbances. Karl Ludwig Kahlbaum first described it in 1874: *Die Katatonie oder das Spannungirresein* (Catatonia or Tension Insanity). In the current *Diagnostic and Statistical Manual of Mental Disorders* published by the American Psychiatric Association (DSM-IV) it is not recognized as a separate disorder, but is associated with psychiatric conditions such as schizophrenia (catatonic type), bipolar disorder, post-traumatic stress disorder, depression and other mental disorders, as well as drug abuse or overdose (or both). It may also be seen in many medical disorders including infections (such as encephalitis), autoimmune disorders, focal neurologic lesions (including strokes), metabolic disturbances and abrupt or overly rapid benzodiazepine withdrawal. It can be an adverse reaction to prescribed medication. It bears similarity to conditions such as encephalitis lethargica and neuroleptic malignant syndrome. There are a variety of treatments available; benzodiazepines are a first-line treatment strategy. Electro-convulsive therapy is also sometimes used. There is growing evidence for the effectiveness of NMDA antagonists for benzodiazepine resistant catatonia. Antipsychotics are sometimes employed but require caution as they can worsen symptoms and have serious adverse effects.

Clinical features

Patients with catatonia may experience an extreme loss of motor skills or even constant hyperactive motor activity. Catatonic patients will sometimes hold rigid poses for hours and will ignore any external stimuli. Patients with catatonic excitement can die of exhaustion if not treated. Patients may also show stereotyped, repetitive movements. They may show specific types of movement such as waxy flexibility, in which they maintain positions after being placed in them by someone else, or *gegenhalten* (lit. "counterhold"), in which they resist movement in proportion to the force applied by the examiner. They may repeat meaningless phrases or speak only to repeat what the examiner says.

While catatonia is only identified as a symptom of schizophrenia in present psychiatric classifications, it is increasingly recognized as a syndrome with many faces. It appears as the Kahlbaum syndrome (retarded catatonia), malignant catatonia (neuroleptic malignant syndrome, toxic serotonin syndrome), and excited forms (delirious mania, catatonic excitement, oneirophrenia). It has also been recognized as grafted on to autism spectrum disorders.

Diagnostic criteria

According to the DSM-IV, the "With catatonic features" specifier can be applied if the clinical picture is dominated by at least two of the following:

- motor immobility as evidenced by catalepsy (including waxy flexibility) or stupor
- excessive motor activity (purposeless, not influenced by external stimuli)
- extreme negativism (motiveless resistance to all instructions or maintenance of a rigid posture against attempts to be moved) or mutism

- peculiarities of voluntary movement as evidenced by posturing, stereotyped movements, prominent mannerisms, or prominent grimacing
- echolalia or echopraxia

Subtypes

- **Stupor** is a motionless, apathetic state in which one is oblivious or does not react to external stimuli. Motor activity is nearly non-existent. Individuals in this state make little or no eye contact with others and may be mute and rigid. One might remain in one position for a long period of time, and then go directly to another position immediately after the first position.

- **Catatonic excitement** is a state of constant purposeless agitation and excitation. Individuals in this state are extremely hyperactive, although, as aforementioned, the activity seems to lack purpose.

Catatonia rating scale

Fink and Taylor developed a catatonia rating scale to identify the syndrome. A diagnosis is verified by a benzodiazepine or barbiturate test. The diagnosis is validated by the quick response to either benzodiazepines or electroconvulsive therapy (ECT). While proven useful in the past, barbiturates are no longer commonly used in psychiatry; thus the option of either benzodiazepines or ECT.

Treatment

Initial treatment is aimed at providing relief from the catatonic state. Benzodiazepines are the first line of treatment, and high doses are often required. A test dose of 1–2 mg of intramuscular lorazepam will often result in marked improvement within half an hour. In France, zolpidem has also been used in diagnosis, and response may occur within the same time period. Ultimately the underlying cause needs to be treated.

Electroconvulsive therapy (ECT) is an effective treatment for catatonia as well as for most of the underlying causes (e.g. psychosis, mania, depression). Antipsychotics should be used with care as they can worsen catatonia and are the cause of neuroleptic malignant syndrome, a dangerous condition that can mimic catatonia and requires immediate discontinuation of the antipsychotic.

Excessive glutamate activity is believed to be involved in catatonia; when first-line treatment options fail, NMDA antagonists such as amantadine or memantine are used. Amantadine may have an increased incidence of tolerance with prolonged use and can cause psychosis, due to its additional effects on the dopamine system. Memantine has a more targeted pharmacological profile for the glutamate system, reduced incidence of psychosis and may therefore be preferred for individuals who cannot tolerate amantadine. Topiramate, is a another treatment option for resistant catatonia; it produces its

therapeutic effects by producing glutamate antagonism via modulation of AMPA receptors.

A version known as "catatonia-like deterioration" occurs in 12-17% of autistic young adults. This form is made worse by antipsychotics. Unlike catatonic stupors, this deterioration happens very gradually. The only way to cure it is to keep the patient constantly active and the activities must have an end goal or they will not work. Stress must be reduced by not pressurising, keeping life predictable and by limiting choice as making choices is very stressful for catatonics.

- **Undifferentiated type**: Psychotic symptoms are present but the criteria for paranoid, disorganized, or catatonic types have not been met. (DSM code 295.9/ICD code F20.3)
- **Residual type**: Where positive symptoms are present at a low intensity only. (DSM code 295.6/ICD code F20.5)

The ICD-10 defines two additional subtypes.

- **Post-schizophrenic depression**: A depressive episode arising in the aftermath of a schizophrenic illness where some low-level schizophrenic symptoms may still be present. (ICD code F20.4)
- **Simple schizophrenia**: Insidious and progressive development of prominent negative symptoms with no history of psychotic episodes. (ICD code F20.6)

Controversies and research directions

The scientific validity of schizophrenia, and its defining symptoms such as delusions and hallucinations, have been criticised. In 2006, a group of consumers and mental health professionals from the UK, under the banner of Campaign for Abolition of the Schizophrenia Label, argued for a rejection of the diagnosis of schizophrenia based on its heterogeneity and associated stigma, and called for the adoption of a biopsychosocial model. Other UK psychiatrists opposed the move arguing that the term schizophrenia is a useful, even if provisional concept.

Similarly, there is an argument that the underlying issues would be better addressed as a spectrum of conditions or as individual dimensions along which everyone varies rather than by a diagnostic category based on an arbitrary cut-off between normal and ill. This approach appears consistent with research on schizotypy, and with a relatively high prevalence of psychotic experiences, mostly non-distressing delusional beliefs, among the general public. In concordance with this observation, psychologist Edgar Jones, and psychiatrists Tony David and Nassir Ghaemi, surveying the existing literature on delusions, pointed out that the consistency and completeness of the definition of delusion have been found wanting by many; delusions are neither necessarily fixed, nor false, nor involve the presence of incontrovertible evidence.

Nancy Andreasen, a leading figure in schizophrenia research, has criticized the current DSM-IV and ICD-10 criteria for sacrificing diagnostic validity for the sake of artificially improving reliability. She argues that overemphasis on psychosis in the diagnostic criteria, while improving diagnostic reliability, ignores more fundamental cognitive impairments that are harder to assess due to large variations in presentation. This view is supported by other psychiatrists. In the same vein, Ming Tsuang and colleagues argue that psychotic symptoms may be a common end-state in a variety of disorders, including schizophrenia, rather than a reflection of the specific etiology of schizophrenia, and warn that there is little basis for regarding DSM's operational definition as the "true" construct of schizophrenia. Neuropsychologist Michael Foster Green went further in suggesting the presence of specific neurocognitive deficits may be used to construct phenotypes that are alternatives to those that are purely symptom-based. These deficits take the form of a reduction or impairment in basic psychological functions such as memory, attention, executive function and problem solving.

The exclusion of affective components from the criteria for schizophrenia, despite their ubiquity in clinical settings, has also caused contention. This exclusion in the DSM has resulted in a "rather convoluted" separate disorder—schizoaffective disorder. Citing poor interrater reliability, some psychiatrists have totally contested the concept of schizoaffective disorder as a separate entity. The categorical distinction between mood disorders and schizophrenia, known as the Kraepelinian dichotomy, has also been challenged by data from genetic epidemiology.

An approach broadly known as the anti-psychiatry movement, most active in the 1960s, opposes the orthodox medical view of schizophrenia as an illness. Psychiatrist Thomas Szasz argues that psychiatric patients are individuals with unconventional thoughts and behavior that society diagnoses as a method of social control, and therefore the diagnosis of "schizophrenia" is merely a form of social construction. The Hearing Voices Movement argues that many people diagnosed as psychotic need their experiences to be accepted and valued rather than medicalized.

Mechanisms

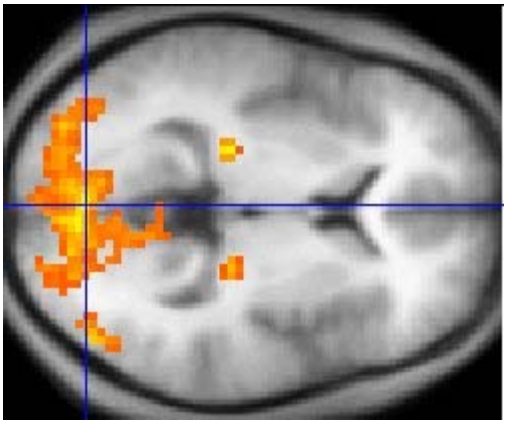
Psychological

A number of psychological mechanisms have been implicated in the development and maintenance of schizophrenia. Cognitive biases that have been identified in those with a diagnosis or those at risk, especially when under stress or in confusing situations, include excessive attention to potential threats, jumping to conclusions, making external attributions, impaired reasoning about social situations and mental states, difficulty distinguishing inner speech from speech from an external source, and difficulties with early visual processing and maintaining concentration. Some cognitive features may reflect global neurocognitive deficits in memory, attention, problem-solving, executive function or social cognition, while others may be related to particular issues and experiences.

Despite a common appearance of "blunted affect", recent findings indicate that many individuals diagnosed with schizophrenia are emotionally responsive, particularly to stressful or negative stimuli, and that such sensitivity may cause vulnerability to symptoms or to the disorder. Some evidence suggests that the content of delusional beliefs and psychotic experiences can reflect emotional causes of the disorder, and that how a person interprets such experiences can influence symptomatology. The use of "safety behaviors" to avoid imagined threats may contribute to the chronicity of delusions. Further evidence for the role of psychological mechanisms comes from the effects of psychotherapies on symptoms of schizophrenia.

Neural

Studies using neuropsychological tests and brain imaging technologies such as fMRI and PET to examine functional differences in brain activity have shown that differences seem to most commonly occur in the frontal lobes, hippocampus and temporal lobes. These differences have been linked to the neurocognitive deficits often associated with schizophrenia.



Functional magnetic resonance imaging and other brain imaging technologies allow for the study of differences in brain activity among people diagnosed with schizophrenia

Particular focus has been placed upon the function of dopamine in the mesolimbic pathway of the brain. This focus largely resulted from the accidental finding that a drug group which blocks dopamine function, known as the phenothiazines, could reduce psychotic symptoms. It is also supported by the fact that amphetamines, which trigger the release of dopamine, may exacerbate the psychotic symptoms in schizophrenia. An influential theory, known as the Dopamine hypothesis of schizophrenia, proposed that excess activation of D_2 receptors was the cause of (the positive symptoms of) schizophrenia. Although postulated for about 20 years based on the D_2 blockade effect common to all antipsychotics, it was not until the mid-1990s that PET and SPET imaging studies provided supporting evidence. This explanation is now thought to be simplistic, partly because newer antipsychotic medication (called atypical antipsychotic medication) can be equally effective as older medication (called typical antipsychotic medication), but also affects serotonin function and may have slightly less of a dopamine blocking effect.

Interest has also focused on the neurotransmitter glutamate and the reduced function of the NMDA glutamate receptor in schizophrenia. This has largely been suggested by abnormally low levels of glutamate receptors found in postmortem brains of people previously diagnosed with schizophrenia and the discovery that the glutamate blocking drugs such as phencyclidine and ketamine can mimic the symptoms and cognitive problems associated with the condition. The fact that reduced glutamate function is linked to poor performance on tests requiring frontal lobe and hippocampal function and that glutamate can affect dopamine function, all of which have been implicated in schizophrenia, have suggested an important mediating (and possibly causal) role of glutamate pathways in schizophrenia. Positive symptoms fail however to respond to glutamatergic medication.

A commonly known side effect associated with schizo-affective patients known as akathisia (mistaken for schizophrenic symptoms) was found to be associated with increased levels of norepinephrine. Data supports the efficacy of novel antipsychotics which deal with agonism of the NDMA glutamate receptors, associated with regulating uptake of norepinephrine, which in turn affects the trafficking of glutamate. This, as well as the data noting exacerbation of positive symptoms in users of norepinephrine-agonizing amphetamine, suggests that schizophrenia may in fact have a greater association with abnormal norepinephrine-reuptake kinetics and less with dopamine, which may in fact be responsible for a large part of the mechanism of glutamate release. It would be greatly beneficial for further research to be done in this area, particularly in the metabolism of various essential amino acids and their pro- and inhibitory effects on neurotransmitter balance.

There have also been findings of differences in the size and structure of certain brain areas in schizophrenia. A 2006 metaanlaysis of MRI studies found that whole brain and hippocampal volume are reduced and that ventricular volume is increased in patients with a first psychotic episode relative to healthy controls. The average volumetric changes in these studies are however close to the limit of detection by MRI methods, so it remains to be determined whether schizophrenia is a neurodegenerative process that begins at about the time of symptom onset, or whether it is better characterised as a neurodevelopmental process that produces abnormal brain volumes at an early age. In first episode psychosis typical antipsychotics like haloperidol were associated with significant reductions in gray matter volume, whereas atypical antipsychotics like olanzapine were not. Studies in non-human primates found gray and white matter reductions for both typical and atypical antipsychotics.

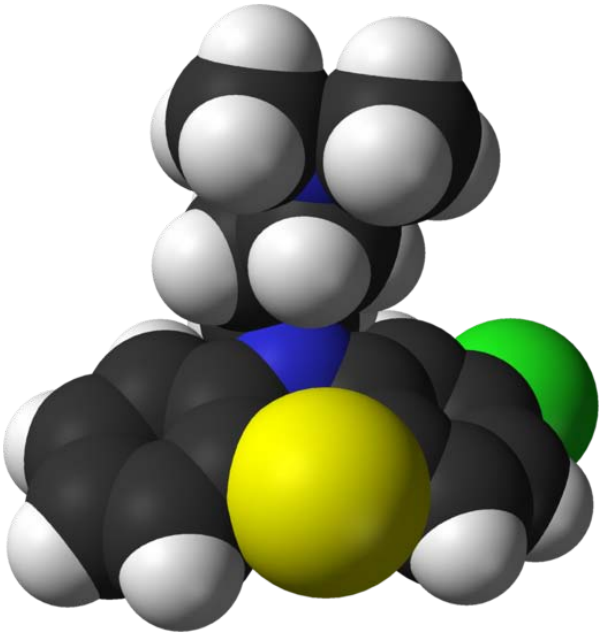
A 2009 meta-analysis of diffusion tensor imaging studies identified two consistent locations of reduced fractional anisotropy (roughly the level of organization of neural connections) in schizophrenia. The authors suggest that two networks of white matter tracts may be affected in schizophrenia, with the potential for "disconnection" of the gray matter regions which they link. During fMRI studies, greater connectivity in the brain's default network and task-positive network has been observed in patients diagnosed with schizophrenia, and may reflect excessive attentional orientation toward introspection and

toward extrospection, respectively. The greater anti-correlation between the two networks suggests excessive rivalry between the networks.

Screening and prevention

There are no reliable markers for the later development of schizophrenia although research is being conducted into how well a combination of genetic risk plus non-disabling psychosis-like experience predicts later diagnosis. People who fulfill the 'ultra high-risk mental state' criteria, that include a family history of schizophrenia plus the presence of transient or self-limiting psychotic experiences, have a 20–40% chance of being diagnosed with the condition after one year. The use of psychological treatments and medication has been found effective in reducing the chances of people who fulfill the 'high-risk' criteria from developing full-blown schizophrenia. However, the treatment of people who may never develop schizophrenia is controversial, in light of the side-effects of antipsychotic medication; particularly with respect to the potentially disfiguring tardive dyskinesia and the rare but potentially lethal neuroleptic malignant syndrome. The most widely used form of preventative health care for schizophrenia takes the form of public education campaigns that provide information on risk factors and early symptoms, with the aim to improve detection and provide treatment earlier for those experiencing delays. The new clinical approach early intervention in psychosis is a secondary prevention strategy to prevent further episodes and prevent the long term disability associated with schizophrenia.

Management



Molecule of chlorpromazine (trade name Thorazine), which revolutionized treatment of schizophrenia in the 1950s

The effectiveness of schizophrenia treatment is often assessed using standardized methods, one of the most common being the Positive and Negative Syndrome Scale (PANSS). Management of symptoms and improving function is thought to be more achievable than a cure. Treatment was revolutionized in the mid-1950s with the development and introduction of chlorpromazine. A recovery model is increasingly adopted, emphasizing hope, empowerment and social inclusion.

Hospitalization may occur with severe episodes of schizophrenia. This can be voluntary or (if mental health legislation allows it) involuntary (called civil or involuntary commitment). Long-term inpatient stays are now less common due to deinstitutionalization, although can still occur. Following (or in lieu of) a hospital admission, support services available can include drop-in centers, visits from members of a community mental health team or Assertive Community Treatment team, supported employment and patient-led support groups.

In many non-Western societies, schizophrenia may be treated with more informal, community-led methods only. Multiple international surveys by the World Health Organization over several decades have indicated that the outcome for people diagnosed with schizophrenia in non-Western countries is on average better there than for people in the West.

Medication

The first line psychiatric treatment for schizophrenia is antipsychotic medication. These can reduce the positive symptoms of psychosis. Most antipsychotics take around 7–14 days to have their main effect. Currently available antipsychotics fail, however, to significantly ameliorate the negative symptoms, and the improvements on cognition may be attributed to the practice effect.

Risperidone (trade name Risperdal) is a common atypical antipsychotic medication

The newer atypical antipsychotic drugs are usually preferred for initial treatment over the older typical antipsychotic, although they are expensive and are more likely to induce weight gain and obesity-related diseases. In 2005–2006, results from a major randomized trial sponsored by the US National Institute of Mental Health (Clinical Antipsychotic Trials of Intervention Effectiveness, or CATIE) found that a representative first-generation antipsychotic, perphenazine, was as effective as and more cost-effective than several newer drugs taken for up to 18 months. The atypical antipsychotic which patients were willing to continue for the longest, olanzapine, was associated with considerable weight gain and risk of metabolic syndrome. Clozapine was most effective for people with a poor response to other drugs, but it had troublesome side effects. Because the trial excluded patients with tardive dyskinesia, its relevance to these people is unclear.

Because of their reportedly lower risk of side effects that affect mobility, atypical antipsychotics have been first-line treatment for early-onset schizophrenia for many years before certain drugs in this class were approved by the Food and Drug Administration for use in children and teenagers with schizophrenia. This advantage comes at the cost of an increased risk of metabolic syndrome and obesity, which is of concern in the context of long-term use begun at an early age. Especially in the case of children and teenagers who have schizophrenia, medication should be used in combination with individual therapy and family-based interventions.

Recent reviews have refuted the claim that atypical antipsychotics have fewer extrapyramidal side effects than typical antipsychotics, especially when the latter are used in low doses or when low potency antipsychotics are chosen. Prolactin elevations have been reported in women with schizophrenia taking atypical antipsychotics. It remains unclear whether the newer antipsychotics reduce the chances of developing neuroleptic malignant syndrome, a rare but serious and potentially fatal neurological disorder most often caused by an adverse reaction to neuroleptic or antipsychotic drugs.

Response of symptoms to medication is variable: treatment-resistant schizophrenia is a term used for the failure of symptoms to respond satisfactorily to at least two different antipsychotics. Patients in this category may be prescribed clozapine, a medication of superior effectiveness but several potentially lethal side effects including agranulocytosis and myocarditis. For other patients who are unwilling or unable to take medication regularly, long-acting depot preparations of antipsychotics may be given every two weeks to achieve control. The United States and Australia are two countries with laws allowing the forced administration of this type of medication on those who refuse, but are otherwise stable and living in the community.

Psychological and social interventions

Psychotherapy is also widely recommended and used in the treatment of schizophrenia, although services may often be confined to pharmacotherapy because of reimbursement problems or lack of training.

Cognitive behavioral therapy (CBT) is used to target specific symptoms and improve related issues such as self-esteem, social functioning, and insight. Although the results of early trials were inconclusive as the therapy advanced from its initial applications in the mid 1990s, CBT has become an effective treatment to reduce positive and negative symptoms of schizophrenia, as well as improving functioning. However, in a 2010 article in *Psychological Medicine* entitled, "Cognitive behavioral therapy for the major psychiatric disorder: does it really work?", Lynch, Laws & McKenna found that no trial employing both blinding and psychological placebo has found CBT to be effective in either reducing symptoms or preventing relapse in schizophrenia.

Another approach is cognitive remediation, a technique aimed at remediating the neurocognitive deficits sometimes present in schizophrenia. Based on techniques of neuropsychological rehabilitation, early evidence has shown it to be cognitively effective,

with some improvements related to measurable changes in brain activation as measured by fMRI. A similar approach known as cognitive enhancement therapy, which focuses on social cognition as well as neurocognition, has shown efficacy.

Family therapy or education, which addresses the whole family system of an individual with a diagnosis of schizophrenia, has been consistently found to be beneficial, at least if the duration of intervention is longer-term. Aside from therapy, the effect of schizophrenia on families and the burden on carers has been recognized, with the increasing availability of self-help books on the subject. There is also some evidence for benefits from social skills training, although there have also been significant negative findings. Some studies have explored the possible benefits of music therapy and other creative therapies.

The Soteria model is alternative to inpatient hospital treatment using a minimal medication approach. It is described as a milieu-therapeutic recovery method, characterized by its founder as "the 24 hour a day application of interpersonal phenomenologic interventions by a nonprofessional staff, usually without neuroleptic drug treatment, in the context of a small, homelike, quiet, supportive, protective, and tolerant social environment." Although research evidence is limited, a 2008 systematic review found the programme equally as effective as treatment with medication in people diagnosed with first and second episode schizophrenia.

Other

Electroconvulsive therapy is not considered a first line treatment but may be prescribed in cases where other treatments have failed. It is more effective where symptoms of catatonia are present, and is recommended for use under NICE guidelines in the UK for catatonia if previously effective, though there is no recommendation for use for schizophrenia otherwise. Psychosurgery has now become a rare procedure and is not a recommended treatment.

Service-user led movements have become integral to the recovery process in Europe and the United States; groups such as the Hearing Voices Network and the Paranoia Network have developed a self-help approach that aims to provide support and assistance outside the traditional medical model adopted by mainstream psychiatry. By avoiding framing personal experience in terms of criteria for mental illness or mental health, they aim to destigmatize the experience and encourage individual responsibility and a positive self-image. Partnerships between hospitals and consumer-run groups are becoming more common, with services working toward remediating social withdrawal, building social skills and reducing rehospitalization.

Regular exercise can have healthful effects on both the physical and mental health and well-being of individuals with schizophrenia.

Prognosis

Course

John Nash, a US mathematician, began showing signs of paranoid schizophrenia during his college years. Despite having stopped taking his prescribed medication, Nash continued his studies and was awarded the Nobel Prize in 1994. His life was depicted in the 2001 film *A Beautiful Mind*.

Coordinated by the World Health Organization and published in 2001, The International Study of Schizophrenia (ISoS) was a long-term follow-up study of 1633 individuals diagnosed with schizophrenia around the world. Of the 75% who were available for follow-up, half had a favourable outcome, and 16% had a delayed recovery after an early

unremitting course. More usually, the course in the first two years predicted the long-term course. Early social intervention was also related to a better outcome. The findings were held as important in moving patients, carers and clinicians away from the prevalent belief of the chronic nature of the condition. A review of major longitudinal studies in North America noted this variation in outcomes, although outcome was on average worse than for other psychotic and psychiatric disorders. A moderate number of patients with schizophrenia were seen to remit and remain well; the review raised the question that some may not require maintenance medication.

A clinical study using strict recovery criteria (concurrent remission of positive and negative symptoms and adequate social and vocational functioning continuously for two years) found a recovery rate of 14% within the first five years. A 5-year community study found that 62% showed overall improvement on a composite measure of clinical and functional outcomes.

World Health Organization studies have noted that individuals diagnosed with schizophrenia have much better long-term outcomes in developing countries (India, Colombia and Nigeria) than in developed countries (United States, United Kingdom, Ireland, Denmark, Czech Republic, Slovakia, Japan, and Russia), despite antipsychotic drugs not being widely available.

Defining recovery

Rates are not always comparable across studies because exact definitions of remission and recovery have not been widely established. A "Remission in Schizophrenia Working Group" has proposed standardized remission criteria involving "improvements in core signs and symptoms to the extent that any remaining symptoms are of such low intensity that they no longer interfere significantly with behavior and are below the threshold typically utilized in justifying an initial diagnosis of schizophrenia". Standardized recovery criteria have also been proposed by a number of different researchers, with the stated DSM definitions of a "complete return to premorbid levels of functioning" or "complete return to full functioning" seen as inadequate, impossible to measure, incompatible with the variability in how society defines normal psychosocial functioning, and contributing to self-fulfilling pessimism and stigma. Some mental health professionals may have quite different basic perceptions and concepts of recovery than individuals with the diagnosis, including those in the Consumer/Survivor/Ex-Patient Movement. One notable limitation of nearly all the research criteria is failure to address the person's own evaluations and feelings about their life. Schizophrenia and recovery often involve a continuing loss of self-esteem, alienation from friends and family, interruption of school and career, and social stigma, "experiences that cannot just be reversed or forgotten". An increasingly influential model defines recovery as a process, similar to being "in recovery" from drug and alcohol problems, and emphasizes a personal journey involving factors such as hope, choice, empowerment, social inclusion and achievement.

Predictors

Several factors have been associated with a better overall prognosis: Being female, rapid (vs. insidious) onset of symptoms, older age of first episode, predominantly positive (rather than negative) symptoms, presence of mood symptoms, and good pre-illness functioning. The strengths and internal resources of the individual concerned, such as determination or psychological resilience, have also been associated with better prognosis. The attitude and level of support from people in the individual's life can have a significant impact; research framed in terms of the negative aspects of this—the level of critical comments, hostility, and intrusive or controlling attitudes, termed high 'Expressed emotion'—has consistently indicated links to relapse. Most research on predictive factors is correlational in nature, however, and a clear cause-and-effect relationship is often difficult to establish.

Mortality

In a study of over 168,000 Swedish citizens undergoing psychiatric treatment, schizophrenia was associated with an average life expectancy of approximately 80–85% of that of the general population; women were found to have a slightly better life expectancy than men, and a diagnosis of schizophrenia was associated with an overall better life expectancy than substance abuse, personality disorder, heart attack and stroke. Other identified factors include smoking, poor diet, little exercise and the negative health effects of psychiatric drugs.

There is a higher than average suicide rate associated with schizophrenia. This has been cited at 10%, but a more recent analysis of studies and statistics revises the estimate at 4.9%, most often occurring in the period following onset or first hospital admission. Several times more attempt suicide. There are a variety of reasons and risk factors.

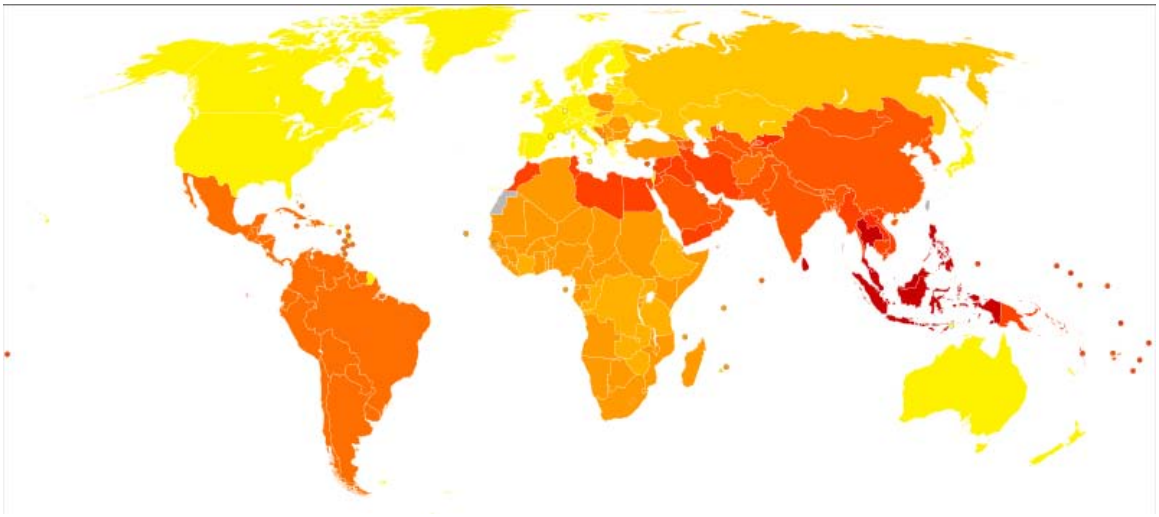
Violence

The relationship between violent acts and schizophrenia is a contentious topic. Current research indicates that the percentage of people with schizophrenia who commit violent acts is higher than the percentage of people without any disorder, but lower than is found for disorders such as alcoholism, and the difference is reduced or not found in same-neighbourhood comparisons when related factors are taken into account, notably sociodemographic variables and substance misuse. Studies have indicated that 5% to 10% of those charged with murder in Western countries have a schizophrenia spectrum disorder.

The occurrence of psychosis in schizophrenia has sometimes been linked to a higher risk of violent acts. Findings on the specific role of delusions or hallucinations have been inconsistent, but have focused on delusional jealousy, perception of threat and command hallucinations. It has been proposed that a certain type of individual with schizophrenia may be most likely to offend, characterized by a history of educational difficulties, low IQ, conduct disorder, early-onset substance misuse and offending prior to diagnosis.

Individuals with a diagnosis of schizophrenia are often the victims of violent crime—at least 14 times more often than they are perpetrators. Another consistent finding is a link to substance misuse, particularly alcohol, among the minority who commit violent acts. Violence by or against individuals with schizophrenia typically occurs in the context of complex social interactions within a family setting, and is also an issue in clinical services and in the wider community.

Epidemiology



Disability-adjusted life year for schizophrenia per 100,000 inhabitants in 2002.
no data ≤ 185 185–197 197–207 207–218 218–229 229–240 240–251 251–262 262–273 273–284 284–295 ≥ 295

Schizophrenia occurs equally in males and females, although typically appears earlier in men—the peak ages of onset are 20–28 years for males and 26–32 years for females. Onset in childhood is much rarer, as is onset in middle- or old age. The lifetime prevalence of schizophrenia—the proportion of individuals expected to experience the disease at any time in their lives—is commonly given at 1%. However, a 2002 systematic review of many studies found a lifetime prevalence of 0.55%. Despite the received wisdom that schizophrenia occurs at similar rates worldwide, its prevalence varies across the world, within countries, and at the local and neighbourhood level. One particularly stable and replicable finding has been the association with living in an urban environment and increased incidence of schizophrenia, even after factors such as drug use, ethnic group and size of social group have been controlled for. Schizophrenia is known to be a major cause of disability. In a 1999 study of 14 countries, active psychosis was ranked the third-most-disabling condition after quadriplegia and dementia and ahead of paraplegia and blindness.

History

Accounts of a schizophrenia-like syndrome are thought to be rare in the historical record before the 1800s, although reports of irrational, unintelligible, or uncontrolled behavior were common. A detailed case report in 1797 concerning James Tilly Matthews, and accounts by Phillipe Pinel published in 1809, are often regarded as the earliest cases of the illness in the medical and psychiatric literature. Schizophrenia was first described as a distinct syndrome affecting teenagers and young adults by Bénédict Morel in 1853, termed *démence précoce* (literally 'early dementia'). The term dementia praecox was used in 1891 by Arnold Pick to in a case report of a psychotic disorder. In 1893 Emil Kraepelin introduced a broad new distinction in the classification of mental disorders between *dementia praecox* and mood disorder (termed manic depression and including both unipolar and bipolar depression). Kraepelin believed that *dementia praecox* was primarily a disease of the brain, and particularly a form of dementia, distinguished from other forms of dementia, such as Alzheimer's disease, which typically occur later in life.

The word *schizophrenia*—which translates roughly as "splitting of the mind" and comes from the Greek roots *schizein* (σχίζειν, "to split") and *phrēn*, *phren-* (φρήν, φρεν-, "mind")—was coined by Eugen Bleuler in 1908 and was intended to describe the separation of function between personality, thinking, memory, and perception. Bleuler described the main symptoms as 4 *A*'s: flattened *Affect*, *Autism*, impaired *Association* of ideas and *Ambivalence*. Bleuler realized that the illness was not a dementia as some of his patients improved rather than deteriorated and hence proposed the term schizophrenia instead.

In the early 1970s, the diagnostic criteria for schizophrenia was the subject of a number of controversies which eventually led to the operational criteria used today. It became clear after the 1971 US-UK Diagnostic Study that schizophrenia was diagnosed to a far greater extent in America than in Europe. This was partly due to looser diagnostic criteria in the US, which used the DSM-II manual, contrasting with Europe and its ICD-9. David Rosenhan's 1972 study, published in the journal *Science* under the title *On being sane in insane places*, concluded that the diagnosis of schizophrenia in the US was often subjective and unreliable. These were some of the factors in leading to the revision not only of the diagnosis of schizophrenia, but the revision of the whole DSM manual, resulting in the publication of the DSM-III in 1980.{subscription required}

The term *schizophrenia* is commonly misunderstood to mean that affected persons have a "split personality". Although some people diagnosed with schizophrenia may hear voices and may experience the voices as distinct personalities, schizophrenia does not involve a person changing among distinct multiple personalities. The confusion arises in part due to the literal interpretation of Bleuler's term *schizophrenia*. The first known misuse of the term to mean "split personality" was in an article by the poet T. S. Eliot in 1933.

Chapter 10

Causes of Schizophrenia

Data from a PET study suggests that the less the frontal lobes are activated (red) during a working memory task, the greater the increase in abnormal dopamine activity in the striatum (green), thought to be related to the neurocognitive deficits in schizophrenia.

While the reliability of the diagnosis introduces difficulties in measuring the relative effect of genes and environment (for example, symptoms overlap to some extent with severe bipolar disorder or major depression), evidence suggests that genetic and environmental factors can act in combination to result in schizophrenia. Evidence suggests that the diagnosis of schizophrenia has a significant heritable component but that onset is significantly influenced by environmental factors or stressors. The idea of an inherent vulnerability (or *diathesis*) in some people, which can be unmasked by biological, psychological or environmental stressors, is known as the *stress-diathesis model*. An alternative idea that biological, psychological and social factors are all important is known as the "biopsychosocial" model.

Genetic

Estimates of the heritability of schizophrenia tend to vary owing to the difficulty of separating the effects of genetics and the environment although twin and adoption studies have suggested a high level of heritability (the proportion of variation between

individuals in a population that is influenced by genetic factors). It has been suggested that schizophrenia is a condition of complex inheritance, with many different potential genes each of small effect, with different pathways for different individuals. Some have suggested that several genetic and other risk factors need to be present before a person becomes affected but this is still uncertain. Candidate genes linked to an increased risk of schizophrenia and bipolar disorder as found in recent genome wide association studies appear to be partly separate and partly overlapping between the two disorders Metaanalyses of genetic linkage studies have produced evidence of chromosomal regions increasing susceptibility, which interacts directly with the Disrupted in Schizophrenia 1 (DISC1) gene protein more recently the zinc finger protein 804A. has been implicated as well as the chromosome 6 HLA region. However, a large and comprehensive genetic study found no evidence of any significant association with any of 14 previously identified candidate genes. Schizophrenia, in a small minority of cases, has been associated with rare deletions or duplications of tiny DNA sequences (known as copy number variants) disproportionately occurring within genes involved in neuronal signaling and brain development/human cognitive, behavioral, and psychological variation. Relations have been found between autism spectrum disorders and schizophrenia based on duplications and deletions of chromosomes; research showed that schizophrenia and autism are significantly more common in combination with 1q21.1 deletion syndrome, velo-cardio-facial syndrome and Phelan-McDermid syndrome. Duplications of parts of the chromosomes which are opposites of these syndromes show more autism-results. Research on autism/schizophrenia relations for chromosome 15 (15q13.3), chromosome 16 (16p13.1) and chromosome 17 (17p12) are inconclusive.

Assuming a hereditary genetic basis, one question for evolutionary psychology is why genes that increase the likelihood of the condition evolved, assuming the condition would have been maladaptive from an evolutionary/reproductive point of view. One theory implicates genes involved in the evolution of language and human nature, but so far all theories have been disproved or remain unsubstantiated.

Prenatal

Causal factors are thought to initially come together in early neurodevelopment to increase the risk of later developing schizophrenia. One curious finding is that people diagnosed with schizophrenia are more likely to have been born in winter or spring, (at least in the northern hemisphere). There is now evidence that prenatal exposure to infections increases the risk for developing schizophrenia later in life, providing additional evidence for a link between in utero developmental pathology and risk of developing the condition.

Social

Living in an urban environment has been consistently found to be a risk factor for schizophrenia. Social disadvantage has been found to be a risk factor, including poverty and migration related to social adversity, racial discrimination, family dysfunction, unemployment or poor housing conditions. Childhood experiences of abuse or trauma

have also been implicated as risk factors for a diagnosis of schizophrenia later in life. Parenting is not held responsible for schizophrenia but unsupportive dysfunctional relationships may contribute to an increased risk.

Substance Abuse

In a recent study of people with schizophrenia and a substance abuse disorder, over a ten year period, "substantial proportions were above cutoffs selected by dual diagnosis clients as indicators of recovery." Although about half of all patients with schizophrenia use drugs or alcohol, and the vast majority use tobacco, a clear causal connection between drug use and schizophrenia has been difficult to prove. The two most often used explanations for this are "substance use causes schizophrenia" and "substance use is a consequence of schizophrenia", and they both may be correct. A 2007 meta-analysis estimated that cannabis use is statistically associated with a dose-dependent increase in risk of development of psychotic disorders, including schizophrenia, though the authors admit that some uncertainty about causality still remains. For example, cannabis use has increased dramatically in several countries over the past few decades, though contrary to predictions the rates of psychosis and schizophrenia have generally *not* increased.

Psychotic individuals may also use drugs to cope with unpleasant states such as depression, anxiety, boredom and loneliness, because drugs increase "feel-good" neurotransmitters level. Various studies have shown that amphetamines increases the concentrations of dopamine in the synaptic cleft, thereby heightening the response of the post-synaptic neuron. However, regarding psychosis itself, it is well understood that methamphetamine and cocaine use can result in methamphetamine- or cocaine-induced psychosis that present very similar symptomatology (sometimes even misdiagnosed as schizophrenia) and may persist even when users remain abstinent. The same can also be said for alcohol-induced psychosis, though to a somewhat lesser extent.

The **causes of schizophrenia** have been the subject of much debate, with various factors proposed and discounted or modified. The language of schizophrenia research under the medical model is scientific. Such studies suggest that genetics, prenatal development, early environment, neurobiology and psychological and social processes are important contributory factors. Current psychiatric research into the development of the disorder is often based on a neurodevelopmental model (proponents of which see schizophrenia as a syndrome.) However, schizophrenia is diagnosed on the basis of symptom profiles. Neural correlates do not provide sufficiently useful criteria. "Current research into schizophrenia has remained highly fragmented, much like the clinical presentation of the disease itself".

Although no common cause of schizophrenia has been identified in all individuals diagnosed with the condition, currently most researchers and clinicians believe it results from a combination of both brain vulnerabilities (either inherited or acquired) and life events. This widely adopted approach is known as the 'stress-vulnerability' model, and much scientific debate now focuses on how much each of these factors contributes to the development and maintenance of schizophrenia. Schizophrenia is most commonly first

diagnosed during late adolescence or early adulthood, suggesting it is often the end process of childhood and adolescent development. There is on average a somewhat earlier onset for men than women, with the possible influence of the female hormone estrogen being one hypothesis and sociocultural influences another.

Most of the factors causing schizophrenia mentioned in this article are mentioned by Philip Seeman who simplified the causes of schizophrenia to d2high, or the highly sensitive d2 receptor: genetics; psychostimulants; caesarian births - hypoxia; lesions and steroids.

Genetics

Evidence suggests that genetic vulnerability and environmental factors can act in combination to result in diagnosis of schizophrenia. Research suggests that genetic vulnerability to schizophrenia is multifactorial, caused by interactions of several genes.

Both individual twin studies and meta-analyses of twin studies estimate the heritability of risk for schizophrenia to be approximately 80% (this refers to the proportion of variation between individuals in a population that is influenced by genetic factors, not the degree of genetic determination of individual risk). Concordance rates between monozygotic twins was close to 50%; whereas dizygotic twins was 17%. Adoption studies have also indicated a somewhat increased risk in those with a parent with schizophrenia even when raised apart. Studies suggest that the phenotype is genetically influenced but not genetically determined; that the variants in genes are generally within the range of normal human variation and have low risk associated with them each individually; and that some interact with each other and with environmental risk factors; and that they may not be specific to schizophrenia.

Some twin studies have found rates as low as 11.0%–13.8% among monozygotic twins, and 1.8%–4.1% among dizygotic twins, however. Tyronne Cannon reviewed the situation, stating: "Previous twin studies have reported estimates of broad heritability ranging from 0.41 to 0.87" Yet, in the "Pairs of Veteran Twins" study, for example, 338 pairs were schizophrenic with only 26 pairs concordant, and it was concluded in one report: "the role of the suggested genetic factor appears to be a limited one; 85 percent of the affected monozygotic pairs in the sample were discordant for schizophrenia". In addition, some scientists criticize the methodology of the twin studies, and have argued that the genetic basis of schizophrenia is still largely unknown or open to different interpretations.

For example, although the concordance of schizophrenia occurrence in monozygotic twins has traditionally been used to estimate a genetic component to the illness, the results could be skewed because of environmental factors like a shared placenta

In fact, researchers, have used the phenomenon of 'fetal programming' to account for familial patterns in epidemiological studies. "Intra-uterine growth is a complex outcome that is influenced by a wide range of factors including fetal genotype, maternal

physiology and behaviour as well as the function of that crucial interface—the placenta," said one journal.

After reviewing techniques like: Genome Wide Association Studies; Single Nucleotide Polymorphisms and Copy Number Variations; the Nature journal reports: the basic observation is that, "You have this clear tangible phenomenon in which children resemble their parents"...."Despite what children get told in elementary school science we just don't know how that works," as Professor of ecology and evolutionary biology at Princeton, Leonid Kruglyak says (in reviewing hereditibility in general). It cites schizophrenia as a trait in which the genes have gone missing.

A great deal of effort has been put into molecular genetic studies of schizophrenia, which attempt to identify specific genes which may increase risk. A 2003 review of linkage studies listed seven genes as likely to increase risk for a later diagnosis of the disorder. Two recent reviews suggested that the evidence was strongest for two genes known as dysbindin (*DTNBP1*) and neuregulin (NRG1), and that a number of other genes (such as *COMT*, *RGS4*, *PPP3CC*, *ZDHHC8*, *DISC1*, and *AKT1*) showed some early promising results. Variations near the gene *FXYD6* have also been associated with schizophrenia in the UK but not in Japan. In 2008, rs7341475 SNP of the reelin gene was associated with an increased risk of schizophrenia in women, but not in men. This female-specific association was replicated in several populations. Still another review found evidence that the protein phosphatase 2B (calcineurin) might be involved in susceptibility to schizophrenia.

The largest most comprehensive genetic study of its kind, involving tests of several hundred single nucleotide polymorphisms (SNPs) in nearly 1,900 individuals with schizophrenia or schizoaffective disorder and 2,000 comparison subjects, reported in 2008 that there was no evidence of any significant association between the disorders and any of 14 previously identified candidate genes (*RGS4*, *DISC1*, *DTNBP1*, *STX7*, *TAAR6*, *PPP3CC*, *NRG1*, *DRD2*, *HTR2A*, *DAOA*, *AKT1*, *CHRNA7*, *COMT*, and *ARVCF*). The statistical distributions suggested nothing more than chance variation. The authors concluded that the findings make it unlikely that common SNPs in these genes account for a substantial proportion of the genetic risk for schizophrenia, although small effects could not be ruled out.

The perhaps largest analysis of genetic associations in schizophrenia is with the *SzGene* database at the *Schizophrenia Research Forum*. One 2008 meta-analysis examined genetic variants in 16 genes and found nominally significant effects.

Other research has suggested that a greater than average number of rare deletions or duplications of tiny DNA sequences within genes (known as copy number variants) are linked to increased risk for schizophrenia, especially in those "sporadic" cases not linked to family history of schizophrenia, and that the genetic factors and developmental pathways can thus be different in different individuals. A genome wide survey of 3,391 individuals with schizophrenia found CNVs in less than 1% of cases. Within them, deletions in regions related to psychosis were observed, as well as deletions on

chromosome 15q13.3 and 1q21.1. CNVs occur due to non-allelic homologous recombination mediated by low copy repeats (sequentially similar regions). This results in deletions and duplications of dosage sensitive genes. It has been speculated that CNVs underlie a significant proportion of normal human variation, including differences in cognitive, behavioral, and psychological features, and that CNVs in at least three loci can result in increased risk for schizophrenia in a few individuals. Epigenetics may also play a role in schizophrenia, with the expression of Protocadherin 11 X/Protocadherin Y playing a possible role in schizophrenia.

A 2009 study was able to create mice matching schizophrenic symptoms by the deletion of only one gene set, those of the neuregulin post-synaptic receptor. The result showed that although the mice mostly developed normally, on further brain development, glutamate receptors brokedown. This theory supports the glutamate hypothesis of schizophrenia. Another study in 2009 by Simon Fraser University researchers identifies a link between Autism and Schizophrenia:

"The SFU group found that variations in four sets of genes are related to both autism and schizophrenia. People normally have two copies of each gene, but in autistics some genome locations have only single copies and in schizophrenics extra copies are present at the same locations."

Obstetric events

It is well established that obstetric complications or events are associated with an increased chance of the child later developing schizophrenia, although overall they constitute a non-specific risk factor with a relatively small effect. Obstetric complications occur in approximately 25 to 30% of the general population and the vast majority do not develop schizophrenia, and likewise the majority of individuals with schizophrenia have not had a detectable obstetric event. Nevertheless, the increased average risk is well-replicated, and such events may moderate the effects of genetic or other environmental risk factors. The specific complications or events most linked to schizophrenia, and the mechanisms of their effects, are still under examination.

One epidemiological finding is that people diagnosed with schizophrenia are more likely to have been born in winter or spring (at least in the northern hemisphere). However, the effect is not large. Explanations have included a greater prevalence of viral infections at that time, or a greater likelihood of vitamin D deficiency. A similar effect (increased likelihood of being born in winter and spring) has also been found with other, healthy populations, such as chess players. Women who were pregnant during the Dutch famine of 1944, where many people were close to starvation (experiencing malnutrition) had a higher chance of having a child who would later develop schizophrenia. Studies of Finnish mothers who were pregnant when they found out that their husbands had been killed during the Winter War of 1939–1940 have shown that their children were significantly more likely to develop schizophrenia when compared with mothers who found out about their husbands' death after pregnancy, suggesting that maternal stress may have an effect.

Fetal growth

Lower than average birth weight has been one of the most consistent findings, indicating slowed fetal growth possibly mediated by genetic effects. Almost any factor adversely affecting the fetus will affect growth rate, however, so the association has been described as not particularly informative regarding causation. In addition, the majority of birth cohort studies have failed to find a link between schizophrenia and low birth weight or other signs of growth retardation.

Animal models have suggested links between intrauterine growth restriction and specific neurological abnormalities similar to those that may be involved in the development of schizophrenia, including ventricular enlargement and reduced hippocampal volume in guinea pigs.

Hypoxia

It has been hypothesized since the 1970s that brain hypoxia (low oxygen levels) before, at or immediately after birth may be a risk factor for the development of schizophrenia. Hypoxia is now being demonstrated as relevant to schizophrenia in animal models, molecular biology and epidemiology studies. One study in Molecular Psychiatry was able to differentiate 90% of schizophrenics from controls based on hypoxia and metabolism. Hypoxia has been recently described as one of the most important of the external factors that influence susceptibility, although studies have been mainly epidemiological. Such studies place a high degree of importance on hypoxic influence, but because of familial pattern of the illness in some families, propose a genetic factor also; stopping short of concluding hypoxia to be the sole cause. Fetal hypoxia, in the presence of certain unidentified genes, has been correlated with reduced volume of the hippocampus, which is in turn correlated with schizophrenia. Although most studies have interpreted hypoxia as causing some form of neuronal dysfunction or even subtle damage, it has been suggested that the physiological hypoxia that prevails in normal embryonic and fetal development, or pathological hypoxia or ischemia, may exert an effect by regulating or dysregulating genes involved in neurodevelopment. A literature review judged that over 50% of the candidate genes for susceptibility to schizophrenia met criteria for "ischemia–hypoxia regulation and/or vascular expression" even though only 3.5% of all genes were estimated to be involved in hypoxia/ischemia or the vasculature.

A longitudinal study found that obstetric complications involving hypoxia were one factor associated with neurodevelopmental impairments in childhood and with the later development of schizophreniform disorders. Fetal hypoxia has been found to predict unusual movements at age 4 (but not age 7) among children who go on to develop schizophrenia, suggesting that its effects are specific to the stage of neurodevelopment. A Japanese case study of monozygotic twins discordant for schizophrenia (one has the diagnosis while the other does not) draws attention to their different weights at birth and concludes hypoxia may be the differentiating factor. The unusual functional laterality in speech production (e.g. right hemisphere auditory processing) found in some individuals with schizophrenia could be due to aberrant neural networks established as a

compensation for left temporal lobe damage induced by pre- or perinatal hypoxia. Prenatal and perinatal hypoxia appears to be important as one factor in the neurodevelopmental model, with the important implication that some forms of schizophrenia may thus be preventable.

Research on rodents seeking to understand the possible role of prenatal hypoxia in disorders such as schizophrenia has indicated that it can lead to a range of sensorimotor and learning/memory abnormalities. Impairments in motor function and coordination, evident on challenging tasks when the hypoxia was severe enough to cause brain damage, were long-lasting and described as a "hallmark of prenatal hypoxia". Several animal studies have indicated that fetal hypoxia can affect many of the same neural substrates implicated in schizophrenia, depending on the severity and duration of the hypoxic event as well as the period of gestation, and in humans moderate or severe (but not mild) fetal hypoxia has been linked to a series of motor, language and cognitive deficits in children, regardless of genetic liability to schizophrenia. One paper restated that cerebellum neurological disorders were frequently found in schizophrenics and speculated hypoxia may cause the subsequent cognitive dysmetria

Whereas most studies find only a modest effect of hypoxia in schizophrenia, a longitudinal study using a combination of indicators to detect possible fetal hypoxia, such as early equivalents of Neurological Soft Signs or obstetric complications, reported that the risk of schizophrenia and other nonaffective psychoses was "strikingly elevated" (5.75% versus 0.39%). Although objective estimates of hypoxia did not account for all schizophrenic cases; the study revealed increasing odds of schizophrenia according to graded increase in severity of hypoxia.

Other factors

There is an emerging literature on a wide range of prenatal risk factors, such as prenatal stress, intrauterine (in the womb) malnutrition, and prenatal infection. Increased paternal age has been linked to schizophrenia, possibly due to "chromosomal aberrations and mutations of the aging germline." Maternal-fetal rhesus or genotype incompatibility has also been linked, via increasing the risk of an adverse prenatal environment. Also, in mothers with schizophrenia, an increased risk has been identified via a complex interaction between maternal genotype, maternal behavior, prenatal environment and possibly medication and socioeconomic factors. References for many of these environmental risk factors have been collected in an online database.

Infections

Numerous viral infections, in utero or in childhood, have been associated with an increased risk of later developing schizophrenia. Schizophrenia is somewhat more common in those born in winter to early spring, when infections are more common.

Influenza has long been studied as a possible factor. A 1988 study found that individuals who were exposed to the Asian flu as second trimester fetuses were at increased risk of

eventually developing schizophrenia. This result was corroborated by a later British study of the same pandemic, but not by a 1994 study of the pandemic in Croatia. A Japanese study also found no support for a link between schizophrenia and birth after an influenza epidemic.

Polio, measles, varicella-zoster, rubella, herpes simplex virus type 2, maternal genital infections, Borna disease virus, and more recently *Toxoplasma gondii*, have been correlated with the later development of schizophrenia. Psychiatrists E. Fuller Torrey and R.H. Yolken have hypothesized that the latter, a common parasite in humans, contributes to some, if not many, cases of schizophrenia. In a meta-analysis of several studies, they found moderately higher levels of Toxoplasma antibodies in those with schizophrenia and possibly higher rates of prenatal or early postnatal exposure to *Toxoplasma gondii*, but not acute infection. However, in another study of postmortem brain tissue, the authors have reported equivocal or negative results, including no evidence of herpes virus or *T. gondii* involvement in schizophrenia.

There is some evidence for the role of autoimmunity in the development of some cases of schizophrenia. A statistical correlation has been reported with various autoimmune diseases and direct studies have linked dysfunctional immune status to some of the clinical features of schizophrenia.

Childhood antecedents

In general, the antecedents of schizophrenia are subtle and those who will go on to develop schizophrenia do not form a readily identifiable subgroup - which would lead to identification of a specific cause. Average group differences from the norm may be in the direction of superior as well as inferior performance. Overall, birth cohort studies have indicated subtle nonspecific behavioral features, some evidence for psychotic-like experiences (particularly hallucinations), and various cognitive antecedents. There have been some inconsistencies in the particular domains of functioning identified and whether they continue through childhood and whether they are specific to schizophrenia.

A prospective study found average differences across a range of developmental domains, including reaching milestones of motor development at a later age, having more speech problems, lower educational test results, solitary play preferences at ages four and six, and being more socially anxious at age 13. Lower ratings of the mother's skills and understanding of the child at age 4 were also related.

Some of the early developmental differences were identified in the first year of life in a study in Finland, although generally related to psychotic disorders rather than schizophrenia in particular. The early subtle motor signs persisted to some extent, showing a small link to later school performance in adolescence. An earlier Finnish study found that childhood performance of 400 individuals diagnosed with schizophrenia was significantly worse than controls on subjects involving motor co-ordination (sports and handcrafts) between ages 7 and 9, but there were no differences on academic subjects (contrary to some other IQ findings). (Patients in this age group with these symptoms

were significantly less likely to progress to high school, despite academic ability) However, reanalysis of the data from the later Finnish study, on older children (14 to 16) in a changed school system, using narrower diagnostic criteria and with less cases but more controls, did not support a significant difference on sports and handicraft performance. However, another study found that unusual motor coordination scores at 7 years of age were associated in adulthood with both those with schizophrenia and their unaffected siblings, while unusual movements at ages 4 and 7 predicted adult schizophrenia but not unaffected sibling status.

A birth cohort study in New Zealand found that children who went on to develop schizophreniform disorder had, as well as emotional problems and interpersonal difficulties linked to all adult psychiatric outcomes measured, significant impairments in neuromotor, receptive language, and cognitive development. A retrospective study found that adults with schizophrenia had performed better than average in artistic subjects at ages 12 and 15, and in linguistic and religious subjects at age 12, but worse than average in gymnastics at age 15.

Some small studies on offspring of individuals with schizophrenia have identified various neurobehavioral deficits, a poorer family environment and disruptive school behaviour, poor peer engagement, immaturity or unpopularity or poorer social competence and increasing schizophrenic symptomology emerging during adolescence.

A minority "deficit syndrome" subtype of schizophrenia is proposed to be more marked by early poor adjustment and behavioral problems, as compared to non-deficit subtypes.

Substance use

The relationship between schizophrenia and drug use is complex, meaning that a clear causal connection between drug use and schizophrenia has been difficult to tease apart. There is strong evidence that using certain drugs can trigger either the onset or relapse of schizophrenia in some people. It may also be the case, however, that people with schizophrenia use drugs to overcome negative feelings associated with both the commonly prescribed antipsychotic medication and the condition itself, where negative emotion, paranoia and anhedonia are all considered to be core features.

The rate of substance use is known to be particularly high in this group. In a recent study, 60% of people with schizophrenia were found to use substances and 37% would be diagnosable with a substance use disorder.

Amphetamines and other stimulants

As amphetamines trigger the release of dopamine and excessive dopamine function is believed to be responsible for many symptoms of schizophrenia (known as the dopamine hypothesis of schizophrenia), amphetamines may worsen schizophrenia symptoms. In addition, amphetamines are known to cause a stimulant psychosis in otherwise healthy

individuals that superficially resembles schizophrenia, and may be misdiagnosed as such by some healthcare professionals.

Hallucinogens

Drugs such as ketamine, PCP, and LSD have been used to mimic schizophrenia for research purposes. Using LSD and other psychedelics as a model has now fallen out of favor with the scientific research community, as the differences between the drug induced states and the typical presentation of schizophrenia have become clear. The dissociatives ketamine and PCP, however, are still considered to produce states that are remarkably similar however, and are considered to be even better models than stimulants since they produce both positive and negative symptoms.

Cannabis

There is some evidence that cannabis use can contribute to schizophrenia. Some studies suggest that cannabis is neither a sufficient nor necessary factor in developing schizophrenia, but that cannabis may significantly increase the risk of developing schizophrenia and may be, among other things, a significant causal factor. Nevertheless, some previous research in this area has been criticised as it has often not been clear whether cannabis use is a cause or effect of schizophrenia. To address this issue, a recent review of studies from which a causal contribution to schizophrenia can be assessed has suggested that cannabis statistically doubles the risk of developing schizophrenia on the individual level, and may, assuming a causal relationship, be responsible for up to 8% of cases in the population.

An older longitudinal study, published in 1987, suggested sixfold increase of schizophrenia risks for high consumers of cannabis (use on more than fifty occasions) in Sweden.

Despite increases in cannabis consumption in the 1960s and 1970s in western society, rates of psychotic disorders such as schizophrenia remained relatively stable. Also, Sweden and Japan, where self-reported marijuana use is very low, do not have lower rates of psychosis than the U.S. and Canada do. For the theory of true causality to be correct, other factors which are thought to contribute to schizophrenia would have to have converged almost flawlessly to mask the effect of increased cannabis usage.

Clues from tobacco use

People with schizophrenia tend to smoke significantly more tobacco than the general population. The rates are exceptionally high amongst institutionalized patients and homeless people. In a UK census from 1993, 74% of people with schizophrenia living in institutions were found to be smokers. A 1999 study that covered all people with schizophrenia in Nithsdale, Scotland found a 58% prevalence rate of cigarette smoking, to compare with 28% in the general population. An older study found that as much as 88% of outpatients with schizophrenia were smokers.

Despite the higher prevalence of tobacco smoking, people diagnosed with schizophrenia have a much lower than average chance of developing and dying from lung cancer. While the reason for this is unknown, it may be because of a genetic resistance to the cancer, a side effect of drugs being taken, or a statistical effect of increased likelihood of dying from causes other than lung cancer.

A 2003 study of over 50,000 Swedish conscripts found that there was a small but significant protective effect of smoking cigarettes on the risk of developing schizophrenia later in life. While the authors of the study stressed that the risks of smoking far outweigh these minor benefits, this study provides further evidence for the 'self-medication' theory of smoking in schizophrenia and may give clues as to how schizophrenia might develop at the molecular level. Furthermore, many people with schizophrenia have smoked tobacco products long before they are diagnosed with the illness, and some groups advocate that the chemicals in tobacco have actually contributed to the onset of the illness and have no benefit of any kind.

It is of interest that cigarette smoking affects liver function such that the antipsychotic drugs used to treat schizophrenia are broken down in the blood stream more quickly. This means that smokers with schizophrenia need slightly higher doses of antipsychotic drugs in order for them to be effective than do their non-smoking counterparts.

The increased rate of smoking in schizophrenia may be due to a desire to self-medicate with nicotine. One possible reason is that smoking produces a short term effect to improve alertness and cognitive functioning in persons who suffer this illness. It has been postulated that the mechanism of this effect is that people with schizophrenia have a disturbance of nicotinic receptor functioning which is temporarily abated by tobacco use.

A study from 1989 and a 2004 case study show that when haloperidol is administered, nicotine limits the extent to which the antipsychotic increases the sensitivity of the dopamine 2 receptor. Dependent on the dopamine system, symptoms of Tardive Dyskinesia are not found in the nicotine administered patients despite a roughly 70% increase in dopamine receptor activity, but the controls have more than 90% and do develop symptoms.A 1997 study showed that akathisia was significantly reduced upon administration of nicotine when the akathisia was induced by antipsychotics. This gives credence to the idea tobacco could be used to self medicate by limiting effects of the illness, the medication, or both.

Life experiences

Social adversity

The chance of developing schizophrenia has been found to increase with the number of adverse social factors (e.g. indicators of socioeconomic disadvantage or social exclusion) present in childhood. Stressful life events generally precede the onset of schizophrenia. A personal or recent family history of migration is a considerable risk factor for schizophrenia, which has been linked to psychosocial adversity, social defeat from being

an outsider, racial discrimination, family dysfunction, unemployment and poor housing conditions. Childhood experiences of abuse or trauma are risk factors for a diagnosis of schizophrenia later in life. Recent large-scale general population studies indicate the relationship is a causal one, with an increasing risk with additional experiences of maltreatment, although a critical review suggests conceptual and methodological issues require further research. There is some evidence that adversities may lead to cognitive biases and/or altered dopamine neurotransmission, a process that has been termed "sensitization". Specific social experiences have been linked to specific psychological mechanisms and psychotic experiences in schizophrenia. In addition, structural neuroimaging studies of victims of sexual abuse and other traumas have sometimes reported findings similar to those sometimes found in psychotic patients, such as thinning of the corpus callosum, loss of volume in the anterior cingulate cortex, and reduced hippocampal volume.

Urbanicity

A particularly stable and replicable finding has been the association between living in an urban environment and the development of schizophrenia, even after factors such as drug use, ethnic group and size of social group have been controlled for. A recent study of 4.4 million men and women in Sweden found an 68%–77% increased risk of diagnosed psychosis for people living in the most urbanized environments, a significant proportion of which is likely to be described as schizophrenia. The effect does not appear to be due to a higher incidence of obstetric complications in urban environments. The risk increases with the number of years and degree of urban living in childhood and adolescence, suggesting that constant, cumulative, or repeated exposures during upbringing occurring more frequently in urbanized areas are responsible for the association. Various possible explanations for the effect have been judged unlikely based on the nature of the findings, including infectious causes or a generic stress effect. It is thought to interact with genetic dispositions and, since there appears to be nonrandom variation even across different neighborhoods, and an independent association with social isolation, it has been proposed that the degree of "social capital" (e.g. degree of mutual trust, bonding and safety in neighborhoods) can exert a developmental impact on children growing up in these environments.

Close relationships

Evidence is consistent that negative attitudes from others increase the risk of schizophrenia relapse, in particular critical comments, hostility, authoritarian, and intrusive or controlling attitudes (termed 'high expressed emotion' by researchers). Although family members and significant others are not held responsible for schizophrenia - the attitudes, behaviors and interactions of all parties are addressed - unsupportive dysfunctional relationships may also contribute to an increased risk of developing schizophrenia.

Neural processes

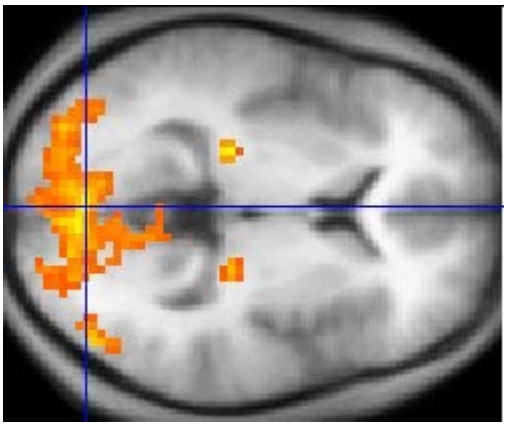
Structural

Studies have tended to show various subtle average differences in the volume of certain areas of brain structure between people with and without diagnoses of schizophrenia, although it has become increasingly clear that there is no single pathological neuropsychological or structural neuroanatomic profile, due partly to heterogeneity within the disorder. The most consistent volumetric findings are (first-onset patient vs control group averages), slightly less grey matter volume and slightly increased ventricular volume in certain areas of the brain. The two findings are thought to be linked. Although the differences are found in first-episode cases, grey matter volumes are partly a result of life experiences, drugs and malnutrition etc., so the exact role in the disorder is unclear. In addition, ventricle volumes are amongst the mostly highly variable and environmentally influenced aspects of brain structure, and the percentage difference in group averages in schizophrenia studies has been described as "not a very profound difference in the context of normal variation." A slightly smaller than average whole-brain volume has also been also been found, and slightly smaller hippocampal volume in terms of group averages. These differences may be present from birth or develop later, and there is substantial variation between individuals.

Most schizophrenia studies have found average reduced volume of the left medial temporal lobe and left superior temporal gyrus, and half of studies have revealed deficits in certain areas of the frontal gyrus, parahippocampal gyrus and temporal gyrus. However, at variance with some findings in individuals with chronic schizophrenia (where use of antipsychotics and other factors may have a confounding effect), significant group differences of temporal lobe and amygdala volumes are not shown in first-episode patients on average. The neurobiological abnormalities are so varied that no single abnormality is observed across the entire group of people with DSM-IV–defined schizophrenia. In addition, it remains unclear whether the structural differences are unique to schizophrenia or cut across the traditional diagnostic boundaries between schizophrenia and affective disorders - though perhaps being unique to conditions with psychotic features.

Studies of the rare childhood-onset schizophrenia (before age 13) indicate a greater-than-normal loss of grey matter over several years, progressing from the back of the brain to the front, levelling out in early adulthood. Such a pattern of "pruning" occurs as part of normal brain development but appears to be exaggerated in childhood-onset psychotic diagnoses, particularly schizophrenia. Abnormalities in the volume of the ventricles or frontal lobes have also been found in several studies but not in others. Volume changes are most likely glial and vascular rather than purely neuronal, and reduction in grey matter may primarily reflect a reduction of neuropil rather than a deficit in the total number of neurons. Other studies, especially some computational studies, have shown that a reduction in the number of neurons can cause psychotic symptoms. Studies to date have been based on small numbers of the most severe and treatment-resistant patients taking antipsychotics.

Functional



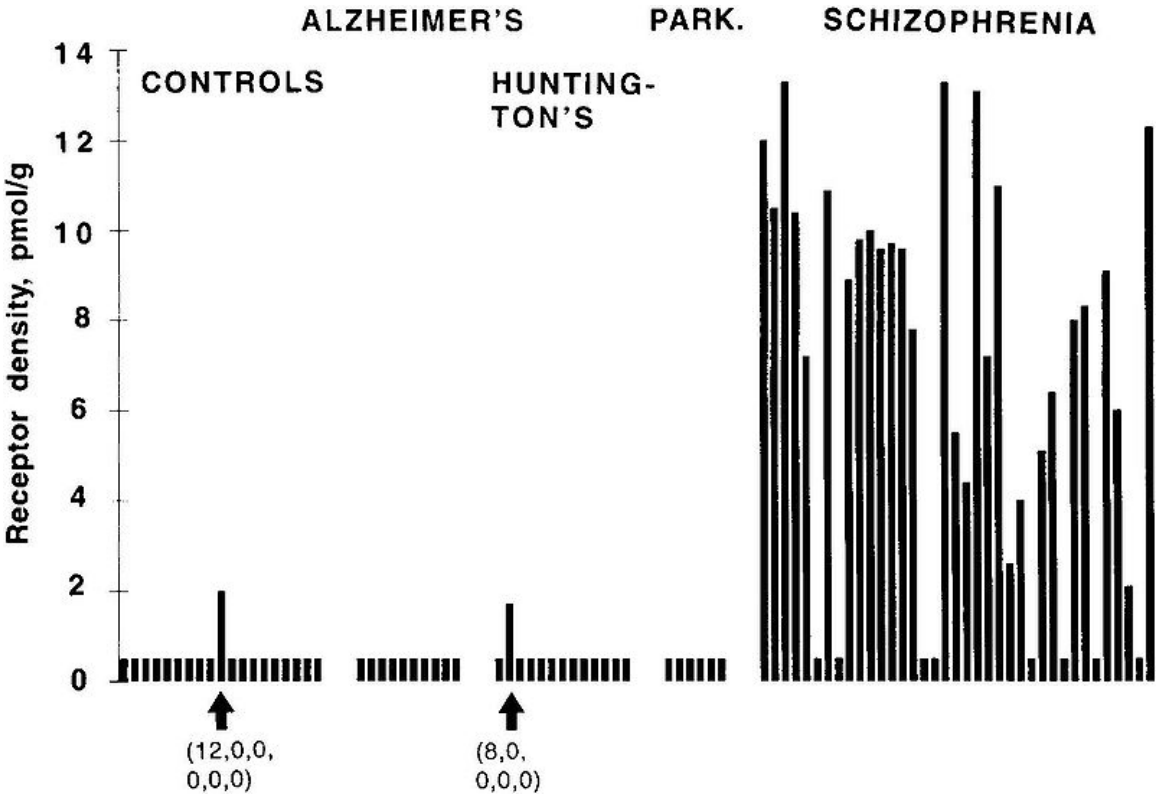
Functional magnetic resonance imaging and other brain imaging technologies allow for the study of differences in brain activity among people diagnosed with schizophrenia.

Some studies using neuropsychological tests and brain imaging technologies such as fMRI and PET to examine functional differences in brain activity have shown that differences seem to most commonly occur in the frontal lobes, hippocampus, and temporal lobes. Abnormalities of the kind shown are linked to the same neurocognitive deficits often associated with schizophrenia, particularly in areas of memory, attention, problem solving, executive function, and social cognition. Observations of the frontal lobe in patients with schizophrenia are inconsistent: While many studies have found abnormalities, others have found no or only a statistically insignificant difference. Data from a PET study suggests that the less the frontal lobes are activated during a working memory task, the greater the increase in abnormal dopamine activity in the striatum, thought to be related to the neurocognitive deficits in schizophrenia.

Electroencephalograph (EEG) recordings of persons with schizophrenia performing perception oriented tasks showed an absence of gamma band activity in the brain, indicating weak integration of critical neural networks in the brain. Those who experienced intense hallucinations, delusions and disorganized thinking showed the lowest frequency synchronization. None of the drugs taken by the persons scanned had moved neural synchrony back into the gamma frequency range. Gamma band and working memory alterations may be related to alterations in interneurons that produce the neurotransmitter GABA.

Atypical connectivity in the default network and other resting-state networks in the brain has been observed in schizophrenic patients. The greater connectivity in the default network and the task-positive network may reflect excessive orientation of attention to introspection and to extrospection, respectively, and the greater anti-correlation between the two networks suggests excessive rivalry between the networks. Increased deactivation of specific default-network regions is associated with the positive symptoms of schizophrenia.

Dopamine



Dopamine D2-Like Sites in Schizophrenia, But Not in Alzheimer's, Huntington's, or Control Brains for [3H]Benzquinoline;Synapse Vol 25 1997; pp137–146, ; copyright 1997 PHILIP SEEMAN, HONG-CHANG GUAN, JOSE NOBREGA, DILSHAD JIWA, RUDOLPH MARKSTEIN, JA-HYUN BALK, ROBERTO PICETTI, EMILIANA BORRELLI, AND HUBERT H.M. VAN TOL Reprinted with permission of John Wiley & Sons, Inc.No rights are granted to use content that appears in the work with credit to another source. The authors say the d2-like sites detected in this diagram could represent the d4-like sites in other replicated experiments and that these are probably d2 monomers. In the 1997 report, Dr Seeman said more research had to be done into the receptors which were marked by GLC 756. Whatever the sites, there is something profoundly different between schizophrenic and other cases. Dr Seeman's decision to call the site dopaminergic was: "Because dopamine was much more effective than norepinephrine or serotonin [at blocking GLC756 binding], the binding site was considered dopaminergic". A 2006 journal reports GLC756 measures: D1, D2, D4, TFNα-1, α-2, 5-HT1A, 5-HT2C, 5-HT1D, 5-HT2 A, adrenoceptors β-1, and β-2 - Dr Seeman tested for all groups by their neurotransmitter (fig 3) except transferring. A crucial part of the method was to measure for non-specific binding. This wasn't done in negative experiments.

Particular focus has been placed upon the function of dopamine in the mesolimbic pathway of the brain. This focus largely resulted from the accidental finding that a drug group which blocks dopamine function, known as the phenothiazines, could reduce psychotic symptoms. An influential theory, known as the "dopamine hypothesis of schizophrenia", proposed that a malfunction involving dopamine pathways was therefore

the cause of (the positive symptoms of) schizophrenia. Evidence for this theory includes findings that the potency of many antipsychotics is correlated with their affinity to dopamine D_2 receptors; and the exacerbatory effects of a dopamine agonist (amphetamine) and a dopamine beta hydroxylase inhibitor (disulfiram) on schizophrenia; and post-mortem studies initially suggested increased density of dopamine D2 receptors in the striatum. Such high levels of D receptors intensify brain signals in schizophrenia and causes positive symptoms such as hallucinations and paranoia. Impaired glutamate (a neurotransmitter which directs neuron to pass along an impulse) activity appears to be another source of schizophrenia symptoms.

However, there was controversy and conflicting findings over whether post-mortem findings resulted from chronic antipsychotic treatment. Compared to the success of postmortem studies in finding profound changes of dopamine receptors, imaging studies using SPET and PET methods in drug naive patients have generally failed to find any difference in dopamine D2 receptor density compared to controls. Comparable findings in longitudinal studies show: " Particular emphasis is given to methodological limitations in the existing literature, including lack of reliability data, clinical heterogeneity among studies, and inadequate study designs and statistic," suggestions are made for improving future longitudinal neuroimaging studies of treatment effects in schizophrenia A recent review of imaging studies in schizophrenia shows confidence in the techniques, while disussing such operator error. In 2007 one report said, "During the last decade, results of brain imaging studies by use of PET and SPET in schizophrenic patients showed a clear dysregulation of the dopaminergic system."

Recent findings from meta-analyses suggest that there may be a small elevation in dopamine D2 receptors in drug-free patients with schizophrenia, but the degree of overlap between patients and controls makes it unlikely that this is clinically meaningful. In addition, newer antipsychotic medication (called atypical antipsychotic medication) can be as potent as older medication (called typical antipsychotic medication) while also affecting serotonin function and having somewhat less of a dopamine blocking effect. In addition, dopamine pathway dysfunction has not been reliably shown to correlate with symptom onset or severity. HVA levels correlate trendwise to symptoms severity. During the application of debrisoquin this correlation becomes significant

Giving a more precise explanation of this discrepancy in d2 receptor radioligand imaging measurements involves the monomer and dimer ratio, Dr Philip Seeman has said: "In schizophrenia, therefore, the density of [11C]methylspiperone sites rises, reflecting an increase in monomers, while the density of [11C]raclopride sites remains the same, indicating that the total population of D2 monomers and dimers does not change.". With this difference in measurement technique in mind; the above mentioned meta analysis uses results from 10 different ligands.

It has been said that, "...Numerous postmortem studies have consistently revealed D2 receptors to be elevated in the striata of patients with schizophrenia". However, the authors were concerned the effect of medication may not have been fully accounted for. The study introduced an experiment by Abi-Dargham et al. in which it was shown

medication free live schizophrenics had more d2 receptors involved in the schizophrenic process and more dopamine. Since then another study has shown such elevated percentages in d2 receptors is brain-wide (using a different ligand, which did not need dopamine depletion) In a 2009 study Annisa Abi-Dagham et al. confirmed the findings of her previous study regarding increased baseline d2 receptors in schizophrenics and showing a correlation between this magnitude and the result of amphetamine stimulation experiments.

Some animal models of psychosis are similar to those for addiction - displaying increased locomotor activity For those female animals with previous sexual experience, amphetamine stimulation happens faster than for virgins. There is no study on male equivalent because the studies are meant to explain why females experience addiction earlier than males.

Even in 1986 the effect of antipsychotics on receptor measurement was controversial. An article in *Science* sought to clarify whether the increase was solely due to medication by using drug naive schizophrenics: "The finding that D2 dopamine receptors are substantially increased in schizophrenic patients who have never been treated with neuroleptic drugs raises the possibility that dopamine receptors are involved in the schizophrenic disease process itself. Alternatively, the increased D2 receptor number may reflect presynaptic factors such as increased endogenous dopamine levels (16). In either case, our findings support the hypothesis that dopamine receptor abnormalities are present in untreated schizophrenic patients." (The experiment used 3-N-[11C]methylspiperone- the same as mentioned by Dr Seeman detects d2 monomers and binding was double that of controls.)

It is still thought that dopamine mesolimbic pathways may be hyperactive, resulting in hyperstimulation of D2 receptors and positive symptoms. There is also growing evidence that, conversely, mesocortical pathway dopamine projections to the prefrontal cortex might be hypoactive (underactive), resulting in hypostimulation of D1 receptors, which may be related to negative symptoms and cognitive impairment. The overactivity and underactivity in these different regions may be linked, and may not be due to a primary dysfunction of dopamine systems but to more general neurodevelopmental issues that precede them. Increased dopamine sensitivity may be a common final pathway.

Another reliable finding, repeatedly found, is that there is a some sixfold excess of binding sites insensitive to a certain testing agent (raclopride) Dr Seeman later said this increase was probably due to the increase in d2 monomers. Such an increase in monomers, occurs via the cooperativity mechanism which is responsible for d2high and d2low, the supersensitive and lowsensitivity states of the d2 dopamine receptor. More specifically, "an increase in monomers, may be one basis for dopamine supersensitivity."

Another one of Philip Seeman's findings was that the dopamine D2 receptor protein looked abnormal in schizophrenia. Proteins change states by flexing. The activating of the protein by folding could be permanent or fluctuating, just like the courses of patients' illnesses waxes and wanes. Increased folding of a protein leads to increased risk of

'additional fragments' forming The schizophrenic d2 receptor has a unique additional fragment when digested by papain in the test-tube, but none of the controls exhibited the same fragment. The D2 receptor in schizophrenia are thus in a highly active state as found by Philip Seeman et al.

Glutamate

Interest has also focused on the neurotransmitter glutamate and the reduced function of the NMDA glutamate receptor in schizophrenia. This has largely been suggested by abnormally low levels of glutamate receptors found in postmortem brains of people previously diagnosed with schizophrenia and the discovery that the glutamate blocking drugs such as phencyclidine and ketamine can mimic the symptoms and cognitive problems associated with the condition. The fact that reduced glutamate function is linked to poor performance on tests requiring frontal lobe and hippocampal function and that glutamate can affect dopamine function, all of which have been implicated in schizophrenia, have suggested an important mediating (and possibly causal) role of glutamate pathways in schizophrenia. Further support of this theory has come from preliminary trials suggesting the efficacy of coagonists at the NMDA receptor complex in reducing some of the positive symptoms of schizophrenia.

Other

Dyregulation of neural calcium homeostasis has been hypothesized to be a link between the glutamate and dopaminergic abnormalities and some small studies have indicated that calcium channel blocking agents can lead to improvements on some measures in schizophrenia with tardive dyskinesia.

There is evidence of irregular cellular metabolism and oxidative stress in the prefrontal cortex in schizophrenia, involving increased glucose demand and/or cellular hypoxia.

Mutations in the gene for brain-derived neurotrophic factor (BDNF) have been reported to be a risk factor for the disease.

Other proposed etiologies

Psychiatrists R. D. Laing, Silvano Arieti, Theodore Lidz and others have argued that the symptoms of what is called mental illness are comprehensible reactions to impossible demands that society and particularly family life places on some sensitive individuals. Laing, Arieti and Lidz were notable in valuing the *content* of psychotic experience as worthy of interpretation, rather than considering it simply as a secondary and essentially meaningless marker of underlying psychological or neurological distress. Laing described eleven case studies of people diagnosed with schizophrenia and argued that the content of their actions and statements was meaningful and logical in the context of their family and life situations. In 1956, Palo Alto, Gregory Bateson and his colleagues Paul Watzlawick, Donald Jackson, and Jay Haley articulated a theory of schizophrenia, related to Laing's work, as stemming from double bind situations where a person receives different or

contradictory messages. Madness was therefore an expression of this distress and should be valued as a cathartic and transformative experience. In the books *Schizophrenia and the Family* and *The Origin and Treatment of Schizophrenic Disorders* Lidz and his colleagues explain their belief that parental behaviour can result in mental illness in children. Arieti's *Interpretation of Schizophrenia* won the 1975 scientific National Book Award in the United States.

The concept of schizophrenia as a result of civilization has been developed further by psychologist Julian Jaynes in his 1976 book *The Origin of Consciousness in the Breakdown of the Bicameral Mind*; he proposed that until the beginning of historic times, schizophrenia or a similar condition was the normal state of human consciousness. This would take the form of a "bicameral mind" where a normal state of low affect, suitable for routine activities, would be interrupted in moments of crisis by "mysterious voices" giving instructions, which early people characterized as interventions from the gods. Researchers into shamanism have speculated that in some cultures schizophrenia or related conditions may predispose an individual to becoming a shaman; the experience of having access to multiple realities is not uncommon in schizophrenia, and is a core experience in many shamanic traditions. Equally, the shaman may have the skill to bring on and direct some of the altered states of consciousness psychiatrists label as illness. Psychohistorians, on the other hand, accept the psychiatric diagnoses. However, unlike the current medical model of mental disorders they may argue that poor parenting in tribal societies causes the shaman's schizoid personalities. Commentators such as Paul Kurtz and others have endorsed the idea that major religious figures experienced psychosis, heard voices and displayed delusions of grandeur.

Psychological explanations

Although psychological theories generally accept biological causes Cognitive Behavioural Therapy has been applied also to schizophrenia. Some experts think autonomy vs intimacy is a motivation for schizophrenic symptoms.

Evolutionary explanations

Psychiatrist Tim Crow has argued that schizophrenia may be the evolutionary price we pay for a left brain hemisphere specialization for language. Since psychosis is associated with greater levels of right brain hemisphere activation and a reduction in the usual left brain hemisphere dominance, our language abilities may have evolved at the cost of causing schizophrenia when this system breaks down. Other approaches have linked schizophrenia to psychological dissociation or states of awareness and identity understood from phenomenological and other perspectives.

Chapter 11

Schizophrenia and Smoking

Studies across 20 countries show a strong association between **schizophrenia and smoking**. For example, in the United States, 80% or more of schizophrenics smoke, compared to 20% of the general population in 2006. Though it is well established that smoking is more prevalent among schizophrenics than the general population as well as those with other psychiatric diagnoses, there is currently no definitive explanation for this difference. Many social, psychological, and biological explanations have been proposed, but today research focuses on neurobiology. Increased rates of smoking among schizophrenics has a number of serious impacts, including increased rates of mortality, increased risk of cardiovascular disease, reduced treatment effectiveness, and greater financial hardship. As a result, researchers believe it is important for mental health professionals to combat smoking among schizophrenics.

Causes

A number of theories have been proposed to explain increased rates of smoking among schizophrenics.

Psychological and social theories

Several psychological and social explanations have been proposed. The earliest explanations were based on psychoanalytic theory. The *psychoanalytic hypothesis* argued that schizophrenics suffer from an oral fixation, resulting in excessive preoccupation with oral gratification.

The *socioeconomic/environmental hypothesis* proposed that smoking results because many schizophrenics are unemployed and inactive, so smoking relieves boredom. Research has found that this explanation alone cannot account for the extreme amount of smoking among schizophrenics.

The *personality hypothesis* focused on the association between smoking and higher level of neuroticism and anxiety. This hypothesis proposed that anxiety as a symptom of schizophrenia may contribute to smoking.

The *psychological tool hypothesis* argues that smokers use nicotine to manipulate their mental state in response to various environmental conditions, such as reducing stress and

managing negative emotions. Research on this hypothesis notes that schizophrenics often have poor coping skills, so use of smoking as psychological tool may result in a vicious cycle of more and more smoking.

The *self-medication hypothesis* argues that schizophrenics use nicotine to compensate for the cognitive deficits that result from schizophrenia, antipsychotic medication used to treat schizophrenia, or both.

The *cognitive effects hypothesis* suggests that nicotine has positive effects on cognition, so smoking is used to improve neurocognitive dysfunction.

In these hypotheses, one factor often implicated is the effects of *institutionalization and boredom*. However, schizophrenics smoke at higher rates and for longer periods than other groups that experience both institutionalization and boredom.

Another factor often implicated is to the *side effects of antipsychotic medications*. Atypical antipsychotics may work against smoking cessation, as symptoms of smoking cessation such as irritable mood, mental dulling, and increased appetite overlap with side effects of atypical antipsychotics. Some also argue that smoking works to reduce the side effects of antipsychotics. However, research shows no association between smoking and antipsychotic use after controlling for schizophrenia.

Another frequently implicated factor is *increased mental acuity* associated with smoking, important because of the mental dulling found over time in schizophrenia. However, both schizophrenics and the general population experience this effect, so it cannot fully explain increased smoking in schizophrenics.

Criticisms

One major criticism of social and psychological explanations of smoking in schizophrenia is that most studies have failed to include personal perspectives of patients with schizophrenia. Studies including personal perspectives find that schizophrenics generally start smoking for the same reasons as the general population, including social pressures and cultural and socioeconomic factors. Schizophrenics who are current smokers also cite similar reasons for smoking as non-schizophrenics, primarily relaxation, force of habit, and settling nerves. However, 28% cite psychiatric issues, including response to auditory hallucinations and reduce the side effects of medication. The major themes found in studies of personal perspectives are habit and routine, socialization, relaxation, and addiction to nicotine. It is argued that smoking provides structure and activity, both of which may be lacking in the lives of those with serious mental illness.

Another major criticism is based on the finding that the association between smoking and schizophrenia is about as strong across all cultures. This finding implies that the association is not solely social or cultural, but rather has a strong biological component.

Biological theories

Neurobiological explanations are generally considered to be strongest, because unlike social and psychological explanations, a direct neurochemical interaction can be demonstrated. Current theory focuses on the role of dopamine in schizophrenia, particularly how negative symptoms such as social withdrawal and apathy may be caused by a deficiency on dopamine in the prefrontal cortex while positive symptoms such as delusions and hallucinations may be caused by excess dopamine in the mesolimbic pathway. Nicotine increases release of dopamine, so it is hypothesized that smoking helps correct dopamine deficiency in the prefrontal cortex and thus relieve negative symptoms.

It is unclear, however, how nicotine interacts with positive symptoms, as it would follow from this theory that nicotine would exacerbate excess dopamine in the mesolimbic pathway and thus positive symptoms as well. One theory argues that the beneficial effects of nicotine on negative symptoms outweigh possible exacerbation of positive symptoms. Another theory is based on animal models showing that chronic nicotine use eventually results in a reduction in dopamine, thus alleviating positive symptoms. However, human studies show conflicting results, including some studies that show that schizophrenic smokers have the most positive symptoms and a reduction in negative symptoms.

Another area of research is the role of nicotinic receptors in schizophrenia and smoking. Studies show increased numbers of exposed nicotinic receptors, which could explain the pathology of both smoking and schizophrenia. However, others argue that the increase in nicotinic receptors is a result of persistent heavy smoking, rather than schizophrenia.

Another source of controversy is the relationship between smoking and sensory gating in schizophrenia. Nicotine may help improve auditory gating, the ability to screen out intrusive environmental sounds. This may help improve attention spans and reduce auditory hallucinations, allowing schizophrenics to perceive the environment more effectively and engage in smoother motor functions. However, research shows this effect alone cannot account for increased smoking rates.

Impacts

Increased smoking among schizophrenics has a number of impacts on this population. One well-documented consequence is the increase in premature death among schizophrenics. Life expectancy among schizophrenics is generally 80-85% that of the general population, which results from both unnatural causes such as suicide but also natural causes such as cardiovascular disease, to which smoking is an important contributor. The schizophrenic populations has a higher incidence of smoking diseases, with heart disease deaths 30% more likely and respiratory disease deaths 60% more likely, two times the general population rate. 2/3 of schizophrenics die from coronary heart disease, versus less than 1/2 of the general population. Ten-year coronary heart disease risk is significantly elevated in schizophrenics, as well as diabetes and hypertension.

Though smoking may help relieve symptoms of schizophrenia, smoking also counteracts the effects of antipsychotic medication. Smoking results in faster metabolism of antipsychotics, which results in smokers being prescribed higher doses. Studies are unclear as to whether changes in smoking are caused by changes in symptoms, side effects of medication, or primary effects of medication.

Besides biological effects, smoking has a profound social impact on schizophrenics. One major impact is financial, as schizophrenics have been found to spend a disproportionate amount of their income on cigarettes. A study of schizophrenics on public assistance found that schizophrenics spent a median amount of $142 per month on cigarettes out of a median monthly public assistance income of $596, or about 27.36%. Some argue that this results in further social impacts as schizophrenics are then unable to spend money on entertainment and social events that would promote well-being, or may even be unable to afford housing or nutrition.

Role of tobacco industry

Though the relationship between smoking and schizophrenia is well established, a factor to be considered in this relationship is the role of the tobacco industry. Research based on internal industry documents shows a concerted effort by the industry to promote belief that schizophrenics need to smoke and that it is dangerous for them to quit. Such promotion includes monitoring or supporting research that endorsed the idea that schizophrenics are uniquely immune to the health consequences of smoking (since proved false) and that tobacco is needed for schizophrenics to self-medicate. The industry also provided cigarettes to hospital wards and supported efforts to block hospital-based smoking bans. Although this does not discredit the effects of nicotine in schizophrenia, it is argued that the efforts of the tobacco industry slowed the decline in smoking prevalence in schizophrenics as well as the development of clinical policies to promote smoking cessation.

Clinical implications

Given conflicting evidence of the costs and benefits of smoking, controversy remains on what the clinical response to smoking in schizophrenics should be. Historically mental health providers have overlooked smoking in schizophrenia, based on the rationale that patients with serious mental illness already suffer from significant stress and disability and as such should be allowed to engage in smoking as an activity that is pleasurable though destructive. There is also historical precedent of mental health providers, particularly in inpatient settings, to use cigarettes as a way to manipulate patient behavior, such as rewarding good behavior with cigarettes or withholding cigarettes to encourage medication compliance. However, research showing that eliminating even one risk factor for disease can significantly improve long-term health outcomes has resulted in the dominant view among clinicians opposing smoking.

Though smoking cessation is generally now a goal of mental health clinicians, there is a lack of empirical research showing successful strategies for accomplishing this goal.

However, all studies have shown a reduction in smoking, though not necessarily elimination. Evidence has been found to support the use of sustained-release buproprion, nicotine replacement therapy, atypical antipsychotics, and cognitive-behavioral therapy. Better outcomes are seen when two or more cessation strategies are employed, as well as for patients using atypical antipsychotics rather than typical antipsychotics. There is also no evidence for an increase in positive symptoms or side effects following smoking cessation, while there is evidence for a decrease in negative symptoms.

Besides smoking cessation, the prevalence of smoking among schizophrenics also calls for additional measures in evaluation by mental health providers. Researchers argue that providers should incorporate tobacco use assessment into everyday clinical practice, as well as continuing assessments of cardiovascular health through measures such as blood pressure and diagnostics such as electrocardiography. Additionally there are ethical and practical concerns if healthcare facilities prohibit smoking without providing alternatives, particularly since withdrawal can alter the presentation of symptoms and response to treatment and may confuse or even exacerbate symptoms. Clinicians should also be aware of the consequences that can result from a lack of cigarettes, such as aggression, prostitution, trafficking, and general disruption. These consequences indicate that providers may need to help patients obtain cigarettes and/or monitor usage, although this may result in ethical concerns as well.

Chapter 12

Treatment of Schizophrenia

Treatment of schizophrenia depends largely on medications and on psychosocial interventions. No single approach is widely considered effective for all patients. A recovery model that emphasizes hope, empowerment and social inclusion is often promoted.

Criteria for the remission of symptoms were suggested in 2006. Management of symptoms and improving function may be more achievable than a permanent cure.

Antipsychotics have been a mainstay of therapy since the introduction of chlorpromazine in the mid-1950s, which revolutionized treatment. Significant adverse effects have attracted controversy. Older concerns of sedation, tardive dyskinesia and neuroleptic malignant syndrome have been largely replaced with those of drug-related obesity and diabetes.

In many non-Western societies, schizophrenia may only be treated with more informal, community-led methods. The outcome for people diagnosed with schizophrenia in non-Western countries may actually be better than for people in the West. The reasons for this effect are not clear, although cross-cultural studies are being conducted.

Prognosis

Numerous international studies have demonstrated favorable long-term outcomes for around half of those diagnosed with schizophrenia, with substantial variation between individuals and regions. One retrospective study found that about a third of people made a full recovery, about a third showed improvement but not a full recovery, and a third remained ill. A clinical study using strict recovery criteria (concurrent remission of positive and negative symptoms and adequate social and vocational functioning continuously for two years) found a recovery rate of 14% within the first five years. A 5-year community study found that 62% showed overall improvement on a composite measure of symptomatic, clinical and functional outcomes. Rates are not always comparable across studies because an exact definition of what constitutes recovery has not been widely accepted, although standardized criteria have been suggested.

The World Health Organization conducted two long-term follow-up studies involving more than 2,000 people suffering from schizophrenia in different countries. These studies

found patients have much better long-term outcomes in developing countries (India, Colombia and Nigeria) than in developed countries (USA, UK, Ireland, Denmark, Czech Republic, Slovakia, Japan, and Russia), despite the fact antipsychotic drugs are typically not widely available in poorer countries, raising questions about the effectiveness of such drug-based treatments.

In many non-Western societies, schizophrenia may only be treated with more informal, community-led methods. Multiple international surveys by the World Health Organization over several decades have indicated that the outcome for people diagnosed with schizophrenia in non-Western countries is on average better there than for people in the West. Many clinicians and researchers suspect the relative levels of social connectedness and acceptance are the difference, although further cross-cultural studies are seeking to clarify the findings.

Several factors are associated with a better prognosis: Being female, acute (vs. insidious) onset of symptoms, older age of first episode, predominantly positive (rather than negative) symptoms, presence of mood symptoms and good premorbid functioning. Most studies done on this subject, however, are correlational in nature, and a clear cause-and-effect relationship is difficult to establish. Evidence is also consistent that negative attitudes towards individuals with schizophrenia can have a significant adverse impact. In particular, critical comments, hostility, authoritarian and intrusive or controlling attitudes (termed high 'Expressed emotion' or 'EE' by researchers) from family members have been found to correlate with a higher risk of relapse in schizophrenia across cultures.

Admission to hospital

Hospitalization may occur with severe episodes of schizophrenia. This can be voluntary or (if mental health legislation allows it) involuntary (called civil or involuntary commitment). Long-term inpatient stays are now less common due to deinstitutionalization, although can still occur. Following (or in lieu of) a hospital admission, support services available can include drop-in centers, visits from members of a community mental health team or Assertive Community Treatment team, supported employment and patient-led support groups.

Specific treatments

Medication

The mainstay of psychiatric treatment for schizophrenia is an antipsychotic medication. These can reduce the "positive" symptoms of psychosis. Most antipsychotics take around 7–14 days to have their main effect.

Risperidone (trade name **Risperdal**) is a common atypical antipsychotic medication

Treatment was revolutionized in the mid 1950s with the development and introduction of the first antipsychotic chlorpromazine. Others such as haloperidol and trifluoperazine soon followed.

Though expensive, the newer atypical antipsychotic drugs are usually preferred for initial treatment over the older typical antipsychotics; they are often better tolerated and associated with lower rates of tardive dyskinesia, although they are more likely to induce weight gain and obesity-related diseases. Of the atypical antipsychotics, olanzapine and clozapine are the most likely to induce weight gain. The effect is more pronounced if high doses of olanzapine are used. Smaller amounts of weight gain are induced by risperidone and quetiapine. Ziprasidone and aripiprazole are considered to be weight neutral antipsychotics.

It remains unclear whether the newer antipsychotics reduce the chances of developing neuroleptic malignant syndrome, a rare but serious and potentially fatal neurological disorder most often caused by an adverse reaction to neuroleptic or antipsychotic drugs.

The two classes of antipsychotics are generally thought equally effective for the treatment of the positive symptoms. Some researchers have suggested that the atypicals offer additional benefit for the negative symptoms and cognitive deficits associated with schizophrenia, although the clinical significance of these effects has yet to be established. Recent reviews have refuted the claim that atypical antipsychotics have fewer extrapyramidal side effects than typical antipsychotics, especially when the latter are used in low doses or when low potency antipsychotics are chosen.

Response of symptoms to medication is variable; "Treatment-resistant schizophrenia" is a term used for the failure of symptoms to respond satisfactorily to at least two different antipsychotics. Patients in this category may be prescribed clozapine, a medication of superior effectiveness but several potentially lethal side effects including agranulocytosis and myocarditis. Clozapine is the only medication proven to be more effective for persons who do not respond to other types of antipsychotics. It also appears to reduce suicide in people with schizophrenia. As clozapine supresses the development of bone marrow,in turn reducing white blood cells which can lead to infection, blood tests are taken for the first six months on this medication. For other patients who are unwilling or unable to take medication regularly, long-acting depot preparations of antipsychotics may be given every two weeks to achieve control. America and Australia are two countries with laws allowing the forced administration of this type of medication on those who refuse but are otherwise stable and living in the community.

Nevertheless, some findings indicate that, in the long term, many schizophrenic individuals function better without antipsychotic medicine. In a 2007 study, only 28% of patients who were not being treated medicinally showed signs of psychotic activity, while 64% of those on antipsychotics had psychotic activity. The authors of the study cautioned that some of this gap may be accounted for by the increased likelihood of symptomatic patients to be placed on antipsychotic medicine, but also noted that some of the difference held even when on-antipsychotic and off-medicine patients of similar prognosis were compared.

Nicotine patch

Following an observation that tobacco smoking eases effects of schizophrenia, it has been proposed nicotine patch as a treatment for schizophrenia.

Psychological and social interventions

Psychotherapy is also widely recommended and used in the treatment of schizophrenia, although services may often be confined to pharmacotherapy because of reimbursement problems or lack of training.

Cognitive behavioral therapy (CBT) is used to target specific symptoms and improve related issues such as self-esteem, social functioning, and insight. Although the results of early trials were inconclusive as the therapy advanced from its initial applications in the mid 1990s, more recent reviews clearly show CBT is an effective treatment for the psychotic symptoms of schizophrenia. Another approach is cognitive remediation therapy, a technique aimed at remediating the neurocognitive deficits sometimes present in schizophrenia. Based on techniques of neuropsychological rehabilitation, early evidence has shown it to be cognitively effective, resulting in the improvement of previous deficits in psychomotor speed, verbal memory, nonverbal memory, and executive function, such improvements being related to measurable changes in brain activation as measured by fMRI. A similar approach known as cognitive enhancement therapy, which focuses on social cognition as well as neurocognition, has shown efficacy.

Metacognitive training: In view of a many empirical findings suggesting deficits of metacognition (thinking about one's thinking, reflecting upon one's cognitive process) in patients with schizophrenia, metacognitive training (MCT) is increasingly adopted as a complementary treatment approach. MCT aims at sharpening the awareness of patients for a variety of cognitive biases (e.g. jumping to conclusions, attributional biases, over-confidence in errors), which are implicated in the formation and maintenance of schizophrenia positive symptoms (especially delusions), and to ultimately replace these biases with functional cognitive strategies. The training consists of 8 modules and can be obtained cost-free from the internet in 15 languages. Studies confirm the feasibility and lend preliminary support to the efficacy of the intervention. Recently, an individualized format has been developed which combines the metacognitive approach with methods derived from cognitive-behavioral therapy.

Family Therapy or Education, which addresses the whole family system of an individual with a diagnosis of schizophrenia, has been consistently found to be beneficial, at least if the duration of intervention is longer-term. Aside from therapy, the impact of schizophrenia on families and the burden on careers has been recognized, with the increasing availability of self-help books on the subject. There is also some evidence for benefits from social skills training, although there have also been significant negative findings. Some studies have explored the possible benefits of music therapy and other creative therapies.

Other

Electroconvulsive therapy is not considered a first line treatment but may be prescribed in cases where other treatments have failed. It is more effective where symptoms of catatonia are present, and is recommended for use under NICE guidelines in the UK for catatonia if previously effective, though there is no recommendation for use for schizophrenia otherwise. Psychosurgery has now become a rare procedure and is not a recommended treatment for schizophrenia.

Alternative approaches

Service-user led movements have become integral to the recovery process in Europe and America; groups such as the Hearing Voices Network and the Paranoia Network have developed a self-help approach that aims to provide support and assistance outside the traditional medical model adopted by mainstream psychiatry. By avoiding framing personal experience in terms of criteria for mental illness or mental health, they aim to destigmatize the experience and encourage individual responsibility and a positive self-image. Partnerships between hospitals and consumer-run groups are becoming more common, with services working toward remediating social withdrawal, building social skills and reducing rehospitalization.

The Soteria model is an alternative treatment to institutionalization and early use of antipsychotics. It is described as a milieu-therapeutic recovery method, characterized by its founder as "the 24 hour a day application of interpersonal phenomenologic interventions by a nonprofessional staff, usually without neuroleptic drug treatment, in the context of a small, homelike, quiet, supportive, protective, and tolerant social environment." Soteria or Soteria-based houses are currently run in Sweden, Germany, Switzerland, and Hungary. The Soteria house in Berne, Switzerland is associated with a psychiatrist who teaches at the University of Berne, and has been featured in the *Schweizerische Aertzezeitung*, the Bulletin of Swiss Physicians.

Orthomolecular psychiatry considers schizophrenia to be a group of disorders, some of which can be treated with megadoses of nutrients, such as niacin (vitamin B_3). Proponents of orthomolecular psychiatry claim that an adverse reaction to gluten is involved in the etiology of some cases. This theory—discussed by one author in three British journals in the 1970s—is unproven. A 2006 literature review suggests that gluten may be a factor for patients with celiac disease and for a subset of patients afflicted with schizophrenia, but that further study is needed to conclusively confirm such a link. In a 2004 Israeli study, anti-gluten antibodies were measured in 50 patients with schizophrenia and a matched control group. All antibody tests in both groups were negative leading to the conclusion that "it is unlikely that there is an association between gluten sensitivity and schizophrenia". Some researchers suggest that dietary and nutritional treatments may hold promise in the treatment of schizophrenia.

Omega-3 fatty acids

An unconventional approach is the use of omega-3 fatty acids, with one study finding some benefits from their use as a dietary supplement.

A 2003 review of four randomized controlled trials of EPA (an omega-3 fatty acid) vs. placebo as adjunctive treatment for schizophrenia found that two of the trials detected a significant improvement on positive and negative symptoms, and suggested that EPA may be an effective adjunct to antipsychotics. The most recent meta-analysis (2006) failed however to find a significant effect. A 2007 review found that studies of omega-3

fatty acids in schizophrenia, despite being mostly of high quality, have produced inconsistent results and small effect sizes of doubtful clinical significance.

Electroconvulsive therapy

Electroconvulsive therapy (**ECT**), previously known as **electroshock**, is a well-established, albeit controversial, psychiatric treatment in which seizures are electrically induced in anesthetized patients for therapeutic effect. Today, ECT is most often used as a treatment for severe major depression which has not responded to other treatment, and is also used in the treatment of mania (often in bipolar disorder), and catatonia. It was first introduced in the 1930s and gained widespread use as a form of treatment in the 1940s and 1950s; today, an estimated 1 million people worldwide receive ECT every year, usually in a course of 6–12 treatments administered 2 or 3 times a week.

Electroconvulsive therapy can differ in its application in three ways: electrode placement, frequency of treatments, and the electrical waveform of the stimulus. These three forms of application have significant differences in both adverse side effects and positive outcomes. After treatment, drug therapy is usually continued, and some patients receive continuation/maintenance ECT. In the United Kingdom and Ireland, drug therapy is continued during ECT. Informed consent is a standard of modern electroconvulsive therapy. Involuntary treatment is uncommon in the United States and is typically only used in cases of great extremity, and only when all other treatment options have been exhausted and the use of ECT is believed to be a potentially life saving treatment. Similarly, national audits of ECT use in Scotland and Ireland have demonstrated that the vast majority of patients treated give informed consent. Although once frowned upon, recent years have seen an increased acceptance of ECT as a safe, effective and economical tool for the treatment of some mental illnesses. Yet it is rarely used as the first line of treatment.

Guidelines for Treatment

Experts disagree on whether ECT is an appropriate first-line treatment or if it should be reserved for patients who have not responded to other interventions such as medication and psychotherapy.

The American Psychiatric Association (APA) 2001 guidelines give the primary indications for ECT among patients with depression as a lack of response to, or intolerance of, antidepressant medications; a good response to previous ECT; and the need for a rapid and definitive response (e.g. because of psychosis or a risk of suicide). The decision to use ECT depends on several factors, including the severity and chronicity of the depression, the likelihood that alternative treatments would be effective, the patient's preference and capacity to consent, and a weighing of the risks and benefits.

Some guidelines recommend cognitive behavioral therapy or other psychotherapy before ECT is used. However, treatment resistance is widely defined as lack of therapeutic response to two antidepressants at adequate doses for an adequate duration and with good

compliance. The APA states that at times patients will prefer to receive ECT over alternative treatments, but commonly the opposite will be the case.

The APA ECT guidelines state that severe major depression with psychotic features, manic delirium, or catatonia are conditions where there is a clear consensus favoring early ECT. The UK's National Institute for Health and Clinical Excellence (NICE) guidelines recommend ECT for patients with severe depression, catatonia, or prolonged or severe mania. Indeed, the updated (2009) NICE guidelines for depression also provide for the use of maintenance ECT (where ECT is given at longer intervals to prevent relapse), although the guidance stresses the need for further study. The 2001 APA guidelines also support the use of ECT for relapse prevention.

The 2001 APA ECT guidelines say that ECT is rarely used as a first-line treatment for schizophrenia but is considered after unsuccessful treatment with antipsychotic medication, and may also be considered in the treatment of patients with schizoaffective or schizophreniform disorder. The 2003 NICE ECT guidelines do not recommend ECT for schizophrenia, and this has been supported by meta-analytic evidence showing no or little benefit versus placebo, or in combination with antipsychotic drugs, including Clozapine.

The NICE 2003 guidelines state that doctors should be particularly cautious when considering ECT treatment for women who are pregnant and for older or younger people, because they may be at higher risk of complications with ECT. The 2001 APA ECT guidelines say that ECT may be safer than alternative treatments in the infirm elderly and during pregnancy, and the 2000 APA depression guidelines stated that the literature supports the safety for mother and fetus, as well as the efficacy during pregnancy.

Non-clinical patient characteristics

About 70 percent of ECT patients are women. This is almost entirely due to women being at twice the risk of depression. Older and more affluent patients are also more likely to receive ECT. The use of ECT treatment is "markedly reduced for ethnic minorities."

Efficacy

Researchers are still divided regarding the validity of ECT, and the publications that argue for its efficacy do so only for short terms of one to six months.

The 1999 U.S. Surgeon General's Report on Mental Health summarized psychiatric opinion at the time about the effectiveness of ECT. It stated that both clinical experience and published studies had determined ECT to be effective (with an average 60 to 70 percent remission rate) in the treatment of severe depression, some acute psychotic states, and mania. Its effectiveness had not been demonstrated in dysthymia, substance abuse, anxiety, or personality disorder. The report stated that ECT does not have a long-term protective effect against suicide and should be regarded as a short-term treatment for an

acute episode of illness, to be followed by continuation therapy in the form of drug treatment or further ECT at weekly to monthly intervals.

A 2004 large multicentre clinical follow-up study of ECT patients in New York—describing itself as the first systematic documentation of the effectiveness of ECT in community practice in the 65 years of its use—found remission rates of only 30 to 47 percent, with 64 percent of those relapsing within six months. However, when patients with co-morbid personality disorders or who were suffering from schizoaffective disorder were removed from the analysis, the remission rates climbed to 60-70%.

ECT on its own does not usually have a sustained benefit. Half those who remit then relapse within six months. This is similar to the rate of relapse after discontinuing antidepressant medication, and is a function of the usual severity and chronicity of pre-existing illness rather than ECT itself. The relapse rate in the first six months is reduced by the use of psychatric medications or further ECT, but remains high.

All systematic published reviews of the literature have concluded that ECT is effective in the treatment of depression. In 2003, The UK ECT Review group published a systematic review and meta-analysis comparing ECT to placebo and antidepressant drugs. This meta-analysis demonstrated a large effect size for ECT versus placebo, and versus antidepressant drugs. In 2006, research psychiatrist Colin A. Ross reviewed the placebo-controlled trials one-by-one and found that no single study showed a significant difference between real and placebo ECT at one month post-treatment. Dr. Ross was highly critical of other published reviews, which concluded that ECT is effective, and Ross stated that these reviews often relied primarily on studies that were not placebo-controlled. However, Dr. Ross's analysis does not include a statistical synthesis in contrast to the well conducted meta-analytic evidence presented by the UK ECT review group in 2003.

Adverse effects

Aside from effects in the brain, the general physical risks of ECT are similar to those of brief general anesthesia; the United States' Surgeon General's report says that there are "no absolute health contraindications" to its use. Immediately following treatment the most common adverse effects are confusion and memory loss. The state of confusion usually disappears after a few hours. It can be tolerated by pregnant women who are not suffering major complications. It can be used with diabetic or obese patients, and with caution in those whose cancers are in remission or under control. It can be used in some immunocompromised patients. It must be used very cautiously in people with epilepsy or other neurological disorders because by its nature it provokes small tonic-clonic seizures, and so would likely not be given to a person whose epilepsy is not well-controlled. Some patients experience muscle soreness after ECT. This is due to the muscle relaxants given during the procedure and rarely due to muscle activity.

Effects on memory

It is the purported effects of ECT on long-term memory that give rise to much of the concern surrounding its use. The acute effects of ECT can include amnesia, both retrograde (for events occurring before the treatment) and anterograde (for events occurring after the treatment). However, the vast majority of these effects are short lived. Memory loss and confusion are more pronounced with bilateral electrode placement rather than unilateral, and with outdated sine-wave rather than brief-pulse currents. The vast majority of modern treatment uses brief pulse currents. Research by Harold Sackeim has shown that excessive current causes more risk for memory loss, and using right-sided electrode placement may reduce verbal memory disturbance.

Retrograde amnesia is most marked for events occurring in the weeks or months before treatment, with one study showing that although some people lose memories from years prior to treatment, recovery of such memories was "virtually complete" by seven months post-treatment, with the only enduring loss being memories in the weeks and months prior to the treatment. Anterograde memory loss is usually limited to the time of treatment itself or shortly afterwards. In the weeks and months following ECT these memory problems gradually improve, but some people have persistent losses, especially with bilateral ECT. One published review summarizing the results of questionnaires about subjective memory loss found that between 29% and 55% of respondents believed they experienced long-lasting or permanent memory changes. In 2000, American psychiatrist Sarah Lisanby and colleagues found that bilateral ECT left patients with more persistently impaired memory of public events as compared to RUL ECT.

Some studies have found that patients are often unaware of cognitive deficits induced by ECT. For example, in June 2008, a Duke University study was published assessing the neuropsychological effects and attitudes in patients after ECT. Forty-six patients participated in the study, which involved neuropsychological and psychological testing before and after ECT. The study documented substantial cognitive impairment after ECT on a variety of memory tests, including "verbal memory for word lists and prose passages and visual memory of geometric designs." The study further found that a significant number of patients believed that their memory had improved after ECT despite the fact that neuropsychological testing clearly showed the opposite. As stated by the researchers, "Indeed, there was a slight trend towards [patients reporting] improved memory functioning, despite the objective neuropsychological data indicating significantly lower recognition and delayed recall." Based on their findings, the authors issued the following recommendation:

"When ECT is provided to adolescents, the potential impact of such cognitive changes should be discussed with the patients and their parents or guardians in terms of implications for not only the patient’s emotional functioning but cognitive functioning as well, particularly upon his or her academic performance. In summary, we argue that an individual cost-benefit analysis should be made in light of the implications of the potential benefits versus costs of ECT upon improving emotional functioning and the

impact that potential memory changes may have on real-world functioning and quality of life."

Severe memory loss from ECT is described in an autobiographical book, *Doctors of Deception: What They Don't Want You to Know about Shock Treatment*.

Controversy over long-term effects on general cognition

According to prominent ECT researcher Harold Sackeim, "despite over fifty years of clinical use and ongoing controversy", until 2007 there had "never been a large-scale, prospective study of the cognitive effects of ECT." In this first-ever large-scale study (347 subjects), Sackeim and colleagues found that at least some forms (namely bilateral application and outdated sine-wave currents) of ECT "routine[ly]" lead to "adverse cognitive effects," including global cognitive deficits and memory loss, that persist for up to six months after treatment, suggesting that the induced deficits may be permanent. The authors also warned that their findings did not suggest that right-unilateral ECT did not also lead to chronic cognitive deficits. However, the several limitations of this study include the lack of a depressed control group with which to compare memory decay over 6 months. The measure of autobiographical memory used, the Columbia Autobiographical Short-Form (AMI-SF) is not capable of showing memory improvement, with scores at followup expressed as percentages of baseline.

Harold Sackeim can be seen in a videotaped deposition briefly discussing the findings of this study and why, in his opinion, earlier studies had failed to find evidence of long-term harm from ECT. Despite over fifty years of clinical use, Sackeim states that prior to 2001, "the field itself never really had an opportunity to have a discussion about patients who have complaints about long-term memory loss." In this video clip, Sackeim also reveals that at a California ECT conference with 200 practitioners present, when polled as to whether they think ECT can lead to chronic cognitive deficits, two-thirds raised their hands. Sackeim says this was "almost a watershed moment for the field", and was the "first time *publicly* that the field itself said 'no' to the position that it can't happen."

In July 2007, a second study was published concluding that ECT routinely leads to chronic, substantial cognitive deficits, and the findings were not limited to any particular forms of ECT. The study, led by psychiatrist Glenda MacQueen and colleagues, found that patients treated with ECT for bipolar disorder show marked deficits across multiple cognitive domains. According to the researchers, "Subjects who had received remote ECT had further impairment on a variety of learning and memory tests when compared with patients with no past ECT. This degree of impairment could not be accounted for by illness state at the time of assessment or by differential past illness burden between patient groups." Despite the findings of chronic, global cognitive deficits in post-ECT patients, MacQueen and colleagues suggest that it is "unlikely that such findings, even if confirmed, would significantly change the risk–benefit ratio of this notably effective treatment."

Six months after the publication of the Sackeim study documenting routine, long-term memory loss after ECT, prominent ECT researcher Max Fink published a review in the journal *Psychosomatics* concluding that patient complaints of memory loss after ECT are "rare" and should be "characterized as somatoform disorders, rather than as evidence of brain damage, thus warranting psychological treatment for such disorders." Based on his findings, Fink suggests that, "Instead of endorsing these reports as the direct consequence of ECT, especially in patients who have recovered from their depressive illness, lost their suicidal drive, and have improved social functioning, is it not more useful to accept the complaint as a somatoform disorder, explore the basis in the individual's history and experience, and offer appropriate supportive treatment?"

Most recent reviews of the literature and other articles continue to characterize ECT as safe and effective. For example, in June 2009, Portuguese researchers published a review on the safety and efficacy of ECT in an article entitled, *Electroconvulsive Therapy: Myths and Evidences.* In their review, the researchers conclude that ECT is an "efficient, safe and even life saving treatment for several psychiatric disorders." In 2008, Yale researchers published a review on the safety and efficacy of ECT in elderly patients. According to the authors, "ECT is well established as a safe and effective treatment for several psychiatric disorders." And in a June 2009 article published in the *Journal of ECT*, Iranian researchers observe that, "Despite the wide consensus over the safety and efficacy of electroconvulsive therapy (ECT), it still faces negative publicity and unfavorable attitudes of patients and families."

Psychiatrist Peter Breggin, chief editor of the journal *Ethical Human Psychology and Psychiatry*, is a leading critic of ECT who believes the procedure is neither safe nor effective. In a published article reviewing the findings of Harold Sackeim's 2007 study on the cognitive effects of ECT, Breggin accuses Max Fink and other pro-ECT researchers of having a history of "systematically covering up damage done to millions of [ECT] patients throughout the world." He disagrees with the position that findings of chronic, global cognitive deficits should have no bearing on the risk-benefit ratio of ECT, and he believes it's important to address the "actual impact of these losses on the lives of individual patients." In a section of his paper entitled *Destroying Lives*, Dr. Breggin writes, "Even when these injured people can continue to function on a superficial social basis, they nonetheless suffer devastation of their identities due to the obliteration of key aspects of their personal lives. The loss of the ability to retain and learn new material is not only humiliating and depressing but also disabling. Even when relatively subtle, these activities can disrupt routine activities of living."

A study published in 2004 in the *Journal of Mental Health* reported that 35 to 42% of patients responding to a questionnaire reported ECT resulted in loss of intelligence. The study also reported, "There is no overlap between clinical and consumer studies on the question of benefit."

Doctors of Deception: What They Don't Want You to Know About Shock Treatment reports before-and-after IQ testing of persons receiving ECT, including the author, that show 30 to 40 point losses.

A recent opinion article by a neuropsychologist and a psychiatrist in Dublin suggests that ECT patients who experience cognitive problems following ECT should be offered some form of cognitive rehabilitation. The authors say that the failure to attempt to rehabilitate patients may be partly responsible for the negative public image of ECT.

Effects on brain structure

Considerable controversy exists over the effects of ECT on brain tissue despite the fact that a number of mental health associations, including the American Psychiatric Association, have concluded that there is no evidence that ECT causes structural brain damage. A 1999 report by the United States Surgeon General states, "The fears that ECT causes gross structural brain pathology have not been supported by decades of methodologically sound research in both humans and animals". However, the word "gross" is a synonym for major, leaving the possibility open for real brain damage which the US Surgeon General considers minor. However, not all experts agree that ECT does not cause brain damage, and two studies have been published since 2007 finding that at least some forms of ECT may result in *widespread, persisting, generalized cognitive dysfunction*, which might support claims that ECT causes brain damage.

A leading critic of ECT, psychiatrist Peter Breggin has published books and journalistic reviews of the literature purporting to show that ECT routinely causes brain damage as evidenced by a considerable list of studies in humans and animals. In particular, Dr. Breggin asserts that animal and human autopsy studies have shown that ECT routinely causes '*widespread pinpoint hemorrhages and scattered cell death*.' According to Dr. Breggin, the 1990 APA task force report on ECT ignored much of the scientific literature pointing out the negative effects of electroshock therapy. For example, in 1952 Hans Hartelius conducted and published an animal study on cats entitled *Cerebral Changes Following Electrically Induced Convulsions* in which a double-blind microscopic pathology examination showed that it was possible to distinguish the 8 shocked animals from the 8 non-shocked animals with remarkable accuracy based on statistically significant structural changes to the brain, including vessel wall changes, gliosis, and nerve cell changes. Based on the detection of shadow cells and neuronophagia, Hartelius determined that there was irreversible damage to neurons associated with electroshock.

Proponents argue that the addition of hyperoxygenation and refinement in technique in the last thirty years has made ECT safe, and a majority of published reviews in recent decades have reflected this position. In a 2004 study designed to evaluate whether modern ECT techniques lead to identifiable brain damage, twelve monkeys underwent daily electroshock for six weeks under conditions meant to simulate human ECT; the animals were then sacrificed and their brains were compared to monkeys undergoing anesthesia alone. According to the researchers, "None of the ECT-treated monkeys showed pathological findings."

There are recent animal studies that have documented significant brain damage after an electroshock series. For example, in 2005, Russian researchers published a study entitled, *Electroconvulsive Shock Induces Neuron Death in the Mouse Hippocampus: Correlation*

of Neurodegeneration with Convulsive Activity. In this study, the researchers found that after an electroshock series, there was a significant loss of neurons in parts of the brain and particularly in defined parts of the hippocampus where up to 10% of neurons were killed. The researchers conclude that "the main cause of neuron death is convulsions evoked by electric shocks." In 2008, Portuguese researchers conducted a rat study aimed at answering the question of whether an electroshock series causes structural changes in vulnerable parts of the brain. According to the authors, "This study answers positively the question of whether repeated administration of ECS seizures can cause brain lesions. Our data are consistent with findings from other animal models and from human studies in showing that neurons located in the entorhinal cortex and in the hilus of the dentate gyrus are particularly vulnerable to repeated seizures." However, they question the applicability of their own research with respect to Electroconvulsive therapy in humans: "An important caveat of our results is that it is unclear to what extent they are relevant to the use of electroconvulsive therapy in psychiatry, because the protocol employed in this study is different from that used clinically. Evidence from previous studies (Gombos et al., [1999]; Vaidya et al., [1999]) and from our pilot experiments indicates that treating rats either with five to ten widely spaced ECS (at 24- or 48-hr schedules) or with two stimulations only 2 hr apart does not lead to loss of hippocampal neurons".

Many expert proponents of ECT maintain that the procedure is safe and does not cause brain damage. Dr. Charles Kellner, a prominent ECT researcher and former chief editor of the *Journal of ECT* states in a recent published interview that, "There are a number of well-designed studies that show ECT does not cause brain damage and numerous reports of patients who have received a large number of treatments over their lifetime and have suffered no significant problems due to ECT." Dr. Kellner cites specifically to a study purporting to show an absence of cognitive impairment in eight subjects after more than 100 lifetime ECT treatments. One of the authors of the cited study, Harold Sackeim, published a large-scale study less than a month after this interview concluding that the type of ECT used in the eight patients receiving the 100 lifetime treatments, bilateral sine wave, routinely leads to persistent, global cognitive deficits (discussed supra). Dr. Kellner states that, "Rather than cause brain damage, there is evidence that ECT may reverse some of the damaging effects of serious psychiatric illness."

Effects in pregnancy

If steps are taken to decrease potential risks, ECT is generally accepted to be relatively safe during all trimesters of pregnancy, particularly when compared to pharmacological treatments. Suggested preparation for ECT during pregnancy includes a pelvic examination, discontinuation of nonessential anticholinergic medication, uterine tocodynamometry, intravenous hydration, and administration of a nonparticulate antacid. During ECT, elevation of the pregnant woman's right hip, external fetal cardiac monitoring, intubation, and avoidance of excessive hyperventilation are recommended. Much of the medical literature in this area is composed of case studies of single or twin pregnancies, and although some have reported serious complications, the majority have found ECT to be safe. ECT is not performed on the fetus.

Administration

Informed consent is sought before treatment. Patients are informed about the risks and benefits of the procedure. Patients are also made aware of risks and benefits of other treatments and of not having the procedure done at all. Depending on the jurisdiction the need for further inputs from other medical professionals or legal professionals may be required. ECT is usually given on an in-patient basis. Prior to treatment a patient is given a short-acting anesthetic such as methohexital, etomidate, or thiopental, a muscle relaxant such as suxamethonium (succinylcholine), and occasionally atropine to inhibit salivation.

Both electrodes can be placed one on the same side of the patient's head. This is known as unilateral ECT. Unilateral ECT is used first to minimize side effects (memory loss). When electrodes are placed on both sides of the head, this is known as bilateral ECT. In bifrontal ECT, an uncommon variation, the electrode position is somewhere between bilateral and unilateral. Unilateral is thought to cause fewer cognitive effects than bilateral but is considered less effective. In the USA most patients receive bilateral ECT. In the UK almost all patients receive bilateral ECT.

The electrodes deliver an electrical stimulus. The stimulus levels recommended for ECT are in excess of an individual's seizure threshold: about one and a half times seizure threshold for bilateral ECT and up to 12 times for unilateral ECT. Below these levels treatment may not be effective in spite of a seizure, while doses massively above threshold level, especially with bilateral ECT, expose patients to the risk of more severe cognitive impairment without additional therapeutic gains. Seizure threshold is determined by trial and error ("dose titration"). Some psychiatrists use dose titration, some still use "fixed dose" (that is, all patients are given the same dose) and others compromise by roughly estimating a patient's threshold according to age and sex. Older men tend to have higher thresholds than younger women, but it is not a hard and fast rule, and other factors, for example drugs, affect seizure threshold.

ECT machines

Most modern ECT machines deliver a brief-pulse current, which is thought to cause fewer cognitive effects than the sine-wave currents which were originally used in ECT. A small minority of psychiatrists in the USA still use sine-wave stimuli. Sine-wave is no longer used in the UK or Ireland. Typically, the electrical stimulus used in ECT is about 800 milliamps and has up to several hundred watts, and the current flows for between one and 6 seconds. In the USA, ECT machines are manufactured by two companies, Somatics, which is owned by psychiatrists Richard Abrams and Conrad Swartz, and Mecta. The Food and Drug Administration has classified the devices used to administer ECT as Class III medical devices. Class III is the highest-risk class of medical devices. In the UK, the market for ECT machines was long monopolized by Ectron Ltd, although in recent years some hospitals have started using American machines. Ectron Ltd was set up by psychiatrist Robert Russell, who together with a colleague from the Three Counties Asylum, Bedfordshire, invented the Page–Russell technique of intensive ECT.

Variations in international practice

There is wide variation in ECT use between different countries, different hospitals, and different psychiatrists. International practice varies considerably from widespread use of the therapy in many western countries to a small minority of countries that do not use ECT at all, such as Slovenia. Guidelines on the use of ECT are stringent in the USA and the UK. Modern standards are not always followed throughout the world and not all countries that use ECT have written technical standards. The use of both anesthesia and muscle relaxants is universally recommended in the administration of ECT. If anesthesia and muscle relaxants are not used the procedure is called unmodified ECT. In a minority of countries such as Japan, India, and Nigeria, ECT may be used without anesthesia. WHO has called for a worldwide ban on unmodified ECT and the topic is currently being debated in countries like India. The practice has been recently abolished in Turkey's largest psychiatric hospital. A major difficulty for developing countries in eliminating unmodified ECT is a lack of trained anesthesiologists available to administer the procedure. A small minority of countries never seek consent before administering ECT. This significantly uneven application of ECT around the world continues to make ECT a controversial procedure.

Sarah Hall reports, "ECT has been dogged by conflict between psychiatrists who swear by it, and some patients and families of patients who say that their lives have been ruined by it. It is controversial in some European countries such as the Netherlands and Italy, where its use is severely restricted".

United States

In the USA, a survey of psychiatric practice in the late 1980s found that an estimated 100,000 people received ECT annually, with wide variation between metropolitan statistical areas. Accurate statistics about the frequency, context and circumstances of ECT in the United States are difficult to obtain because only a few states have reporting laws that require the treating facility to supply state authorities with this information. One state which does report such data is Texas, where in the mid-1990s ECT was used in about one third of psychiatric facilities and given to about 1,650 people annually. Usage of ECT has since declined slightly; in 2000–01 ECT was given to about 1,500 people aged from 16 to 97 (in Texas it is illegal to give ECT to anyone under sixteen). ECT is more commonly used in private psychiatric hospitals than in public hospitals, and minority patients are underrepresented in the ECT statistics. In the United States, ECT is usually given three times a week; in the UK, it is usually given twice a week. Occasionally it is given on a daily basis. A course usually consists of 6–12 treatments, but may be more or fewer. Following a course of ECT some patients may be given continuation or maintenance ECT with further treatments at weekly, fortnightly or monthly intervals. A few psychiatrists in the USA use multiple-monitored ECT (MMECT) where patients receive more than one treatment per anesthetic. Electroconvulsive therapy is not a required subject in US medical schools and not a required skill in psychiatric residency training. Privileging for ECT practice at institutions

is a local option, no national certification standards are established, and no ECT-specific continuing training experiences are required of ECT practitioners.

United Kingdom

In the United Kingdom in 1980, an estimated 50,000 people received ECT annually, with use declining steadily since then to about 12,000 per annum. It is still used in nearly all psychiatric hospitals, with a survey of ECT use from 2002 finding that 71 percent of patients were women and 46 percent were over 65 years of age. Eighty-one percent had a diagnosis of mood disorder; schizophrenia was the next most common diagnosis. Sixteen percent were treated without their consent. In 2003, the National Institute for Clinical Excellence, a government body which was set up to standardize treatment throughout the National Health Service, issued guidance on the use of ECT. Its use was recommended "only to achieve rapid and short-term improvement of severe symptoms after an adequate trial of treatment options has proven ineffective and/or when the condition is considered to be potentially life-threatening in individuals with severe depressive illness, catatonia or a prolonged manic episode". The guidance received a mixed reception. It was welcomed by an editorial in the British Medical Journal but the Royal College of Psychiatrists launched an unsuccessful appeal. The NICE guidance, as the British Medical Journal editorial points out, is only a policy statement and psychiatrists may deviate from it if they see fit. Adherence to standards has not been universal in the past. A survey of ECT use in 1980 found that more than half of ECT clinics failed to meet minimum standards set by the Royal College of Psychiatrists, with a later survey in 1998 finding that minimum standards were largely adhered to, but that two-thirds of clinics still fell short of current guidelines, particularly in the training and supervision of junior doctors involved in the procedure. A voluntary accreditation scheme, ECTAS, was set up in 2004 by the Royal College, but as of 2006 only a minority of ECT clinics in England, Wales, Northern Ireland and the Republic of Ireland have signed up.

Mechanism of action

The aim of ECT is to induce a therapeutic clonic seizure (a seizure where the person loses consciousness and has convulsions) lasting for at least 15 seconds. Although a large amount of research has been carried out, the exact mechanism of action of ECT remains elusive. The main reasons for this are that the human brain can not be studied directly before and after ECT and therefore scientists rely on animal models of depression and ECT, with major limitations. While animal models are acknowledged to model merely aspects of depressive illness, human and animal brains are very similar at a molecular level, enabling detailed study of the molecular mechanisms involved in ECT

There is a vast literature on the effects of Electroconvulsive Shock (ECS) in animals. In animal models of depression, particularly "Learned helplessness" and "Social defeat", there is evidence of pruning of normally dense synaptic connections in the hippocampus, a richly connected area deep in the temporal lobe which is vital in controlling both mood and memory. ECS has been shown to increase levels of Brain-derived neurotrophic factor (BDNF) and Vascular Endothelial Growth Factor (VEGF) in the rodent hippocampus.

This reverses the toxic effects of depression on this area of the brain, increasing both new synapse formation and the formation of new brain cells (hippocampal neurogenesis). Both these effects have been noted to be present in antidepressant-treated animals, however they are neither necessary nor sufficient for antidepressant response. ECT is a more robust inducer of these neuroplastic effects than antidepressants. Electroconvulsive Therapy (ECT) has also been shown to increase serum brain-derived neurotrophic factor (BDNF) in drug resistant depressed patients. This suggests a common molecular mechanism of action, albeit in need of much further study.

Legal status

Informed consent

It is widely acknowledged internationally that obtaining the written, informed consent of the patient is important before ECT is administered. The World Health Organization, in its 2005 publication "Human Rights and Legislation WHO Resource Book on Mental Health," specifically states, "ECT should be administered only after obtaining informed consent."

In the US, this doctrine places a legal obligation on a doctor to make a patient aware of: the reason for treatment, the risks and benefits of a proposed treatment, the risks and benefits of alternative treatment, and the risks and benefits of receiving no treatment. The patient is then given the opportunity to accept or reject the treatment. The form states how many treatments are recommended and also makes the patient aware that the treatment may be revoked at anytime during a course of ECT. The Surgeon General's Report on Mental Health states that patients should be warned that the benefits of ECT are short-lived without active continuation treatment in the form of drugs or further ECT, and that there may be some risk of permanent, severe memory loss after ECT. The report advises psychiatrists to involve patients in discussion, possibly with the aid of leaflets or videos, both before and during a course of ECT.

To demonstrate what he believes should be required to fully satisfy the legal obligation for informed consent, one psychiatrist, working for an anti-psychiatry organisation, has formulated his own consent form using the consent form developed and enacted by the Texas Legislature as a model.

In the UK, in order for consent to be valid it requires an explanation in "broad terms" of the nature of the procedure and its likely effects. One review from 2005 found that only about half of patients felt they were given sufficient information about ECT and its adverse effects and another survey found that about fifty percent of psychiatrists and nurses agreed with them.

A 2005 study published in the *British Journal of Psychiatry* described patients' perspectives on the adequacy of informed consent before ECT. The study found that, "About half (45–55%) of patients reported they were given an adequate explanation of ECT, implying a similar percentage felt they were not." The authors also stated:

"Approximately a third did not feel they had freely consented to ECT even when they had signed a consent form. The proportion who feel they did not freely choose the treatment has actually increased over time. The same themes arise whether the patient had received treatment a year ago or 30 years ago. Neither current nor proposed safeguards for patients are sufficient to ensure informed consent with respect to ECT, at least in England and Wales."

Involuntary ECT

Procedures for involuntary ECT vary from country to country depending on local mental health laws. Legal proceedings are required in some countries, while in others ECT is seen as another form of treatment that may be given involuntarily as long as legal conditions are observed. Involuntary electroshock contravenes the principle of autonomy in medical ethics. The maxim of autonomy is "Voluntas aegroti suprema lex." This rule states that the will of the patient is supreme. It implies that a patient has the right to consent to, or to refuse a medical treatment, such as ECT. Persons considered not to be of sound mind are in many jurisdictions considered incapable of giving true consent. In such a case, the patient's "assent" may be sought; opinions are divided as to whether this should be routinely done, or whether a patient who is not competent to consent to therapy should retain the right to refuse it.

Citizens in western societies often undergo emergency medical procedures when they have lost the capacity to consent (such as neurosurgery after head injury). Under these circumstances, the principles of benificence and non-maleficence must be adhered to.

United States

In most states in the USA, a judicial order following a formal hearing is needed before a patient can be forced to undergo involuntary ECT. Patients may be represented by legal counsel at the hearing. Oregon Revised Statutes allow for involuntary ECT with the signature of a physician independent of the patient's facility, and no judicial order or legal counsel are required. According to the Surgeon General's Report on Mental Health, "As a rule, the law requires that such petitions are granted only where the prompt institution of ECT is regarded as potentially lifesaving, as in the case of a person in grave danger because of lack of food or fluid intake caused by catatonia." However, there are legal loopholes that thwart strict adherence to this principle. For example, an American citizen was being forced to undergo ECT against his will in 2009, even though his life was not in danger. In this March 17, 2009 video, the man, his mother, and advocates, speak out against his forced ECT. The description of the video states that "Though Sandford, 54, is not charged with any crime, he has received over 40 such rounds of shocks on an outpatient basis so far – even after his original mental problems have long since subsided and he has repeatedly asked for the shocks to stop. Over the objections of Sandford, his mother and friends, his legal conservator at Lutheran Social Service of MN (LSSMN) has gone to court and succeeded in mandating a continuation of the procedure." Twin Cities Indymedia asserts "Like all other USA states, Minnesota has [legal] loopholes allowing [its] citizens to receive electroshock over their expressed wishes."

Great Britain

Until 2009 in England and Wales, the Mental Health Act 1983 allowed the use of ECT on detained patients whether or not they had capacity to consent to it, so long as the treatment was likely to alleviate or prevent deterioration in a condition and was authorized by a psychiatrist from the Mental Health Act Commission's panel. However, following amendments which took effect in 2009, ECT may not be given to a patient who has capacity to refuse to consent to it, irrespective of his or her detention under the Act, although treatment may still be given to capacious patients in an emergency under Section 62 of the Act. If the treating psychiatrist thinks the need for treatment is urgent they may start a course of ECT before authorization. About 2,000 people a year in England and Wales are treated without their consent under the Mental Health Act. In Scotland the Mental Health (Care and Treatment) (Scotland) Act 2003 also gives patients with capacity the right to refuse ECT.

History

As early as the 16th century, agents to produce seizures were used to treat psychiatric conditions. In 1785, the therapeutic use of seizure induction was documented in the London Medical Journal. Convulsive therapy was introduced in 1934 by Hungarian neuropsychiatrist Ladislas J. Meduna who, believing mistakenly that schizophrenia and epilepsy were antagonistic disorders, induced seizures with first camphor and then metrazol (cardiazol). Within three years metrazol convulsive therapy was being used worldwide. In 1937, the first international meeting on convulsive therapy was held in Switzerland by the Swiss psychiatrist Muller. The proceedings were published in the American Journal of Psychiatry and, within three years, cardiazol convulsive therapy was being used worldwide. Italian Professor of neuropsychiatry Ugo Cerletti, who had been using electric shocks to produce seizures in animal experiments, and his colleague Lucio Bini developed the idea of using electricity as a substitute for metrazol in convulsive therapy and, in 1937, experimented for the first time on a person. Sherwin B. Nuland, having discussed the matter with a first-hand observer in the 1970s, gave the following description of the results of the first use of ECT on a person:

> "They thought, 'Well, we'll try 55 volts, two-tenths of a second. That's not going to do anything terrible to him.' So they did that. [...] This fellow — remember, he wasn't even put to sleep — after this major grand mal convulsion, sat right up, looked at these three fellows and said, 'What the fuck are you assholes trying to do?' Well, they were happy as could be, because he hadn't said a rational word in the weeks of observation."

ECT soon replaced metrazol therapy all over the world because it was cheaper, less frightening and more convenient. Cerletti and Bini were nominated for a Nobel Prize but did not receive one. By 1940, the procedure was introduced to both England and the US. Through the 1940s and 1950s the use of ECT became widespread. ECT is the only form of shock treatment still performed by modern medicine.

In the early 1940s, in an attempt to reduce the memory disturbance and confusion associated with treatment, two modifications were introduced: the use of unilateral electrode placement and the replacement of sinusoidal current with brief pulse. It took many years for brief-pulse equipment to be widely adopted Unilateral ECT has never been popular with psychiatrists and is still only given to a minority of ECT patients. In the 1940s and early 1950s ECT was usually given in "unmodified" form, without muscle relaxants, and the seizure resulted in a full-scale convulsion. A rare but serious complication of unmodified ECT was fracture or dislocation of the long bones. In the 1940s psychiatrists began to experiment with curare, the muscle-paralysing South American poison, in order to modify the convulsions. The introduction of suxamethonium (succinylcholine), a safer synthetic alternative to curare, in 1951 led to the more widespread use of "modified" ECT. A short-acting anesthetic was usually given in addition to the muscle relaxant in order to spare patients the terrifying feeling of suffocation that can be experienced with muscle relaxants.

The steady growth of antidepressant use along with negative depictions of ECT in the mass media led to a marked decline in the use of ECT during the 1950s to the 1970s. The Surgeon General stated there were problems with electroshock therapy in the initial years before anesthesia was routinely given and, *these now antiquated practices contributed to the negative portrayal of ECT in the popular media.* The New York Times described the public's negative perception of ECT as being caused mainly by one movie, "For Big Nurse in *One Flew Over the Cuckoo's Nest,* it was a tool of terror, and in the public mind *shock therapy* has retained the tarnished image given it by Ken Kesey's novel: dangerous, inhumane and overused".

In 1976, Dr. Blatchley demonstrated the effectiveness of his constant current, brief pulse device ECT. This device eventually largely replaced earlier devices because of the reduction in cognitive side effects, although some ECT clinics in the US still use sine-wave devices. The 1970s saw the publication of the first American Psychiatric Association task force report on electroconvulsive therapy (to be followed by further reports in 1990 and 2001). The report endorsed the use of ECT in the treatment of depression. The decade also saw criticism of ECT. Specifically critics pointed to shortcomings such as noted side effects, the procedure being used as a form of abuse, and uneven application of ECT. The use of ECT declined until the 1980s, "when use began to increase amid growing awareness of its benefits and cost-effectiveness for treating severe depression". In 1985 the National Institute of Mental Health and National Institutes of Health convened a consensus development conference on ECT and concluded that, whilst ECT was the most controversial treatment in psychiatry and had significant side-effects, it had been shown to be effective for a narrow range of severe psychiatric disorders.

Due to the backlash noted previously, national institutions reviewed past practices and set new standards. In 1978, The American Psychiatric Association released its first task force report in which new standards for consent were introduced and the use of unilateral electrode placement was recommended. The 1985 NIMH Consensus Conference confirmed the therapeutic role of ECT in certain circumstances. The American Psychiatric Association released its second task force report in 1990 where specific

details on the delivery, education, and training of ECT were documented. Finally in 2001 the American Psychiatric Association released its latest task force report. This report emphasizes the importance of informed consent, and the expanded role that the procedure has in modern medicine.

Patient experience

The APA ECT taskforce guidelines report findings that most patients find ECT no worse than going to the dentist, and many found it less stressful than the dentist. They report that other research finds that most patients would voluntarily receive ECT again if needed.

NICE ECT guidelines report that some individuals consider ECT to have been a beneficial and lifesaving treatment, while others reported feelings of terror, shame and distress, and found it positively harmful and an abusive invasion of personal autonomy, especially when administered without their consent.

Individual positive depictions

Kitty Dukakis, wife of politician Michael Dukakis, reports in a *Newsweek* article mostly positive effects from electroconvulsive therapy, and regards memory loss as an acceptable price to pay for relief from depression.

For me, the memory issues are real but manageable. Things I lose generally come back. Other memories I prefer to lose, including those about the depression I was suffering. But there are some memories—of meetings I have attended, people's homes I have visited—that I don't want to lose but I can't help it. They generally involve things I did two weeks before and two weeks after ECT. Often they are just wiped out....I have learned ways to partly compensate for whatever loss I still experience. I call my sister Jinny, Michael and my kids, asking what my niece Betsy's phone number is, what we did yesterday and what we are planning to do tomorrow. I apologize prior to asking. I wonder when they are going to run out of patience with "Kitty being Kitty." I hate losing memories, which means losing control over my past and my mind, but the control ECT gives me over my disabling depression is worth this relatively minor cost. It just is.

American psychotherapist Martha Manning's autobiographical *Undercurrents* acknowledges the downside of treatment: "I felt like I'd been hit by a truck for a while, but that was, comparatively speaking, not so bad," as well as the upside: "Afterwards, I thought, do regular people feel this way all the time? It's like you've not been in on a great joke for the whole of your life."

In his autobiographical book *Electroboy*, American writer Andy Behrman describes undergoing ECT as a treatment for bipolar disorder while under house-arrest: "I wake up thirty minutes later and think I am in a hotel in Acapulco. My head feels as if I have just downed a frozen margarita too quickly. My jaws and limbs ache. But I am elated."

Curtis Hartmann, a lawyer in western Massachusetts, stated: "ECT, a treatment of last resort for severe, debilitating depression, is all that has ever worked for me. I awaken about 20 minutes later, and although I am still groggy with anesthesia, much of the hellish depression is gone. It is a disease that for me, literally steals me from myself—a disease that executes me and then forces me to stand and look down at my corpse. Thankfully, ECT has kept my monster at bay, my hope intact".

Beverley Callard is a British actress, best known for her role as Liz McDonald in Coronation Street. In her recently published autobiography titled "Unbroken", she describes her experience with ECT for severe depression, stating that the treatment was responsible, in part for her recovery.

Individual negative depictions

Negative effects of ECT have been reported by noteworthy individuals.

Ernest Hemingway, American author, committed suicide shortly after ECT at the Menninger Clinic in 1961. He is reported to have said to his biographer, "Well, what is the sense of ruining my head and erasing my memory, which is my capital, and putting me out of business? It was a brilliant cure but we lost the patient...."

In 2005, "Peggy S. Salters, 60, sued Palmetto Baptist Medical Center in Columbia, as well as the three doctors responsible for her care. As the result of an intensive course of outpatient ECT in 2000, she lost all memories of the past 30 years of her life, including all memories of her husband of three decades, now deceased, and the births of her three children. Ms. Salters held a Masters of Science in nursing and had a long career as a psychiatric nurse, but lost her knowledge of nursing skills and was unable to return to work after ECT." The jury awarded Salters $635,177 in compensation for her inability to work. The judgement was upheld upon appeal.

Registered nurse Barbara C. Cody reports in a letter to the *Washington Post* that her life was forever changed by 13 outpatient ECTs she received in 1983. "Shock 'therapy' totally and permanently disabled me. EEGs [electroencephalograms] verify the extensive damage shock did to my brain. Fifteen to 20 years of my life were simply erased; only small bits and pieces have returned. I was also left with short-term memory impairment and serious cognitive deficits. [deletion] Shock 'therapy' took my past, my college education, my musical abilities, even the knowledge that my children were, in fact, my children. I call ECT a rape of the soul."

In 2007, a judge canceled a two year old court order that allowed the involuntary electroshock of Simone D., a psychiatric patient at Creedmoor Psychiatric Center in the state of New York. Although Simone spoke only Spanish, she rarely received access to staff fluent in her language. Simone previously had 200 electroshocks. However, she communicated that she did not want more electroshock. Simone stated, "Electroshock causes more pain. I suffer more from shock treatment! "

In 2008, David Tarloff, a psychiatric patient who had received electroshock, assaulted two therapists in the city of New York. Tarloff injured one therapist and killed the other. One of the therapists was Kent Shinbach, a psychiatrist who had an interest in electroconvulsive therapy. "It is not clear whether Dr. Shinbach played any role in Mr. Tarloff's shock therapy". However, Tarloff told investigators that Shinbach had given Tarloff psychiatric treatment at a psychiatric facility initially in 1991.

In an interview with *Houston Chronicle* in 1996, Melissa Holliday, a former extra on *Baywatch* and model for *Playboy* stated the ECT she received in 1995, "ruined her life." She went on to state, "I've been through a rape, and electroshock therapy is worse. If you haven't gone through it, I can't explain it."

Liz Spikol, the senior contributing editor of *Philadelphia Weekly*, wrote of her ECT in 1996, "Not only was the ECT ineffective, it was incredibly damaging to my cognitive functioning and memory. But sometimes it's hard to be sure of yourself when everyone 'credible' — scientists, ECT docs, researchers — are telling you that your reality isn't real. How many times have I been told my memory loss wasn't due to ECT but to depression? How many times have I been told that, like a lot of other consumers, I must be perceiving this incorrectly? How many times have people told me that my feelings of trauma related to the ECT are misplaced and unusual? It's as if I was raped and people kept telling me not to be upset—that it wasn't that bad."