# Psychosis and Neurological Disorders

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# Chapter 1

# Psychosis

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**Psychosis** (from the Greek ψυχή "psyche", for mind/soul, and -ωσις "-osis", for abnormal condition) means abnormal condition of the mind, and is a generic psychiatric term for a mental state often described as involving a "loss of contact with reality". People suffering from psychosis are described as *psychotic.* Psychosis is given to the more severe forms of psychiatric disorder, during which hallucinations and delusions and impaired insight may occur. Some professionals say that the term psychosis is not sufficient as some illnesses grouped under the term "psychosis" have nothing in common (Gelder, Mayou & Geddes 2005)

People experiencing psychosis may report hallucinations or delusional beliefs, and may exhibit personality changes and thought disorder. Depending on its severity, this may be accompanied by unusual or bizarre behavior, as well as difficulty with social interaction and impairment in carrying out the daily life activities.

A wide variety of central nervous system diseases, from both external poisons and internal physiologic illness, can produce symptoms of psychosis.

## *Signs and symptoms*

People with psychosis may have one or more of the following: hallucinations, delusions, or a thought disorder, as described below.

### Hallucinations

A hallucination is defined as sensory perception in the absence of external stimuli. Hallucinations are different from illusions, or perceptual distortions, which are the misperception of external stimuli. Hallucinations may occur in any of the five senses and take on almost any form, which may include simple sensations (such as lights, colors, tastes, and smells) to more meaningful experiences such as seeing and interacting with fully formed animals and people, hearing voices, and having complex tactile sensations.

Auditory hallucinations, particularly experiences of hearing voices, are a common and often prominent feature of psychosis. Hallucinated voices may talk about, or to, the person, and may involve several speakers with distinct personas. Auditory hallucinations tend to be particularly distressing when they are derogatory, commanding or preoccupying. However, the experience of hearing voices need not always be a negative one. One research study has shown that the majority of people who hear voices are not in need of psychiatric help. The Hearing Voices Movement has subsequently been created to support voice hearers, regardless of whether they are considered to have a mental illness or not.

### Delusions

Psychosis may involve delusional beliefs, some of which are paranoid in nature. Karl Jaspers has classified psychotic delusions into *primary* and *secondary* types. Primary delusions are defined as arising suddenly and not being comprehensible in terms of normal mental processes, whereas secondary delusions may be understood as being influenced by the person's background or current situation (e.g., ethnic or sexual orientation, religious beliefs, superstitious belief).

### Thought disorder

Thought disorder describes an underlying disturbance to conscious thought and is classified largely by its effects on speech and writing. Affected persons show loosening of associations, that is, a disconnection and disorganization of the semantic content of speech and writing. In the severe form speech becomes incomprehensible and it is known as "word-salad".

## *Causes*

Causes of symptoms of mental illness were customarily classified as "organic" or "functional". Organic conditions are primarily medical or pathophysiological, whereas, functional conditions are primarily psychiatric or psychological. The DSM-IV-TR no longer classifies psychotic disorders as functional or organic. Rather it lists traditional psychotic illnesses, psychosis due to General Medical conditions, and Substance induced psychosis.

## Psychiatric

Functional causes of psychosis include the following:

- brain tumors
- drug abuse amphetamines, cocaine, marijuana, alcohol among others
- brain damage
- schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic disorder
- bipolar disorder (manic depression)
- severe clinical depression
- severe psychosocial stress
- sleep deprivation
- some focal epileptic disorders especially if the temporal lobe is affected
- exposure to some traumatic event (violent death, etc.)
- abrupt or over-rapid withdrawal from certain recreational or prescribed drugs

A psychotic episode can be significantly affected by mood. For example, people experiencing a psychotic episode in the context of depression may experience persecutory or self-blaming delusions or hallucinations, while people experiencing a psychotic episode in the context of mania may form grandiose delusions.

Stress is known to contribute to and trigger psychotic states. A history of psychologically traumatic events, and the recent experience of a stressful event, can both contribute to the development of psychosis. Short-lived psychosis triggered by stress is known as brief reactive psychosis, and patients may spontaneously recover normal functioning within two weeks. In some rare cases, individuals may remain in a state of full-blown psychosis for many years, or perhaps have attenuated psychotic symptoms (such as low intensity hallucinations) present at most times.

Sleep deprivation has been linked to psychosis. However, this is not a risk for most people, who merely experience hypnagogic or hypnopompic hallucinations, i.e. unusual sensory experiences or thoughts that appear during waking or drifting off to sleep. These are normal sleep phenomena and are not considered signs of psychosis.

Vitamin $B_{12}$ deficiency can also cause symptoms of mania and psychosis.

Vitamin D overdose can cause altered thinking and psychosis.

Genetics may also have a role in psychosis. The Genain quadruplets were identical quadruplets who were all diagnosed with schizophrenia. Although having grown up in the same environment means it could be any other common factor, like for example having the same parents with the same behavior towards them.

## General medical

Psychosis arising from "organic" (non-psychological) conditions is sometimes known as **secondary psychosis**. It can be associated with the following pathologies:

- neurological disorders, including:
  - brain tumour
  - dementia with Lewy bodies
  - multiple sclerosis
  - sarcoidosis
  - Lyme Disease
  - syphilis
  - Alzheimer's Disease
  - Parkinson's Disease
  - Anti-NMDA receptor encephalitis

- electrolyte disorders such as:
  - hypocalcemia
  - hypernatremia
  - hyponatremia
  - hypokalemia
  - hypomagnesemia
  - hypermagnesemia
  - hypercalcemia
  - hypophosphatemia
- hypoglycemia
- lupus
- AIDS
- leprosy
- malaria
- Adult-onset vanishing white matter leukoencephalopathy
- Late-onset metachromatic leukodystrophy
- Cerebral involvement of scleroderma (a single case report).
- Hashimoto's encephalopathy, an extremely rare condition (about 100 reported cases).

Psychosis can even be caused by apparently innocuous ailments such as flu or mumps.

## Psychoactive drugs

Various psychoactive substances (both legal and illegal) have been implicated in causing, exacerbating, and/or precipitating psychotic states and/or disorders in users. Frequent use of cannabis doubles both the risk of psychosis and schizophrenia Older studies indicate that certain strains containing large proportions of THC and low proportions of CBD, merely lowers the threshold for psychosis, and thus helps to trigger full-blown psychosis in some people. On the other hand, cannabis use has increased dramatically over the past

few decades but declined in the last decade, whereas the rate of psychosis has not increased. This suggests that a direct causal link is unlikely for all users.

### Prescription medication

Some medications such as bromocriptine and phenylpropanolamine may also cause or worsen psychotic symptoms.

## *Pathophysiology*

The first brain image of an individual with psychosis was completed as far back as 1935 using a technique called pneumoencephalography (a painful and now obsolete procedure where cerebrospinal fluid is drained from around the brain and replaced with air to allow the structure of the brain to show up more clearly on an X-ray picture).

The purpose of the brain is to collect information from the body (pain, hunger, etc.), and from the outside world, interpret it to a coherent world view, and produce a meaningful response. The information from the senses enter the brain in the primary sensory areas. They process the information and send it to the secondary areas where the information is interpreted. Spontaneous activity in the primary sensory areas may produce hallucinations which are misinterpreted by the secondary areas as information from the real world.

For example, a PET or fMRI scan of a person who claims to be hearing voices may show activation in the primary auditory cortex, or parts of the brain involved in the perception and understanding of speech.

Tertiary brain cortex collects the interpretations from the secondary cortexes and creates a coherent world view of it. A study investigating structural changes in the brains of people with psychosis showed there was significant grey matter reduction in the right medial temporal, lateral temporal, and inferior frontal gyrus, and in the cingulate cortex bilaterally of people before and after they became psychotic. Findings such as these have led to debate about whether psychosis itself causes excitotoxic brain damage and whether potentially damaging changes to the brain are related to the length of psychotic episode. Recent research has suggested that this is not the case although further investigation is still ongoing.

Studies with sensory deprivation have shown that the brain is dependent on signals from the outer world to function properly. If the spontaneous activity in the brain is not counterbalanced with information from the senses, loss from reality and psychosis may occur after some hours. A similar phenomenon is paranoia in the elderly when poor eyesight, hearing and memory causes the person to be abnormally suspicious of the environment.

On the other hand, loss from reality may also occur if the spontaneous cortical activity is increased so that it is no longer counterbalanced with information from the senses. The 5-

HT2A receptor seems to be important for this, since drugs which activate them produce hallucinations.

However, the main feature of psychosis is not hallucinations, but the inability to distinguish between internal and external stimuli. Close relatives to psychotic patients may hear voices, but since they are aware that they are unreal they can ignore them, so that the hallucinations do not affect their reality perception. Hence they are not considered to be psychotic.

Psychosis has been traditionally linked to the neurotransmitter dopamine. In particular, the dopamine hypothesis of psychosis has been influential and states that psychosis results from an overactivity of dopamine function in the brain, particularly in the mesolimbic pathway. The two major sources of evidence given to support this theory are that dopamine receptor D2 blocking drugs (i.e., antipsychotics) tend to reduce the intensity of psychotic symptoms, and that drugs which boost dopamine activity (such as amphetamines and cocaine) can trigger psychosis in some people. However, increasing evidence in recent times has pointed to a possible dysfunction of the excitory neurotransmitter glutamate, in particular, with the activity of the NMDA receptor. This theory is reinforced by the fact that dissociative NMDA receptor antagonists such as ketamine, PCP and dextromethorphan/detrorphan (at large overdoses) induce a psychotic state more readily than dopinergic stimulants, even at "normal" recreational doses. The symptoms of dissociative intoxication are also considered to mirror the symptoms of schizophrenia, including negative psychotic symptoms, more closely than amphetamine psychosis. Dissociative induced psychosis happens on a more reliable and predictable basis than amphetamine psychosis, which usually only occurs in cases of overdose, prolonged use or with sleep deprivation, which can independently produce psychosis. New antipsychotic drugs which act on glutamate and its receptors are currently undergoing clinical trials.

The connection between dopamine and psychosis is generally believed to be complex. While dopamine receptor D2 suppresses adenylate cyclase activity, the D1 receptor increases it. If D2-blocking drugs are administered the blocked dopamine spills over to the D1 receptors. The increased adenylate cyclase activity affects genetic expression in the nerve cell, a process which takes time. Hence antipsychotic drugs take a week or two to reduce the symptoms of psychosis. Moreover, newer and equally effective antipsychotic drugs actually block slightly less dopamine in the brain than older drugs whilst also blocking 5-HT2A receptors, suggesting the 'dopamine hypothesis' may be oversimplified. Soyka and colleagues found no evidence of dopaminergic dysfunction in people with alcohol-induced psychosis and Zoldan et al. reported moderately successful use of ondansetron, a 5-$HT_3$ receptor antagonist, in the treatment of levodopa psychosis in Parkinson's disease patients.

Psychiatrist David Healy has criticised pharmaceutical companies for promoting simplified biological theories of mental illness that seem to imply the primacy of pharmaceutical treatments while ignoring social and developmental factors which are known to be important influences in the aetiology of psychosis.

Some theories regard many psychotic symptoms to be a problem with the perception of ownership of internally generated thoughts and experiences. For example, the experience of hearing voices may arise from internally generated speech that is mislabeled by the psychotic person as coming from an external source.

One clear finding is that persons with bipolar disorder seem to have increased activity of the left hemisphere compared to the right hemisphere of the brain, while persons with schizophrenia have increased activity in the right hemisphere.

Increased level of right hemisphere activation has also been found in people who have high levels of paranormal beliefs and in people who report mystical experiences. It also seems to be the case that people who are more creative are also more likely to show a similar pattern of brain activation. Some researchers have been quick to point out that this in no way suggests that paranormal, mystical or creative experiences are in any way *by themselves* a symptom of mental illness, as it is still not clear what makes some such experiences beneficial and others distressing.

## *Diagnosis*

The Brief Psychiatric Rating Scale (BPRS) assesses the level of 18 symptom constructs of psychosis such as hostility, suspicion, hallucination, and grandiosity. It is based on the clinician's interview with the patient and observations of the patient's behavior over the previous 2–3 days. The patient's family can also provide the behavior report. During the initial assessment and the follow-up, both positive and negative symptoms of psychosis can be assessed using the 30 item Positive and Negative Symptom Scale (PANSS).

## *Treatment*

The treatment of psychosis depends on the cause or diagnosis or diagnoses (such as schizophrenia, bipolar disorder and/ or substance intoxication). The first line treatment for many psychotic disorders is antipsychotic medication (oral or intramuscular injection), and sometimes hospitalization is needed. There is growing evidence that cognitive behavior therapy and family therapy can be effective in managing psychotic symptoms. When other treatments for psychosis are ineffective, electroconvulsive therapy (ECT) (aka shock treatment) is sometimes applied to relieve the underlying symptoms of psychosis due to depression. There is also increasing research suggesting that animal-assisted therapy can contribute to the improvement in general well-being of people with schizophrenia.

### Early intervention

Early intervention in psychosis is a relatively new concept based on the observation that identifying and treating someone in the early stages of a psychosis can significantly improve their longer term outcome. This approach advocates the use of an intensive multi-disciplinary approach during what is known as the critical period, where

intervention is the most effective, and prevents the long term morbidity associated with chronic psychotic illness.

Newer research into the effectiveness of cognitive behavioural therapy during the early pre-cursory stages of psychosis (also known as the "prodrome" or "at risk mental state") suggests that such input can prevent or delay the onset of psychosis.

One of the international paradigms aimed at researching the prodrome is the North American Prodrome Longitudinal Study (NAPLS). The study is concerned with brain development, hormones, and neuropsychological functions that may play a role in risk for and prevention of mental illness in young adulthood. Specifically, the goal is to determine the neurobiological indicators present in prodromal patients that may contribute to the onset of severe mental illness as compared with those of control individuals.

## *History*

The word *psychosis* was first used by Ernst von Feuchtersleben in 1845 as an alternative to insanity and mania and stems from the Greek *ψύχωσις* (*psychosis*), "a giving soul or life to, animating, quickening" and that from *ψυχή* (*psyche*), "soul" and the suffix *-ωσις* (*-osis*), in this case "abnormal condition". The word was used to distinguish disorders which were thought to be disorders of the mind, as opposed to "neurosis", which was thought to stem from a disorder of the nervous system. The psychoses thus became the modern equivalent of the old notion of madness, and hence there was much debate on whether there was only one (unitary) or many forms of the new disease.

The division of the major psychoses into manic depressive illness (now called bipolar disorder) and dementia praecox (now called schizophrenia) was made by Emil Kraepelin, who attempted to create a synthesis of the various mental disorders identified by 19th century psychiatrists, by grouping diseases together based on classification of common symptoms. Kraepelin used the term 'manic depressive insanity' to describe the whole spectrum of mood disorders, in a far wider sense than it is usually used today. In Kraepelin's classification this would include 'unipolar' clinical depression, as well as bipolar disorder and other mood disorders such as cyclothymia. These are characterised by problems with mood control and the psychotic episodes appear associated with disturbances in mood, and patients will often have periods of normal functioning between psychotic episodes even without medication. Schizophrenia is characterized by psychotic episodes which appear to be unrelated to disturbances in mood, and most non-medicated patients will show signs of disturbance between psychotic episodes.

During the 1960s and 1970s, psychosis was of particular interest to counterculture critics of mainstream psychiatric practice, who argued that it may simply be another way of constructing reality and is not necessarily a sign of illness. For example, R. D. Laing argued that psychosis is a symbolic way of expressing concerns in situations where such views may be unwelcome or uncomfortable to the recipients. He went on to say that psychosis could be also seen as a transcendental experience with healing and spiritual

aspects. Arthur J. Deikman suggested use of the term "mystical psychosis" to characterize first-person accounts of psychotic experiences that are similar to reports of mystical experiences. Thomas Szasz focused on the social implications of labeling people as psychotic, a label he argues unjustly medicalises different views of reality so such unorthodox people can be controlled by society. Psychoanalysis has a detailed account of psychosis which differs markedly from that of psychiatry. Freud and Lacan outlined their perspective on the structure of psychosis in a number of works.

Since the 1970s, the introduction of a recovery approach to mental health, which has been driven mainly by people who have experienced psychosis (or whatever name is used to describe their experiences), has led to a greater awareness that mental illness is not a lifelong disability, and that there is an expectation that recovery is possible, and probable with effective support.

# Chapter 2

# Brain Damage

"**Brain damage**" or "brain injury" (BI) is the destruction or degeneration of brain cells. Brain injuries occur due to a wide range of internal and external factors. A common category with the greatest number of injuries is traumatic brain injury (TBI) following physical trauma or head injury from an outside source, and the term acquired brain injury (ABI) is used in appropriate circles, to differentiate brain injuries occurring after birth from injury due to a disorder or congenital malady.

## *Causes*

Brain injuries occur due to a very wide range of conditions, illnesses, injuries, and as a result of iatrogenesis (adverse effects of medical treatment). Possible causes of widespread (*diffuse*) brain damage include prolonged hypoxia (shortage of oxygen), poisoning by teratogens (including alcohol), infection, and neurological illness. Chemotherapy can cause brain damage to the neural stem cells and oligodendrocyte cells that produce myelin. Common causes of focal or localized brain damage are physical trauma (traumatic brain injury, stroke, aneurysm, surgery, other neurological disorder, and heavy metals poisoning including by mercury and its compounds of lead or blows to the back of skull.

## *Signs and symptoms*

Brain injuries often create long-term impairment or disability which can vary greatly in severity. In cases of serious brain injuries, the likelihood of areas with permanent disability is great, including neurocognitive deficits, delusions (often specifically monothematic delusions), speech or movement problems, and mental handicap. There will also be personality changes. The most severe cases result in coma or even persistent vegetative state. Even a mild incident can have long term effects or cause symptoms to appear years later.

Mental fatigue is a common debilitating experience and may not be linked by the patient to the original (minor) incident. Narcolepsy and sleep disorders are common misdiagnoses.

Brain injury whether from stroke, alcohol abuse, traumatic brain injury, or vitamin B deficiency can sometimes result in Korsakoff's Psychosis, where the individual engages in confabulations. Confabulations involve the inability to separate daydream memory from real memory and the filling in of memory lapses with daydreams. Like all other symptoms of brain injuries, Korsakoff's Psychosis is often mis-diagnosed, in this case as schizophrenia.

## *Management*

Various professions may be involved in the medical care and rehabilitation of someone who suffers impairment after a brain injury. Neurologists, neurosurgeons, and physiatrists are physicians who specialise in treating brain injury. neuropsychologists (especially clinical neuropsychologists) are psychologists who specialise in understanding the effects of brain injury and may be involved in assessing the severity or creating rehabilitation strategies. occupational therapists may be involved in running rehabilitation programs to help restore lost function or help re-learn essential skills. Registered nurses, such as those working in hospital intensive care units, are able to maintain the health of the severely brain-injured with constant administration of medication and neurological monitoring, including the use of the Glasgow Coma Scale used by other health professionals to quantify extent of orientation.

The effects of impairment or disability resulting from brain injury may be treated by a number of methods, including medication, psychotherapy, neuropsychological rehabilitation, snoezelen, surgery, or physical implants such as deep brain stimulation.

In the case of brain damage from traumatic brain injury, dexamethasone and/or Mannitol may be used.

## *Prognosis*

Prognosis, or the likely progress of a disorder, depends on the nature, location and cause of the brain damage.

In general, neuroregeneration can occur in the peripheral nervous system but is much rarer and more difficult to assist in the central nervous system (brain or spinal cord). However, in neural development in humans, areas of the brain can learn to compensate for other damaged areas, and may increase in size and complexity and even change function, just as someone who loses a sense may gain increased acuity in another sense - a process termed neuroplasticity.

It is a common misconception that a brain injury sustained during childhood always has a better chance of successful recovery than similar injury acquired in adult life. It is contested that in recent studies, severe brain injuries inflicted upon children can be alleviated by the interaction of nicotinamide repropagation in nerve cells. However, the consequences of childhood injury may simply be more difficult to detect in the short term. This is because different cortical areas mature at different stages, with some major

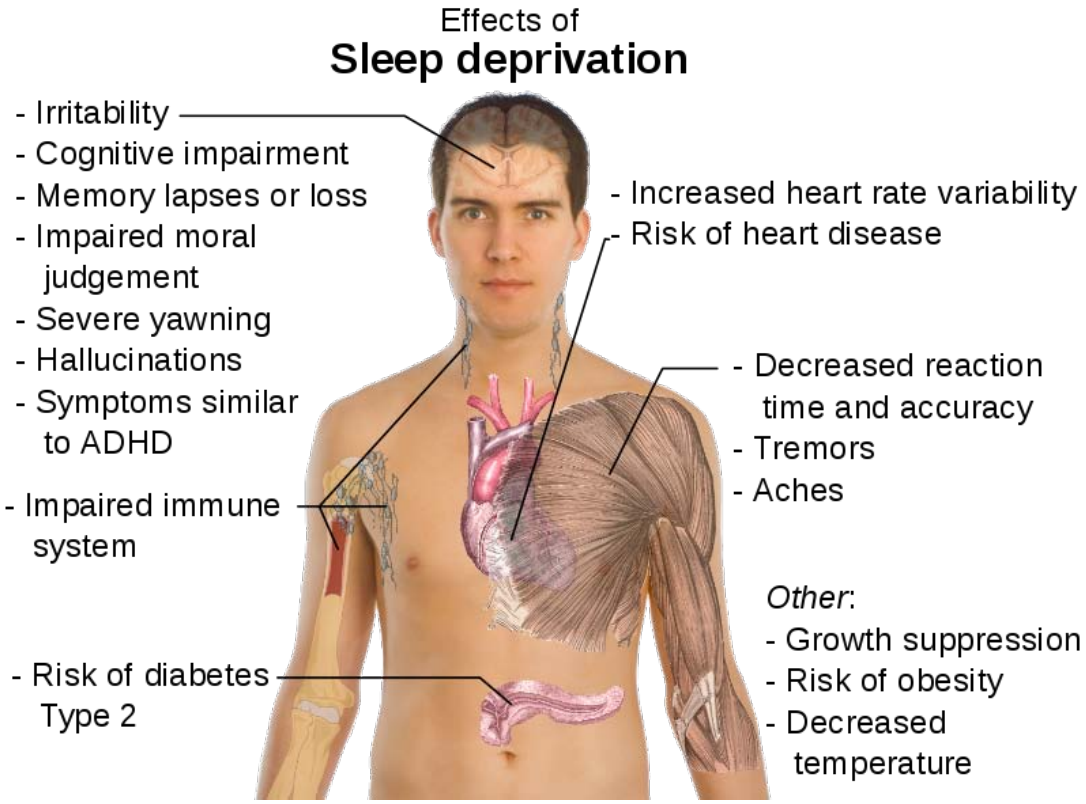
cell populations and their corresponding cognitive faculties remaining unrefined until early adulthood. In the case of a child with frontal brain injury, for example, the impact of the damage may be undetectable until that child fails to develop normal executive functions in his or her late teens and early twenties.

# Chapter 3

# Sleep Deprivation

**Sleep deprivation** is the condition of not having enough sleep; it can be either chronic or acute. A chronic sleep-restricted state can cause fatigue, daytime sleepiness, clumsiness and weight loss or weight gain. It adversely affects the brain and cognitive function. Few studies have compared the effects of acute total sleep deprivation and chronic partial sleep restriction. Complete absence of sleep over long periods is impossible for humans to achieve (unless they suffer from fatal familial insomnia); brief microsleeps cannot be avoided. Long-term total sleep deprivation has caused death in lab animals.

## *Physiological effects*




Main health effects of sleep deprivation

Minor dark circles, in addition to a hint of eye bags, a combination suggestive of minor sleep deprivation.

Generally, lack of sleep may result in:

- aching muscles
- confusion, memory lapses or loss
- depression
- hallucinations
- hand tremors
- headaches
- increased blood pressure
- increased stress hormone levels
- increased risk of diabetes
- increased risk of fibromyalgia
- irritability
- nystagmus (rapid involuntary rhythmic eye movement)
- obesity
- temper tantrums in children
- yawning
- symptoms similar to:
    - Attention-deficit hyperactivity disorder(ADHD)
    - Psychosis

## Diabetes

In 2005, a study of over 1400 participants showed that participants who habitually slept few hours were more likely to have associations with diabetes type 2. However, because this study was merely correlational, the direction of cause and effect between little sleep and diabetes is uncertain. The authors point to an earlier study which showed that experimental rather than habitual restriction of sleep resulted in impaired glucose tolerance (IGT).

## Effects on the brain

Sleep deprivation can adversely affect the brain and cognitive function. A 2000 study, by the UCSD School of Medicine and the Veterans Affairs Healthcare System in San Diego, used functional magnetic resonance imaging (fMRI) technology to monitor activity in the

brains of sleep-deprived subjects performing simple verbal learning tasks. The study showed that regions of the brain's prefrontal cortex displayed more activity in sleepier subjects. Depending on the task at hand, the brain would sometimes attempt to compensate for the adverse effects caused by lack of sleep.

The temporal lobe, which is a brain region involved in language processing, was activated during verbal learning in rested subjects but not in sleep-deprived subjects. The parietal lobe, not activated in rested subjects during the verbal exercise, was more active when the subjects were deprived of sleep. Although memory performance was less efficient with sleep deprivation, greater activity in the parietal region was associated with better memory.

A 2001 study at Chicago Medical Institute suggested that sleep deprivation may be linked to serious diseases, such as heart disease and mental illnesses including psychosis and bipolar disorder. The link between sleep deprivation and psychosis was further documented in 2007 through a study at Harvard Medical School and the University of California at Berkeley. The study revealed, using MRI scans, that lack of sleep causes the brain to become incapable of putting an emotional event into the proper perspective and incapable of making a controlled, suitable response to the event. Sleep deprivation may have been the underlying cause of the overdose deaths of celebrities Heath Ledger, Anna Nicole Smith and Michael Jackson.

A noted 2002 University of California animal study indicated that non-rapid eye movement sleep (NREM) is necessary for turning off neurotransmitters and allowing their receptors to "rest" and regain sensitivity which allows monoamines (norepinephrine, serotonin and histamine) to be effective at naturally-produced levels. This leads to improved regulation of mood and increased learning ability. The study also found that REM (rapid eye movement) sleep deprivation may alleviate clinical depression because it mimics selective serotonin reuptake inhibitors (SSRIs). This is because the natural decrease in monoamines during REM is not allowed to occur, which causes the concentration of neurotransmitters in the brain, that are depleted in clinically depressed persons, to increase. Sleep outside of the REM phase may allow enzymes to repair brain cell damage caused by free radicals. High metabolic activity while awake damages the enzymes themselves preventing efficient repair. This study observed the first evidence of brain damage in rats as a direct result of sleep deprivation.

Animal studies suggest that sleep deprivation increases stress hormones, which may reduce new cell production in adult brains.

## Effects on growth

A 1999 study found that sleep deprivation resulted in reduced cortisol secretion the next day, driven by increased subsequent slow-wave sleep. Sleep deprivation was found to enhance activity on the hypothalamic-pituitary-adrenal axis (which controls reactions to stress and regulates body functions such as digestion, the immune system, mood, sex, or

energy usage) while suppressing growth hormones. The results supported previous studies, which observed adrenal insufficiency in idiopathic hypersomnia.

## Effects on the healing process

A study conducted in 2005 showed that a group of rats which were deprived of REM sleep for five days had no significant effect on their ability to heal wounds, compared to a group of rats not deprived of "dream" sleep. The rats were allowed deep (NREM) sleep. However, another study conducted by Gumustekin et al. in 2004 showed sleep deprivation hindering the healing of burns on rats.

## Attention and working memory

Among the numerous physical consequences of sleep deprivation, deficits in attention and working memory are perhaps the most important; such lapses in mundane routines can lead to unfortunate results, from forgetting ingredients while cooking to missing a sentence while taking notes. Working memory is tested by such methods as choice-reaction time tasks.

The attentional lapses also extend into more critical domains in which the consequences can be literally life-or-death; car crashes and industrial disasters can result from inattentiveness attributable to sleep deprivation. To empirically measure the magnitude of attention deficits, researchers typically employ the psychomotor vigilance task (PVT) which requires the subject to press a button in response to a light at pseudo-random intervals. Failure to press the button in response to the stimulus (light) is recorded as an error, attributable to the microsleeps that occur as a product of sleep deprivation.

Crucially, individuals' subjective evaluations of their fatigue often do not predict actual performance on the PVT. While totally sleep-deprived individuals are usually aware of the degree of their impairment, lapses from chronic (lesser) sleep deprivation can build up over time so that they are equal in number and severity to the lapses occurring from total (acute) sleep deprivation. Chronically sleep-deprived people, however, continue to rate themselves considerably less impaired than totally sleep-deprived participants. Since people usually evaluate their capability on tasks like driving subjectively, their evaluations may lead them to the false conclusion that they are able to perform tasks that require constant attention when their abilities are in fact impaired.

## Impairment of ability

The dangers of sleep deprivation are apparent on the road; the American Academy of Sleep Medicine reports that one in every five serious motor vehicle injuries is related to driver fatigue, with 80,000 drivers falling asleep behind the wheel every day and 250,000 accidents every year related to sleep, though the National Highway Traffic Safety Administration suggests the figure for traffic accidents may be closer to 100,000. The AASM recommends pulling off the road and taking a 15- or 20-minute nap to alleviate drowsiness.

According to a 2000 study published in the *British Medical Journal*, researchers in Australia and New Zealand reported that sleep deprivation can have some of the same hazardous effects as being drunk. People who drove after being awake for 17–19 hours performed worse than those with a blood alcohol level of .05 percent, which is the legal limit for drunk driving in most western European countries and Australia. Another study suggested that performance begins to degrade after 16 hours awake, and 21 hours awake was equivalent to a blood alcohol content of .08 percent, which is the blood alcohol limit for drunk driving in Canada, the U.S., and the U.K.

In addition, as a result of continuous muscular activity without proper rest time, effects such as cramping are much more frequent in sleep-deprived individuals. Extreme cases of sleep deprivation have been reported to be associated with hernias, muscle fascia tears, and other such problems commonly associated with physical overexertion.

A 2006 study has shown that while total sleep deprivation for one night caused many errors, the errors were not significant until after the second night of total sleep deprivation. However, combining alcohol with acute sleep deprivation results in a trebled rate of driving off the road when using a simulator.

The National Sleep Foundation identifies several warning signs that a driver is dangerously fatigued, including rolling down the window, turning up the radio, trouble keeping eyes open, head-nodding, drifting out of the lane, and daydreaming. At particular risk are lone drivers between midnight and 6 a.m.

Sleep deprivation can negatively impact performance in professional fields as well, potentially jeopardizing lives. Due largely to the February 2009 crash of a regional jet in Buffalo, NY, which killed 50 people and was partially attributed to pilot fatigue, the FAA is reviewing its procedures to ensure pilots are sufficiently rested. A 2004 study also found medical residents with less than four hours of sleep a night made more than twice as many errors as residents who slept for more than seven hours a night, an especially alarming trend given that less than 11% of surveyed residents were sleeping more than seven hours a night.

Great sleep deprivation mimics psychosis: distorted perceptions can lead to inappropriate emotional and behavioral responses.

## Microsleeps

Microsleeps occur when a person has a significant sleep deprivation. The brain automatically shuts down, falling into a sleep state for a period that can last from a second to half a minute. The person falls asleep no matter what activity he or she is engaged in. Microsleeps are similar to blackouts and a person experiencing them is not consciously aware that they are occurring.

### Weight gain/loss

In rats, prolonged, complete sleep deprivation increases both food intake and energy expenditure, however a hormone imbalance is observed, leading to weight gain and ultimately death.

Several large studies using nationally representative samples suggest that the obesity problem in the United States might have as one of its causes a corresponding decrease in the average number of hours that people are sleeping. The findings suggest that this might be happening because sleep deprivation could be disrupting hormones that regulate glucose metabolism and appetite.

The association between sleep deprivation and obesity appears to be strongest in young and middle-age adults. Other scientists hold that the physical discomfort of obesity and related problems, such as sleep apnea, reduce an individual's chances of getting a good night's sleep.

## *Uses*

### Scientific study of laboratory animals

This rat is being deprived of restful REM sleep by an animal researcher using a single platform ("flower pot") technique. The water is within 1 cm of the small flower pot

bottom platform where the rat sits. At the onset of REM sleep, the exhausted rat will either fall into the deep water only to clamber back to its pot to avoid death from drowning, or its nose will become submerged into the water startling it back to an awakened state.

In science, sleep deprivation (of rodents, e.g.) is used in order to study the function(s) of sleep and the biological mechanisms underlying the effects of sleep deprivation.

**Some sleep deprivation techniques are as follows:**

- Gentle handling: During the sleep deprivation period, the animal and its polysomnograph record are continuously observed; when the animal displays sleep electrophysiological signals or assumes a sleep posture, it is given objects to play with and activated by acoustic and if necessary tactile stimuli. Although subjective, this technique is used for total sleep deprivation as well as REM or NREM sleep deprivation. This technique often requires polysomnography.
- Single platform: During the sleep deprivation period, the animal is placed on an inverted flower pot, the bottom diameter of which is small relative to the animal's size (usually 7 cm for adult rats). The pot is placed in a large tub filled with water to within 1 cm of the flower pot bottom. The animal is able to rest on the pot and is even able to get NREM sleep. But at the onset of REM sleep, with its ensuing muscular relaxation, it will either fall into the water and clamber back to its pot or will get its nose wet enough to awaken it. Thus, this technique is only useful for studying REM sleep deprivation. This was one of the first scientific methods developed.
- Multiple platform: In an effort to reduce the elevated stress response induced by the single platform method, researchers developed the "multiple platform" technique of REM sleep deprivation. In this configuration, the animal is placed within a large tank containing multiple platforms, thereby eliminating the movement restriction in the earlier setup.
- Modified multiple platform: Modification of the multiple platform method where several animals together experience sleep deprivation (Nunes and Tufik, 1994).
- Pendulum: Animals are prevented from entering into REM sleep by allowing them to sleep for only brief periods of time. This is accomplished by an apparatus that moves the animals' cages backwards and forwards in a pendular motion. At the extremes of the motion, the animals experience postural imbalance, forcing them to walk back and forth to retain their balance.

## Interrogation

Sleep deprivation can be used as a means of interrogation, which has resulted in court trials over whether or not the technique is a form of torture.

Under one interrogation technique, a subject might be kept awake for several days and when finally allowed to fall asleep, suddenly awakened and questioned. Menachem

Begin, the Prime Minister of Israel from 1977–83, described his experience of sleep deprivation as a prisoner of the NKVD in Russia as follows:

In the head of the interrogated prisoner, a haze begins to form. His spirit is wearied to death, his legs are unsteady, and he has one sole desire: to sleep... Anyone who has experienced this desire knows that not even hunger and thirst are comparable with it.

Sleep deprivation was one of the five techniques used by the British government in the 1970s. The European Court of Human Rights ruled that the five techniques "did not occasion suffering of the particular intensity and cruelty implied by the word torture ... [but] amounted to a practice of inhuman and degrading treatment", in breach of the European Convention on Human Rights.

The Justice Department released four memos in August 2002 describing interrogation techniques used by the Central Intelligence Agency. They first described 10 techniques used in the interrogations of Abu Zubaydah. Among them included sleep deprivation. Memos from May 2005 introduced four more techniques and confirmed the combination of interrogation methods were not constituted as torture under United States law.

The question of extreme use of sleep deprivation as torture has advocates on both sides of the issue. In 2006, Australian Federal Attorney-General Philip Ruddock argued that sleep deprivation does not constitute torture. Nicole Bieske, a spokeswoman for Amnesty International Australia, has stated, "At the very least, sleep deprivation is cruel, inhumane and degrading. If used for prolonged periods of time it is torture."

## Treatment for depression

Recent studies show sleep deprivation has some potential in the treatment of depression, About 60% of patients, when sleep-deprived, show immediate recovery, with most relapsing the following night. The effect has been shown to link to increases in brain-derived neurotrophic factor (BDNF). It has been shown that chronotype is related to the effect of sleep deprivation on mood in normal people; those with morningness circadian preference show an increase in depression-dejection scores while those with eveningness preference show a significant decrease.

The incidence of relapse can be decreased by combining sleep deprivation with medication. Many tricyclic antidepressants happen to suppress REM sleep, providing additional evidence for a link between mood and sleep. Similarly, tranylcypromine has been shown to completely suppress REM sleep at adequate doses.

## Voluntary

Sleep deprivation has sometimes been self-imposed to achieve personal notoriety in the context of record-breaking stunts.

## *Causes*

### Psychostimulant drugs

Psychostimulant drugs, predominantly methamphetamine, are capable of keeping users awake for 3–15 days at a time with repeated dosing.

### Mental illness

The specific causal relationships between sleep loss and effects on psychiatric disorders have been most extensively studied in patients with mood disorders. Shifts into mania in bipolar patients are often preceded by periods of insomnia, and sleep deprivation has been shown to induce a manic state in susceptible individuals. Sleep deprivation may represent a final common pathway in the genesis of mania, and sleep loss is both a precipitating and reinforcing factor for the manic state.

### School

A National Sleep Foundation survey found that college/university-aged students get an average of 6.8 hours of sleep each night. Sleep deprivation is common in college freshmen as they adjust to the stress and social activities of college life. A study performed by the Department of Psychology at the National Chung Cheng University in Taiwan concluded that freshmen received the shortest amount of sleep during the week. In 1997 the University of Minnesota did research that compared students who went to school at 7:15 a.m. and those who went to school at 8:40 a.m. They found that students who went to school at 8:40 got higher grades and more sleep on weekday nights. One in four U.S. high school students admits to falling asleep in class at least once a week. It is known that during human adolescence, circadian rhythms and therefore sleep patterns typically undergo marked changes. Electroencephalogram (EEG) studies indicate a 50% reduction of deep (stage 4) sleep and a 75% reduction in the peak amplitude of delta waves during NREM sleep in adolescence. School schedules are often incompatible with a corresponding delay in sleep offset, leading to a less than optimal amount of sleep for the majority of adolescents.

## *Counteracting the effects of sleep deprivation*

Several strategies are common in attempting to increase alertness and counteract the effects of sleep deprivation. Caffeine is often used over short periods to boost wakefulness when acute sleep deprivation is experienced; however, caffeine is less effective if taken routinely. Other strategies recommended by the American Academy of Sleep Medicine include prophylactic sleep before deprivation, naps, other stimulants, and combinations thereof. However, the only sure and safe way to combat sleep deprivation is to increase nightly sleep time.

Recovery of cognitive function is accomplished more rapidly after acute total sleep deprivation than after chronic partial sleep restriction. Chronic deprivation is the more

common in everyday life. Just one night of recovery sleep can reverse adverse effects of total sleep deprivation. Recovery sleep is more efficient than normal sleep with shorter sleep latency and increased amounts of deep and REM sleep.

## *Longest period without sleep*

Randy Gardner holds the scientifically documented record for the longest period of time a human being has intentionally gone without sleep not using stimulants of any kind. Gardner stayed awake for 264 hours (11 days), breaking the previous record of 260 hours held by Tom Rounds of Honolulu. Lt. Cmdr. John J. Ross of the U.S. Navy Medical Neuropsychiatric Research Unit later published an account of this event, which became well-known among sleep-deprivation researchers.

Other sources claim that the Guinness World Records record stands at 449 hours (18 days, 17 hours), held by Maureen Weston, of Peterborough, Cambridgeshire in April, 1977, in a rocking-chair marathon.

Claims of not having slept in years have been made at times, for certain individuals, but either without scientific verification, or contradicted in independent verification:

- **Never scientifically verified**: Thai Ngoc, born 1942, claimed in 2006 to have been awake for 33 years or 11,700 nights, according to Vietnamese news organization Thanh Nien. It was said that Ngoc acquired the ability to go without sleep after a bout of fever in 1973, but other reports indicate he stopped sleeping in 1976 with no known trigger. At the time of the Thanh Nien report, Ngoc suffered from no apparent ill effect (other than a minor decline in liver function), was mentally sound and could carry 100 kg of pig feed down a 4 km road, but another report indicates that he was healthy before the sleepless episode but that now he was not feeling well because of the lack of sleep.
- **Contradicted by claimant himself**: In January 2005, the RIA Novosti published an article about Fyodor Nesterchuk from the Ukrainian town of Kamen-Kashirsky who claimed to have not slept in more than 20 years. Local doctor Fyodor Koshel, chief of the Lutsk city health department, claimed to have examined him extensively and failed to make him sleep. Koshel also said however that Nesterchuck did not suffer any of the normally deleterious effects of sleep deprivation. However, when a reporter from *The Guardian* followed up on this report, Nesterchuk said he was getting 2–3 hours of sleep per night, and that "[h]e did not appear to notice the marked difference between never getting to sleep once in 240 months, and getting fewer than the recommended number of hours each week."
- **Contradicted in more accurate reporting**: Rhett Lamb of St. Petersburg, Florida, was initially reported to not sleep at all, but actually has a rare condition permitting him to sleep only one to two hours per day in the first three years of his life. He has a rare abnormality called an Arnold-Chiari malformation where brain tissue protrudes into the spinal canal; the skull puts pressure on the protruding

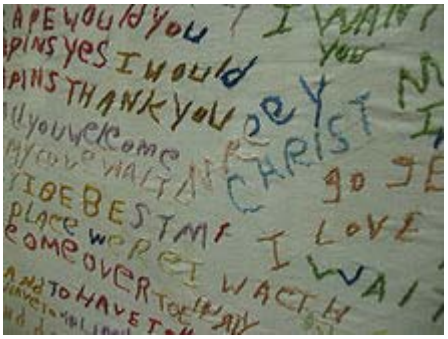
part of the brain. The boy was operated on at All Children's Hospital in St. Petersburg in May 2008. Two days after surgery he slept through the night.

- **Pathological condition**: French sleep expert Michel Jouvet and his team reported the case of a patient who was quasi-sleep-deprived for 4 months, as confirmed by repeated polygraphic recordings showing less than 30 min (of stage I sleep) per night, a condition they named "agrypnia". The 27-year-old man was suffering from Morvan's fibrillary chorea, a rare disease that leads to involuntary movements, and in this particular case extreme insomnia. The researchers found that treatment with 5-HTP restored almost normal sleep stages, however some months after this recovery the patient died during a relapse which was unresponsive to 5-HTP. Despite the extreme insomnia, psychological investigation showed no sign of cognitive deficits, except for some hallucinations.

# Chapter 4

# 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 thought processes 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 about 0.3–0.7%. Diagnosis is based on observed behavior and the patient's reported experiences.

Genetics, early environment, neurobiology, and psychological and social processes appear to be important contributory factors; some recreational and prescription drugs appear to cause or worsen symptoms. Current research is focused on the role of neurobiology, although no single isolated organic cause has been found. The many possible combinations of symptoms have triggered 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.

The mainstay of treatment is antipsychotic medication, which primarily works by suppressing dopamine activity. 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 now shorter and less frequent than they were.

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 almost 50%. Social problems, such as long-term unemployment, poverty and homelessness, are common. The average life expectancy of people with the disorder is 12 to 15 years less than those without, the result of increased physical health problems and a higher suicide rate (about 5%).

## *Signs and symptoms*

A person diagnosed with schizophrenia may experience hallucinations (most reported are 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. Social withdrawal, sloppiness of dress and hygiene, and loss of motivation and judgement are all common in schizophrenia. There is often an observable pattern of emotional difficulty, for example lack of responsiveness. Impairment in social cognition is associated with schizophrenia, as are symptoms of paranoia; social isolation commonly occurs. In one uncommon subtype, the person may be largely mute, remain motionless in bizarre postures, or exhibit purposeless agitation, all signs of catatonia.

Late adolescence and early adulthood are peak periods for the onset of schizophrenia, critical years in a young adult's social and vocational development. In 40% of men and 23% of women diagnosed with schizophrenia the condition manifested itself before the age of 19. 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. Those who go on to develop schizophrenia may experience transient or self-limiting psychotic symptoms and the non-specific symptoms of social withdrawal, irritability and dysphoria during the prodromal phase.

## 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 they 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. Positive symptoms are those that most individuals do not normally experience but are present in people with schizophrenia. They can include delusions, disordered thoughts and speech, and tactile, auditory, visual, olfactory and gustatory hallucinations, typically regarded as manifestations of psychosis. Hallucinations are also typically related to the

content of the delusional theme. Positive symptoms generally respond well to medication. Negative symptoms are deficits of normal emotional responses or of other thought processes, and respond less well to medication. They commonly 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. People with prominent negative symptoms often have a history of poor adjustment before the onset of illness, and response to medication is often limited.

## *Causes*

A combination of genetic and environmental factors play a role in the development of schizophrenia. People with a family history of schizophrenia who suffer a transient or self-limiting psychosis have a 20–40% chance of being diagnosed one year later.

### Genetic

Estimates of heritability vary because of the difficulty in separating the effects of genetics and the environment. The greatest risk for developing schizophrenia is having a first-degree relative with the disease (risk is 6.5%); more than 40% of monozygotic twins of those with schizophrenia are also affected. It is likely that many genes are involved, each of small effect. Many possible candidates have been proposed, including specific copy number variations, NOTCH4 and histone protein loci. A number of genome-wide associations such as zinc finger protein 804A have also been linked. There appears to be significant overlap in the genetics of schizophrenia and bipolar disorder.

Assuming a hereditary basis, one question from evolutionary psychology is why genes that increase the likelihood of psychosis evolved, assuming the condition would have been maladaptive from an evolutionary 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.

### Environment

Environmental factors associated with the development of schizophrenia include the living environment, drug use and prenatal stressors. Parenting style seems to have no effect, although people with supportive parents do better than those with critical parents. Living in an urban environment during childhood or as an adult has consistently been found to increase the risk of schizophrenia by a factor of two, even after taking into account drug use, ethnic group, and size of social group. Other factors that play an important role include social isolation and immigration related to social adversity, 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.

**Substance abuse**

A number of drugs have been associated with the development of schizophrenia including cannabis, cocaine and amphetamines. About half of those with schizophrenia use drugs and/or alcohol excessively. The role of cannabis could be causal, but other drugs may be used only as coping mechanisms to deal with depression, anxiety, boredom, and loneliness.

Cannabis is associated with a dose-dependent increase in the risk of developing a psychotic disorder. Frequent use has been found to double the risk of psychosis and schizophrenia. Some research has however questioned the causality of this link. Amphetamine, cocaine, and to a lesser extent alcohol, can result in psychosis that presents very similarly to schizophrenia.

**Prenatal**

Factors such as hypoxia and infection, or stress and malnutrition in the mother during fetal development, may result in a slight increase in the risk of schizophrenia later in life. People diagnosed with schizophrenia are more likely to have been born in winter or spring (at least in the northern hemisphere), which may be a result of increased rates of viral exposures in utero. This difference is about 5 to 8%.

## *Mechanisms*

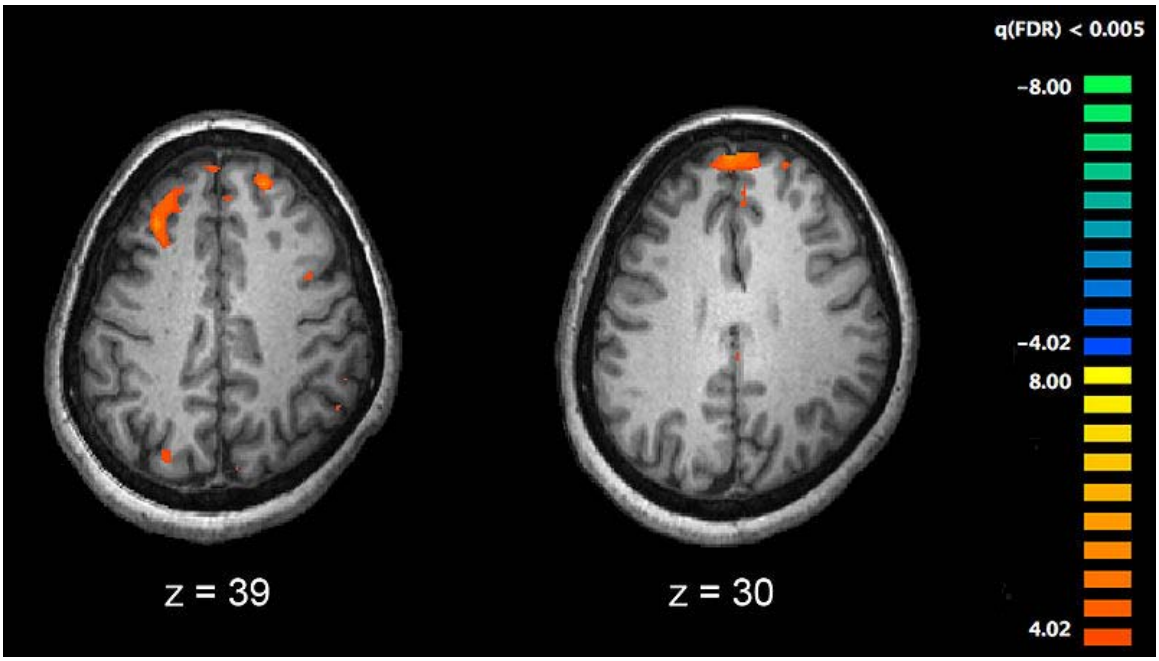
A number of attempts have been made to explain the link between altered brain function and schizophrenia. One of the most common is the dopamine hypothesis, which attributes psychosis to the mind's faulty interpretation of the misfiring of dopaminergic neurons.

### Psychological

Many psychological mechanisms have been implicated in the development and maintenance of schizophrenia. Cognitive biases have been identified in those with the diagnosis or those at risk, especially when under stress or in confusing situations. Some cognitive features may reflect global neurocognitive deficits such as memory loss, while others may be related to particular issues and experiences.

Despite a demonstrated 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.

## Neurological



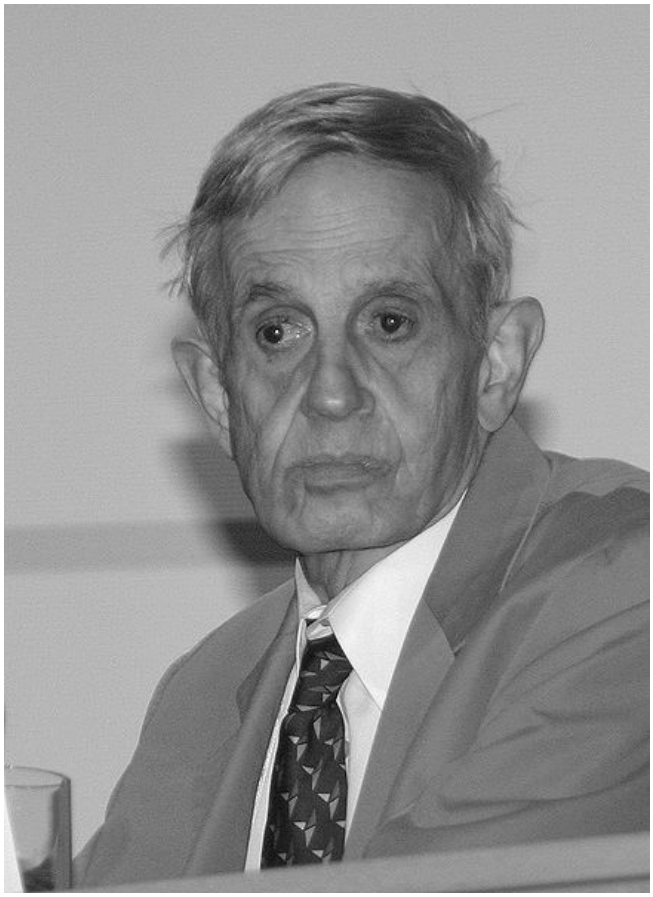

Functional magnetic resonance imaging (fMRI), and other brain imaging technologies, allow for the study of differences in brain activity in people diagnosed with schizophrenia. The image shows two levels of the brain, with areas that were more active in healthy controls than in schizophrenia patients shown in red, during an fMRI study of working memory.

Those with a diagnosis of schizophrenia have changes in both brain structure and chemistry. 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. Because neural circuits are altered, it has alternatively been suggested that schizophrenia should be thought of as a collection of neurodevelopmental disorders.

Particular attention has been paid to the function of dopamine in the mesolimbic pathway of the brain. This focus largely resulted from the accidental finding that phenothiazine drugs, which block dopamine function, 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. The influential dopamine hypothesis of schizophrenia proposed that excessive 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. The dopamine hypothesis is now thought to be simplistic, partly because newer antipsychotic medication (atypical antipsychotic medication) can be just as effective as older

medication (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, largely because of the abnormally low levels of glutamate receptors found in the postmortem brains of those diagnosed with schizophrenia, and the discovery that glutamate-blocking drugs such as phencyclidine and ketamine can mimic the symptoms and cognitive problems associated with the condition. Reduced glutamate function is linked to poor performance on tests requiring frontal lobe and hippocampal function, and glutamate can affect dopamine function, both of which have been implicated in schizophrenia, have suggested an important mediating (and possibly causal) role of glutamate pathways in the condition. But positive symptoms fail to respond to glutamatergic medication. A common side effect associated with schizo-affective patients, known as akathisia (mistaken for schizophrenic symptoms), was found to be associated with increased levels of norepinephrine.

## *Diagnosis*



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*.

Schizophrenia is diagnosed based on criteria in either the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*, version DSM-IV-TR, or the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, the ICD-10. These criteria use the self-reported experiences of the person and reported abnormalities in behavior, followed by a clinical assessment by a mental health professional. Symptoms associated with schizophrenia occur along a continuum in the population and must reach a certain severity before a diagnosis is made. As of 2009 there is no objective test.

## Criteria

The ICD-10 criteria are typically used in European countries, while the DSM-IV-TR criteria are used in the United States and the rest of the world, and are prevailing in research studies. The ICD-10 criteria put more emphasis on Schneiderian first-rank symptoms. 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 or 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. Significant 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.

## 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)
- 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)
- 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)
- 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)

## Differential

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.

## *Prevention*

Evidence for the effectiveness of early intervention is inconclusive. While there is some evidence that early intervention in those with a psychotic episode may improve short term outcomes, there is little benefit from these measures after five years. Attempting to prevent schizophrenia in the prodrome phase is of uncertain benefit and therefore as of 2009 is not recommended. Prevention is difficult as there are no reliable markers for the later development of the disease.

## *Management*

The primary treatment of schizophrenia is antipsychotic medications, often in combination with psychological and social supports. Hospitalization may occur for severe episodes either voluntarily or (if mental health legislation allows it) involuntarily. Long-term hospitalization is uncommon since deinstitutionalization beginning in the 1950s, although still occasionally occurs. Community support services including drop-in centers, visits by members of a community mental health team, supported employment and support groups are common. Some evidence indicates that regular exercise has a positive effect on the physical and mental health of those with schizophrenia.

## Medication


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

The first-line psychiatric treatment for schizophrenia is antipsychotic medication, which can reduce the positive symptoms of psychosis in about 7–14 days. Antipsychotics however fail to significantly ameliorate the negative symptoms and cognitive dysfunction.

The choice of which antipsychotic to use is based on benefits, risks, and costs. It is debatable whether as a class typical or atypical antipsychotics are better. Both have equal drop-out and symptom relapse rates when typicals are used at low to moderate dosages. There is a good response in 40–50%, a partial response in 30–40%, and treatment resistance (failure of symptoms to respond satisfactorily after six weeks to two of three different antipsychotics) in 20% of people. Clozapine is an effective treatment for those who respond poorly to other drugs, but it has the potentially serious side effect of agranulocytosis (lowered white blood cell count) in 1–4%.

With respect to side effects typical antipsychotics are associated with a higher rate of extrapyramidal side effects while atypicals are associated with considerable weight gain, diabetes and risk of metabolic syndrome. While atypicals have fewer extrapyramidal side

effects these differences are modest. Some atypicals such as quetiapine and risperidone are associated with a higher risk of death compared to the atypical perphenazine, while clozapine is associated with the lowest risk of death. It remains unclear whether the newer antipsychotics reduce the chances of developing neuroleptic malignant syndrome, a rare but serious neurological disorder.

For people who are unwilling or unable to take medication regularly, long-acting depot preparations of antipsychotics may be used to achieve control. When used in combination with psychosocial interventions they may improve long-term adherence to treatment.

### Psychosocial

A number of psychosocial interventions may be useful in the treatment of schizophrenia including: family therapy, assertive community treatment, supported employment, skills training, cognitive behavioral therapy (CBT), token economic interventions, and psychosocial interventions for substance use and weight management. Family therapy or education, which addresses the whole family system of an individual, may reduce relapses and hospitalizations. The evidence for CBT's effectiveness in either reducing symptoms or preventing relapse is minimal. The benefits of art or drama therapy are currently unknown.

## *Prognosis*

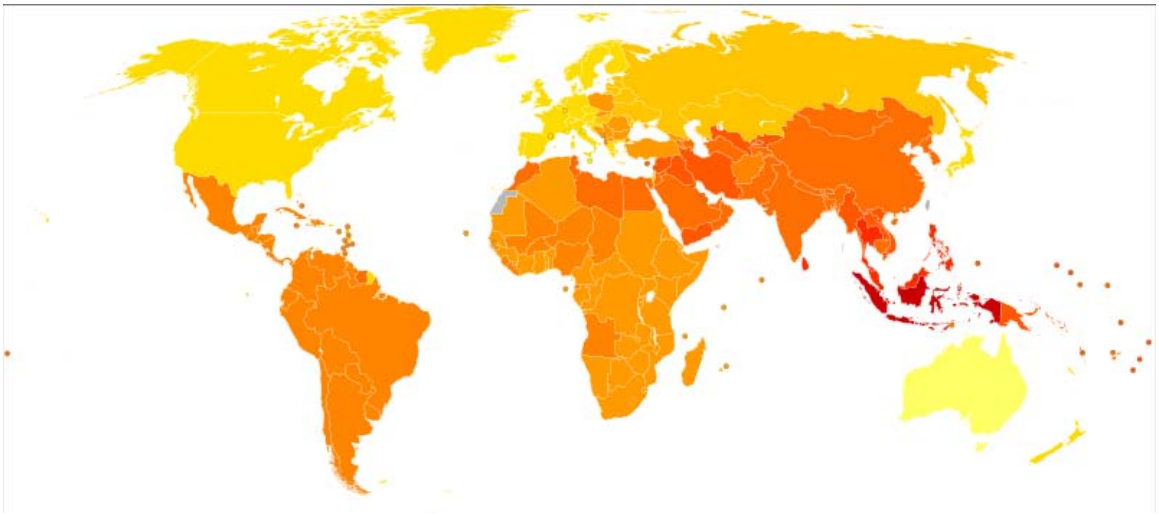
Schizophrenia has great human and economic costs. It results in a decreased life expectancy of 12–15 years, primarily because of its association with obesity, sedentary lifestyles, and smoking, with an increased rate of suicide playing a lesser role. These differences in life expectancy increased between the 1970s and 1990s, and between the 1990s and first decade of the 21st century did not change substantially in a health system with open access to care (Finland).

Schizophrenia is a major cause of disability, with active psychosis ranked as the third-most-disabling condition after quadriplegia and dementia and ahead of paraplegia and blindness. Approximately three-fourths of people with schizophrenia have ongoing disability with relapses. Some people do recover completely and others function well in society. Most people with schizophrenia live independently with community support. In people with a first episode of psychosis a good long-term outcome occurs in 42%, an intermediate outcome in 35% and a poor outcome in 27%. Outcomes for schizophrenia appear better in the developing than the developed world. These conclusions however have been questioned.

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 to 4.9%, most often occurring in the period following onset or first hospital admission. Several times more (20 to 40%) attempt suicide at least once. There are a variety of risk factors, including male gender, depression, and a high intelligence quotient.

Schizophrenia and smoking have shown a strong association in studies world-wide. Use of cigarettes is especially high in individuals diagnosed with schizophrenia, with estimates ranging from 80% to 90% being regular smokers, as compared to 20% of the general population. Those who smoke tend to smoke heavily, and additionally smoke cigarettes with high nicotine content.

## *Epidemiology*



Disability-adjusted life year for schizophrenia per 100,000 inhabitants in 2004.

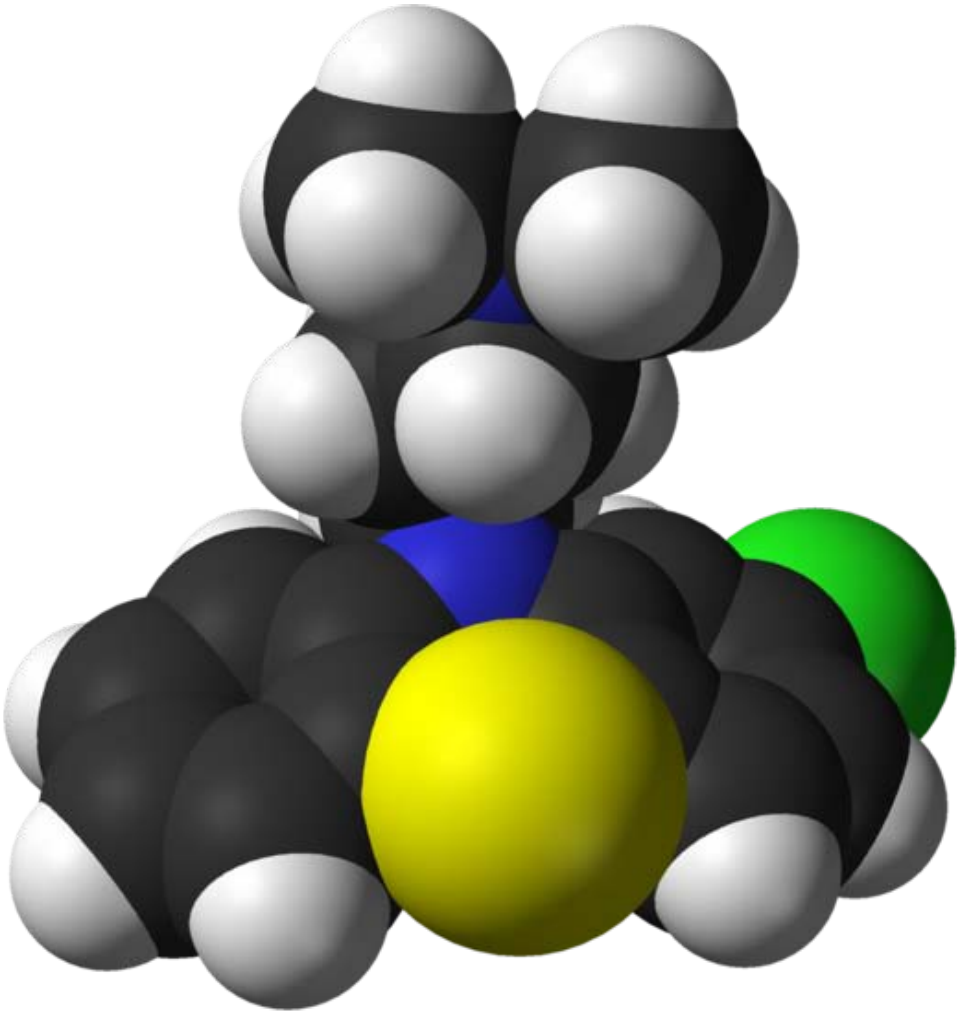
- no data
- ≤ 185
- 185–197
- 197–207
- 207–218
- 218–229
- 229–240
- 240–251
- 251–262
- 262–273
- 273–284
- 284–295
- ≥ 295

Schizophrenia affects around 0.3–0.7% of people at some point in their life, or 24 million people worldwide as of 2011. It occurs 1.4 times more frequently in males than females and 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. Despite the received wisdom that schizophrenia occurs at similar rates worldwide, its prevalence varies across the world, within countries, and at the local and neighborhood level. It causes approximately 1% of worldwide disability adjusted life years. The rate of schizophrenia varies up to threefold depending on how it is defined.

## *History*

Accounts of a schizophrenia-like syndrome are thought to be rare in the historical record before the 19th century, 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 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 thus proposed the term schizophrenia instead. Treatment was revolutionized in the mid-1950s with the development and introduction of chlorpromazine.



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

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 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.

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 5

# Schizophreniform Disorder

## Schizophreniform disorder

| | |
|---|---|
| **ICD-10** | F20.8 |
| **ICD-9** | 295.40 |
| **eMedicine** | article/292885 |
| **MeSH** | D011618 |

**Schizophreniform disorder** is a mental disorder diagnosed when symptoms of schizophrenia are present for a significant portion of the time within a one-month period, but signs of disruption are not present for the full six months required for the diagnosis of schizophrenia.

The symptoms of both disorders can include delusions, hallucinations, disorganized speech, disorganized or catatonic behavior, and social withdrawal. While impairment in social, occupational, or academic functioning is required for the diagnosis of schizophrenia, in schizophreniform disorder an individual's level of functioning may or may not be affected. While the onset of schizophrenia is often gradual over a number of months or years, the onset of schizophreniform disorder can be relatively rapid.

Like schizophrenia, schizophreniform disorder is often treated with antipsychotic medications, especially the atypicals, along with a variety of social supports (such as individual psychotherapy, family therapy, occupational therapy, etc.) designed to reduce the social and emotional impact of the illness. The prognosis varies depending upon the nature, severity, and duration of the symptoms, but about two-thirds of individuals diagnosed with schizophreniform disorder go on to develop schizophrenia.

### *Symptoms and Diagnosis*

Schizophreniform disorder is a type of mental illness that is characterized by psychosis and closely related to schizophrenia. Both schizophrenia and schizophreniform disorder, as defined by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), have the same symptoms and essential features except for two differences: the level of functional impairment and the duration of symptoms. Impairment in social, occupational,

or academic functioning is always present in schizophrenia, but such impairment may or may not be present in schizopheniform disorder. In schizophreniform disorder, the symptoms (including prodromal, active, and residual phases) must last at least 1 month but not more than 6 months, while in schizophrenia the symptoms must be present for a minimum of 6 months.

If the symptoms have persisted for at least one month, a provisional diagnosis of schizophreniform disorder can be made while waiting to see if recovery occurs. If the symptoms resolve within 6 months of onset, the provisional qualifier is removed from the diagnosis. However, if the symptoms persist for 6 months or more, the diagnosis of schizophreniform disorder must be revised. The diagnosis of brief psychotic disorder may be considered when the duration of symptoms is less than one month.

The main symptoms of both schizophreniform disorder and schizophrenia can include:

- delusions,
- hallucinations,
- disorganized speech resulting from formal thought disorder,
- disorganized or catatonic behavior, and negative symptoms, such as
- an inability to show emotion (flat affect),
- an inability to experience pleasure (anhedonia),
- impaired or decreased speech (aphasia),
- a lack of desire to form relationships (asociality), and
- a lack of motivation (avolition).

## Prognosis

The following specifiers for schizophreniform disorder may be used to indicate the presence or absence of features that may be associated with a better prognosis:

- With Good Prognostic Features, used if at least two of the following features are present:
    - onset of prominent psychotic symptoms within 4 weeks of the first noticeable change in usual behavior or functioning,
    - confusion or perplexity at the height of the psychotic episode,
    - good premorbid social and occupational functioning, and
    - absence of blunted or flat affect.
- Without Good Prognostic Features, used if two or more of the above features have not been present.

The presence of negative symptoms and poor eye contact both appear to be prognostic of a poor outcome. Many of the anatomic and functional changes seen in the brains of patients with schizophrenia also occur in patients with schizophreniform disorder. However, at present there is no consensus among scientists regarding whether or not ventricular enlargement, a poor prognostic factor in schizophrenia, has any prognostic value in patients with schizophreniform disorder. According to the American Psychiatric

Association, approximately two-thirds of patients diagnosed with schizophreniform disorder are subsequently diagnosed with schizophrenia.

## Etiology

The exact etiology of the disorder remains unknown, and relatively few studies have focused exclusively on the etiology of schizophreniform disorder. Like other psychotic disorders, a two-hit hypothesis has been proposed, suggesting that some individuals have an underlying multifactorial genetic vulnerability to the disorder that can be triggered by certain environmental factors. Schizophreniform disorder is more likely to occur in people with family members who have schizophrenia or bipolar disorder.

## Prevalence

Schizophreniform disorder is equally prevalent among men and women. The most common ages of onset are 18-24 for men and 18-35 for women. While the symptoms of schizophrenia often develop gradually over a period of years, the diagnostic criteria for schizophreniform disorder require a much more rapid onset.

Available evidence suggests variations in incidence across sociocultural settings. In the United States and other developed countries, the incidence is low, possibly fivefold less than that of schizophrenia. In developing countries, the incidence is substantially higher, especially for the subtype "With Good Prognostic Features". In some of these settings schizophreniform disorder may be as common as schizophrenia.

## Treatment

Various modalities of treatment, including pharmacotherapy, psychotherapy, and various other psychosocial and educational interventions, are used in the treatment of schizophreniform disorder. Pharmacotherapy is the most commonly used treatment modality as psychiatric medications can act quickly to both reduce the severity of symptoms and shorten their duration. The medications used are largely the same as those used to treat schizophrenia, with an atypical antipsychotic) as the usual drug of choice. Patients who do not respond to the initial atypical antipsychotic may benefit from being switched to another atypical antipsychotic, the addition of a mood stabilizer such as lithium or an anticonvulsant, or being switched to a typical antipsychotic.

Treatment of schizophreniform disorder can occur in inpatient, outpatient, partial hospitalization settings. In selecting the treatment setting, the primary aims are to minimize the psychosocial consequences for the patient and maintain the safety of the patient and others. While the need to quickly stabilize the patient's symptoms almost always exists, consideration of the patient's severity of symptoms, family support, and perceived likelihood of compliance with outpatient treatment can help determine if stabilization can occur in the outpatient setting. Patients who receive inpatient treatment may benefit from a structured intermediate environment, such as a sub-acute unit, step-

down unit, partial hospital, or day hospital, during the initial phases of returning to the community.

As improvement progresses during treatment, help with coping skills, problem-solving techniques, psychoeducational approaches, and eventually occupational therapy and vocational assessments are often very helpful for patients and their families. Virtually all types of individual psychotherapy are used in the treatment of schizophreniform disorder, except for insight-oriented therapies as patients often have limited insight as a symptom of their illness.

Since schizophreniform disorder has such rapid onset of severe symptoms, patients are sometimes in denial about their illness, which also would limit the efficacy of insight-oriented therapies. Supportive forms of psychotherapy such as interpersonal psychotherapy, supportive psychotherapy, and cognitive behavior therapy are particularly well suited for the treatment of the disorder. Group psychotherapy is usually not indicated for patients with schizophreniform disorder because they may be distressed by the symptoms of patients with more advanced psychotic disorders.

# Chapter 6

# Hallucination

A **hallucination**, in the broadest sense of the word, is a perception in the absence of a stimulus. In a stricter sense, hallucinations are defined as perceptions in a conscious and awake state in the absence of external stimuli which have qualities of real perception, in that they are vivid, substantial, and located in external objective space. The latter definition distinguishes hallucinations from the related phenomena of dreaming, which does not involve wakefulness; illusion, which involves distorted or misinterpreted real perception; imagery, which does not mimic real perception and is under voluntary control; and pseudohallucination, which does not mimic real perception, but is not under voluntary control. Hallucinations also differ from "delusional perceptions", in which a correctly sensed and interpreted genuine perception is given some additional (and typically bizarre) significance.

Hallucinations can occur in any sensory modality — visual, auditory, olfactory, gustatory, tactile, proprioceptive, equilibrioceptive, nociceptive, thermoceptive and chronoceptive.

A mild form of hallucination is known as a **disturbance**, and can occur in any of the senses above. These may be things like seeing movement in peripheral vision, or hearing faint noises and/or voices. Auditory hallucinations are very common in paranoid schizophrenia. They may be benevolent (telling the patient good things about themselves) or malicious, cursing the patient etc. Auditory hallucinations of the malicious type are frequently heard like people talking about the patient behind their back. Like auditory hallucinations, the source of their visual counterpart can also be behind the patient's back. Their visual counterpart is the feeling of being looked-stared at, usually with malicious intent. Frequently, auditory hallucinations and their visual counterpart are experienced by the patient together.

Hypnagogic hallucinations and hypnopompic hallucinations are considered normal phenomena. Hypnagogic hallucinations can occur as one is falling asleep and hypnopompic hallucinations occur when one is waking up.

Hallucinations can also be associated with drug use (particularly deliriants), sleep deprivation, psychosis, neurological disorders, and delirium tremens.

## *Classification*

Hallucinations may be manifested in a variety of forms. Various forms of hallucinations affect different senses, sometimes occurring simultaneously, creating multiple sensory hallucinations for those experiencing them.

### Visual

The most common modality referred to when people speak of hallucinations. These include the phenomena of seeing things which are not present or visual perception which does not reconcile with the consensus reality. There are many different causes, which have been classed as psychophysiologic (a disturbance of brain structure), psychobiochemical (a disturbance of neurotransmitters), and psychological (e.g. meaningful experiences consciousness). Numerous disorders can involve visual hallucinations, ranging from psychotic disorders to dementia to migraine, but experiencing visual hallucinations does not in itself mean there is necessarily a disorder. Visual hallucinations are associated with organic disorders of the brain and with drug and alcohol related illness.

### Auditory

Auditory hallucinations (also known as **Paracusia**), particularly of one or more talking voices, are particularly associated with psychotic disorders such as schizophrenia or mania, and hold special significance in diagnosing these conditions, although many people not suffering from diagnosable mental illness may sometimes hear voices as well. Auditory hallucinations of non-organic origin are most often met with in paranoid schizophrenia. Their visual counterpart in that disease is the non-reality-based feeling of being looked or stared at.

Other types of auditory hallucination include exploding head syndrome and musical ear syndrome, and may occur during sleep paralysis. In the latter, people will hear music playing in their mind, usually songs they are familiar with. Recent reports have also mentioned that it is also possible to get musical hallucinations from listening to music for long periods of time. This can be caused by: lesions on the brain stem (often resulting from a stroke); also, tumors, encephalitis, or abscesses. Other reasons include hearing loss and epileptic activity. Auditory hallucinations are also a result of attempting wake-initiation of lucid dreams.

### Olfactory

Phantosmia is the phenomenon of smelling odors that aren't really present. The most common odors are unpleasant smells such as rotting flesh, vomit, urine, feces, smoke, or others. Phantosmia often results from damage to the nervous tissue in the olfactory system. The damage can be caused by viral infection, brain tumor, trauma, surgery, and possibly exposure to toxins or drugs. Phantosmia can also be induced by epilepsy affecting the olfactory cortex and is also thought to possibly have psychiatric origins.

Phantosmia is different from parosmia, in which a smell is actually present, but perceived differently from its usual smell.

Olfactory hallucinations have also been reported in migraine, although the frequency of such hallucinations is unclear.

### Tactile

Other types of hallucinations create the sensation of tactile sensory input, simulating various types of pressure to the skin or other organs. This type of hallucination is often associated with substance use, such as someone who feels bugs crawling on them (known as formication) after a prolonged period of cocaine or amphetamine use.

### Gustatory

This type of hallucination focuses typically on food and is common to individuals presenting persecutory perceptions along with the experience of epileptic aura.

### General Somatic Sensations

General Somatic Sensations of a hallucinatory nature is experienced when an individual feels that his body is being mutilated i.e. twisted, torn, or disembowelled. Other reported cases are invasion by animals in the person's internal organs such as snakes in the stomach or frogs in the rectum. The general feeling that one's flesh is decomposing is also classified under this type of hallucination.

## *Stages of a hallucination*

1. Emergence of surprising or warded-off memory or fantasy images
2. Frequent reality checks
3. Last vestige of insight as hallucinations become "real"
4. Fantasy and distortion elaborated upon and confused with actual perception
5. Internal-external boundaries destroyed and possible pantheistic experience

## *Cause*

Hallucinations can be caused by a number of factors.

### Hypnagogic hallucination

These hallucinations occur just before falling asleep, and affect a surprisingly high proportion of the population. The hallucinations can last from seconds to minutes, all the while the subject usually remains aware of the true nature of the images. These may be associated with narcolepsy. Hypnagogic hallucinations are sometimes associated with brainstem abnormalities, but this is rare.

## Peduncular hallucinosis

Peduncular means pertaining to the peduncle, which is a neural tract running to and from the pons on the brain stem. These hallucinations usually occur in the evenings, but not during drowsiness, as in the case of hypnagogic hallucination. The subject is usually fully conscious and then can interact with the hallucinatory characters for extended periods of time. As in the case of hypnagogic hallucinations, insight into the nature of the images remains intact. The false images can occur in any part of the visual field, and are rarely polymodal.

## Delirium tremens

One of the more enigmatic forms of visual hallucination is the highly variable, possibly polymodal delirium tremens. Individuals suffering from delirium tremens may be agitated and confused, especially in the later stages of this disease. Insight is gradually reduced with the progression of this disorder. Sleep is disturbed and occurs for a shorter period of time, with rapid eye movement sleep.

## Parkinson's disease and Lewy body dementia

Parkinson's disease is linked with Lewy body dementia for their similar hallucinatory symptoms. The symptoms strike during the evening in any part of the visual field, and are rarely polymodal. The segue into hallucination may begin with illusions where sensory perception is greatly distorted, but no novel sensory information is present. These typically last for several minutes, during which time the subject may be either conscious and normal or drowsy/inaccessible. Insight into these hallucinations is usually preserved and REM sleep is usually reduced. Parkinson's disease is usually associated with a degraded substantia nigra pars compacta, but recent evidence suggests that PD affects a number of sites in the brain. Some places of noted degradation include the median raphe nuclei, the noradrenergic parts of the locus coeruleus, and the cholinergic neurons in the parabrachial and pedunculopontine nuclei of the tegmentum.

## Migraine coma

This type of hallucination is usually experienced during the recovery from a comatose state. The migraine coma can last for up to two days, and a state of depression is sometimes comorbid. The hallucinations occur during states of full consciousness, and insight into the hallucinatory nature of the images is preserved. It has been noted that ataxic lesions accompany the migraine coma.

## Charles Bonnet syndrome

Charles Bonnet syndrome is the name given to visual hallucinations experienced by blind patients. The hallucinations can usually be dispersed by opening or closing the eyelids until the visual images disappear. The hallucinations usually occur during the morning or evening, but are not dependent on low light conditions. These prolonged hallucinations

usually do not disturb the patients very much, as they are aware that they are hallucinating. A differential diagnosis are opthalmopathic hallucinations.

### Focal epilepsy

The visual hallucinations from focal epilepsy are characterized by being brief and stereotyped. They are usually localized to one part of the visual field, and last only a few seconds. Other epileptic features may present themselves between visual episodes. Consciousness is usually impaired in some way, but nevertheless, insight into the hallucination is preserved. Usually, this type of focal epilepsy is caused by a lesion in the posterior temporoparietal.

### Schizophrenic hallucination

Hallucinations caused by schizophrenia.

### Drug-induced hallucination

Hallucinations caused by the consumption of psychoactive substances such as LSD or DMT.

## *Pathophysiology*

Various theories have been put forward to explain the occurrence of hallucinations. When psychodynamic (Freudian) theories were popular in psychiatry, hallucinations were seen as a projection of unconscious wishes, thoughts and wants. As biological theories have become orthodox, hallucinations are more often thought of (by psychologists at least) as being caused by functional deficits in the brain. With reference to mental illness, the function (or dysfunction) of the neurotransmitters glutamate and dopamine are thought to be particularly important. The Freudian interpretation may have an aspect of truth, as the biological hypothesis explains the physical interactions in the brain, while the Freudian deals with the origin of the flavor of the hallucination. Psychological research has argued that hallucinations may result from biases in what are known as metacognitive abilities.

These are abilities that allow us to monitor or draw inferences from our own internal psychological states (such as intentions, memories, beliefs and thoughts). The ability to discriminate between internal (self-generated) and external (stimuli) sources of information is considered to be an important metacognitive skill, but one which may break down to cause hallucinatory experiences. Projection of an internal state (or a person's own reaction to another's) may arise in the form of hallucinations, especially auditory hallucinations. A recent hypothesis that is gaining acceptance concerns the role of overactive top-down processing, or strong perceptual expectations, that can generate spontaneous perceptual output (that is, hallucination).

## *Treatments*

There are few treatments for many types of hallucinations. However, for those hallucinations caused by mental disease, a psychologist or psychiatrist should be alerted, and treatment will be based on the observations of those doctors. Antipsychotic and atypical antipsychotic medication may also be utilized to treat the illness if the symptoms are severe and cause significant distress. For other causes of hallucinations there is no factual evidence to support any one treatment is scientifically tested and proven. However, abstaining from hallucinogenic drugs, managing stress levels, living healthily, and getting plenty of sleep can help reduce the prevalence of hallucinations. In all cases of hallucinations, medical attention should be sought out and informed of one's specific symptoms.

## *Epidemiology*

One study from as early as 1895 reported that approximately 10% of the population experienced hallucinations. A 1996-1999 survey of over 13,000 people reported a much higher figure, with almost 39% of people reporting hallucinatory experiences, 27% of which were daytime hallucinations, mostly outside the context of illness or drug use. From this survey, olfactory (smell) and gustatory (taste) hallucinations seem the most common in the general population.

# Chapter 7

# Thought Disorder

In psychiatry, **thought disorder** or **formal thought disorder** is a term used to describe incomprehensible language, either speech or writing, that is presumed to reflect thinking. There are different types. For example, language may be difficult to understand if it switches quickly from one unrelated idea to other (flight of ideas) or if it is long-winded and very delayed at reaching its goal (circumstantiality) or if words are inappropriately strung together resulting in gibberish (word salad).

Psychiatrists consider Formal Thought Disorder as being one of two types of "thinking" or "thought" disorders. The other type being delusions. The latter involves "content" while the former involves "form". Although the term "thought disorder" can refer to either type, in common parlance it refers most often to a disorder of thought "form" also known as Formal Thought Disorder.

It is usually considered a symptom of psychotic mental illness, although it occasionally appears in other conditions. For example, pressured speech and flight of ideas may be present in mania. Clanging or echolalia may be present in Tourette syndrome. Eugen Bleuler, who named schizophrenia, held that its defining characteristic was a disorder of the thinking process. However, Formal thought disorder is not unique to schizophrenia or psychosis. So-called “organic” patients with a clouded consciousness, like that found in delirium, also have a formal thought disorder. However, there is a distinct clinical difference between the two. Schizophrenic or psychotic patients never demonstrate awareness nor concern about it because it results from a fundamental inability to use the same type of Aristotelian logic as everyone else does whereas so-called “organic” patients with a clouded consciousness usually do demonstrate awareness and concern about it, by complaining about being “confused” or “unable to think straight” because it results, instead, from various cognitive deficits.

## *Possible signs and symptoms of thought disorder*

Thought is revealed through speech. Thus, observation of patterns of thought naturally involves close observation of the speech of the individual being considered. Although it is normal to exhibit some of the following during times of extreme stress (e.g. a cataclysmic event or the middle of a war) it is the degree, frequency, and the resulting functional impairment that leads to the conclusion that the person being observed has a thought disorder.

- *Blocking* - Interruption of train of speech before completion. e.g. "Am I early?" "No, you're just about on..."*(silence)* This is commonly seen when a joke is being told and the speaker forgets the punchline. At an extreme degree, after blocking occurs, the speaker does not recall the topic he or she was discussing. True blocking is a common sign of schizophrenia.

- *Circumstantiality* - Speech that is highly detailed and very delayed at reaching its goal. Speaking about many concepts related to the point of the conversation before eventually returning to the point and concluding the thought. Excessive long-windedness. e.g. "What is your name?" "Well, sometimes when people ask me that I have to think about whether or not I will answer because some people think it's an odd name even though I don't really because my mom gave it to me and I think my dad helped but it's as good a name as any in my opinion, I think it's a little weird to have the same name as two of my other names, but the fact that I like it, is a good thing... but yeah, it's Tom."

- *Clanging* - Sounds, rather than meaningful relationships, appear to govern words or topics. Excessive rhyming. e.g. "I'm not trying to make noise. I'm trying to make sense. If you can't make sense out of nonsense, well, have fun." "I heard the bell. Well, hell, I heard the bell."

- *Derailment* (also *Loose Association* and *Knight's Move thinking*) - Ideas slip off the topic's track on to another which is obliquely related or unrelated. e.g. "The next day when I'd be going out you know, I took control, like uh, I put bleach on my hair in California."

- *Distractible speech* - During mid speech, the subject is changed in response to a stimulus. e.g. "Then I left San Francisco and moved to... where did you get that tie?"

- *Echolalia* - Echoing of one's or other people's speech that may only be committed once, or may be continuous in repetition. This may involve repeating only the last few words or last word of the examiner's sentences. This can be a symptom of Tourette's Syndrome. e.g. "What would you like for dinner?", "That's a good question. *That's a good question*. *That's a good question*. *That's a good question*."

- *Evasive Interaction* - Attempts to annunciate ideas and/or feelings about another individual comes out as evasive or in a diluted form, e.g.: "I... er ah... you are uh... I think you have... uh-- acceptable erm... uh... hair."

- *Flight of Ideas* - A sequence of loose associations or extreme tangentiality where the speaker goes quickly from one idea to another seemingly unrelated idea. To the listener, the ideas seem unrelated and do not seem to repeat. Often pressured speech is also present. e.g. "I own five cigars. I've been to Havana. She rose out of the water, in a bikini."

- *Illogicality* - Conclusions are reached that do not follow logically (non-sequiturs or faulty inferences). e.g. "Do you think this will fit in the box?" draws a reply like "Well duh; it's brown isn't it?"

- *Incoherence (word salad)* - Speech that is unintelligible because, though the individual words are real words, the manner in which they are strung together results in incoherent gibberish, e.g. the question "Why do people comb their hair?" elicits a response like "Because it makes a twirl in life, my box is broken help me blue elephant. Isn't lettuce brave? I like electrons. Hello, beautiful."

- *Loss of goal* - Failure to show a train of thought to a natural conclusion. e.g. "Why does my computer keep crashing?", "Well, you live in a stucco house, so the pair of scissors needs to be in another drawer."

- *Neologisms* - New word formations. These may also involve elisions of two words that are similar in meaning or in sound. e.g. "I got so angry I picked up a dish and threw it at the geshinker."

- *Perseveration* - Persistent repetition of words or ideas. e.g. "It's great to be here in Nevada, Nevada, Nevada, Nevada, Nevada." This may also involve repeatedly giving the same answer to different questions. e.g. "Is your name Mary?" "Yes." "Are you in the hospital?" "Yes." "Are you a table?" "Yes."

- *Phonemic paraphasia* - Mispronunciation; syllables out of sequence. e.g. "I slipped on the lice and broke my arm."

- *Pressure of speech* - An increase in the amount of spontaneous speech compared to what is considered customary. This may also include an increase in the rate of speech. Alternatively it may be difficult to interrupt the speaker; the speaker may continue speaking even when a direct question is asked.

- *Self-reference* - Patient repeatedly and inappropriately refers back to self. e.g. "What's the time?", "It's 7 o'clock. That's my problem."

- *Semantic paraphasia* - Substitution of inappropriate word. e.g. "I slipped on the coat, on the ice I mean, and broke my book."

- *Stilted speech* - Speech excessively stilted and formal. e.g. "The attorney comported himself indecorously."

- *Tangentiality* - Replying to questions in an oblique, tangential or irrelevant manner. e.g.:

  Q: "What city are you from?"
  A: "Well, that's a hard question. I'm from Iowa. I really don't know where my relatives came from, so I don't know if I'm Irish or French."

- *Word approximations* - Old words used in a new and unconventional way. e.g. "His boss was a seeover."

## *Diagnosis*

The concept of thought disorder has been criticized as being based on circular or incoherent definitions. For example, thought disorder is inferred from disordered speech, however it is assumed that disordered speech arises because of disordered thought. Similarly the definition of 'Incoherence' (word salad) is that speech is incoherent.

Furthermore, although thought disorder is typically associated with psychosis, similar phenomena can appear in different disorders, potentially leading to misdiagnosis—for example, in the case of incomplete yet potentially fruitful thought processes.

It has been suggested that individuals with autism spectrum disorders (ASD) display language disturbances like those found in schizophrenia. A 2008 study found that children and adolescents with ASD showed significantly more illogical thinking and loose associations than control subjects. The illogical thinking was related to cognitive functioning and executive control; the loose associations were related to communication symptoms and to parent reports of stress and anxiety.

# Chapter 8

# Early Intervention in Psychosis

**Early intervention in psychosis** is a clinical approach to those experiencing symptoms of psychosis for the first time. It forms part of the new prevention paradigm for psychiatry and is leading to reform of mental health services, especially in the United Kingdom. There has been considerable academic interest over the past decade.

This approach centers on the early detection and treatment of early symptoms of psychosis during the formative years of the psychotic condition. The first three to five years are believed to be a critical period. The aim is to reduce the usual delays to treatment for those in their first episode of psychosis. The provision of optimal treatments in these early years is thought to prevent relapses and reduce the long term impact of the condition. It is considered a secondary prevention strategy.

The duration of untreated psychosis (DUP) has been shown as an indicator of prognosis, with a longer DUP associated with more long term disability.

## *Components of the model*

There are a number of functional components of the early psychosis model, and they can be structured as different sub-teams within early psychosis services. The emerging pattern of sub-teams are currently:

### Early psychosis treatment teams

Multiple discipline clinical teams providing an intensive case management approach for the first three to five years. The approach is similar to assertive community treatment, but with an increased focus on the engagement and treatment of this previously untreated population and the provision of evidence based, optimal interventions for clients in their first episode of psychosis. For example, the use of low-dose antipsychotic medication is promoted ("start low, go slow"), with a need for monitoring of side effects and an intensive and deliberate period of psycho-education for patients and families that are new to the mental health system. Interventions to prevent a further episodes of psychosis (a "relapse") and strategies that encourage a return to normal vocation and social activity are a priority. There is a concept of phase specific treatment for acute, early recovery and late recovery periods in the first episode of psychosis.

### Early detection function

Interventions aimed at improving the detection and engagement of those early in the course of their psychotic conditions. Key tasks include being aware of early signs of psychosis and improving pathways into treatment. Teams provide information and education to the general public and assist GPs with recognition and response to those with suspected signs, for example: EPPIC's Youth Access Team (YAT) (Melbourne); OPUS (Denmark); TIPS (Norway); REDIRECT (Birmingham); LEO CAT (London).

### Prodrome or "at risk mental state" clinics

There are specialist services for those with subclinical symptoms of psychosis or other strong indicators of risk of transition to psychosis. The Pace Clinic in Melbourne, Australia, is considered one of the origins of this strategy, along with the Institute of Psychiatry based service OASIS in South London, Yale Medical School based clinic, PRIME, The Center of Prevention and Evaluation (COPE) at the Columbia University Medical Center in New York City, the Recognition and Prevention Program based at the Zucker Hillside Hospital in Glen Oaks, New York, and the NAPLS site based at the Emory University Department of Clinical Psychology in Atlanta, Georgia. These services are able to reliably identify those at high risk of developing psychosis and are beginning to publish encouraging outcomes from randomised controlled trials that reduce the chances of becoming psychotic, including evidence that psychological therapy and high doses of fish oil have a role in the prevention of psychosis.

## *History*

Early intervention in psychosis is a preventative approach for psychosis that has evolved as contemporary recovery views of psychosis and schizophrenia have gained acceptance. It subscribes to a "post Kraepelin" concept of schizophrenia, challenging the current assumptions originally promoted by Emil Kraepelin in the 19th century, that schizophrenia (or dementia praecox) was a condition with a progressing and deteriorating course. Psychosis is now formulated within a diathesis–stress model, allowing a more hopeful view of prognosis, and expects full recovery for those with early emerging psychotic symptoms. It is more aligned with psychosis as continuum (such as with the concept of schizotypy) with multiple contributing factors, rather than schizophrenia as simply a neurobiological disease.

Within this changing view of psychosis and schizophrenia, the model has developed from a divergence of several different ideas, and from a number of sites beginning with the closure of psychiatric institutions signaling move toward community based care. In 1986, the Northwick Park study discovered an association between delays to treatment and disability, questioning the service provision for those with their first episode of schizophrenia. In the 1990s, evidence began to emerge that cognitive behavioural therapy was an effective treatment for delusions and hallucinations. The next step came with the development of the EPPIC early detection service in Melbourne, Australia in 1996 and the prodrome clinic led by Alison Yung. This service was an inspiration to other services,

such as the West Midlands IRIS group, including the consumer non-governmental organisation Rethink; the TIPS early detection randomised control trial in Norway; and the Danish OPUS trial. In 2001, the United Kingdom Department of Health called the development of early psychosis teams "a priority". The International Early Psychosis Association, founded in 1998, issued an international consensus declaration together with the World Health Organisation in 2004. Clinical practice guidelines have been written by consensus.

## *Clinical outcome evidence*

An early psychosis approach has been shown in formal studies to reduce the severity of symptoms, improve relapse rates, and decrease the use of inpatient care, in comparison to standard care, at 18 months follow up. These studies also clearly show greater levels of user satisfaction with the service. Although the evidence for an ongoing positive impact has yet to be established, some have noted that the underlying assumptions and lack of evidence for the current *late intervention* standard service approaches make the rationale early intervention "overwhelming".

The earlier 2006 Cochrane review continues to report a lack of strong research evidence for specific early detection and early intervention programmes, although it does acknowledge the need to intervene earlier for those with psychosis. Since that time, the emerging evidence on treatment outcome for early psychosis is positive.

## *Current literature on cost*

Evidence from the United Kingdom suggests that the costs of an early psychosis service are considerably less compared to standard care with one year costs for early psychosis teams (£9,422) two thirds the cost of standard teams (£14,394). This is maintained at Year 3 and is thought to be due to the reduced inpatient costs with the more intensive community follow up provided by early psychosis services.

An Australian historical comparison of direct health costs found a clear economic advantage for an early psychosis approach compared to standard care, at 12 month follow up. Another report, commissioned by Orygen Research Centre in Melbourne, concludes: EI not only costs nearly AU$2000 less per person annually than TAU (treatment as usual) in trial-related costs, it also saves nearly AU$1500 in health system and other financial costs...total saving to society of nearly AU$9000 per patient per year. This does not take into account the potential benefits of EI in reducing suicides and positive impact on vocational outcomes.

## *Reform of mental health services*

### United Kingdom

The United Kingdom has probably made the most significant service reform with their adoption of early psychosis teams, with early psychosis now considered as an integral

part of comprehensive community mental health services. *The Mental Health Policy Implementation Guide* outlines service specifications and forms the basis of a newly developed fidelity tool. There is a requirement for services to reduce the duration of untreated psychosis, as this has been shown to be associated with better long term outcome. The implementation guideline recommends:

- 14 to 35 year age entry criteria
- First three years of psychotic illness
- Aim to reduce the duration of untreated psychosis to less than 3 months
- Maximum caseload ratio of 1 care coordinator to 10–15 clients
- For every 250,000 (depending on population characteristics), one team
    - Total caseload 120 to 150
    - 1.5 doctors per team
    - Other specialist staff to provide specific evidence based interventions

## Australia and New Zealand

Services have spread from the origin founding EPPIC initiative in Melbourne (Victoria, Australia) since the 1990s.

New Zealand has operated significant early psychosis teams for more than ten years, following the inclusion of early psychosis in a mental health policy document in 1997. There is a national early psychosis professional group, New Zealand Early Intervention in Psychosis Steering Group, organising training events and producing local resources.

## Scandinavia

Early psychosis programmes have continued to develop from the original TIPS services in Norway and the OPUS randomised trial in Denmark.

## North America

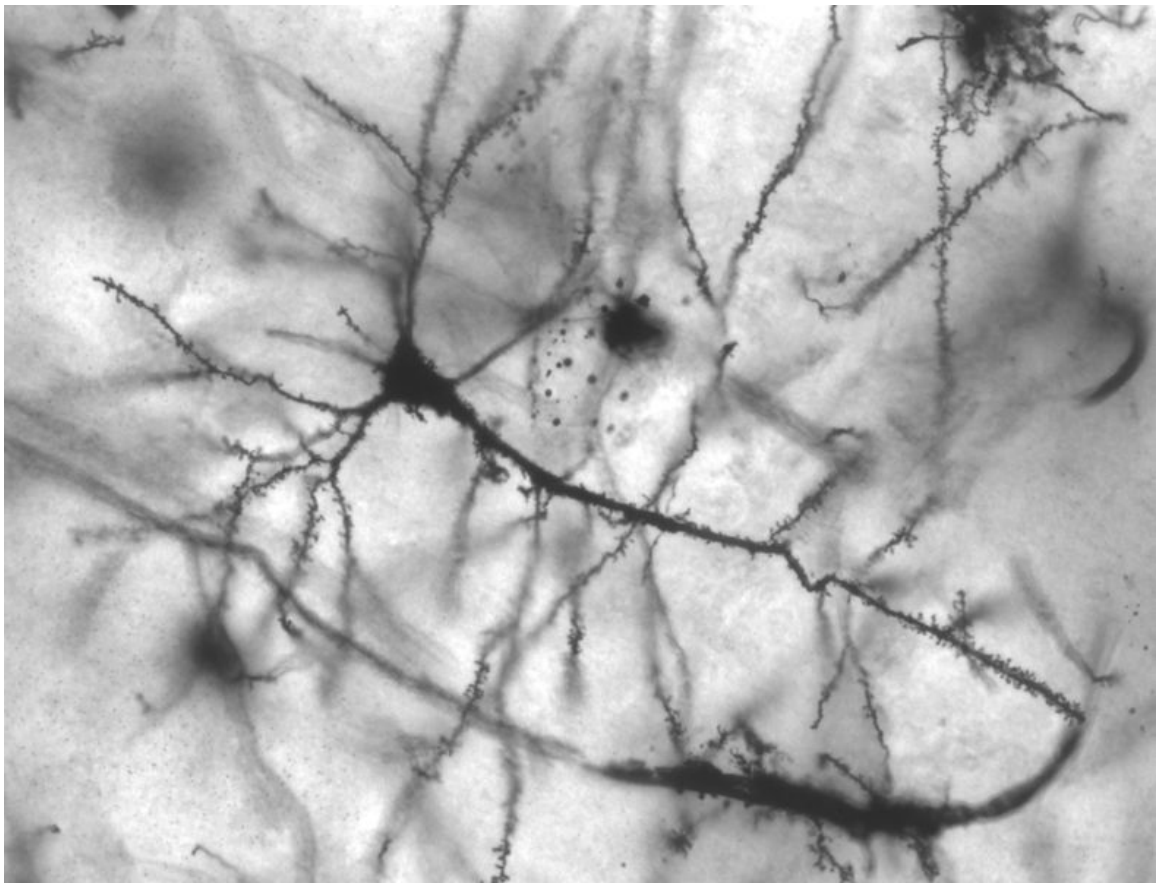
Canada has extensive coverage across most provinces, including established clinical services and comprehensive academic research in British Columbia (Vancouver), Alberta (EPT in Calgary), and Ontario (PEPP, FEPP). In the United States, the Early Assessment and Support Alliance is implementing early psychosis intervention statewide.

## Asia

The first meeting of the Asian Network of Early Psychosis (ANEP) was held in 2004. There are now established services in Singapore and Hong Kong.

## Chapter 9

# Neurological Disorder

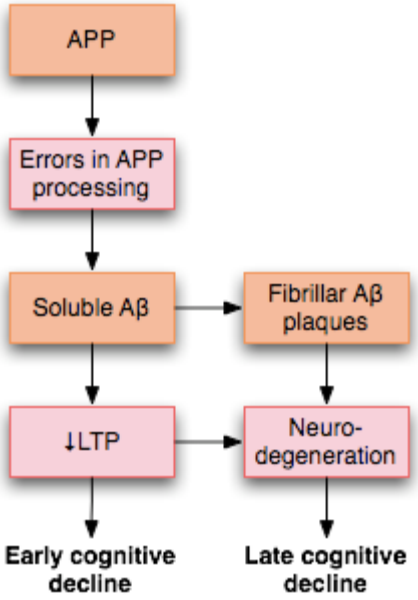


Neurons in patient with epilepsy, 40x

A **neurological disorder** is a disorder of the body's nervous system. Structural, biochemical or electrical abnormalities in the brain or spinal cord, or in the nerves leading to or from them, can result in symptoms such as paralysis, muscle weakness, poor coordination, loss of sensation, seizures, confusion, pain and altered levels of consciousness. There are many recognized neurological disorders, some relatively common, but many rare. They may be revealed by neurological examination and studied and treated within the specialities of neurology and clinical neuropsychology. Interventions include preventative measures, lifestyle changes, physiotherapy or other

therapy, neurorehabilitation, pain management, medication, or operations performed by neurosurgeons. The World Health Organization estimated in 2006 that neurological disorders and their sequelae affect as many as one billion people worldwide, and identified health inequalities and social stigma/discrimination as major factors contributing to the associated disability and suffering.

## *Causes*



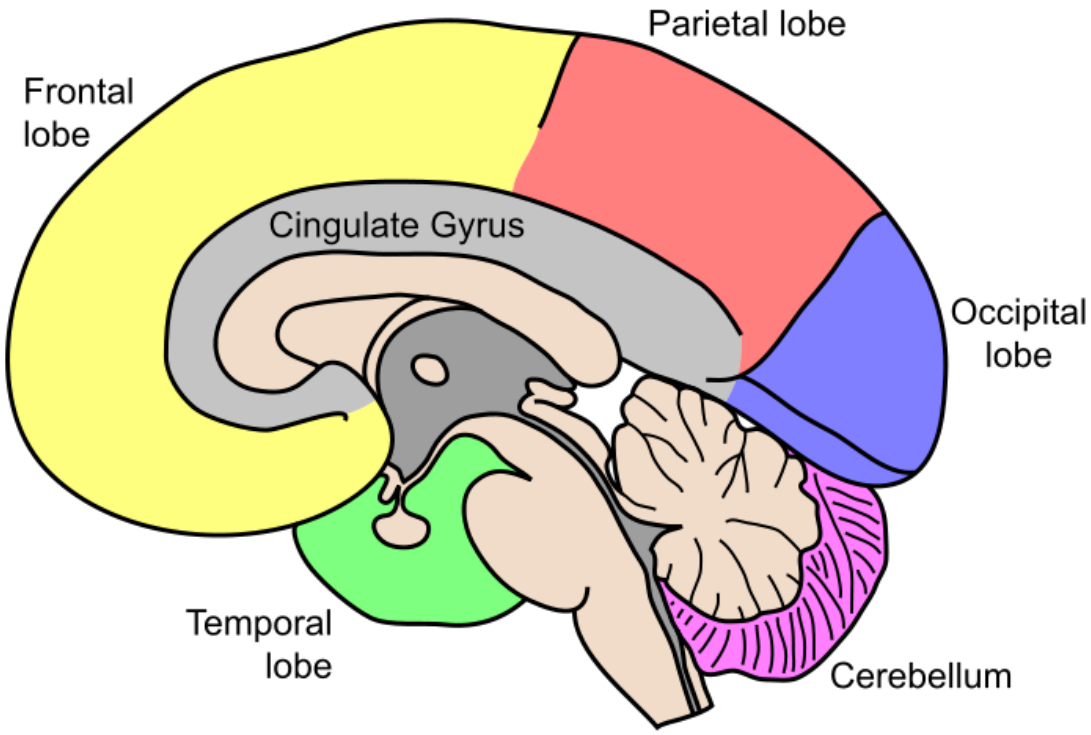

Part of the causal chain leading to Alzheimer's disease

Although the brain and spinal cord are surrounded by tough membranes, enclosed in the bones of the skull and spinal vertebrae, and chemically isolated by the so-called blood-brain barrier, they are very susceptible if compromised. Peripheral nerves tend to lie deep under the skin but are also still relatively exposed to damage. And individual neurons, the building blocks of the nervous system, and the neural networks into which they form, are susceptible to electrochemical and structural disruption. While neuroregeneration may occur in the peripheral nervous system, it is thought to be rare in the brain and spinal cord.

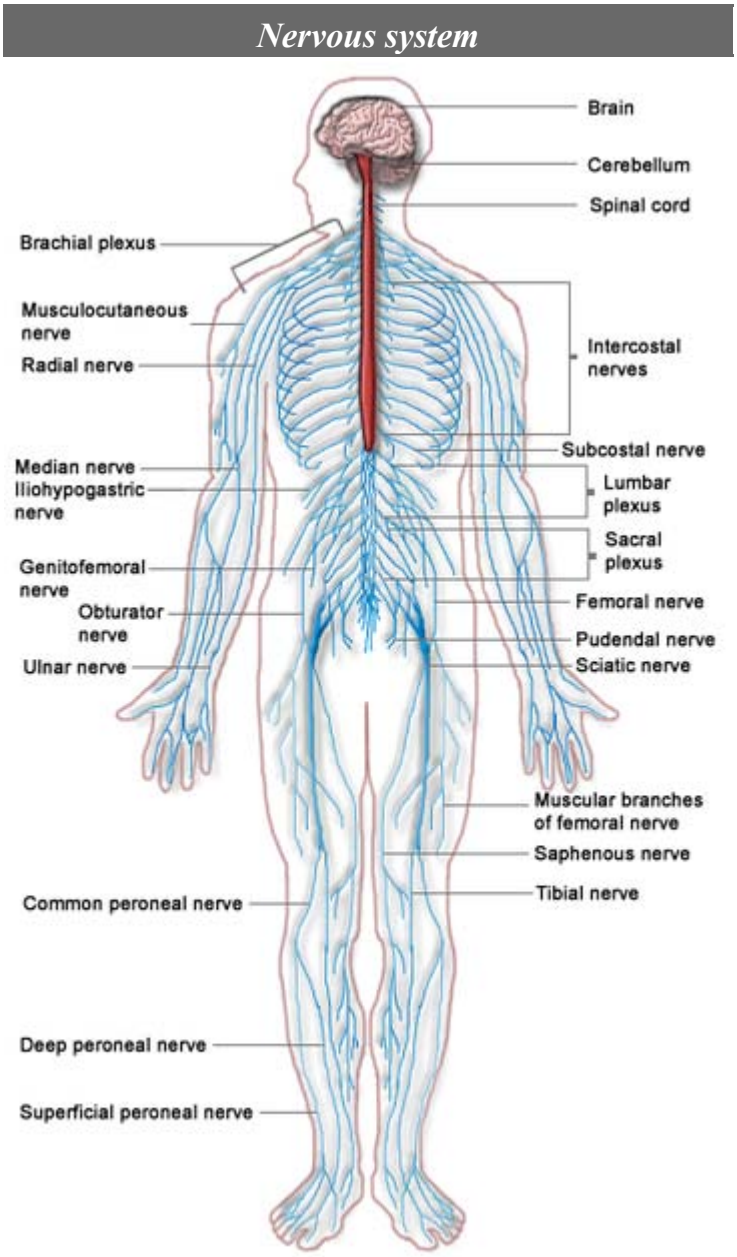
The specific causes vary by disorder and sometimes by individual case, but can include genetic disorders; congenital abnormalities or disorders; infections; lifestyle or environmental health problems including malnutrition; and brain injury, spinal cord injury or nerve injury. The problem may start in another body system that interacts with the nervous system; for example cerebrovascular disorders involve brain injury due to problems with the blood vessels (cardiovascular system) supplying the brain, and autoimmune disorders involve damage caused by the body's own immune system.

In a substantial minority of cases of neurological symptoms, no neural cause can be identified using current testing procedures, and such "idiopathic" conditions can invite different theories about what is occurring.

## *Classification*




Anatomy of the human brain




The Human Nervous System.

Neurological disorders can be categorized according to the primary location affected, the primary type of dysfunction involved, or the primary type of cause. The broadest division is between central nervous system (CNS) disorders and peripheral nervous system (PNS) disorders. The Merck Manual lists brain, spinal cord and nerve disorders in the following overlapping categories:

- Brain:
    - Brain damage according to cerebral lobe:
        - Frontal lobe damage
        - Parietal lobe damage

        - Temporal lobe damage
        - Occipital lobe damage
    - Brain dysfunction according to type:
        - Aphasia (language)
        - Dysarthria (speech)
        - Apraxia (patterns or sequences of movements)
        - Agnosia (identifying things/people)
        - Amnesia (memory)
- Spinal cord disorders
- Peripheral nervous system disorders
- Cranial nerve disorders
- Autonomic nervous system disorders
- Seizure disorders such as epilepsy
- Movement disorders such as Parkinson's disease
- Sleep disorders
- Headaches (including migraine)
- Lower back and neck pain
- Other pain
- Delirium and dementia such as Alzheimer's disease
- Dizziness and vertigo
- Stupor and coma
- Head injury
- Stroke (CVA, cerebrovascular attack)
- Tumors of the nervous system (e.g. cancer)
- Multiple sclerosis (MS) and other demyelinating diseases
- Infections of the brain or spinal cord (including meningitis)
- Prion diseases (a type of infectious agent)
- Complex regional pain syndrome (CRPS) (a chronic pain condition.)

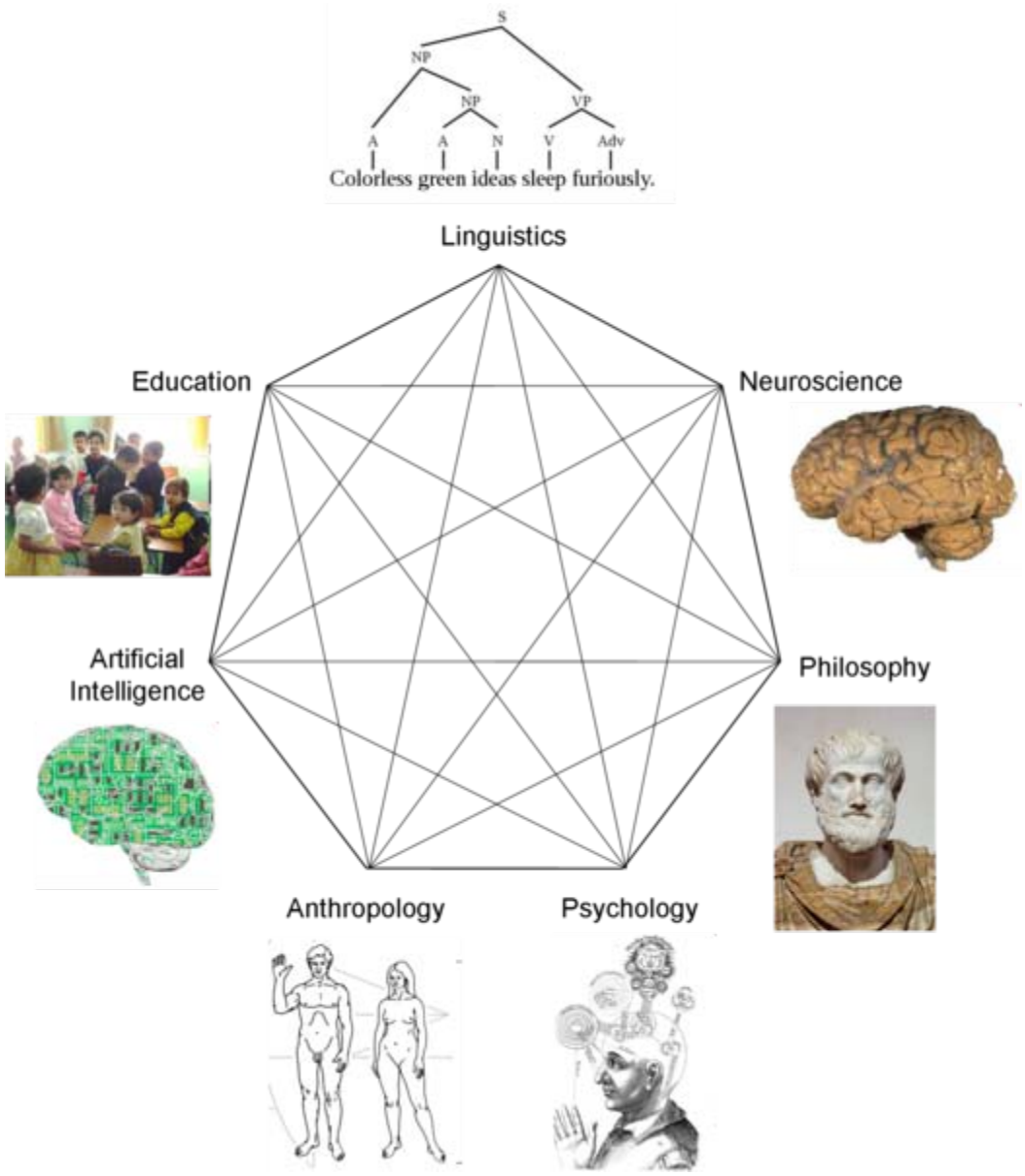
Neurological disorders in non-human animals are treated by veterinarians.

## *Neural and mental dysfunction*

Mental disorders, learning disabilities and mental retardation are not usually classed as primarily neurological. However the distinction can be a matter of some debate, either in regard to specific facts about the cause of a condition or in regard to the general understanding of brain and mind. Furthermore the definition of disorder can be contested in regard to what is considered abnormal, dysfunctional, harmful or unnatural in neurological, evolutionary, psychometric or social terms.

While certain types of mental condition are not usually classified primarily as neurological disorders, and certain types of brain disorder are not usually classified primarily as mental conditions, there are now an array of basic sciences that deal with the continuum between the neural and the mental, including subspecialities of psychology and neuroscience such as neuropsychology, cognitive neuropsychology or cognitive (thought) neuroscience, affective (emotion) neuroscience, behavior neuroscience (also

known as biopsychology), social neuroscience, and neurophenomenology (subjective experience and consciousness).




Different levels of analysis in the understanding of cognition in the brain

These basic fields inform the applied medical and clinical disciplines of neurology, psychiatry and clinical psychology, whose theories and treatments now routinely encompass a biopsychosocial model. These disciplines in turn comprise subspecialities such as behavioral neurology, neuropsychiatry and clinical neuropsychology that deal with cases where a connection between mental/behavioral problems and brain dysfunction is particularly called for. Biopsychiatry is the general term for the approach in psychiatry that seeks to explain all mental disorders primarily in terms of the biological functioning of the nervous system.

The conventional distinctions drawn between mind, brain and nervous system are to some extent mirrored by the various overlapping categories of clinical examination, namely mental state examination, neuropsychological assessment and neurological examination. At the present time a brain scan alone cannot accurately diagnose a mental disorder or tell the risk of developing one, but can be used to rule out other medical conditions such as a brain tumor.

Such distinctions can affect the explanation given for idiopathic (of unknown origin) neurological symptoms if it is thought (perhaps by exclusion of any other diagnosis) that higher brain/mental activity is causing symptoms that usually originate in other areas of the nervous system. Classic examples are "functional" seizures, sensory numbness, "functional" limb weakness and functional neurological deficit ("functional" in this context is usually contrasted with the old term "organic disease"). Such cases may be contentiously interpreted as being "psychological" rather than "neurological". In psychiatry some cases may then be classified as mental disorders, for example conversion disorder if the symptoms appear to be causally linked to emotional states or responses to social stress. However there are also accepted neurological conditions of dissociation where the brain/mind appears to register neurological stimuli that cannot possibly be coming from the part of the nervous system to which they would normally be attributed, such as phantom pain or synesthesia, or where limbs act without conscious direction as in alien hand syndrome.

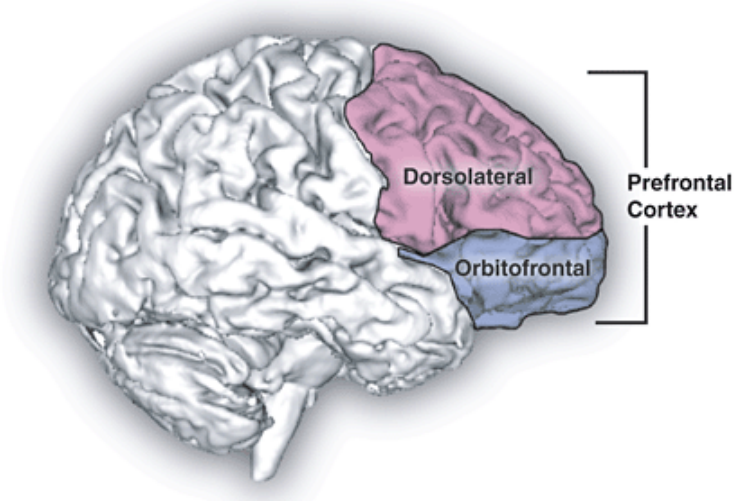
# Chapter 10

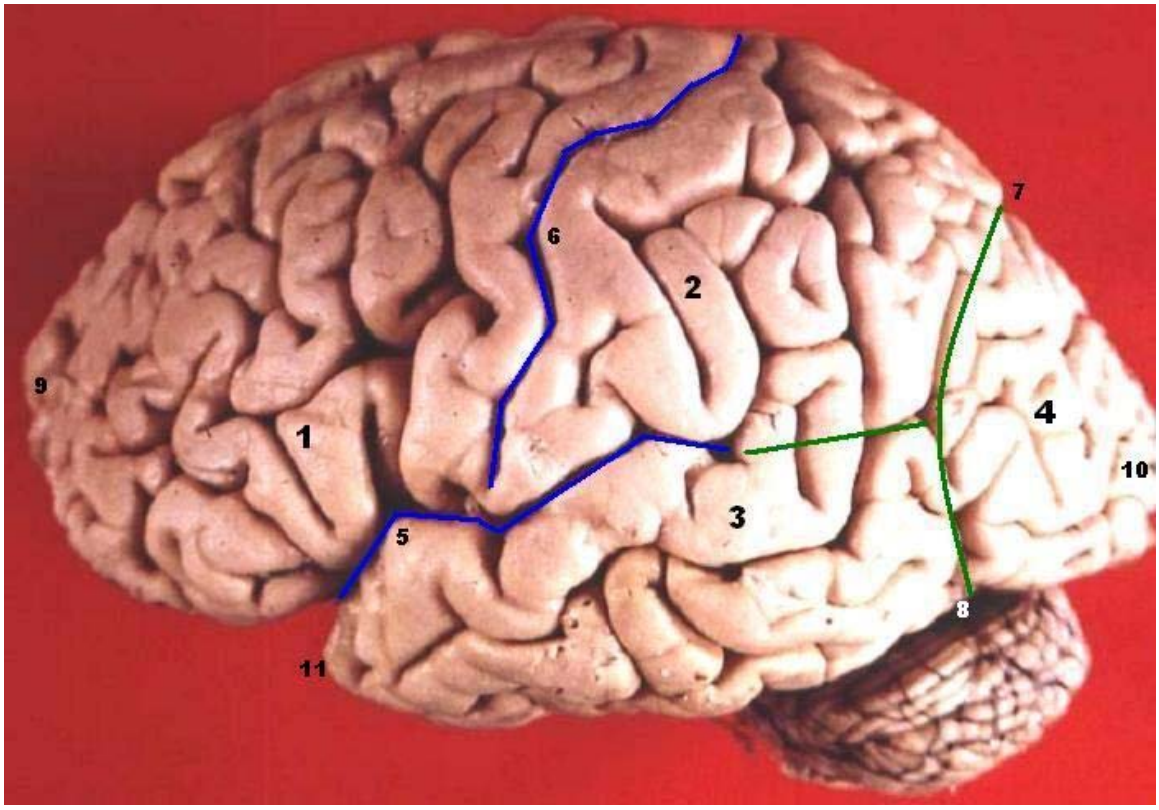
# Frontal Lobe Disorder

| Frontal lobe disorder | |
|---|---|
| **ICD-10** | F07. |
| **eMedicine** | article/1135866 |

**Frontal lobe disorder** is an impairment of the frontal lobe that occurs as a result of a number of diseases as well as head trauma. The frontal lobe of the brain plays a key role in higher mental functions such as motivation, planning, social behaviour, and speech production. A frontal lobe syndrome can result from a range of causes including head trauma, tumours, degenerative diseases,neurosurgery and cerebrovascular disease. Impairment of frontal lobe functioning is also found in a range of psychiatric conditions including schizophrenia, attention deficit disorder and antisocial personality disorder. Frontal lobe impairment can be detected by recognition of typical clinical signs, use of simple screening tests, and specialist neuropsychiatric testing.

## *Anatomy and functions*






The top blue line denotes the central sulcus

The frontal lobe has three main areas, known as the precentral cortex, prefrontal cortex and the orbitofrontal cortex. These three areas are represented in both the left and the right cerebral hemispheres.

The precentral cortex or primary motor cortex is concerned with the planning, initiation and control of physical movement. The dorsolateral part of the frontal lobe is concerned with planning, strategy formation, and other executive functions. The prefrontal cortex in the left hemisphere is involved with verbal memory while the prefrontal cortex in the right hemisphere is involved in spatial memory. The left frontal operculum region of the prefrontal cortex, or Broca's area, is responsible for expressive language, i.e. language production. The orbitofrontal cortex is concerned with response inhibition, impulse control, and social behaviour.

## *Clinical assessment*

### History

Frontal lobe disorders may be recognized through a sudden and dramatic change in a person's personality, for example with loss of social awareness, disinhibition, emotional instability, aggression, irritability or impulsiveness (for example sexually inappropriate behaviour or spending money impulsively). Alternatively the disorder may become apparent because of mood changes such as depression, anxiety or apathy.

## Examination

On mental state examination a person with frontal lobe damage may show reduced speech, with reduced verbal fluency and impaired expressive language. The person might have flattened or blunted affect. Typically the person is lacking in insight and judgment, but does not have marked cognitive abnormalities or memory impairment (as measured for example by the mini-mental state examination). With more severe impairment there may be echolalia or mutism. Neurological examination may show primitive reflexes (also known as frontal release signs) such as the grasp reflex or the rooting reflex. These are reflexes normally found in babies, but normally suppressed and absent in adults. Akinesia (lack of spontaneous movement) and urinary incontinence will be present in more severe and advanced cases. The frontal assessment battery (FAB), which includes simple tests of sequencing, behavioural inhibition, planning and frontal release signs, can be used as a screening test to elicit typical neurological and cognitive features.

## Further investigation

A range of neuropsychological tests are available for clarifying the nature and extent of frontal lobe dysfunction. For example, concept formation and ability to shift mental sets can be measured with the Wisconsin card sort test, planning can be assessed with the Mazes subtest of the WISC, switching between plans is assessed with the Trail-making test, and screening out distracting stimuli is assessed with the Stroop test.

Individuals with frontotemporal dementia and Pick's disease will show frontal cortical atrophy on CT scans or MRIs. Frontal impairment due to head injuries, tumours or cerebrovascular disease will also be apparent on brain imaging.

## *Dysexecutive syndrome*

Dysexecutive syndrome consists of a number of symptoms which tend to occur together (hence it being described as a syndrome). Broadly speaking, these symptoms fall into three main categories; cognitive, emotional and behavioural. Although many of these symptoms regularly co-occur, it is common to encounter patients who have several, but not all of these symptoms. This is one reason why some researchers are beginning to argue that dysexecutive syndrome is not the best term to describe these various symptoms. The fact that many of the dysexecutive syndrome symptoms can occur alone has led some researchers to suggest that the symptoms should not be labelled as a "syndrome" as such. Some of the latest imaging research on frontal cortex areas suggests that executive functions may be more discrete than was previously thought. The argument is that rather than damage to the frontal cortex areas causing dysexecutive functions in general, that damage to multiple frontal cortex areas that are close together (but responsible for different cognitive functions) can cause the various symptoms of dysexecutive syndrome.

The counterargument is that there is a central executive corresponding to areas within the frontal lobes which is responsible for much of the executive system and executive function in general, and that damage to this area causes dysexecutive syndrome.

## Cognitive symptoms

- Short attention span
- Poor working memory
- Poor short term memory
- Difficulty in planning and reasoning
- Environmental dependence syndrome

## Emotional symptoms

- Difficulty in inhibiting emotions, anger, excitement, sadness etc...
- Depression, possibly due to above.
- Occasionally, difficulty in understanding others' points of view, leading to anger and frustration.

## Behavioural symptoms

- Utilization behaviour
- Perseveration behaviour
- Inappropriate aggression
- Inappropriate sexual behaviour
- Inappropriate humour and telling of pointless and boring stories (Witzelsucht)

Phineas Gage, who suffered a severe frontal lobe injury in 1848, has been called a case of dysexecutive syndrome. But Gage's psychological changes are typically grossly exaggerated: of the symptoms listed above, the only ones Gage can even *arguably* be said to have exhibited (based on primary sources) are "anger and frustration," slight memory impairment, and "difficulty in planning".

In particular, the primary sources do not report utilisation behaviour, depression, aggression, inappropriate sexual behaviour, or "inappropriate humour and telling of pointless and boring stories" (in fact, his audience was said to have found his stories entertaining). The oft-quoted statement by friends—that after the accident he was "no longer Gage"—admits interpretation as any number of behavioural or personality changes, not even necessarily of organic etiology. Although he was not able to return to his work for the railroad, after his physical recovery he was socially functional and self-supporting for the remainder of his life.

## *Causes of frontal lobe dysfunction*

### Head trauma

Closed head injuries, for example from motor vehicle accidents, can cause damage to the orbitofrontal cortex. Pre-frontal lobotomies severing connections between the pre-frontal cortex and the rest of the brain, were effectively a form of iatrogenic trauma resulting in a frontal lobe syndrome.

### Cerebrovascular disease

Cerebrovascular disease may cause a stroke in the frontal lobe.

### Tumours

Tumours such as meningiomas may present with a frontal lobe syndrome.

### Degenerative diseases

Frontal lobe impairment is a feature of Alzheimer's disease, frontotemporal dementia and Pick's disease.

### Psychiatric disorders

There is evidence for frontal lobe impairment in schizophrenia, depression, attention-deficit hyperactivity disorder (ADHD), and antisocial personality disorder or psychopathy.

A large number of studies have documented abnormalities in working memory in schizophrenia, associated with disrupted functioning of the dorso-lateral prefrontal cortex. There is also evidence for disruption of neuronal connections between the temporal and frontal lobes in people with schizophrenia. The characteristic dorso-lateral prefrontal cortex morphological abnormalities are said to be related to a general impaired ability to control and regulate behaviour, which would correspond to deficits in several functional areas in schizophrenia. A study of people with schizophrenia using MRI scanning and psychological assessment has also found that longer duration of illness was associated with lower gray matter volume in the left dorsomedial prefrontal cortex and the right middle frontal cortex, and these changes were associated with impaired working memory, attention and psychomotor speed. Another MRI study of schizophrenia has found an association between orbitofrontal cortex volume reduction and a longer duration of illness, impaired executive functioning, and greater formal thought disorder.

Research on children with ADHD has shown a general reduction of brain volume, but with a proportionally greater reduction in the volume of the left-sided prefrontal cortex. These findings are in keeping with the core ADHD features of inattention, hyperactivity, and impulsivity, but other brain regions have also been implicated in the causation of

ADHD. The prefrontal cortex is also implicated by functional magnetic resonance imaging (fMRI) studies which examine brain activation during tasks such as motor response inhibition; reduced prefrontal cortex activation is associated with higher ADHD behavioural scores.

# Chapter 11

# Dysarthria and Apraxia

# Dysarthria

| Dysarthria | |
|---|---|
| **ICD-10** | R47.1 |
| **ICD-9** | 784.5 |
| **DiseasesDB** | 4015 |
| **MeSH** | D004401 |

**Dysarthria** is a motor speech disorder resulting from neurological injury, characterized by poor articulation (cf. aphasia: a disorder of the content of speech). Any of the speech subsystems (respiration, phonation, resonance, prosody, and articulation) can be affected.

Dysarthric speech is due to some disorder in the nervous system, which in turn hinders control over, for example, the tongue, throat, lips or lungs. Swallowing problems (dysphagia) are often present.

Cranial nerves that control these muscles include the trigeminal nerve's motor branch (V), the facial nerve (VII), the glossopharyngeal nerve (IX), the vagus nerve (X), and the hypoglossal nerve (XII).

## *Classification*

Dysarthrias are classified in multiple ways based on the presentation of symptoms. Specific dysarthrias include spastic (resulting from bilateral damage to the upper motor neuron), flaccid (resulting from bilateral or unilateral damage to the lower motor neuron), ataxic (resulting from damage to cerebellum), unilateral upper motor neuron (presenting milder symptoms than bilateral UMN damage), hyperkinetic and hypokinetic (resulting from damage to parts of the basal ganglia, such as in Huntington's disease or Parkinsonism), and the mixed dysarthrias (where symptoms of more than one type of dysarthria are present). The majority of dysarthric patients are diagnosed as having

'mixed' dysarthria, as neural damage resulting in dysarthria is rarely contained to one part of the nervous system - for example, multiple strokes, traumatic brain injury, and some kinds of degenerative illnesses (such as amyotrophic lateral sclerosis) usually damage many different sectors of the nervous system.

## Causes

The causes of dysarthria can be many, including toxic, metabolic, degenerative diseases (such as Parkinsonism, ALS, Huntington's Disease, Niemann Pick disease, Ataxia etc.), traumatic brain injury, or thrombotic or embolic stroke. These result in lesions to key areas of the brain involved in planning, executing, or regulating motor operations in skeletal muscles (i.e. muscles of the limbs), including muscles of the head and neck (dysfunction of which characterises dysarthria). These can result in dysfunction, or failure of: the motor or somatosensory cortex of the brain, corticobulbar pathways, the cerebellum, basal nuclei (consisting of the putamen, globus pallidus, caudate nucleus, substantia nigra etc.), brainstem (from which the cranial nerves originate), or the neuro-muscular junction (in diseases such as Myasthenia Gravis) which block the nervous system's ability to activate motor units and effect correct range and strength of movements.

## Treatment

Articulation problems resulting from dysarthria are treated by speech language pathologists, using a variety of techniques. Techniques used depend on the effect the dysarthria has on control of the articulators. Traditional treatments target the correction of deficits in rate (of articulation), prosody (appropriate emphasis and inflection, affected e.g. by apraxia of speech, right hemisphere brain damage, etc.), intensity (loudness of the voice, affected e.g. in hypokinetic dysarthrias such as in Parkinson's), resonance (ability to alter the vocal tract and resonating spaces for correct speech sounds) and phonation (control of the vocal folds for appropriate voice quality and valving of the airway). These treatments have usually involved exercises to increase strength and control over articulator muscles (which may be flaccid and weak, or overly tight and difficult to move), and using alternate speaking techniques to increase speaker intelligibility (how well someone's speech is understood by peers).

More recent techniques based on the principles of motor learning (PML), such as LSVT (Lee Silverman Voice Treatment) Speech therapy and specifically LSVT may improve voice and speech function in PD. for Parkinson's, aim to retrain speech skills through building new generalised motor programs, and attach great importance to regular practice, through peer/partner support and self-management. Regularity of practice, and when to practice, are the main issues in PML treatments, as they may determine the likelihood of generalisation of new motor skills, and therefore how effective a treatment is.

Augmentative and Alternative Communication (AAC) devices that make coping with a dysarthria easier include speech synthesis software and text-based telephones. These

allow people who are unintelligible, or may be in the later stages of a progressive illness, continue to be able to communicate without the need for fully intelligible speech. Some cases of dysarthria, as in children are of no known causes. It is a speech motor disorder causing high pitch and tone, mis pronunciation of words and fast talking. Children benefit from a speech and language therapist to help them slow down, practice beginning and end sounds of words. It is not genetic. Children sometimes cannot chew properly,thus over stuffing their mouths since there is no sensation of fullness. Early in childhood, some show signs of dysarthria but it takes years to get the correct diagnosis. A case of a 4 yo diagnosed December 2009 in which in hindsight, the pieces came together. Late talker, seemed to have acid reflux ( projectile vomiting), smile was irregular and always talked in "gibberish". Children also do well when introduced to others their age to socialize and "pick up" correct word usage. This 4 yo in particular always sounded "deaf" to her parents since she always talked loud and off key. Word books could be helpful for hard to understand words, but require training on both ends( the parent and child). Speech therapy is very beneficial to the child. After a year of SLP; the 4 yo is talking more but has difficulty with ending sounds and slow speaking. She sounds different than a typical 4 yo but has made remarkable progress. A hearing test as well as any other should be done to rule out hearing loss or a developmental delay. Dysarthria in children is classified as a learning disability. Before entering a school program, a parent should and must have all information on the child, the treatment plan and request weekly SLP sessions as well as an Individualized Education Plan (IEP) in place to ensure the child gets the correct education and assistance if needed. Dysarthria in children without a genetic or brain disorder are more common than first believed and the least attention as to why this disorder affects an other wise health child.

# Apraxia

| Apraxia | |
|---|---|
| **ICD-10** | R48.2 |
| **ICD-9** | 438.81, 784.69 |
| **DiseasesDB** | 31600 |
| **MedlinePlus** | 003203 |
| **eMedicine** | neuro/438 |
| **MeSH** | D001072 |

**Apraxia** is a disorder caused by damage to specific areas of the cerebrum, characterized by loss of the ability to execute or carry out learned purposeful movements, despite having the desire and the physical ability to perform the movements. It is a **disorder of**

**motor planning** which may be acquired or developmental, but may not be caused by incoordination, sensory loss, or failure to comprehend simple commands (which can be tested by asking the person to recognize the correct movement from a series). Apraxia should not be confused with aphasia, an inability to produce and/or comprehend language; abulia, the lack of desire to carry out an action; or allochiria, in which patients perceive stimuli to one side of the body as occurring on the other.

The root word of apraxia is *praxis*, Greek for an act, work, or deed. It is preceded by a privative a, meaning *without*.

## *Types*

There are several types of apraxia including:

- *ideomotor* (inability to carry out a motor command; for example, "act as if you are brushing your teeth" or "salute") - the form most frequently encountered by physicians;
    - *limb apraxia* when movements of the arms and legs are involved;
    - *nonverbal-oral* or *buccofacial* (inability to carry out facial movements on command; e.g., lick lips, whistle, cough, or wink);
- *ideational* (inability to create a plan for or idea of a specific movement; for example, "pick up this pen and write down your name");
- *limb-kinetic* (inability to make fine, precise movements with a limb);
- *verbal* (difficulty planning the movements necessary for speech), also known as Apraxia of Speech (see below);
- *constructional* (inability to draw or construct simple configurations), such as intersecting pentagons;
- *oculomotor* (difficulty moving the eye, especially with saccade movements).
- *gait apraxia*

Each type may be tested at decreasing levels of complexity; if the person tested fails to execute the commands, you can make the movement yourself and ask that the person mimic it, or you can even give them a real object (like a toothbrush) and ask them to use it.

Apraxia may be accompanied by a language disorder called aphasia.

### Apraxia of speech

Symptoms of Acquired Apraxia of speech (AOS) and Childhood Apraxia of Speech (CAS) include inconsistent articulatory errors, groping oral movements to locate the correct articulatory position, and increasing errors with increasing word and phrase length. AOS often co-occurs with Oral Apraxia (during both speech and non-speech movements) and Limb Apraxia.

Childhood Apraxia of Speech (CAS) presents in children who have no evidence of difficulty with strength or range of motion of the articulators, but are unable to execute speech movements because of motor planning and coordination problems. This is not to be confused with phonological impairments in children with normal coordination of the articulators during speech.

Acquired apraxia of speech involves the loss of previously acquired speech levels. It occurs in both children and adults who have (prior to the onset of apraxia) acquired some level of speaking ability. Unlike Childhood Apraxia of Speech, AOS is typically the result of a stroke, tumor, or other known neurological illness or injury.

## *Causes*

Ideomotor apraxia is almost always caused by lesions in the language-dominant (usually left) hemisphere of the brain; and, as such, these patients often have concomitant aphasia, especially of the Broca or conduction type. Left-side ideomotor apraxia may be caused by a lesion of the anterior corpus callosum.

Ideational apraxia is commonly associated with confusion states and dementia.

Constructional apraxia is associated with hepatic encephalopathy due to cerebral edema.

## *Treatment*

Recommended treatment for individuals with apraxia includes physical therapy, occupational therapy and/or speech therapy.

## *Prognosis*

The prognosis for individuals with apraxia varies. With therapy, some patients improve significantly, while others may show very little improvement. Some individuals with apraxia may benefit from the use of a communication aid.

# Chapter 12

# Agnosia and Dysautonomia

## Agnosia

| Agnosia | |
|---|---|
| **ICD-10** | R48.1 |
| **ICD-9** | 784.69 |
| **MeSH** | D000377 |

**Agnosia** (*a-gnosis*, or loss of knowledge) is a loss of ability to recognize objects, persons, sounds, shapes, or smells while the specific sense is not defective nor is there any significant memory loss. It is usually associated with brain injury or neurological illness, particularly after damage to the occipitotemporal border, which is part of the ventral stream.

### *Types*

| Name | Description |
|---|---|
| Alexia | Inability to recognize text. |
| Akinetopsia | The loss of motion perception. |
| Alexithymia | While not strictly a form of agnosia, Alexithymia may be difficult to distinguish from or co-occur with social-emotional agnosia. Alexithymia is deficiency in understanding, processing, or describing emotions common to around 85% of people on the autism spectrum. Alexithymia is believed to be due to an information processing delay in the combined processing of information in the left and right hemispheres, resulting in poor differentiation between body messages and emotions. |
| Amusia or Receptive amusia | Is agnosia for music. It involves loss of the ability to recognize musical notes, rhythms, and intervals and the inability to experience music as musical. |
| Anosognosia | This is the inability to gain feedback about one's own condition and |

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| | can be confused with lack of insight but is caused by problems in the feedback mechanisms in the brain. It is caused by neurological damage and can occur in connection with a range of neurological impairments but is most commonly referred to in cases of paralysis following stroke. Those with Anosognosia with multiple impairments may even be aware of some of their impairments but completely unable to perceive others. |
| Apperceptive agnosia | Patients are unable to distinguish visual shapes and so have trouble recognizing, copying, or discriminating between different visual stimuli. Unlike patients suffering from associative agnosia, those with apperceptive agnosia are unable to copy images. |
| Apraxia | Is a form of motor (body) agnosia involving the neurological loss of ability to map out physical actions in order to repeat them in functional activities. It is a form of body-disconnectedness and takes several different forms; Speech-Apraxia in which ability to speak is impaired, Limb-Kinetic Apraxia in which there is a loss of hand or finger dexterity and can extend to the voluntary use of limbs, Ideomotor Apraxia in which the gestures of others can't be easily replicated and can't execute goal-directed movements, Ideational Apraxia in which one can't work out which actions to initiate and struggles to plan and discriminate between potential gestures, Apraxia of Gait in which co-ordination of leg actions is problematic such as kicking a ball, Constructional Apraxia in which a person can't co-ordinate the construction of objects or draw pictures or follow a design, Oculomotor Apraxia in which the ability to control visual tracking is impaired and Buccofacial Apraxia in which skilled use of the lips, mouth and tongue is impaired. |
| Associative agnosia | Patients can describe visual scenes and classes of objects but still fail to recognize them. They may, for example, know that a fork is something you eat with but may mistake it for a spoon. Patients suffering from associative agnosia are still able to reproduce an image through copying. |
| Auditory agnosia | With Auditory Agnosia there is difficulty distinguishing environmental and non-verbal auditory cues including difficulty distinguishing speech from non-speech sounds even though hearing is usually normal. |
| Autotopagnosia | Is associated with the inability to orient parts of the body, and is often caused by a lesion in the parietal part of the posterior thalmic radiations. |
| Color agnosia | Refers to the inability to recognize a color, while being able to perceive or distinguish it. |
| Cortical deafness | Refers to people who do not perceive any auditory information but whose hearing is intact. |
| Finger agnosia | Is the inability to distinguish the fingers on the hand. It is present in lesions of the dominant parietal lobe, and is a component of |

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| | Gerstmann syndrome. |
| Form agnosia | Patients perceive only parts of details, not the whole object. |
| Integrative agnosia | This is where one has the ability to recognize elements of something but yet be unable to integrate these elements together into comprehensible perceptual wholes |
| Mirror agnosia | One of the symptoms of Hemispatial neglect. Patients with Hemispatial neglect were placed so that an object was in their neglected visual field but a mirror reflecting that object was visible in their non-neglected field. Patients could not acknowledge the existence of objects in the neglected field and so attempted to reach into the mirror to grasp the object. |
| Pain agnosia | Also referred to as **Analgesia**, this is the difficulty perceiving and processing pain; thought to underpin some forms of self injury. |
| Phonagnosia | Is the inability to recognize familiar voices, even though the hearer can understand the words used. |
| Prosopagnosia | Also known as **faceblindness** and **facial agnosia**: Patients cannot consciously recognize familiar faces, sometimes even including their own. This is often misperceived as an inability to remember names. |
| Semantic agnosia | Those with this form of agnosia are effectively 'object blind' until they use non-visual sensory systems to recognise the object. For example, feeling, tapping, smelling, rocking or flicking the object, may trigger realisation of its semantics (meaning). |
| Simultanagnosia | Patients can recognize objects or details in their visual field, but only one at a time. They cannot make out the scene they belong to or make out a whole image out of the details. They literally "cannot see the forest for the trees." Simultanagnosia is a common symptom of Balint's syndrome. |
| Social emotional agnosia | Sometimes referred to as Expressive Agnosia, this is a form of agnosia in which the person is unable to perceive facial expression, body language and intonation, rendering them unable to non-verbally perceive people's emotions and limiting that aspect of social interaction. |
| Somatosensory agnosia | Or **Astereognosia** is connected to tactile sense - that is, touch. Patient finds it difficult to recognize objects by touch based on its texture, size and weight. However, they may be able to describe it verbally or recognize same kind of objects from pictures or draw pictures of them. Thought to be connected to lesions or damage in somatosensory cortex. |
| Tactile agnosia | Impaired ability to recognize or identify objects by touch alone. |
| Time agnosia | Is the loss of comprehension of the succession and duration of events. |
| Topographical agnosia | This is a form of visual agnosia in which a person cannot rely on visual cues to guide them directionally due to the inability to recognise objects. Nevertheless, they may still have an excellent |

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| | capacity to describe the visual layout of the same place |
| Verbal auditory agnosia | This presents as a form of meaning 'deafness' in which hearing is intact but there is significant difficulty recognising spoken words as semantically meaningful. |
| Visual agnosia | Is associated with lesions of the left occipital lobe and temporal lobes. Many types of visual agnosia involve the inability to recognize objects. |
| Visual verbal agnosia | Difficulty comprehending the meaning of written words. The capacity to read is usually intact but comprehension is impaired. |

### *Causes*

Agnosia can result from strokes, dementia, or other neurological disorders. It may also be trauma-induced by a head injury, brain infection, or hereditary. Some forms of agnosia have been found to be genetic.

Patients who experience dramatic recovery from blindness experience significant to total Agnosia.

### *Treatment*

For all practical purposes, there is no direct cure. Patients may improve if information is presented in other modalities than the damaged one. Different types of therapies can help to reverse the effects of Agnosia. In some cases, occupational therapy or speech therapy can improve agnosia, depending on its etiology.

# Dysautonomia

| Dysautonomia | |
|---|---|
| **ICD-10** | G90. |
| **ICD-9** | 337.9 |
| **MeSH** | D001342 |

**Dysautonomia** (autonomic dysfunction) is a broad term that describes any disease or malfunction of the autonomic nervous system. This includes postural orthostatic tachycardia syndrome (POTS), inappropriate sinus tachycardia (IST), vasovagal syncope, mitral valve prolapse dysautonomia, pure autonomic failure, neurocardiogenic syncope (NCS), neurally mediated hypotension (NMH), autonomic instability and a number of

lesser-known disorders such as cerebral salt-wasting syndrome. Dysautonomia is associated with Lyme disease, primary biliary cirrhosis, multiple system atrophy (Shy-Drager syndrome), Ehlers-Danlos syndrome, and Marfan syndrome for reasons that are not fully understood. In a study on orthostatic intolerance and EDS it is suggested the occurrence of these syndromes together can be attributed to the abnormal connective tissue in dependent blood vessels of those with EDS, which permits veins to distend excessively in response to ordinary hydrostatic pressures. This in turn leads to increased venous pooling and its hemodynamic and symptomatic consequences.

## *Presentation*

Symptoms of dysautonomia are numerous and vary widely from person to person. Since dysautonomia is a full-body condition, a large number of symptoms may be present that can greatly alter a person's quality of life. Each patient with dysautonomia is different—some are affected only mildly while others are left completely bedridden and disabled.

The primary symptoms that present in patients with dysautonomia are:

- Excessive fatigue
- Excessive thirst (polydipsia)
- Lightheadedness, dizziness or vertigo
- Feelings of anxiety or panic (not mentally induced)
- Rapid heart rate or slow heart rate
- Orthostatic hypotension, sometimes resulting in syncope (fainting)

Other symptoms frequently associated with dysautonomia include: headaches, pallor, malaise, facial flushing, salt cravings, constipation, diarrhea, nausea, acid reflux, visual disturbances, orthostatic hypotension, numbness, nerve pain, trouble breathing, chest pains, in some cases loss of consciousness and seizures. A full list of symptoms may be found at the Dysautonomia Information Network.

## *Causes*

Causes of dysautonomias are not fully understood, but they are thought to include:

- Autoimmune disorders, especially Lyme disease and Type I diabetes
- Bad body posture (causes compression of important arteries and/or nerves)
- Brain injury
- Degenerative neurological diseases such as Parkinson's disease
- Exposure to chemicals
- Genetic factors
- Hereditary connective tissue diseases, especially Ehlers-Danlos Syndrome
- Pregnancy
- Physical trauma or injury which damages the autonomic nervous system, as with Cerebral salt-wasting syndrome.
- Viral illness

## Management

In some cases, a procedure called "cardiac ablation" can be performed to stop the heart symptoms completely. It is not recommended in POTS patients, and can in fact worsen tachycardia. Medications are also used to stabilize the condition on a long-term basis. Benzodiazepines can be used for some of the physical problems such as anxiety. In many cases treatment of primary dysautonomia is symptomatic and supportive. Measures to combat orthostatic intolerance include elevation of the head of the bed, frequent small meals, a high-salt diet, fluid intake, and compression stockings. Drugs such as fludrocortisone, midodrine, ephedrine and SSRIs can also be used to treat symptoms. Treating dysautonomia can be difficult and usually requires a combination of drug therapies.

## Prognosis

The outlook for patients with dysautonomia depends on the particular diagnostic category. There is no way of predicting whether symptoms of dysautonomia will resolve over time, or continue over the entire course of one's lifespan. Some forms of dysautonomia are not life threatening, even if life changing in the form of minor to major limitations in activities of daily living. However patients with Ehlers-Danlos Syndrome, Marfan Syndrome or Parkinson's disease have a chronic, progressive, generalized form of dysautonomia in the setting of central nervous system degeneration, leading to a generally poor long-term prognosis. Patients can die from pneumonia, acute respiratory failure, or sudden cardiopulmonary arrest.

There is some evidence that dysautonomia may be a factor in SIDS (sudden infant death syndrome).

## History

In the nineteenth and earlier twentieth centuries, a diagnosis that was almost solely given to women was called "neurasthenia," or a "weak nervous system." (During World War One, doctors began to apply it to men exhibiting symptoms of what is now called post-traumatic stress disorder.) These women would present symptoms of fatigue, weakness, dizziness and fainting, and the doctor's orders would simply be bed rest. Some of these women died, while many others recovered. No one understood where the problems came from. With the advances in modern medicine, diagnostic criteria and treatment for various forms of dysautonomia have sharpened. Doctors and researchers are including males in their subject population for this disorder.

The prototype of dysautonomia is the ancient scourge of beriberi,a nutritional deficiency disease due to excess of simple carbohydrate and concomitant vitamin $B_1$ deficiency. In the early stages this results in loss of functional efficiency in the central control mechanisms of the autonomic nervous system. If the nutritional deficiency continues, there is gradual degeneration of the system. Other vitamin deficiencies have been

implicated in causing dysautonomia and unlike the genetically determined forms of the disease, are treatable.

# Chapter 13

# Movement Disorders

# Hypokinesia

| Hypokinesia | |
|---|---|
| **MeSH** | D018476 |

**Hypokinesia** refers to decreased bodily movement. It is associated with basal ganglia diseases (such as Parkinson's disease), mental health disorders and prolonged inactivity due to illness, amongst other diseases.

Hypokinesia describes a spectrum of disorders:

- **Akinesia** (*a-*, "without", *kinisi*, "motion") is the inability to initiate movement due to difficulty selecting and/or activating motor programs in the central nervous system. Common in severe cases of Parkinson's disease, akinesia is a result of severely diminished dopaminergic cell activity in the direct pathway of movement.
- **Bradykinesia** (*brady-*, "slow", *kinisi*, "motion") is characterized by slowness of movement and has been linked to Parkinson's disease and other disorders of the basal ganglia. Rather than being a slowness in initiation (akinesia), bradykinesia describes a slowness in the execution of movement. It is one of the 3 key symptoms of parkinsonism, which are bradykinesia, tremor and rigidity. Bradykinesia is also the cause of what is normally referred to as "stone face" (expressionless face) among those with Parkinson's.
- **Freezing** is characterized by an inability to move muscles in any desired direction.
- **Rigidity** results when there is an increase in muscle tone that causes resistance to passive movement throughout the whole range of motion. There are different types of rigidity. The form just described is the so-called 'lead-pipe' rigidity seen especially in Parkinson's disease. 'Cogwheel' rigidity is a combination of rigidity and tremor which presents as a jerky resistance to passive movement. Spasticity is a special form of rigidity that is present only at the start of passive movement. It is rate dependent and only elicited upon a high speed movement. These various

forms of rigidity can be seen in different forms of movement disorders, such as Parkinson's disease.
- **Postural instability** is the loss of ability to maintain an upright posture.

# Ataxia

**Ataxia** (from Greek *α-* [used as a negative prefix] + *-τάξις* [order], meaning "lack of order") is a neurological sign and symptom that consists of gross lack of coordination of muscle movements. Ataxia is a non-specific clinical manifestation implying disfunction of the parts of the nervous system that coordinate movement, such as the cerebellum. Several possible causes exist for these patterns of neurological dysfunction. The term "dystaxia" is a rarely-used synonym.

The International Ataxia Awareness Day is observed on September 25 each year.

## *Types*

### Cerebellar

The term cerebellar ataxia is used to indicate ataxia that is due to dysfunction of the cerebellum. This causes a variety of elementary neurological deficits, such as antagonist hypotonia, asynergy, dysmetria, dyschronometria, and dysdiadochokinesia. How and where these abnormalities manifest themselves depends on which cerebellar structures have been damaged, and whether the lesion is bilateral or unilateral.

- **Dysfunction of the vestibulocerebellum** impairs the balance and the control of eye movements. This presents itself with postural instability, in which the person tends to separate his/her feet upon standing, in order to gain a wider base and to avoid bodily oscillations (especially forward-backward ones). The instability is therefore worsened when standing with the feet together, regardless of whether the eyes are open or closed. This is a negative Romberg's test, or more accurately, it denotes the individual's inability to carry out the test, because the individual feels unstable even with open eyes.
- **Dysfunction of the spinocerebellum** presents itself with a wide-based "drunken sailor" gait, characterised by uncertain starts and stops, lateral deviations, and unequal steps. This part of the cerebellum regulates body and limb movements.
- **Dysfunction of the cerebrocerebellum** presents with disturbances in carrying out voluntary, planned movements. These include:
    - intention tremor (coarse trembling, accentuated over the execution of voluntary movements, possibly involving the head and eyes as well as the limbs and torso);

- peculiar writing abnormalities (large, unequal letters, irregular underlining);
- a peculiar pattern of dysarthria (slurred speech, sometimes characterised by explosive variations in voice intensity despite a regular rhythm).

### Sensory

The term sensory ataxia is employed to indicate ataxia due to loss of proprioception - the loss of sensitivity to the positions of joint and body parts. This is generally caused by dysfunction of the dorsal columns of the spinal cord, because they carry proprioceptive information up to the brain. In some cases, the cause of sensory ataxia may instead be dysfunction of the various parts of the brain which receive positional information, including the cerebellum, thalamus, and parietal lobes.

Sensory ataxia presents itself with an unsteady "stomping" gait with heavy heel strikes, as well as a postural instability that is usually worsened when the lack of proprioceptive input cannot be compensated for by visual input, such as in poorly lit environments.

Physicians can find evidence of sensory ataxia during physical examination by having the patient stand with his/her feet together and eyes shut. In affected patients, this will cause the instability to worsen markedly, producing wide oscillations and possibly a fall. This is called a positive Romberg's test. Worsening of the finger-pointing test with the eyes closed is another feature of sensory ataxia. Also, when the patient is standing with arms and hands extended toward the physician, if the eyes are closed, the patient's finger will tend to "fall down" and then be restored to the horizontal extended position by sudden muscular contractions (the "ataxic hand").

### Vestibular

The term vestibular ataxia is employed to indicate ataxia due to dysfunction of the vestibular system, which in acute and unilateral cases is associated with prominent vertigo, nausea and vomiting. In slow-onset, chronic bilateral cases of vestibular dysfunction, these characteristic manifestations may be absent, and dysequilibrium may be the sole presentation.

## *Causes*

The three types of ataxia have overlapping causes, and therefore can either coexist or occur in isolation.

### Focal lesions

Any type of focal lesion of the central nervous system (such as stroke, brain tumour, multiple sclerosis) will cause the type of ataxia corresponding to the site of the lesion: cerebellar if in the cerebellum, sensory if in the dorsal spinal cord (and rarely in the

thalamus or parietal lobe), vestibular if in the vestibular system (including the vestibular areas of the cerebral cortex).

## Exogenous substances

Exogenous substances that cause ataxia mainly do so because they have a depressant effect on central nervous system function. The most common example is ethanol, which is capable of causing reversible cerebellar and vestibular ataxia. Other examples include various prescription drugs (e.g. most antiepileptic drugs have cerebellar ataxia as a possible adverse effect), Lithium level over 1.5mEq/L, cannabis ingestion and various other recreational drugs (e.g. ketamine, PCP or dextromethorphan, all of which are NMDA receptor antagonists that produce a dissociative state at high doses). Exposure to high levels of methylmercury, through consumption of fish with high mercury concentrations, is also a known cause of ataxia and other neurological disorders

## Vitamin $B_{12}$ deficiency

Vitamin $B_{12}$ deficiency may cause, among several neurological abnormalities, overlapping cerebellar and sensory ataxia.

## Causes of isolated sensory ataxia

Peripheral neuropathies may cause generalised or localised sensory ataxia (e.g. a limb only) depending on the extent of the neuropathic involvement. Spinal disorders of various types may cause sensory ataxia from the lesioned level below, when they involve the dorsal columns.

## Non-hereditary cerebellar degeneration

Non-hereditary causes of cerebellar degeneration include chronic ethanol abuse, paraneoplastic cerebellar degeneration, high altitude cerebral oedema, coeliac disease, normal pressure hydrocephalus and cerebellitis.

## Hereditary ataxias

Ataxia may depend on hereditary disorders consisting of degeneration of the cerebellum and/or of the spine; most cases feature both to some extent, and therefore present with overlapping cerebellar and sensory ataxia, even though one is often more evident than the other. Hereditary disorders causing ataxia include autosomal dominant ones such as spinocerebellar ataxia, episodic ataxia, and dentatorubropallidoluysian atrophy, as well as autosomal recessive disorders such as Friedreich's ataxia (sensory and cerebellar, with the former predominating) and Niemann Pick disease, ataxia-telangiectasia (sensory and cerebellar, with the latter predominating), and abetalipoproteinaemia. An example of X-linked ataxic condition is the rare fragile X-associated tremor/ataxia syndrome.

### Arnold-Chiari Malformation

Arnold-Chiari malformation is a malformation of the brain. It consists of a downward displacement of the cerebellar tonsils and the medulla through the foramen magnum, sometimes causing hydrocephalus as a result of obstruction of cerebrospinal fluid outflow.

## *Treatment*

The movement disorders related to ataxia are primarily treated with physical therapy. As ataxia involves a loss of coordinated and efficient action of stabilising muscles in the trunk, exercise training typically includes a focus on stability exercise. There is often an array of other motor deficits requiring exercise treatment including weakness, balance impairment and decreased endurance. It is also possible that treatment will include strategies to manage difficulties with everyday activities, such as a cane or walker to decrease the risk of falls associated with a balance impairment, or prescription of a wheelchair.

## *Other uses of the term*

The term "ataxia" is sometimes used in a broader sense to indicate lack of coordination in some physiological process. Examples include **optic ataxia** (lack of coordination between visual inputs and hand movements, resulting in inability to reach and grab objects. Optic ataxia may be caused by lesions to the posterior parietal cortex. The posterior parietal cortex is responsible for combining and expressing positional information and relating it to movement. Outputs of the posterior parietal cortex include the spinal cord, brain stem motor pathways, pre-motor and pre-frontal cortex, basal ganglia and the cerebellum. Some neurons in the posterior parietal cortex are modulated by intention. Optic ataxia is usually part of Balint's syndrome, but can be seen in isolation with injuries to the superior parietal lobule, as it represents a disconnection between visual-association cortex and the frontal premotor and motor cortex), and **ataxic respiration** (lack of coordination in respiratory movements, usually due to dysfunction of the respiratory centres in the medulla oblongata).

# Hemiballismus

| Hemiballismus | |
|---|---|
| **ICD-10** | G25.5 |
| **ICD-9** | 333.5 |
| **MeSH** | D020820 |

**Hemiballismus** is a very rare movement disorder. It is five hundred times rarer than Parkinson's disease. Its effects can sometimes be severe enough to prevent patients from being able to perform daily functions. It is usually associated with structural brain lesions but can occur with metabolic abnormalities. The symptoms can also decrease while the patient is asleep, unlike some movement disorders.

## *General Definition*

Hemiballismus is usually characterized by involuntary flinging motions of the extremities. The movements are often violent and have wide amplitudes of motion. They are continuous and random and can involve proximal and/or distal muscles on one side of the body. Some cases even include the facial muscles. It is common for arms and legs to move together. The more a patient is active, the more the movements increase. With relaxation comes a decrease in movements. Physicians can measure the severity of the disorder by having the patient perform a series of basic, predetermined tasks and counting the hemiballistic movements during a set time session. The physicians then rate the patient on a severity scale. This scale gives scientists and clinicians a way to compare patients and determine the range of the disorder.

The name 'hemiballismus' literally means 'half ballistic', referring to the violent, flailing movements observed on one side of the body.

## *Anatomy*

**Basal ganglia**
The basal ganglia are a collection of nuclei that connects to several other areas of the brain. Due to the diverse nuclei that they contain, the basal ganglia are involved in numerous functions, including motor control. It is within this structure that hemiballismus primarily occurs in the brain.

**Subthalamic Nucleus**
This structure within the basal ganglia innervates other structures, including a very important connection to the inside of the globus pallidus. The subthalamic nucleus essentially provides the excitement needed to drive the globus pallidus. Injury to this area or its efferent or afferent connections can induce this disorder. The structure itself is a

regulator of motor function and is also involved in associative and limbic functions. It was traditionally thought that the disorder was only caused by injury to the subthalamic nucleus, but new studies are showing that damage to other areas of the brain can also be responsible for causing this disorder. Hemiballismus caused by lesions in the subthalamic nucleus is more severe than other forms of the disorder.

**Globus Pallidus**
From recent studies, it is now thought that hemiballismus can be associated with a decreased output of the globus pallidus. This is because studies have shown that firing rates decrease from 70/s to 40/s. In addition to a decreased firing rate, degenerative neurological disorders that cause patients to exhibit hemiballistic movements show a marked decrease in the globus pallidus mass as well. Increases in activity in this area causes there to be an inhibition of the motor thalamus. This causes cortical activation and thus a movement inhibition. In the case of hemiballismus, the opposite occurs, leading to the characteristic large, irregular movements.

**Putamen**
The putamen is also part of the basal ganglia and can be involved in hemiballismus due to the fact that it projects to the premotor cortex through the globus pallidus. As a result, damage to this area can also cause hemiballistic movements to be seen as it is also part of the chain in movement.

**Caudate Nucleus**
The caudate nucleus is the portion of the basal ganglia that helps control voluntary movement. Damage to this area can also result in hemiballismus as it is directly related to voluntary movement.

**Cortical Structures**
While the majority of damage that causes hemiballismus occurs within the basal ganglia, there are still cases that have been documented on which damage to cortical structures has caused hemiballistic movements.

## *History*

The work of J.R. Whittier, F.A. Mettler, and M.B. Carpenter in the mid 1900s helped scientists and clinicians form a more complete picture of hemiballismus. In their experiments, several lesions were made in the basal ganglia structures in monkeys and then they monitored the results. They noticed that the majority of the time, the monkeys did not have any unusual movements. However, when at least twenty percent of the subthalamic nucleus was damaged, abnormal movements were seen in the limbs opposite to the side of the brain that was damaged. This observation caused scientists to believe that hemiballismus outside the subthalamic nucleus did not occur. It was not until much later that this classical model began to expand to include other areas of the basal ganglia and even some cortical structures. They also noticed that unlike human patients, the unusual movements in the monkeys were mainly in the lower extremeites. In about half of the monkeys, the hemiballismus continued until the monkey died.

Other scientists have also worked on this perplexing disorder and have found that the symptoms can be induced by injecting kainic acid or ibotenic acid into the subthalamic nucleus. I. Hamada and M.R. DeLong found that by using these chemicals, they could destroy only four percent of the subthalamic nucleus and still see hemiballistic movements. However, the abnormal movements would usually disappear within four to five hours even though it did not appear as though the damaged tissue had healed. This suggests that the subthalamic nucleus is plastic enough to adapt to small amounts of damage in order to resume normal function.

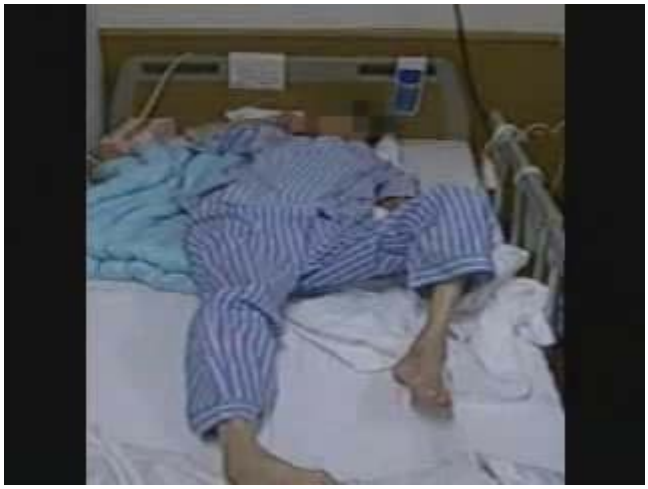
## *Causes*

In examining the causes of hemiballismus, it is important to remember that this disorder is extremely rare. While hemiballismus can result from the following list, just because a patient suffers from one of these disorders does not mean they will also suffer from hemiballismus.

**Stroke**
Hemisballismus as a result of stroke occurs in only about 0.45 cases per hundred thousand stroke victims. Even at such a small rate, stroke is by far the most common cause of hemiballismus. A stroke causes tissue to die due to a lack of oxygen resulting from an impaired blood supply. In the basal ganglia, this can result in the death of tissue that helps to control movement. As a result, the brain is left with damaged tissue that sends damaged signals to the skeletal muscles in the body. The result is occasionally a patient with hemiballismus.

**Traumatic Brain Injury**
Hemiballismus can also occur as a result of a traumatic brain injury. There are cases in which victims of assault or other forms of violence have developed hemiballismus. Through these acts of violence, the victim's brain has been damaged and the hemiballistic movements have developed.

**Amyotrophic Lateral Sclerosis**
This disease causes neuronal loss and gliosis, which can include the subthalamic nucleus and other areas of the brain. Essentially any disorder that causes some form of neuronal loss or gliosis in the basal ganglia has the potential to cause hemiballismus.



Hyperglycemia-induced involuntary movements (in this case, not hemiballismus, but hemichorea (chorea of one side of the body) and bilateral dystonia) in a 62-year-old Japanese woman with type 1 diabetes.

**Nonketotic Hyperglycemia**

Patients with nonketotic hyperglycemia can develop hemiballismus as a complication to the disease through the development of a subthalamic nucleus lesion. This is the second most common reported cause of hemiballismus. It can be found primarily in the elderly and many of the reported cases have come from East Asian origin, which suggests that there may be some genetic disposition to development of hemiballismus as a result of hyperglycemia. Hemiballistic movements appear when blood glucose levels get too high and then subside once glucose levels return to normal. This time scale for this is usually several hours. In patients with this type of hemiballismus, imaging reveals abnormalities in the putamen contralateral to the movements as well as the globus pallidus and caudate nucleus. While the hyperglycemia itself is not the cause of the hemiballistic movements, it has been suggested that petechial hemorrhage or a decreased production of GABA and acetylcholine could result secondary to the hyperglycemia. One of these issues could be responsible for the hemiballistic movements.

**Neoplasms**

A neoplasm is an abnormal growth of cells. Cases have shown that if this occurs somewhere in the basal ganglia, hemiballismus can result.

**Vascular malformations**

Vascular malformations can cause abnormal blood flow to areas of the brain. If too little blood is delivered to the basal ganglia, a stroke can occur.

**Tuberculomas**

This is another form of tumor that can result in the brain as a result of a tuberculous meningitis infection. This type of tumor can also damage parts of the basal ganglia, sometimes resulting in hemiballismus.

**Demyelinating plaques**
Demyelinating plaques attack the myelin sheaths on neurons. This decreases the conduction velocity of the neurons, making the signals received by the basal ganglia garbled and incomplete. This disorganized signal can also cause the chaotic movements characterized by hemiballismus.

**Complications from HIV infection**
Patients with HIV often have complications that arise along with AIDS. Hypoglycemia due to pentamidine use in patients with AIDS has been known to cause hemiballismus. In some patients, hemiballismus has been the only visible symptom to alert the physician that the patients may have AIDS. It is typically a result of a secondary infection that occurs due to the compromised immune system and the most common infection causing hemiballismus is cerebral toxoplasmosis. Most of the lesions that result from this infection are found in the basal ganglia. As long as the diagnosis is not missed, this type of hemiballismus can be treated just as well as in patients without HIV.

## *Treatments*

When treating hemiballismus, it is first important to treat whatever may be causing the manifestation of this disorder. This could be hyperglycemia, infections, or neoplastic lesions. Some patients may not even need treatment because the disorder is not severe and can be self – limited.

**Dopamine Blockers**
When pharmacological treatment is necessary, the most standard type of drug to use is an antidopaminergic drug. Blocking dopamine is effective in about ninety percent of patients. Perphenazine, pimozide, haloperidol, and chlorpromazine are standard choices for treatment. Scientists are still unsure as to why this form of treatment works, as dopamine has not been directly linked to hemiballismus.

**Anticonvulsants**
An anticonvulsant called topiramate has helped patients in three cases and may be a viable treatment for the future.

**ITB Therapy**
Intrathecal baclofen (ITB) therapy is used to treat a variety of movement disorders such as cerebral palsy and multiple sclerosis. It can also be a possibility to help treat hemiballismus. In one case, before ITB the patient had an average of 10-12 ballism episodes of the right lower limb per hour. During episodes, the right hip would flex up to about 90 degrees, with a fully extended knee. After an ITB pump was implanted and the correct dosage was found, the frequency of ballistic right leg movements decreased to about three per day, and the right hip flexed to only 30 degrees. The patient was also able to better isolate individual distal joint movements in the right lower limb. The patient currently receives 202.4 microg/day of ITB and continues to benefit almost 6 years after the ITB pump was implanted.

**Botulinum Injections**
New uses for botulinum toxin have included treatment of hemiballismus. However, this is still in the early stages of testing. This treatment deals with the muscular manifestations of hemiballismus as opposed to the neurological causes.

**Tetrabenazine**
Tetrabenazine has been used to treat other movement disorders, but is now being used to treat hemiballismus. Patients using this medication have had a dramatic response. However, lowering the dosage leads to a return of symptoms. This drug works by depleting dopamine.

**Antipsychotics**
In one case, a patient had not been responding to haloperidol, thus the physician tried olanzapine. The patient made a significant recovery. More research is being performed on the use of these types of drugs in treating hemiballismus.

**Functional Neurosurgery**
Surgery as a treatment should only be used on patients with severe hemiballismus that has not responded to treatment. Lesioning of the globus pallidus or deep brain stimulation of the globus pallidus are procedures that can be used on humans. Usually, lesioning is favored over deep brain stimulation because of the maintenance required to continue stimulating the brain correctly and effectively.

## *Prognosis*

In the past, the prognosis for patients with this disease had been very poor; with many patients suffering from severe disability or death. Now, patients are responding remarkably well to current treatments and the majority of patients go into spontaneous remission. For those that do not go into remission, the symptoms of hemiballismus can generally be very well controlled with medication.

## *Further Questions*

Due to the rarity of this disorder, scientists know very little about the details of hemiballismus. There are still many unanswered questions such as:

•There appears to be a discrepancy between this disorder in humans and animals that has yet to be explained.

•Hemiballismus can also be induced by damage to other areas of the basal ganglia besides the subthalamic nucleus. Why is this? Research is being done in these areas in order to give scientists and clinicians a better model for this disease that will ultimately lead to better diagnosis and treatment of this disorder.

•Research is also being done on why certain treatments seem to help hemiballistic patients when they should seemingly do more harm. An example of this is why lesioning the globus pallidus seems to reduce hemiballistic movements.

•Why does blocking dopamine help reduce patients' symptoms?

### *Conclusion*

Hemiballismus is a rare movement disorder that is caused primarily by damage to various areas in the basal ganglia. While a classical model for this disorder was developed in the 1950s, new discoveries are causing that model to shift. New treatments are also emerging, allowing for better control of symptoms as well as affecting those who did not respond to standard treatment. The prognosis for patients with this disorder is very good, as research in the area is continuing to reveal new insights into the pathophysiology. However, there are still many unanswered questions about this unusual movement disorder and scientists and clinicians are still learning new information as they probe deeper into the brain.

# Choreia

| Choreia (disease) | |
|---|---|
| **ICD-10** | G25.5 |
| **ICD-9** | 333.5 |
| **DiseasesDB** | 16662 |
| **eMedicine** | neuro/62 |
| **MeSH** | D002819 |

**Choreia** (or **chorea**) is an abnormal involuntary movement disorder, one of a group of neurological disorders called dyskinesias. The term *choreia* is derived from the Greek word *χορεία* (=dance), as the quick movements of the feet or hands are vaguely comparable to dancing or piano playing.

The term **hemichoreia** refers to choreia of one side of the body, such as choreia of one arm and not both (comparable to hemiballismus).

## Presentation

Choreia is characterized by brief, quasi-purposeful, irregular contractions that are not repetitive or rhythmic, but appear to flow from one muscle to the next.

These 'dance-like' movements of choreia (from the same root word as "choreography") often occur with athetosis, which adds twisting and writhing movements.

## Causes

Choreia can occur in a variety of conditions and disorders.

- Choreia is a primary feature of Huntington's disease, a progressive neurological disorder.
- Twenty percent of children and adolescents with rheumatic fever develop Sydenham's chorea as a complication.
- Choreia gravidarum is rare type of choreia which is a complication of pregnancy.
- Choreia may also be caused by drugs (levodopa, anti-convulsants, anti-psychotics), metabolic disorders, endocrine disorders, and vascular incidents.
- Ataxia telangiectasia
- Wilson's disease, a genetic disorder that leads to toxic levels of copper in the body

## Ballism

When choreia is serious, slight movements will become thrashing motions; this form of severe choreia is referred to as ballism. Walking may become peculiar, and include odd postures and leg movements. Unlike ataxia and dystonia, which affect the quality of voluntary movements or parkinsonism, which is a hindrance of voluntary movements, the movements of choreia and ballism occur on their own, without conscious effort.

## Treatment

There is no standard course of treatment for choreia. Treatment depends on the type of choreia and the associated disease. Although there are many drugs that can control it, no cure has yet been identified.

| Form | Treatment |
|---|---|
| Huntington's-related | A common treatment is dopaminergic antagonists, although treatment is largely supportive. |
| Sydenham's chorea | Haloperidol, carbamazepine and valproic acid.Usually involves antibiotic drugs to treat the infection, followed by drug therapy to prevent recurrence. |
| Choreia gravidarum | haloperidol, chlorpromazine alone or in combination with diazepam, also pimozide can also be used. |
| Wilson's disease | Reducing levels of copper in the body using D-penicillinamine, |

| | |
|---|---|
| | trientine hydrochloride, tetrathiomolybdate, and other chelating agents |
| Drug-induced choreia | Adjusting medication dosages. |
| Metabolic and endocrine-related choreias | Treated according to their causes. |

# Chapter 14

# Sleep Disorder

| Sleep disorder | |
|---|---|
| **ICD-10** | F51., G47. |
| **ICD-9** | 307.4, 327, 780.5 |
| **DiseasesDB** | 26877 |
| **eMedicine** | med/609 |
| **MeSH** | D012893 |

A **sleep disorder** (somnipathy) is a medical disorder of the sleep patterns of a person or animal. Some sleep disorders are serious enough to interfere with normal physical, mental and emotional functioning. A test commonly ordered for some sleep disorders is the polysomnography.

Disruptions in sleep can be caused by a variety of issues, from teeth grinding (bruxism) to night terrors. When a person suffers from difficulty in sleeping with no obvious cause, it is referred to as insomnia. In addition, sleep disorders may also cause sufferers to sleep excessively, a condition known as hypersomnia. Management of sleep disturbances that are secondary to mental, medical, or substance abuse disorders should focus on the underlying conditions.

## *Common disorders*

The most common sleep disorders include:

- Primary insomnia: Chronic difficulty in falling asleep and/or maintaining sleep when no other cause is found for these symptoms.
- Bruxism: Involuntarily grinding or clenching of the teeth while sleeping.
- Delayed sleep phase syndrome (DSPS): inability to awaken and fall asleep at socially acceptable times but no problem with sleep maintenance, a disorder of circadian rhythms. (Other such disorders are advanced sleep phase syndrome (ASPS), non-24-hour sleep-wake syndrome (Non-24), and irregular sleep wake

rhythm, all much less common than DSPS, as well as the transient jet lag and shift work sleep disorder.)

- Hypopnea syndrome: Abnormally shallow breathing or slow respiratory rate while sleeping.
- Narcolepsy: Excessive daytime sleepiness (EDS) often culminating in falling asleep spontaneously but unwillingly at inappropriate times.
- Cataplexy: a sudden weakness in the motor muscles that can result in collapse to the floor.
- Night terror: *Pavor nocturnus*, sleep terror disorder: abrupt awakening from sleep with behavior consistent with terror.
- Parasomnias: Disruptive sleep-related events involving inappropriate actions during sleep; sleep walking and night-terrors are examples.
- Periodic limb movement disorder (PLMD): Sudden involuntary movement of arms and/or legs during sleep, for example kicking the legs. Also known as nocturnal myoclonus.
- Rapid eye movement behavior disorder (RBD): Acting out violent or dramatic dreams while in REM sleep.
- Restless legs syndrome (RLS): An irresistible urge to move legs. RLS sufferers often also have PLMD.
- Situational circadian rhythm sleep disorders: shift work sleep disorder (SWSD) and jet lag.
- Sleep Apnea, and mostly Obstructive sleep apnea: Obstruction of the airway during sleep, causing lack of sufficient deep sleep; often accompanied by snoring. Other forms of sleep apnea are less common.
- Sleep paralysis: is characterized by temporary paralysis of the body shortly before or after sleep. Sleep paralysis may be accompanied by visual, auditory or tactile hallucinations. Not a disorder unless severe. Often seen as part of Narcolepsy.
- Sleepwalking or *somnambulism*: Engaging in activities that are normally associated with wakefulness (such as eating or dressing), which may include walking, without the conscious knowledge of the subject.
- Nocturia: A frequent need to get up and go to the bathroom to urinate at night. It differs from Enuresis, or bed-wetting, in which the person does not arouse from sleep, but the bladder nevertheless empties.
- Somniphobia: a dread of sleep.

## *Classifications*

- Dyssomnias - A broad category of sleep disorders characterized by either hypersomnolence or insomnia. The three major subcategories include intrinsic (i.e., arising from within the body), extrinsic (secondary to environmental conditions or various pathologic conditions), and disturbances of circadian rhythm. MeSH
    - Insomnia
    - Narcolepsy
    - Sleep Disordered Breathing (SDB), including (non exhaustive):
        - Several types of Sleep apnea

        - Snoring
        - Upper airway resistance syndrome
    - Restless leg syndrome
    - Periodic limb movement disorder
    - Hypersomnia
        - Recurrent hypersomnia - including Kleine-Levin syndrome
        - Posttraumatic hypersomnia
        - "Healthy" hypersomnia
    - Circadian rhythm sleep disorders
        - Delayed sleep phase syndrome
        - Advanced sleep phase syndrome
        - Non-24-hour sleep-wake syndrome
- Parasomnias - A category of sleep disorders that involve abnormal and unnatural movements, behaviors, emotions, perceptions, and dreams in connection with sleep.
    - REM sleep behaviour disorder
    - Sleep terror
    - Sleepwalking (or somnambulism)
    - Bruxism (Tooth-grinding)
    - Bedwetting or sleep enuresis.
    - Sleep talking (or somniloquy)
    - Sleep sex (or sexsomnia)
    - Exploding head syndrome - Waking up in the night hearing loud noises.
- Medical or Psychiatric Conditions that may produce sleep disorders
    - Psychosis (such as Schizophrenia)
    - Mood disorders
        - Depression
        - Anxiety
    - Panic
    - Alcoholism
- Sleeping sickness - a parasitic disease which can be transmitted by the Tsetse fly.

## *General principles of treatment*

Treatments for sleep disorders generally can be grouped into four categories:

- behavioral/ psychotherapeutic treatments
- rehabilitation/management
- medications
- other somatic treatments

None of these general approaches is sufficient for all patients with sleep disorders. Rather, the choice of a specific treatment depends on the patient's diagnosis, medical and psychiatric history, and preferences, as well as the expertise of the treating clinician. Often, behavioral/psychotherapeutic and pharmacological approaches are not incompatible and can effectively be combined to maximize therapeutic benefits.

Management of sleep disturbances that are secondary to mental, medical, or substance abuse disorders should focus on the underlying conditions.

Medications and somatic treatments may provide the most rapid symptomatic relief from some sleep disturbances. Some disorders, such as narcolepsy, are best treated pharmacologically. Others, such as chronic and primary insomnia, may be more amenable to behavioral interventions, with more durable results.

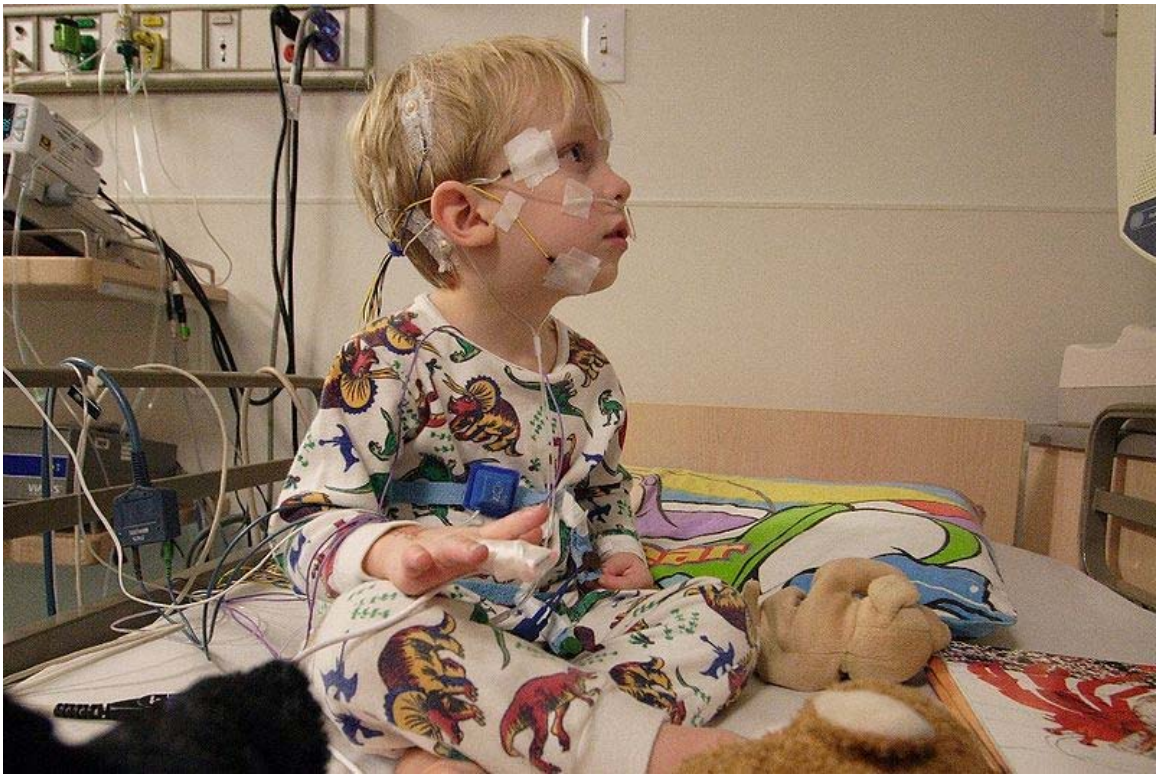
Chronic sleep disorders in childhood, which affect some 70% of children with developmental or psychological disorders, are under-reported and under-treated. Sleep-phase disruption is also common among adolescents, whose school schedules are often incompatible with their natural circadian rhythm. Effective treatment begins with careful diagnosis using sleep diaries and perhaps sleep studies. Modifications in sleep hygiene may resolve the problem, but medical treatment is often warranted.

Special equipment may be required for treatment of several disorders such as obstructive apnea, the circadian rhythm disorders and bruxism. In these cases, when severe, an acceptance of living with the disorder, however well managed, is often necessary.

Some sleep disorders have been found to compromise glucose metabolism.

## *Sleep medicine*

Due to rapidly increasing knowledge about sleep in the 20th century, including the discovery of REM sleep and sleep apnea, the medical importance of sleep was recognized. The medical community began paying more attention than previously to primary sleep disorders, such as sleep apnea, as well as the role and quality of sleep in other conditions. By the 1970s in the USA, clinics and laboratories devoted to the study of sleep and sleep disorders had been founded, and a need for standards arose.



Pediatric Polysomnography

Sleep Medicine is now a recognized subspecialty within internal medicine, family medicine, pediatrics, otolaryngology, psychiatry and neurology in the United States. Certification in Sleep Medicine shows that the specialist:

"has demonstrated expertise in the diagnosis and management of clinical conditions that occur during sleep, that disturb sleep, or that are affected by disturbances in the wake-sleep cycle. This specialist is skilled in the analysis and interpretation of comprehensive polysomnography, and well-versed in emerging research and management of a sleep laboratory."

Competence in sleep medicine requires an understanding of a myriad of very diverse disorders, many of which present with similar symptoms such as excessive daytime sleepiness, which, in the absence of volitional sleep deprivation, "is almost inevitably caused by an identifiable and treatable sleep disorder", such as sleep apnea, narcolepsy, idiopathic central nervous system (CNS) hypersomnia, Kleine-Levin syndrome, menstrual-related hypersomnia, idiopathic recurrent stupor, or circadian rhythm disturbances. Another common complaint is insomnia, a set of symptoms which can have a great many different causes, physical and mental. Management in the varying situations differs greatly and cannot be undertaken without a correct diagnosis.

Sleep dentistry (bruxism, snoring and sleep apnea), while not recognized as one of the nine dental specialties, qualifies for board-certification by the American Board of Dental Sleep Medicine (ABDSM). The resulting Diplomate status is recognized by the American

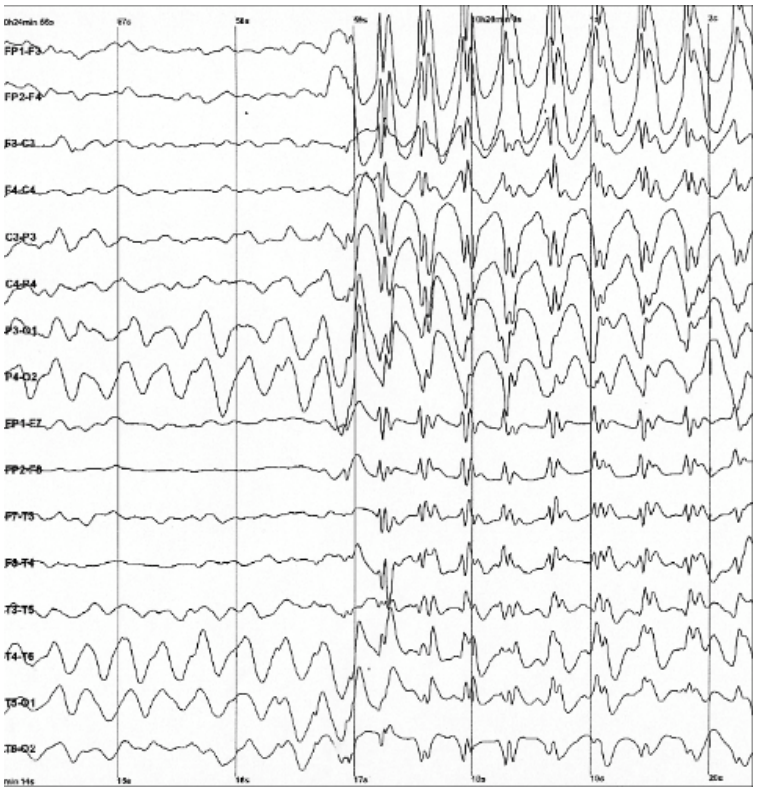
Academy of Sleep Medicine (AASM), and these dentists are organized in the Academy of Dental Sleep Medicine (USA). The qualified dentists collaborate with sleep physicians at accredited sleep centers and can provide oral appliance therapy and upper airway surgery to treat or manage sleep-related breathing disorders.

In the UK, knowledge of sleep medicine and possibilities for diagnosis and treatment seem to lag. Guardian.co.uk quotes the director of the Imperial College Healthcare Sleep Centre: "One problem is that there has been relatively little training in sleep medicine in this country – certainly there is no structured training for sleep physicians." The Imperial College Healthcare site shows attention to obstructive sleep apnea syndrome (OSA) and very few other sleep disorders.

# Chapter 15

# Epilepsy

| Epilepsy |
| --- |




Generalized 3 Hz spike and wave discharges in EEG

| | |
| --- | --- |
| **ICD-10** | G40.-G41. |
| **ICD-9** | 345 |
| **DiseasesDB** | 4366 |
| **MedlinePlus** | 000694 |
| **eMedicine** | neuro/415 |
| **MeSH** | D004827 |

**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, with almost 90% of these people being 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.

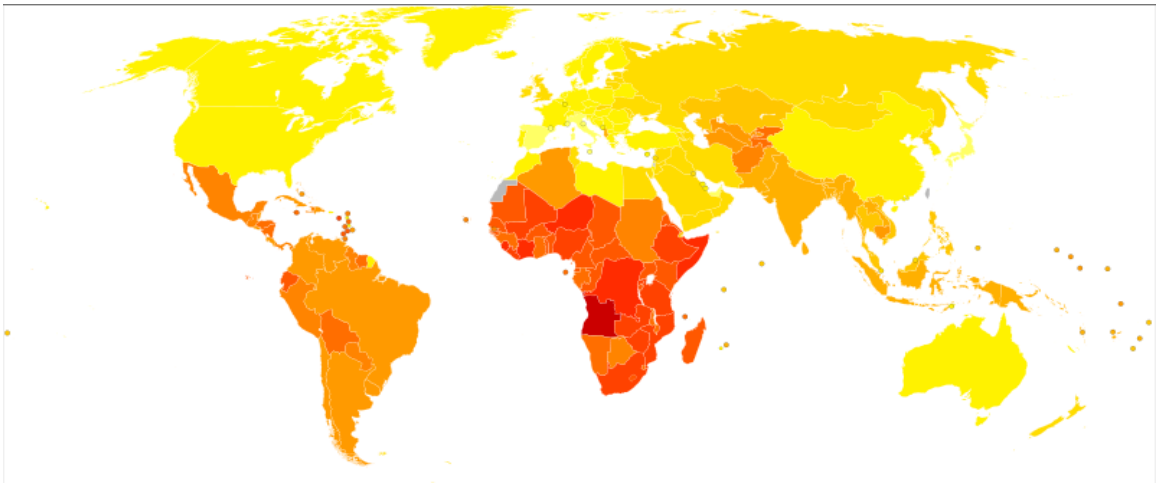
**Avoidance therapy** consists of minimizing or eliminating triggers in patients whose seizures are particularly susceptible to seizure precipitants (see above). For example, sunglasses that counter exposure to particular light wavelengths can improve seizure control in certain photosensitive epilepsies.

**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.
no data
less than 50
50-72.5
72.5-95
95-117.5
117.5-140
140-162.5
162.5-185
185-207.5
207.5-230
230-252.5
252.5-275
more than 275

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.

## *Society and culture*

### Legal implications

Many jurisdictions forbid certain activities to persons suffering from epilepsy. The most commonly prohibited activities involve operation of vehicles or machinery, or other

activities in which continuous vigilance is required. However, there are usually exceptions for those who can prove that they have stabilized their condition. Those few whose seizures do not cause impairment of consciousness, have a lengthy aura preceding impairment of consciousness, or whose seizures only arise from sleep, may be exempt from such restrictions, depending on local laws. There is an ongoing debate in bioethics over *who* should bear the burden of ensuring that an epilepsy patient does not drive a car or fly an airplane.

**Automobiles**

In the U.S., people with epilepsy can drive if their seizures are controlled with treatment and they meet the licensing requirements in their state. The amount of time someone needs to be free of seizures varies in different states, but is most likely to be between three months and a year. The majority of the 50 states place the burden on patients to report their condition to appropriate licensing authorities so that their privileges can be revoked where appropriate. A minority of states place the burden of reporting on the patient's physician. After reporting is carried out, it is usually the driver's licensing agency that decides to revoke or restrict a driver's license.

In the UK, it is the responsibility of the patients to inform the Driver and Vehicle Licensing Agency (DVLA) if they have epilepsy. The DVLA rules are quite complex, but in summary, those that continue to have seizures or who are within 6 months of medication change may have their licence revoked. A person must be seizure free of an 'awake' seizure for 12 months (or had only 'sleep' seizures for 3 years or more) before they can apply for a license. A doctor who becomes aware that a patient with uncontrolled epilepsy is continuing to drive has, after reminding the patient of their responsibility, a duty to break confidentiality and inform the DVLA. The doctor should advise the patient of the disclosure and the reasons why their failure to notify the agency obliged the doctor to act.

**Aircraft**

In many countries, persons with any history of epilepsy are generally disqualified for the medical certifications required for all classes of pilot licenses. In the United States, FAA regulations disqualify applicants for medical certification with a history of epilepsy, although the final decision is made by FAA headquarters, and rare exceptions are sometimes made for persons who have had only an isolated seizure or two in childhood and have remained free of seizures in adulthood without medication.

## Notable cases

Many notable people, past and present, have carried the diagnosis of epilepsy. In many cases, their epilepsy is a footnote to their accomplishments; for some, it played an integral role in their fame. Historical diagnoses of epilepsy are not always certain; there is controversy about what is considered an acceptable amount of evidence in support of such a diagnosis.