

The disease once sacred: A brief history of epilepsy

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All who drink of this remedy recover in a short time, except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases - Galen (2nd century AD)

When King Charles II of England (1630-1684/85) suffered convulsions during his final days, he underwent the best treatments Europe had to offer a monarch: the letting of 24 oz of blood from his arm and shoulder, purgatives to induce vomiting, blistering of the scalp, sneezing powder to relieve the pressure of humors on his brain, cowslip flower powders to strengthen the brain, pigeon dung plastered to the soles of his feet to calm him, an enema made of rock salt and flowers, drinks of barley water, white wine, and absinthe – finally something helpful... along with various medicaments like melon seeds, dissolved pearls, nutmeg, cloves, human skull extracts, powdered stone, and cannonball sweat. Okay, the last was added by me, but this list amounted to the best treatments 17th century medicine had available at its disposal. That the man who restored the English monarchy in his youth was medically tortured the last few days of his life did not escape the notice of dignitaries present during the procedure, including Sir Charles Scarborough, one of a dozen physicians attending the dying king who recorded this list of “treatments” for us. (Crawford, 1909).

Treatments for epilepsy have improved since the days of Charles II and ironically he may have actually suffered from a kidney ailment, as some scholars believe, and it was this ailment that caused seizures. If so, drinking flowers and bone probably didn't help his condition. In other words, if people suffered a serious ailment in the 17th century, they could only hope that no doctors were available for their care.

There are few things associated with EEG as much as epilepsy, a term which encompasses a range of brain breakdowns that manifest by loss or change of consciousness with or without convulsions. We've known about epilepsy since we've known about ourselves; seizures are described in the earliest medical writings we have. In fact few conditions have attracted so much attention and generated so much controversy as epilepsy. The maladies of epilepsy and aphasia were the dysfunctional engine that propelled behavioral and clinical sciences into the modern era.

People have written about seizure disorder and its mysteries for nearly 4,000 years, starting with Assyrian, Akkadian, and Babylonian accounts (Stol, 1993; Eadie, 1995; Magiorkinis et al., 2010). The Code of Hammurabi of the 2nd millenia BC even mentions epilepsy in slave sale contracts, a buyer-beware notice (Stol, 1993). The Babylonians believed all diseases had supernatural causes, as did the Sumerians, whose name for epilepsy was "what has fallen from heaven," a word similar to their word for meteorite. They also called it the "Hand of God" with the god being given an angry adjective such as debilitating, fierce, devouring, or raging. An epilepsy sufferer was said to be struck by the "Hand of the Fierce God," for instance.

Plato added his two cents on the etiology of seizures in *Timaeus*, considering its cause to be a mixture of phlegm and black bile which confused the divine circles of the head – not bad for the 4th century BC. If he had predicted distortion of divine circles of electromagnetism, he could be describing modern-day identification of nonconvulsant seizures with EEG. Aristotle, on the other hand, believed that food in the stomach produced vapors that rose to the head in the veins to cause seizures, relating the body to brain as he tended to do (Eadie & Bladin, 2001).

I am about to discuss the disease called "sacred." It is not, in my opinion, any more divine or more sacred than any other diseases, but has a natural cause Its origin, like that of other diseases, lies in heredity The fact is that the cause of this affection is the brain. My own view is that those who first attributed a sacred character to this malady were like the magicians, purifiers, charlatans, and quacks of our own day. Being at a loss, and having no treatment which would help, they concealed and sheltered themselves behind superstition, and called the disease sacred, in order that their utter ignorance might not be manifest. -- Hippocrates 430 BC

Epilepsy was regarded in ancient times with awe and superstition until Hippocrates revolutionized our understanding and care of diseases with his careful system of observation and treatment. The Hippocratic school separated rational methods from magical and religious practices in a number of texts; nevertheless, the association with demons and spirits remained for hundreds of years (Daras et al., 1994; Riggs & Riggs, 2005). In ancient Rome people suffering from epilepsy were avoided or spat at for fear of contagion (Todman, 2008). Saint Paul of the 1st century writes of this habit, in regard to himself (Landsborough, 1987), and three of the Gospels describe a clear case of seizure considered demonic possession. "Teacher, I brought you my son, who is possessed by a spirit that has robbed him of speech. Whenever it seizes him, it throws him to the ground. He foams at the mouth, gnashes his teeth, and becomes rigid. I asked your disciples to drive the spirit out, but they could not." (Mark 9:14-29, NIV). Jesus resolved the problem but not Paul's. In fact the great Christian missionary of the first century may have himself suffered from temporal lobe epilepsy (TLE).

Were Paul's ecstatic visions, his conversion on the road to Damascus, the "light from heaven" which went off in his head, a product of TLE and temporal lobe disinhibition? It is always difficult to diagnose a patient, especially one who died prior to the invention of the MMPI or MRI, but Paul alludes to his illness in his writings and from this sparse evidence scholars have presumed something about his life and his condition. Paul describes an estatic personal experience in his letter to the Church in Corinth in which he felt "caught up to paradise." He was "caught up to the third heaven. In the body or out of the body? That I do not know... and (here he) heard sacred secrets which no human lips can repeat." A sense of unreality in relation to one's body in space and a dreamy state of auditory hallucinations reminded Landsborough (1987) of his patients' experiences with TLE.

You are all healthy people, but you have no idea what joy that joy is which we epileptics experience the second before a seizure... I do not know whether this joy lasts for seconds or

*hours or months, but believe me, I would not exchange it for all the delights of this world." -
Fyodor Dostoyevsky*

The great Russian novelist of the 19th century, Fyodor Dostoyevsky, likely inherited his condition as both his father and his son had seizures, but he was fortunate in having ecstatic auras which are not typical of most individuals with epilepsy. He incorporated such experiences into his novels, and many of his major characters were epileptic such as Prince Myshkin of *The Idiot*. Like Saint Paul, Fyodor spent much time working on theological issues, as his books can attest to. Many sufferers of TLE are hyperreligious and religious conversion following ecstatic auras is not uncommon (Dewhurst & Beard, 1970; LaPlante, 2000; Trimble & Freeman, 2006; Devinsky & Lai, 2004). Much of Western religious and mystical imagery may be explained as limbic contents temporarily brought to verbal awareness, from William Blake and Dante Alighieri to the Prophets of Judaism. We may never know what exactly transpired on that road to Damascus in the case of Saint Paul, but we do know that it changed the course of human history, transforming a persecuted and poverty-stricken Galilean sect of Judaism into the most dominant force of history. But what interests the applied neuroscientist part of me is that his ecstatic experience clearly would have neurological correlates, which given the right circumstances might be replicated. (Which is not to say that on that dusty road Paul experienced something science can explain, only that we may eventually be able to replicate some of the brain state.)

Of course not all religious figures were epileptic (Paul may not have been) and not all individuals with epilepsy are religious, although TLE patients tend to exhibit hyperreligiosity and hypergraphia (excessive writing) and other attributes helpful in starting followings including a belief in a "greater awareness" they have been exposed to. Joseph Smith, Jr (1805–1844), founder of the Latter Day Saint movement, exhibited signs of seizure (or spiritual rapture) in a famous incident he related to others from the spring of 1820. In the woods of western New York he was seized with some strange power that rendered him speechless and then he saw a light as bright as the sun (Dewhurst & Beard, 1970). He went on to found a religion with millions of adherents. Other well-known religious figures who may have suffered seizures include the Judaic prophet Ezekiel (6th century BC; cf. Altschuler, 2002) who wrote of his fainting spells, speechlessness, and compulsive writing, Emanuel Swedenborg (1688–1772; cf. Foote-Smith & Smith, 1996), numerous saints including Saint Teresa of Ávila and Saint Joan, and possibly even Muhammad, founder of Islam. It may be that TLE, particularly of the right hemisphere, enables an individual to break free of conventional organization of experience and allow individuals to experience the earliest moments of Creation, what Gnostics call the Plemora. Joan D'Arc (1412–1431) often felt that the secrets of the universe were about to be revealed to her, an experience shared by many of the physicists working at the Large Hadron Collider outside of Geneva, where the early universe is being simulated with powerful magnets. Joan said her visions were triggered by ringing church bells, i.e., musicogenic, and like Dostoyevsky she had an ecstatic aura. Musicogenic epilepsy is often triggered by music with emotional significance, and my own mother had a similar experience of visions in response to church music after alpha-theta training

years ago. Joan's voices propelled this teenager onto the world's stage and led the charge in ejecting English rule from French soil. But like many female TLE sufferers of her day, she was tried as a witch, as well as a heretic, and burned at the stake.

Individuals with epilepsy were often considered witches in Medieval Europe. One of the most popular publications of this time was the *Malleus Maleficarum*, published in Germany in 1487, which instructed magistrates on how to identify, interrogate and convict witches, and it included convulsions as a common feature of witches. The de-facto handbook for witch-hunting was published 13 times between 1487 and 1520, and many more times as the Renaissance dawned. Some scholars estimate that more than 200,000 women were murdered in large part because they exhibited the symptoms of epilepsy (Temkin, 1945). The treatment of King Charles' convulsions 200 years later seems tame in comparison

In the Middle Ages, epilepsy was called the "falling sickness" and people looked to saints and relics for cures (Diamantis et al., 2009). Some interpreted epileptic seizures as a transient form of death followed by a resurrection, a Christ-like experience for the lucky or unlucky (Mann, 2009). Religious and magical remedies were the norm for epilepsy, despite the Hippocratic legacy. Theodorus Priscianus (c.380 AD) recommended occult remedies such as amulets alongside more rational remedies including a healthy diet, massage, daily exercise, and bathing. Alexandros of Tralleis (525–605 BC) recommended "the plant peony plucked during the waning of the moon" or to "wash the head of the patient and burn a ram's horn under his nose and he will fall down" or to wear a ring of jasper (Stol, 1993; Eadie & Bladin, 2001). A thousand years and the same remedies were still being suggested by medical authorities. The step-daughter of George Washington, "Patsy" Custis, wore an iron ring to treat her seizures, and she subsequently died from a brief seizure in 1773 (Doherty, 2004). The famed Roman physician Galen thought that the moon governed periods of epileptic fits. He also divided epilepsy into three forms (incorrectly), assuming that seizures could originate in the body and travel up to the brain.

The chief factor in the cure of epilepsy in the young is change, especially that due to growing up, but seasonal change of climate, or change of place or mode of life, are also important. - Hippocrates 430 BC

Galen's medicinal ideas held sway over most of Europe for a millenia. According to Galen epileptogenesis occurred when substances (humors) blocked the lateral ventricles. Caelius Aurelianus, a 5th century physician, added to this the following factors: drinking too much wine, indigestion, compression of the brain, and sudden frights, and he believed it could be transmitted to nursing infants through mother's milk. Arnold of Villanova (14th century) believed that different humors resulted in seizures at difference phases of the moon and the etiology of seizure included "bites of mad dogs or reptiles, or from poisoned, corrupt, and pestiferous air" which filled up of the chief ventricles of the brain. John of Gaddesden (1492) added wind as a moderating influence "such as the South Wind, or the East Wind, and the North Wind when they

follow a South Wind. Also, everything that comes suddenly and quickly heats the head, such as a long stay in the south, or bath, or close to a fire..."

The Renaissance ushered in new ideas about the world and humanity and this included new conceptions of epilepsy. Paracelsus, a pioneer in alchemy/medicinal chemistry, challenged Galenism in the 16th century and he believed that epilepsy was present in all of nature including plants: "Earthquakes and falling sickness have the same causes," he was known to say. English anatomist Thomas Willis (1667) believed that "(e)pilepsy is caused by contractions of the membrances around the brain compressing and constricting its substance and preventing the proper and equable expansion of the (animal) spirits..." -- an explosion of 'animal spirits' in the brain that resembles the internal combustion engine. As the concept of animal spirits died in neuroscience, the role of electricity in epileptogenesis grew, especially after Galvani (1780) demonstrated electrical activation in his frog preparations, until we reach the semblance of modern-day thinking on this topic.

Epileptic convulsions can be understood, as 'the result of experiments made by disease on the brain of man'. (John Hughlings Jackson, 1875).

By the late 1870s the modern era of epilepsy research and treatment had begun with the work of three English neurologists, John Hughlings Jackson, Russell Reynolds, and Sir William Richard Gowers. In 1904 the term "epileptologist" was coined by American William Spratling, a neurologist who specialized in epilepsy (Dasheiff, 1994). However we were not yet free of the stigma of epilepsy despite our modern sensibilities. An ugly chapter of eugenics followed, and 33 states enacted laws that allowed for the sterilization of epileptics, notably those under the care of state institutions (e.g., Virginia Sterilization Act of 1925). Many states also enacted laws that forbade people with epilepsy to marry. Only when Congress passed the Americans with Disabilities Act of 1990 were these laws overturned in toto, but not before 60,000 involuntary sterilizations of American citizens had taken place.

Unfortunately there remains misinformation and misunderstanding about epilepsy and seizure disorders to this day, including the notion of an epileptogenic focus. A third of all patients who undergo surgery for intractable epilepsy continue to have seizures postoperatively (e.g., Kim et al., 2008). Brain areas are removed and the patient is no better off. That the supposed starting point for a seizure is removed and convulsions continue reflects how little we actually do know about epilepsy. It may be that the entire brain runs fast in such cases, making training the best option. As many as 50,000 Americans die each year from seizures and related causes (e.g., drownings, car accidents) and 1 in 10 people will suffer a seizure during their lifetime. The mortality rate is 2 to 3 times higher and the risk of sudden death is 24 times greater than that of the general population, yet research funding lags far behind many other neurological afflictions, with \$35 a patient for epilepsy compared to \$129 for Alzheimer's and \$280 for multiple sclerosis (Meacham, 2009).

Epilepsy reflects a hyperexcitability to brain state changes or transient sensory stimuli due to an inhibitory deficiency in neural regulation. Common seizure triggers include sleep deprivation, stress, drugs or alcohol, menstruation, nutritional deficiencies such as low blood sugar, medications, hyperventilation, photic stimulation (flashing lights or sounds), and sleep transitions (e.g., waking, falling to sleep). We have had descriptions of seizure triggers and symptoms for centuries, in ancient records in clay cuneiform tablets and Egyptian papyrus. Epilepsy was called *bennu* in ancient Babylonia and "*apasmara*" (loss of consciousness) or "*rupa*" in Ayurvedic (Indian) texts (Jain & Tandon, 2004). An ancient medical treatise from China, the The Yellow Emperor's Inner Canon (or Classic of Internal Medicine), included epileptic symptomatology (Scott, 1993). A 4th century account of a generalized tonic-clonic seizure belongs in a modern-day textbook: "After various premonitory signs the patient falls down, stretched out or twisted, and in this condition he remains for some time. After these tonic convulsions he passes into the stage of clonic convulsions and a condition where he appears to be sleeping. The attack is followed by complete amnesia." (Temkin, 1945).

Epilepsy advanced the field of neurology and in no small part produced Western civilization as we know it. Julius Caesar, Socrates, Napoleon, and Saint Paul all suffered seizures from what we can tell. As Tennyson put it, "*All at once, out of the intensity of the consciousness of individuality, the individuality itself seemed to dissolve and fade away into boundless being; and this not a confused state, but the clearest of the clearest, the surest of the surest, the weirdest of the weirdest, utterly beyond words.*" From such moments of clarity may come lifelong motivation to change the world.

The story of the treatment of epilepsy with neurofeedback begins in the 1960s, when Mercury astronauts claimed they saw Polynesian natives waving at them as they flew over the Pacific. In 1967 Gordon Allie, inventor of amphetamine, was contracted to test toxicity of the Mercury capsule rocket fuel with David Fairchild to determine if it caused what were clearly hallucinations on the part of the astronauts, but Gordon died before the contract was over and Fairchild asked his friend M Barry Sterman to help finish the work. At the time Sterman was studying EEG activity in cats and using operant conditioning to see whether brain behavior (i.e., EEG) behaved like motor behavior in terms of acquisition, consolidation, and extinction. The rest of the story is well known in our field: Sterman trained 10 cats to produce SMR (sensorimotor activity) over the motor strip for chicken broth & milk, then Fairchild came knocking at his door and they needed cats to test rocket fuel on. Fifty cats were injected with NASA's rocket fuel monomethylhydrazine (MMH), which resembles gamma-aminobutyric acid (GABA) molecularly and thereby blocks its synthesis in the central nervous system. Without the brain's primary inhibitory neurotransmitter, GABA, the cats' brains were unable to diminish response to stimulation, even mild stimulation such as blowing in the face, so that any stimulation would lead to convulsions (Sterman, personal communication). Of the 50 cats injected with MMH at 100 mg/kg, 10 had undergone SMR training and it happened that these culprits blew the expected toxicity curve. Typically, cats went into a grand mal seizure within

one hour after injection of MMH but those trained to increase SMR in the past showed a different pattern: Seven took significantly longer to seize and 3 did not convulse at all, the seizure thresholds changed in response to EEG training. I suspect that SMR training increased GABA-ergic receptor density in the motor or afferent pathways, thereby dampening sensorimotor excitability and blocking any runaway activity or seizure. These results cannot be explained by placebo (“I shall please” in Latin) as cats didn’t know what to expect nor did the experimenter.

Neurofeedback now has a 40-year history for treating seizures (Sterman et al., 1969; Tan et al., 2009) and this technology and approach (operant conditioning) has since been adapted to treat an astounding array of human frailties including mood and sleep problems, attention and learning difficulties, as well as brain injury and drug abuse. The mysteries of brain function still remain with us 4,000 years into our investigation, but with neurofeedback we’ve added an extremely powerful tool to resolving its disorders.

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