Epilepsy: A way from Herodotus to Hippocrates

Article *in* Epilepsy & Behavior · August 2013

DOI: 10.1016/j.yebeh.2012.04.003

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Epilepsy & Behavior xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Epilepsy, behavior, and art (Epilepsy, Brain, and Mind, part 1)

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ARTICLE INFO

Article history:
Accepted 28 February 2013
Available online xxxx

Keywords:
Epilepsy
Art
Music
Behavior
Mind
Psychiatry
Hallucinations
Cognition
Stress
Crime

ABSTRACT

Epilepsy is both a disease of the brain and the mind. Brain diseases, structural and/or functional, underlie the appearance of epilepsy, but the notion of epilepsy is larger and cannot be reduced exclusively to the brain. We can therefore look at epilepsy from two angles. The first perspective is intrinsic: the etiology and pathophysiology, problems of therapy, impact on the brain networks, and the "mind" aspects of brain functions — cognitive, emotional, and affective. The second perspective is extrinsic: the social interactions of the person with epilepsy, the influence of the surrounding environment, and the influences of epilepsy on society. All these aspects reaching far beyond the pure biological nature of epilepsy have been the topics of two International Congresses of Epilepsy, Brain, and Mind that were held in Prague, Czech Republic, in 2010 and 2012 (the third Congress will be held in Brno, Czech Republic on April 3–5, 2014; www.epilepsy-brain-mind2014.eu). Here, we present the first of two papers with extended summaries of selected presentations of the 2012 Congress that focused on epilepsy, behavior, and art.

1. Introduction

Extended summaries of presentations at the Second International Conference of Epilepsy, Brain, and Mind (Prague, Czech Republic, 2012) that focused on epilepsy, behavior, and art are featured in this paper. This part of the Congress was devoted to humanistic aspects of epilepsy — history, visual art, and music. Hippocrates made one of the most important and evolutionary contributions to the history of medicine by stating that epilepsy is not a sacred disease and by fighting against superstition. The interesting and notable Joseph Wenzel founded the first medical society for research in epilepsy in Mainz in 1802. The 16th-century state-of-the-art in epilepsy treatment could be found in a monastery formula of 1511. According to an analysis of Raphael's The Transfiguration, the picture of the boy

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1525-5050/$ – see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.yebeh.2013.03.011

with epilepsy may be interpreted as prefiguring the Passion of Christ. Further, the interpretation of Epileptic Woman, an extraordinary painting by Bohumil Kubišta (1884–1918), a leading figure of early Czech modernist art, conveyed psychosocial insights that are relevant today. The influence of epilepsy on popular music composers was shown with the example of Neil Perceval Young; Prince and Adam Horovitz are two others who have acknowledged their seizures. There is evidence of the use of epilepsy-based terminology in popular/contemporary music. Some composers/performers have used music as a means of nonverbal expression of the experience of seizures and living with epilepsy, while others use song format as a means of third-person autobiographical expression. Music should be further studied as a potential add-on therapy in the treatment of persons with epilepsy.

Several sessions were devoted to the behavioral aspects of epilepsy. In patients with epilepsy, control of nocturnal seizures is essential for memory. However, other factors, including sleep disorders and possibly particular anticonvulsant drugs, may be important in improving the sleep of patients with epilepsy and thereby improving their learning and memory. When analyzing criminal violent behavior, the presence of aggression during epileptic automatisms should be verified in a videotape-recorded seizure in which ictal epileptiform patterns are also recorded. Because of the paroxysmal character of déjà vu and the possible impact of environmental and molecular factors on hippocampal neurogenesis and excitability, the role of "small seizures" in the genesis of nonpathological déjà vu experiences deserves consideration. Typical aspects of self-induction behavior are an irresistible, compulsive attraction to a (visual) stimulus, frequently associated with pleasure, that interferes with school and social activities. Standardized photic stimulation and long-term video-EEG monitoring can reveal that blinking and slow eye closures precede epileptiform discharges. The recognition of preictal and periictal psychiatric symptoms requires a thorough appreciation of psychiatric phenomena in patients with epilepsy, including insights to guide the interpretation of treatment response. Feeling-of-a-presence refers to the illusion that somebody is close by although nobody actually is. The parietal lobe and the temporo-parietal junction are known to be involved in self-processing, self–other distinction, the integration of multisensory body-related information, and other illusory own-body perceptions. Although the classical clinical picture of forced normalization is that of a psychosis, which can resemble schizophrenia, often a mixed picture is seen, with marked affective components. The answer to the question as to whether neuroimaging can solve the mind–body problem is that the existence of a correlation between mental activities and brain activation does not, and cannot, prove that the two are identical. Questions about stress and epilepsy were also analyzed. Preliminary studies have pointed out the role of sympathetic arousal modulation on the pathophysiology of seizures. Some authors conducted clinical studies on the use of relaxation techniques as a treatment of seizures. Population-based studies provide the best evidence for the association between stressful life events and the development of epilepsy or exacerbation in the number of seizures in persons with established epilepsy.

In sessions devoted to age and developmental factors, it was suggested that early identification of potential sources of epileptogenesis (e.g., focal cortical dysplasia) followed by an appropriate intervention, respecting developmental connectomics, might offer a better prognosis for successful completion of cerebral development and, thus, normal development of the human mind. Certain cognitive skills of aged patients who have undergone temporal lobe resection (TLR) remain significantly impaired compared to those of their age-matched peers, but patterns of strengths and weaknesses of patients with TLR remain stable over time. The rate of age-related memory decline is not greater in people who have undergone surgical treatment of TLE than in the healthy aging population. An older age at the time of TLE surgery did not increase the risk for postsurgical memory decline.

The following extended summaries explore these issues and more in greater detail.

2. Epilepsy, art, and history

2.1. Epilepsy: a way from Herodotus to Hippocrates

Stavros J. Baloyannis

From an etymological point of view, the word "epilepsy" is derived from the Greek verb *epilambanein* (επιλαμβάνειν), meaning to seize or take hold of. Epilepsy therefore means "a condition of getting over, seized, attacked, or possessed". People in the time of Homer had the feeling that seizures were induced by gods, and epilepsy, therefore, might be considered as a sacred disease.

During the Minoan (3500–1700 B.C.) and Mycenaean (1600–1100 B.C.) periods of Greek history, medicine was closely connected to religion, since disease was attributed to gods who had control of human health, life, and death. Alcmaeon of Croton (6th century B.C.) was the first of the Greek physicians who ascertained that the brain was the organ of cognition, the source of memory and thoughts [1], and probably the source of epileptic phenomena [2]. Democritus of Abdera (5th century B.C.) wrote a book on epilepsy (Περί επιληψίας), claiming that the brain houses the soul and that cognition and senses originate from the same force [3].

Herodotus, the "Father of History", was born in Halicarnassus. He traveled to the Mediterranean world as a pilgrim of knowledge and wisdom and described the cultures and the customs of the many people he met, spending many years writing his History, which is recognized as the first textbook of history of the ancient world. In his History [4] (III, 27–29), Herodotus described the case of the Persian king Cambyses, whose great crime was killing Apis the bull god during an epileptic seizure in Egypt. Because of that criminal and sacrilegious act, Cambyses was punished with madness [4] (III, 30) and further committed many other homicides and atrocities, ruining his kingdom and eventually dying from a wound at the same place where he had mortally wounded Apis. Herodotus concluded [4] (III, 33),

> "Such were Cambyses' mad acts to his own household, whether they were done because of Apis or grew from some of the many troubles that are wont to beset men; for indeed he is said to have been afflicted from his birth with that grievous disease which some call "sacred." It is not unlikely then that when his body was grievously afflicted his mind too should be diseased".

Hippocrates, the "Father of Medicine" and the most predominant physician of the classical period of Greek history (480–323 B.C.E.), was born on the island of Cos. He studied medicine under his father Heraclides and traveled to many countries. He created a famous medical school on Cos at around 430 B.C.E. Hippocrates was the first physician who introduced and applied the physical examination of the patient, including observation, palpation, and auscultation. He was above superstition and believed that diseases are natural phenomena provoked by any deviation from health, and he viewed the doctor as "Nature's helper". On epilepsy, Hippocrates wrote [5],

> "I do not believe that the sacred disease is any more divine or sacred than any other disease but, on the contrary, just as other diseases have a nature from which they arise, so this one has a nature and a definite cause. Nevertheless, because it is completely different from other diseases, it has been regarded as a divine visitation by those who, being only human, view it with ignorance and astonishment".

> "This so-called sacred disease is due to the same causes as all other diseases… each disease has its own nature and power and there is

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nothing in any disease which is unintelligible or which is insusceptible to treatment…"

Hippocrates claimed that those cases of epilepsy which come on before puberty may be treatable but those which come on after twenty-five years of age, for the most part, terminate in death. He recognized that there are signs of the onset of a seizure, which only the patient is aware of, and called such a sign the aura. This is the first time that the term "aura" was used in medical literature. In addition, Hippocrates wrote, "Melancholics ordinarily become epileptics, and epileptics, melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy". Hippocrates' postulation that "epileptics become melancholics" reflects current concepts of a relation between depression and epilepsy, since depression is the most frequent psychiatric comorbidity in epilepsy.

Hippocrates observed diseases as they progressed in time and established rules by which the physician would know what to expect and what to do at the right time. Many years later, Galen from Pergamon, c. 130–c. 200 A.D., the most famous physician of the Hellenistic period, combined anatomical knowledge, experimental research, and clinical practice and stated that the tonic–clonic convulsions or spasms (σπασμός) are phenomena of intensive activation or irritation of the brain, sometimes related to obstruction of the ventricles, the pores, and the channels of the brain.

By stating that epilepsy is not a sacred disease and fighting against superstition, Hippocrates made one of the most important and evolutionary contributions to the history of medicine. He outlined the true medical approach, associating it with scientific knowledge, humanism, and medical ethics, recognizing that the relationship between doctor and patient must be dictated by human concepts and by the crucial ethical principle "benefit and do no harm to the patient".

Interested readers are referred to [1–12].

2.2. Epilepsy and the paradigm of death in Christian painting

Michael W. Mann

Sex and death, i.e., the beginning and the end of life, are fundamental themes of human interrogation. Here, I deal with the latter one.

The original fruit of the "tree of knowledge" is not the distinction of good and evil, but the knowledge of our death. The gods are immortal and know it, whereas the animal is mortal and ignores it. Only man is mortal and conscious of it. That worries man, and he has to rely on cultural creation to overcome this intolerable knowledge. This is where epilepsy enters my discussion.

In many different times, places, and cultures, epilepsy is seen as something close to death [13]. The Inca named epilepsy "wind of the dead" or "disease of the dead", the Maya named it "pseudo-death", and the Aztec called medicines against epilepsy "medicine or herb of the dead" and "medicine of those who are dying". In China, Cao (Tsao) Yuan Fang of the Sui Dynasty (610 A.D.) wrote the following about Yang epilepsy, one of the five types of epilepsy: "During the attack, the patient appears as if dead, becomes incontinent, and then recovers spontaneously in a few moments". In Swahili, a native language in Tanganyika, epilepsy is called Kifafa, meaning "half dead and stiff". The Christian scholar of the Middle Ages, Thomas Aquinas, wrote, "those labouring under the falling sickness who are quasi dead…" [14–18].

Clearly, epilepsy was, and still is, related to death in the experiences of patients and their families. Apart from sleep (Hypnos [sleep] in Greek mythology is the younger brother of Thanatos [death]), epilepsy is the major human experience that looks much like death. After the violent convulsions of a tonic–clonic seizure, the person with epilepsy lies motionless, eyelids closed and unresponsive … and then progressively recovers, stands up, and walks, talks, and lives again. How can this be? How can a person, lying without a sign of life, recover from that state? The myth of Hyakinthos, Apollo's friend, reborn in the form of a flower that bears his name [19,20], has been linked to the "renaissance" after an epileptic seizure.

In the Western world, the fate of Christ is a major example. The crucifixion and the subsequent resuscitation of Christ, celebrated as Easter, is the hallmark of Christian tradition, and the fate of the son of God has been linked in painting to the fate of a son suffering with epilepsy (Saint Mark 9.14-29, Saint Matthew 17.14-21, and Saint Luke 9.37-43). The manuscript Laur. VI. 23, kept in the Medicea-Laurenziana library (Florence) [21], and the manuscript Grec. 74, kept in the Bibliothèque Nationale (Paris) [22], both illustrate step by step the verses of the Bible from the four evangelists, hence the biblical story of the epileptic son. In the gospel of the epileptic son, the Bible contains a fairly typical description of a generalized seizure, which is reported by all the evangelists in the same chronological order, following the transfiguration of Christ.

In 1516, Giulio di Medici, the future Pope Clement VII, commissioned a transfiguration from Raphael de Sanzio, but Raphael's genius dared to go beyond by bringing together in one single painting two subsequent verses from the Bible. The relationship between the transfigured son (Christ) and the seized one seems to be the reason for this dramatic innovation. Raphael's painting, "The Transfiguration", exemplifies the evolution from teaching mnemonic to rhetoric function in Christian painting (Fig. 1).

The epileptic boy's body forms the shape of the Greek letter χ (chi) (Fig. 2) which resembles the letter X of our alphabet. The chi

Fig. 1. The Transfiguration, Raphael de Sanzio, Vatican Museum, Rome, Italy.

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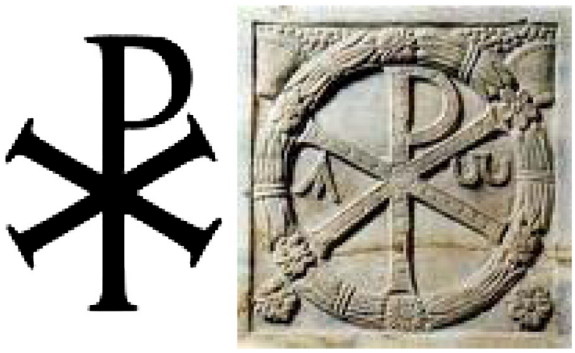

Fig. 2. Two examples of the Greek letters χ (chi) and P (rho) superimposed.

corresponds to the first letter of the name of Christ. Used alone, but especially superimposed over the second letter in Christos, the Greek P (rho), the chi forms a Christogram, the Chrismon (Fig. 2). The chi evokes Christ, thus replacing his image and his name.

The position of Jesus' arms and left foot reproduces the shape of the letter τ (tau), the last letter in the Hebrew alphabet, which was associated with the saving cross in the tradition of Christian symbols. It symbolized death conquered by sacrifice [23].

Nevertheless, Raphael did not paint the Chrismon as such. Dramatizing his painting, he staged the epileptic boy in the shape of a chi cross and Jesus in the shape of a tau cross (Fig. 3) symbolizing their partial identity, as did Pieter Paul Rubens, later, through white color [13].

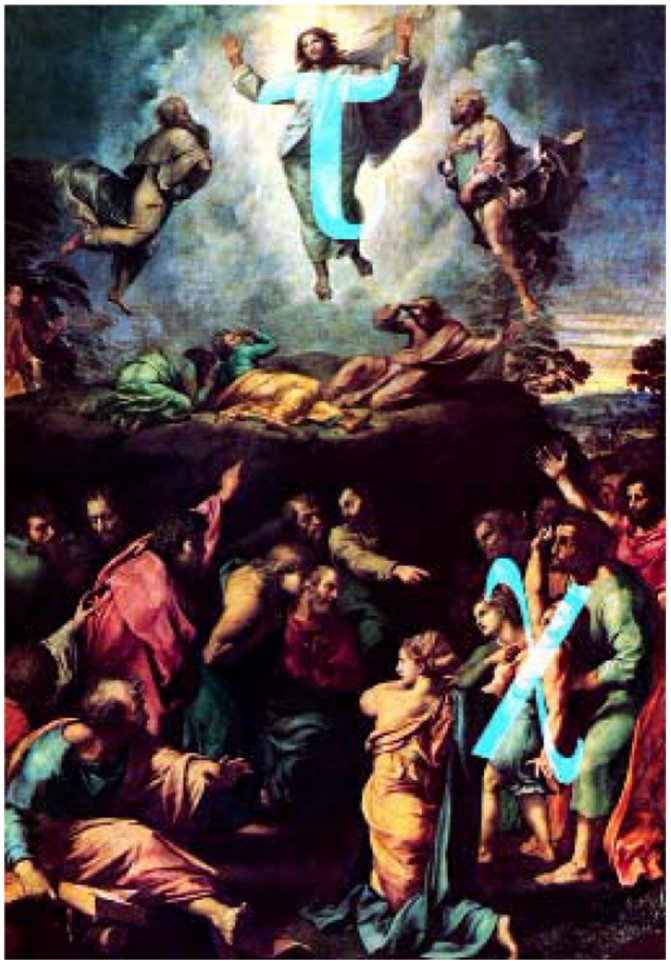

Fig. 3. The Transfiguration, Raphael de Sanzio, Vatican Museum, Rome, Italy. τ and χ superimposed by the author.

The hypothesis emerges that the epileptic son, who implores with his look the son of God, symbolizes the latter's future Passion through his posture, which combines the posture of a motor seizure [24,25] and a chi cross. This pathic identity has yet another dimension, since, as the Bible tells us, the boy will arise after his seizure, as will Christ in the dynamics of his resurrection.

Aside from the medical (epileptic seizure as a transient form of death) and religious (chi cross as a representation of Christ) arguments, data from art history support this interpretation of the epileptic boy prefiguring the Passion of Christ. The art historian Karl Oberhuber reconstructed a sarcophagus, like the one from “The Crowning of Mary” (Fig. 4), an early painting of Raphael, within this strange diagonal which separates the group of the apostles in the lower part of The Transfiguration from the family (Fig. 5) [26]. A person right above a sarcophagus is a person resurrected. Therefore, Jesus, at the very moment of his divine glory of transfiguration, is presented by Raphael as mortal, which means human.

Thus, this Christian painting interprets, in the framework of the biblical story of Jesus, the epileptic seizure as a circle leading to "death" and ressurection. In his last painting, “The Transfiguration”, Raphael brings together the son of God and the “possessed” son

Fig. 4. The Crowning of Mary.

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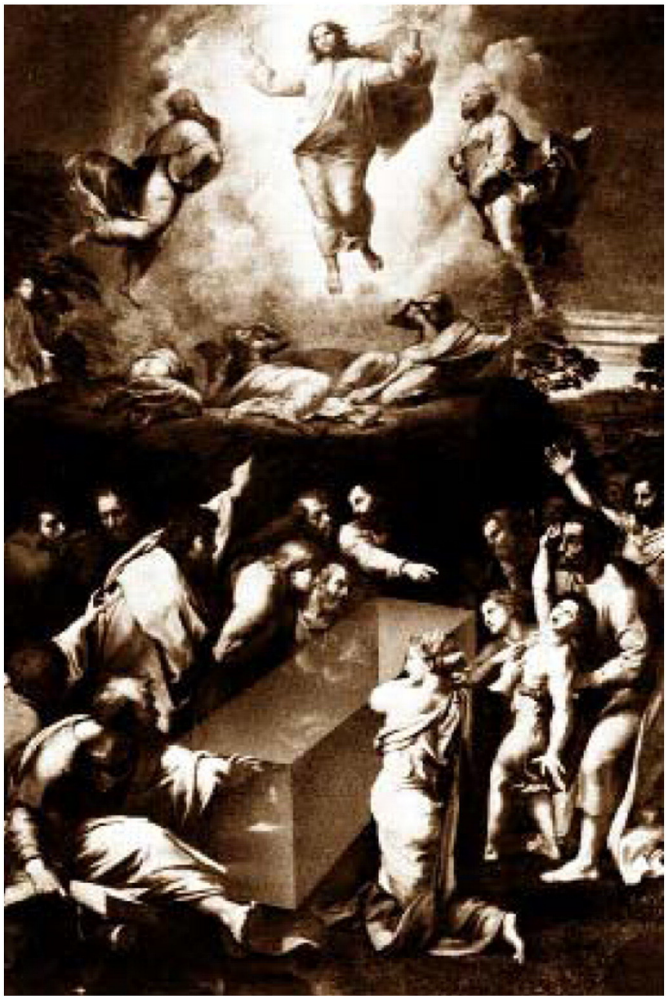

Fig. 5. The Transfiguration, Raphael, interpretation by Karl Oberhuber. Raphael — Vatican Museum, Rome.

with epilepsy, standing up as a bold figure of renaissance. Renaissance and its concept of the individual, expressed through the genius of Raphael, comprise the revolutionary idea of an oscillatory relationship between the son with epilepsy and the son of God.

The disruption of the continuity of life is the hallmark of the epileptic seizure, just as the crucifixion is the hallmark of the life of Christ. The idea of death as the nadir of a movement leading to rebirth is an Indo-European concept which appears in Christian eschatology as the belief in the resurrection of the flesh. Jesus is resurrected three days after his death and exemplifies at Easter this promise to the ones who believe.

Three lines of argument (medical (the epileptic seizure as a transient form of death), religious (the distorted body of the seized boy in the form of a chi cross as a representation of Christ) and art history (reconstruction of the sarcophagus) data) support the interpretation of the two sons linked in a distinct, yet similar fate — the boy with epilepsy prefiguring the Passion of Christ.

2.3. Epilepsy and apoplexy in a monastery formulary of 1511

Gerhard Helmstaedter

The general theme of *Epilepsy and apoplexy in a monastery formula* is here seen through the eyes of the Benedictine monk P. Henricus Breyell, with special emphasis on disease management. His medicinal handbook of 1511 included a directory on diverse ailments, among them cerebral diseases, and gives an idea of what people felt and suffered. What is interesting here is the development of traditional medicine since antiquity, which is a mixture of advice and therapies. Further, one can retrace the medicinal agents, mostly herbal, that were used and the printed sources when available. The knowledge of herbal medicine developed either as the consequence of humeral pathology or as linked with medieval lore.

2.3.1. A monk's manuscript of 1511

In the northern part of Germany near Cologne, the 16th century monk P. Henricus Breyell composed a medicinal textbook at the Benedictine Abbey in Brauweiler in 1511 containing information about herbal medicines, cures, and recipes, with additional sections on distilled waters and medicated wines.

For the reference list and receptarium, the author used his own scheme of ailments, *a capite ad calcem* (from head to toe), cross-referenced to his herbal information by annotating the relevant passage in the herbs (cf. text beginning with *Aristologia rotunda* (smearwort)/14 *Anthos* (rosemary) 5). Furthermore, he added recipes he himself knew. One chapter in his Formulary concerns cerebral ailments, with sections on the severe forms of *epilepsia* and *apoplexia* and the slighter form of *melancholia*. This paper transcribes and comments on the sections dealing with epilepsy and apoplexy.

2.3.2. State of the art in 1500

It can be assumed that the author acquired his medicinal expertise most likely in Cologne, where medicine was one of the founding faculties of the university. In addition, he might have had access to medicinal literature available at around 1500, the pharmaceutical handbooks on drugs, the *Circa instans* for simple drugs, and the *Antidotarium Nicolai* for compound medicines.

While medieval medicine brought new insights into the physiology and topography of the brain, the medical treatment of cerebral diseases and proposed cures were founded in the Hippocratic/Galenic tradition. This assertion is supported by the citations of Aulus Celsus (c. 25 B.C.–c. 50 A.D.), a Roman encyclopedist known for his extant medical work *De Medicina*.

> Ch. 23 That malady which is called comitialis… is one of the best known. The man suddenly falls down and foam issues out of his mouth; after an interval he returns to himself, and actually gets up by himself. And usually it persists even until the day of death without danger to life; nevertheless occasionally, whilst still recent, it is fatal to the man.
>
> Ch 27 Palsy, on the other hand, is a frequent disease, prevalent everywhere. It attacks at times the whole body, at times part of it. Those, whose limbs are seriously paralyzed, are as a rule quickly carried off […].

Similarly, Constantinus Africanus (c. 1010–1087, Monte Casino), says in his *Pan tegni libri* "*Est autem epilepsia apoplexia vicina. Medici vocant epilepsiami apoplexia parva.*" (*Epilepsy is also related to apoplexy. Physicians call epilepsy the minor apoplexy*).

2.3.3. Excerpts from the Monk's Formulary

The 1511 Formulary states "*Was dy vallende sucht verdrivet epilencia genant*". This rubrified headline, "*What banishes the falling sickness, called epilepsy*", emphasizes the term πλῆψία ("attack"). Here, we find a recipe from the treatment devised by Galen, cited in accordance with the later English translation by William Turner in his book *Herball*, printed in London and Cologne in 1568.

> "Peonye Part II fol. 84v "Out of Galene" […] By reason where I would not doubt, but if it be hanged about a child's neck, it would heal in them the falling sickness. I saw once a boy delivered viii months from the falling sickness/by the hanging of the root about his neck: and when as by chance it fell off, he fell into the sickness

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again. And the same after the roots were hanged up again he was well again […]".

But there is no denying the fact that all the mentioned medical measures were of scarce therapeutic use, except as tools of a physician's bedside manner. One can, of course, say that the physicians of the time followed the traditional scientific mindset and were reluctant to leave their patients to the institutions of the medieval church, which saw them as 'possessed individuals'.

[Transcription from the manuscript of Henricus Breyell, written in a low German idiom and completed in 1511 (Ha1 UB Halle, Germany).]

[fol 314v] *Was dy vallende sucht verdrivet epilencia genant*
Aristologia rotunda 14 Anthos 5 Auricula muris, dysser saff mit wyn gesoych is gut 17 Alchimilla synauwe 20 Ambra 30 Betonica 35 Balsamus 43 Coriander 56 Cubebe 72 Ferula 99 Maiorana 122 Peonia 144 Penthaphyllon 154 Verbena 193
Aurum golt. Item gefelt golt is gut genutz in spyse ader gemenget mit eynem electuarium genant anacardinum ad[er] ieralogodium. Ind ouch in wyn genutz is güt.
Syseleos velt kuymel, den gedruncken mit wyn. Ind dar under gemenget langen peyffer is gut epilenticis.
Weder dy vallende sucht, dar XPS [XPIΣTOΣ] uns vur behuyde. Nym smeer wurtzel, yt heystz ouch smyrgel ader smys krut, dat dy lynen wever plegent tzo nemen, yr doech tzo stercken. Nym dye wurtzel van dem krut. Ind schon weyssen broet. Ind snyt das in eyn kanne. Ind guys dar oever guyden wyn. Ind eysse des alle dach nuchteren iij guyde leyffel vol. Ind heyrde dat yt hylft.
[315r] *So wilch kynt, das vallende oevel hait, dem bynt pyonia wurtzel umb den hals, yt vergeyt ym. Galenus spricht, dat eyn kynt van viij jaeren, das vallende hait, ind druge der pyonia wurtzel an dem haltze. Ind dy veyl tzo eynre ave, van stunt veyl dat kynt der suychten halven nyeder. Doe sy weder gebunden wart, doe stunt yt weder up. Doe wolde dat krut beys versuygen, ind bant yt weder ave, doe vil aver dat kynt weder, doe man sy weder bant, doe stundt yd weder up. So wart dy kraft der wurtzelen bekant.*
[313v] *Vur den slach apoplexia genant* […]

Manuscript and sources can be requested from the author.

2.4. Joseph Wenzel and the first medical society for research in epilepsy

Günter Krämer

Joseph (Franz Ignaz Aloysius) Wenzel was born on March 3, 1768 in Mainz, Germany. His father had been a member of the Medical Faculty of the local university since 1759, becoming Associate Professor of Surgery in 1763. In addition, he had been Dean twice. Joseph had seven siblings, only three of whom reached the age of six. He studied philosophy together with his brother Carl (Karl) at the University of Mainz and then showed some interest in theology. Out of curiosity, both attended medical lectures and thereafter opted for medical school, which they attended from 1786 to 1791. One of their teachers as professor of anatomy and physiology was Samuel Thomas von Sömmering (1755–1830), who was the first to describe the 12 pairs of cranial nerves.

After graduation in 1791, Wenzel proceeded with extensive studies abroad (e.g., in Vienna, Zürich, and Pavia), where he prepared the basis for his later works, including neuropathology. He was in favor of a strictly empirical approach ("present only observed facts and not unreasonable ideas"). In 1804, Wenzel became professor of anatomy and physiology at the University of Mainz.

In November 30, 1802, Joseph Wenzel and several other physicians in Mainz founded the so-called private medical society, whose goal was "to collect observations on and to distribute light about the nature and the healing of a disease so far generally known to be incurable, epilepsy…" [27]. The society pioneered clinical trials for the treatment of epilepsy and tried to recruit as many patients as possible: "Every patient with epilepsy in Mainz under the care of members of the society was visited in regular intervals, and if necessary more frequently…. Each seizure was exactly documented in the clinical records of the patients…. Drugs were distributed to the poor patients…. On the account of the society, we just did everything every member and the little group was capable to do" [28].

The agents tested for effectiveness were pure (eau de) cologne, valerian prepared with the spirit of Hofmann, dissolution of ammonia in distilled water, saturated aqueous infusion of valerian, spangle (zinc flowers), and electricity. Because of the frustrating results with all these methods, it "… was decided before new therapeutic trials would be performed … to explore with a lot of diligence, whether or not there is a local defect, or visible destruction of any part of the brain present in this disease which might explain why treatment attempts had been useless or even had exacerbated the disease and increased the seizures" [28].

Between 1804 and 1808, autopsies were performed on 20 patients with epilepsy who had been under the care of members of the society. The observations were compared to a control group of 20 deceased people without epilepsy, which was comprised of Johannes Bückler (1778–1803), called Schinderhannes (the German Robin Hood), captured in 1802 and executed in 1803 together with 19 of his followers with the guillotine. In all the patients with epilepsy, pathological changes in the pituitary gland (swelling and "yellow material" between the atrophic anterior and posterior lobes) were described, and these findings were published in 1810 in a book of 120 pages, posthumously edited by his brother Karl.

Although it is now clear that these findings were most probably postmortem artifacts, the scientific strategy of Joseph Wenzel and his society seems to be an example of a very early rational approach to epilepsy research. For centuries, predominantly extracerebral origins or causes of epilepsy had been described, such as sympathic epilepsy (with origins in the stomach). The theory of spinal epilepsy of C.-E. Brown-Séquard and Marshall Hall was not yet created (first published by M. Hall in 1841) and even in 1859, the Dutch anatomist, physiologist, and psychiatrist Johannes L. C. Schroeder van der Kolk localized the origin of epilepsy in the medulla oblongata. The experiments of the German scientists G. Frisch and E. Hitzig, which led to the recognition of epilepsy as a cortical disease, were not performed prior to 1870. Therefore, the contributions of Wenzel are extraordinary in this historical context.

In addition, Wenzel was self-critical in regard to his findings: "Either the seed which I present here thrives fruit, and then mankind will be grateful, or, after this germ has been destroyed due to more investigations, another idea may sprout which will be welcomed by science. In no case, our efforts will have been in vain" [28].

The following conclusions can be drawn about Joseph Wenzel:

- He was an early pioneer of experimental as well as clinical epileptology.
- In 1802, he founded what appears to be the world's first professional society for epilepsy research in Mainz, Germany.
- He was very critical about his own findings.
- He deserves increased recognition in the history of epileptology.

2.5. Popular music in epilepsy: Neil Perceval Young

Jerome Engel, Jr.

It is said that many famous creative people had epilepsy. Cited examples usually include artists like Van Gogh and writers like Dostoevsky, but composers are not often mentioned. A question has been raised as to whether composers are less likely to have epilepsy than other creative people. There is one contemporary composer of

Please cite this article as: Rektor I, et al, Epilepsy, behavior, and art (Epilepsy, Brain, and Mind, part 1), Epilepsy Behav (2013), http://dx.doi.org/10.1016/j.yebeh.2013.03.011

popular music, Neil Young, whose epilepsy condition is well-known. Neil Young is the cofounder of the band Buffalo Springfield and a member of several other important bands, including Crosby, Stills, Nash & Young, and Crazy Horse. He is widely regarded as one of the most influential songwriters and performers of his generation. His epileptic seizures began in 1966, shortly after he moved to Los Angeles from his native Canada. His seizures were most likely temporal lobe onset with secondarily generalized seizures and were poorly controlled for many years, explaining his erratic behavior when he would occasionally get up and leave the stage in the middle of a performance. At these times, he would commonly have a seizure backstage or in the parking lot. Some of these events are described in his biography [29].

Neil Young has three children: two sons with cerebral palsy, at least one of whom had seizures, and a daughter who also has a diagnosis of epilepsy. His risk factors for epilepsy include polio at age six. He also has type I diabetes and underwent surgery for a cerebral aneurysm in 2005, which was probably unrelated to his epilepsy condition.

Neil Young helped found The Bridge School for children with severe verbal and physical disabilities, which is partially supported by annual benefit concerts. He was inducted into the Rock and Roll Hall of Fame twice, in 1995 and 1997, and received the Order of Canada in 2009. No information is available to assess the possible influence of Neil Young's seizures on his compositions, but a review of his highly prolific body of work suggests very few, if any, songs that might reflect his epilepsy — in contrast to concerns about death before his aneurysm surgery, which stimulated an entire album ("Prairie Wind").

What does this say about popular music and epilepsy? Actually very little; apart from this clearly anecdotal case, it is difficult to survey the landscape of modern popular music to search for evidence of epilepsy. It is impossible to know who is a performer/composer and who is just a performer. Most performers now write at least some of their music. The best composers are actually poets (e.g., Bob Dylan, Paul Simon, the Beatles, rap and hip-hop artists). Consequently, composing music cannot be easily divorced from writing. The modern popular music scene contains many risk factors for brain injury and seizures: alcohol, drugs, and violent behavior. Furthermore, living artists are protective of their reputations, and few would disclose epileptic seizures if they had them, preferring to be considered drug addicts rather than "epileptics." It is, therefore, not possible to know who has epilepsy and even more difficult to know what type. In order to discuss the influence of epilepsy on musical creativity, it is essential to discriminate different types of epilepsy. In any event, most epileptic seizures that occur in pop musicians could result from lifestyle factors and begin too late to influence the formative stages of their musical careers.

The following conclusions can be drawn:

- It is impossible to know what percentage of popular musicians might have epilepsy — Prince, Adam Horovitz and Lil Wayne are three musicians who have acknowledged their seizures.
- It is impossible to comment on the types of seizures, their causes, or their age of onset with respect to the artists' musical careers.
- Most popular musicians are also poets, so analysis of this population would pertain to literature as much as, if not more than, music composition.
- There is no basis, from available data, to comment on the relationship between epilepsy and popular composers and no reason to believe that epilepsy is less prevalent among popular composers than among other creative artists.

2.6. Epilepsy in popular/contemporary music

Guy W. Stoker

At the 2009 Epilepsy, Brain, and Mind conference in Prague, it was observed that while there were papers on the use of visual art, choreography, and literature as nonverbal methods for expressing the experiences of those living with epilepsy, both from the patient's and family's points of view, papers on the use of music as such a chosen medium were noticeably absent.

This prompted me to research this situation for my master's dissertation (Stoker, GW. An investigation into the place of music in the field of epileptic art; University College Falmouth, 2010). I found over 50 examples of musical compositions in which terminology about epilepsy and seizures is either in the title, the lyrics, the artist's name, or a combination of these. There were several examples, such as Epilepsy by 187 (Darkside album), whereby use of the word "seizure" in the lyrics was intended to draw a parallel to orgasm. Likewise, the album covers of the Baphomet and Baphomet II albums featuring Peter Gschwend, with 2 tracks entitled Hosanna and Gobanga, show a graphic image of sexual penetration by a demonic figure, suggesting reference to the belief in earlier times that a seizure was a sign of demonic possession.

On further investigation including conversations and emails with the performers and writers, I found that in many cases, the music or the composer/performer did not have a direct connection to epilepsy. The following, however, are notable exceptions:

- A Danish composer with epilepsy, with the writing/recording name of Son of Mom, whose album The Story of Epilepsy conveys his experiences of seizures and living with epilepsy;
- The singer Jerry King, who took a lighthearted look at epilepsy in his song Epilepsy Betsy, from the Ain't Rocket Science 202 album, making reference to his girlfriend having seizures in the car at a drive-in movie and on the dance floor during the high school dance;
- The Canadian singer/songwriter Jim Armstrong, an artist with epilepsy, who conveyed his experiences through his music, including the song Angel In Our Corner from the Mudtown album;
- The American composer Dr. Cynthia Folio, who wrote a work on the 3 stages of her daughter's seizures (preictal, ictal, and postictal) called When The Spirit Catches You. When asked why this piece lasts for approximately 20 min, she explained that in talking to many people who have gone through a traumatic experience such as seeing their loved one or child having a seizure, they will say that during this event, time slows down or stops, and this is what she is conveying. The music is accompanied by a voice-over from her daughter expressing in her own words what she feels during each stage of a seizure;
- Dr. Kip Haaheim of Kansas State University, who collaborated with the epileptologist Ivan Osorio to create a musical explanatory model of the 3 ictal stages called Epileptic Seizure Metaphor (2009). To achieve this, Dr. Haaheim started with Mozart's Symphony Number 40, partly because of its global recognition, representing the preictal stage. He then manipulated the score by elongating and shortening phrases and adding and removing instrumentation and notation, which send the piece into chaos and dysfunction, clearly indicative of the ictal stage. Then, through a reversal of some of these orchestral and instrumental manipulations, the piece starts to gradually recover its musical form and recognition, indicative of the postictal recovery stage. This is all achieved in the space of under 2 min and is an excellent nonverbal explanation of before, during, and after a seizure, and, as such, has won awards.

Following my research, I composed an album called Ictal Variations Project, which was recorded in 2009–2010 and subsequently created the website www.projectmea.ning.com.

The following conclusions can be drawn:

- There is evidence of the use of epilepsy-based terminology in popular/contemporary music.
- Some composers/performers have used music as a means of nonverbal expression of the experience of seizures and living with epilepsy, with some using song format as a means of third-person or autobiographical expression.

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- Many title or lyrical references to epilepsy or seizures are not connected directly with the experience of the condition.
- There is evidence of the use of music as an explanatory tool for the stages of an epileptic seizure.

The interested reader may wish to explore the following.

1 Armstrong, J. (2007) 'Angel In Our Corner' (Mudtown) [CD] Toronto: Sonic Deli Records
2 Folio, C. (2004) 'When The Spirit Catches You' (Press Play) [CD] New Jersey: Meyer Records
3 Gschwend, P. (1997) 'Gobanga' (Baphomet II: The Unanswered Questions, The 7 Seals of Baphomet) [CD] Alpheric 666
4 Gschwend, P. (1997) 'Hosannah' (Baphomet) [CD] Alpheric 666
5 Haaheim, K. (2009) 'Epileptic Seizure Metaphor' [mp3] Kansas: Kansas State University
6 King, J. (2006) 'Epilepsy Betsy' (Ain't Rocket Science 202) [mp3] Berkley Springs: Wild Hare Records
7 Son of Mom (2009) 'The Story of Epilepsy' [mp3] Belgium: J. Cloesen
8 Stoker, G. W. (2010) 'An investigation into the place of music in the field of epileptic art' University College Falmouth
9 187 (1995) 'Epilepsy' [mp3] Babenhausen: Black October Records

2.7. Music in the brain and epilepsy

Ivan Rektor

Music is thought to have evolutionary adaptive value as a reward system, fostering interpersonal attachment and cooperative behaviors within social groups. Most people believe that music is a universal human attribute and that it has a neurobiological basis [30].

According to the late eminent American composer and conductor, Leonard Bernstein, an analogy can be drawn between Chomsky's innate grammatical competence and the innate musical–grammatical competence we all possess (cited by [30]). Music operates on abstract representations of sounds. A PET-based model assumes that music and language show parallel combinatorial generativity for complex sound structures (phonology) but distinctly different informational content (semantics) [31]. Functional magnetic resonance imaging and PET studies display a considerable overlap of the regions implicated in the perception of music and the areas involved in perceiving, memorizing, and producing abstract sequences as well as language and syntax [32]. It may be that when the brain processes music, organization comes first and sound only follows [33]. As evaluated with fMRI, jazz improvisation is characterized by the widespread deactivation of lateral portions of the prefrontal cortex together with focal activation of the medial prefrontal cortex. This unique pattern may be intrinsic to the creative process [34]. Musical stimuli heard without a conscious goal elicit strongly positive feelings and limbic activations. Esthetic responses reflect its rewarding or aversive properties. It was suggested that there is a direct route for such esthetic responses, one that may serve as the initial basis for our preferences [35].

Music is an abstract stimulus that can arouse feelings of euphoria and craving. Intense pleasure in response to music can lead to dopamine release in the striatal system. In one study, the caudate was more involved during the anticipation and the nucleus accumbens was more involved during the experience of peak emotional responses to music. These results help to explain why music has such high value across all human societies [36].

Listening to Mozart's Sonata for Two Pianos in D major, K.448 produces significant short-term enhancement of spatial–temporal reasoning, a phenomenon called the "Mozart effect" [37]. Mozart's music, by activating task-relevant brain areas, enhances the learning of spatial–temporal rotation tasks [37]. Right frontal and left temporal–parietal coherent activity was induced by listening to Mozart [38]. Functional magnetic resonance imaging showed significant differences in the activation by this Mozart sonata (in comparison to Beethoven's "Für Elise") in the dorsolateral prefrontal cortex, occipital cortex, and cerebellum (all important for spatial–temporal reasoning) [32].

Further, a beneficial influence of Mozart's music on epileptiform activity in patients with seizures has been reported. Frequencies of discharges in EEG recorded before, during, and after exposure to Mozart's Sonata for Two Pianos in D major, K.448 were counted. It was shown that the effect depended on the number of times that a given note sequence appeared within the entire score and the repetition of a melodic interval (the same tonal distance, rather than the exact same notes). Assuming that this characteristic may also account for seizure reduction, values for the two characteristics of long-lasting periodicity and repetition of the melodic line may be taken together. Mozart's music scored significantly higher in the repetition of melody than selections from five other composers (J. S. Bach, Wagner, Beethoven, Chopin, and Liszt) [39,40]. Long-term listening to Mozart K.448 may be effective in decreasing epileptiform discharges in children with epilepsy in a chronologically progressive manner [41,42]. Epileptiform discharges significantly decreased after listening to Mozart K.448 for 1, 2, and 6 months.

The ratio of lower to higher harmonics may also play a role in the effect of the Mozart K.448 on epileptiform discharges. In one study [43], interictal discharges were reduced in most patients as they listened to the Mozart sonata played on two pianos. A week later, the testing was repeated, using a digitally computerized string version (string K.448), in patients whose epileptiform discharges had responded to the version played on a piano. Although the string K.448 had a larger number of higher harmonics in the spectrogram analysis, the discharges were not at all reduced when patients listened to this music. It was suggested that more fundamental tones and fewer higher harmonics may reduce the number of epileptiform discharges.

We conclude that music should be further studied as a potential add-on therapy in the treatment of persons with epilepsy.

The study was supported by CEITEC - Central European Institute of Technology, CZ.1.05/1.1.00/02.0068).

Fig. 6. *Epileptic Woman*, by Bohumil Kubišta.

Please cite this article as: Rektor I, et al, Epilepsy, behavior, and art (Epilepsy, Brain, and Mind, part 1), Epilepsy Behav (2013), http://dx.doi.org/10.1016/j.yebeh.2013.03.011

2.8. Looking at *Epileptic Woman*

Ladislav Kesner

Epileptic Woman (1911) (Fig. 6) is an extraordinary painting by Bohumil Kubišta (1884–1918), a leading figure of early Czech modernist art, whose artistic achievements are now being recognized as equal to those of his more famous contemporaries such as Egon Schiele, Oskar Kokoschka, or Richard Gerstl. Kubišta was one of several major Central European artists who, at around 1910, sought to capture emotional and mental states and psychopathologies — both their own and those of other people. His portraits and self-portraits from this period suggest that the problem of painterly rendering of emotional and mental states and personal identity was a centerpiece of his artistic intention.

Epileptic Woman reportedly depicts a spirit medium whom Kubišta met at a spiritistic seance. Kubišta's friend and artistic soulmate, another important Czech modernist painter named Jan Zrzavý, who accidently may have been present at the very same event, memorably characterized this painting three decades after Kubišta's premature death: "Epileptic woman, with eyes heavy with faintness and grief, with a face withered and despondent by debilitating fatigue and illness! And yet, there is so much humility in her image, a saintliness radiates from this picture, which is a prayer of sympathy over the misery of a lost human life" [44].

Although this painting has generated many commentaries over the years, it is still pertinent to ask: what is to be seen in it? And how does it perhaps contribute to the understanding of the phenomenon of epilepsy? To begin with, there is the possibility of seeing the painting with the diagnostic eye. It has been suggested that *Epileptic Woman* captures the moment of an epileptic seizure (Ivan Rektor, personal communication). Extending this essentially clinical gaze, based on mimetic reading of the painting as a record of an event, one might go a step further and argue that what is depicted is an epileptic aura. The woman's face seems to radiate that moment of "strangeness overcoming consciousness" which has been recognized as a hallmark of the epileptic aura [45].

But this is certainly not the whole story and probably not even the main part of Kubišta's artistic intention. More is at stake.

A viewer's response to a picture is powerfully conditioned by the innate capacity of mind-reading or theory of mind. In making sense of *Epileptic Woman*, most viewers will inevitably engage in inferring mental state from the formal configuration of the woman's facial expression. The protocubist, crystal-like fractures suggest deep wrinkles, deeply set eyes, and sagging corners of the mouth, thus for many viewers turning the face into a picture of mind tormented by devastating illness. Previous comments indeed testify to such implicit understanding, based on theory of mind. We have already seen Jan Zrzavý's comments; in a similar vein another early commentator, František Kubišta (the painter's uncle), wrote in 1940: "The spirit of epileptic woman is symbolized by chiaroscuro, which emphasizes emaciated features of the face, so that suffering and mental lethargy prompted by unbearable fate comes through" [46]. Similarly, the leading Czech art critic Miroslav Lamač wrote that Kubišta intended to depict "a disrupted psyche of epileptic woman" [47].

But the power of mind-reading notwithstanding, I would once again suggest that Kubišta's intention was not simply, or at least not only, to depict misery and grief and to portray the epileptic mind as suffering, lethargic, and disrupted. There are indeed clues that his intention may have been just the opposite, namely, to suggest spiritual power. Earlier commentators of the painting have noted its symbolic dimensions. There is an expressive effect of depressively monochromatic color and spectral yellowish-green radiation; the association of yellow color with light and eternity could best symbolize the "sacred illness" [48]. Again, according to Zrzavý's reminiscences, Kubišta revealed to him that the color in his paintings of the period "…is to have purely spiritual effects, a role to symbolise mental state of beings depicted…".

Of equal importance is the formal construction of the painting. *Epileptic Woman* belongs to a group of several portraits in which Kubišta rendered psychically intense states, using an expressive modification of cubist structure. In several important paintings done between 1908 and 1913, he was preoccupied with creating a visual metaphor of what he conceived as the spiritual force of human beings. In his own theoretical texts, Kubišta coined a concept of "transcendental form", which is geometric and has symbolic functions, intimating that "motions of the mind regulate this form". Such transcendental form is made visible in several of his paintings of this period, most notably in *St. Sebastian* (1912), considered to be his own spiritual self-portraiture, as well as in *Epileptic Woman*. Kubišta used protocubist deformations and linear fracturing of geometric planes of the head in order to reinforce concentration on the head as a locus of the spirit/intellect. The emphasis on the head allowed him to visualize the sitter's spirit conveyed through transcendental forms [49]. Moreover, the hexagon itself on which the composition is based has a symbolic connotation of spiritual potency. This link is further enhanced by the concave cut on the forehead, as if some force deformed the head by the blow of a hammer, as seen in several other paintings of this time (*Double*, *St. Sebastian*), which evokes a wound or stigma and – by extension – exceptionality of the spirit. At the time Kubišta was painting *Epileptic Woman*, the connection between epileptic seizures and spirituality was well established, and Kubišta himself was aware of the culturally sanctified view that considered epilepsy a sacred illness — he knew, for example, Dostoyevsky's musing on the subject.

In the figure of the epileptic woman – whom he very well may have met and observed during a seizure – Kubišta found an embodiment and manifestation of his concept of exceptional spiritual power. Conversely, one can say that he experienced a woman with an epileptic seizure through the prism of his conception of spiritual potency. His painting is a powerful artistic reinforcement of the link between epileptic consciousness and spirituality, which has been confirmed by contemporary research [50].

Kubišta's achievement in this work – a testimony to his artistic greatness – can be seen in the way he managed to convey simultaneously, within one image, a sympathetic and empathetic portrait of psychic trauma and suffering and, at the same time, a portrait of mind not destroyed by its illness, challenging the viewer not to be reduced to an objective clinical gaze or pity. It is most interesting to observe this achievement in light of contemporary scientific views, which argue against any sharply defined "epileptic personality" and stress the multidimensional nature of mental experiential phenomena, or ictal consciousness, occurring during an epileptic aura [51]. Indeed, it seems to me that Kubišta's painting is a powerful visual metaphor of ictal experience or ictal consciousness. In this painting, Kubišta succeeded in making visible the person suffering from epilepsy while in no way being reduced to it. He shows us the distance, mentioned by Raymond Tallis [52], between epilepsy as a brain condition and the human being struggling with it; in other words, the gap between the brain and the mind.

3. Epilepsy and behavior

3.1. Impact of seizures on sleep and memory

Carl Bazil

The purpose of sleep is not just to ward off drowsiness nor is it only to allow the brain to rest. The brain is very active during sleep, particularly with regard to memory and procedural learning. Although the exact processes involved are not known, sleep – particularly slow-wave sleep – appears to be critical for learning. This has implications for optimal cognitive functioning in healthy people but has particular relevance in persons with neurological diseases, particularly epilepsy, where learning may already be impaired.

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Memory dysfunction is one of the most prevalent complaints in patients with epilepsy; however, physicians rarely consider sleep and sleep deprivation as potential contributors to the problem. Understanding the potential influences of sleep on learning can help physicians to address the concerns of patients who report cognitive problems.

3.1.1. Effects of seizures on sleep

Even a brief seizure is known to cause significant sleep disruption. Studies of patients in an epilepsy monitoring unit show that complex partial seizures, even brief ones, cause reductions in sleep efficiency, slow-wave sleep, and particularly REM sleep. This is especially significant if a seizure occurs early in the sleep period [53]. Other epileptic conditions have an even more profound impact on sleep, including the Landau–Kleffner syndrome and electrical status epilepticus in sleep.

The impact of interictal epileptiform discharges on sleep is less clear; however, it is suspected that very frequent discharges may also affect sleep. Therefore, it is likely that if sleep is required for learning, seizures and potentially interictal discharges may indirectly disrupt learning by interfering with sleep.

3.1.2. Sleep and learning

There is not one type of memory nor is there a single process that accounts for the many aspects of what we call memory and learning. Depending on the direct nature of learning, there are different neurological systems involved. Short-term memory occurs over the course of seconds to minutes, and sleep is clearly not involved or required for this. Long-term memory may be either explicit (conscious recall of either facts or events) or implicit (memory for procedural skills). Either may be influenced by attention, motivation, mood, and sleep. These are, of course, not independent; for example, lack of sleep clearly affects attention, sometimes making study of this area complicated.

Motor learning has been studied in healthy subjects in relation to sleep, with results strongly suggesting that motor learning requires sleep [54]. Healthy subjects were taught a sequential finger tapping task (somewhat analogous to playing a musical instrument). Both the accuracy and number of correct sequences were evaluated. Subjects were tested at 12 and 24 h after learning and were evaluated such that they may have slept in the first 12 h after training or the second 12-hour period. More learning was evident when subjects were tested after the sleep period compared to when subjects remained awake, regardless of whether sleep occurred early or late. No improvement occurred when 12 h of wakefulness elapsed between learning and retesting, suggesting that the improvement was specifically due to sleep and not to elapsed time. This improvement seemed to specifically correlate with the last quarter of sleep, suggesting that a full night's sleep is optimal for motor learning.

Some types of learning may be particularly associated with slow-wave sleep. In an interesting experiment, Rasch et al. [55] used the scent of a rose as a cue during sleep. They used a card-pair task in which subjects needed to learn where each card presented had a pair in an array of cards. There were four testing paradigms: presentation of the scent during learning, then again during slow-wave sleep; presentation of scent during slow-wave sleep only; presentation of scent during learning and during REM sleep; and presentation of scent during learning and during wakefulness. There was also a control group where vehicle, rather than scent, was used in each condition. Learning was only enhanced if and only if the same scent was used during learning and during slow-wave sleep. Other studies show that a motor learning task is associated with focal enhancement of slow-wave sleep and that learning is directly associated with increased slow-wave sleep (and does not occur during wakefulness) [56].

Sleep deprivation is common and may also affect the ability to learn. In a study of healthy individuals, the ability to learn word pairs was compared when subjects were fully rested and when they were sleep-deprived for 36 h. Learning efficiency in this declarative memory task was decreased by nearly half in those who were sleep-deprived. Word pairs could be neutral, positive, or negative in connotation. Disturbingly, the authors found that it was mainly the recall of positive word pairs that suffered; recall of neutral word pairs suffered less, and recall of negative word pairs was not significantly affected. The study suggests that sleep deprivation may result in selectively recalling negative stimuli [57].

3.1.3. Impact of anticonvulsant drugs

Obviously, anticonvulsant drugs may improve sleep by preventing seizures. It is also possible that some agents have independent properties that either improve or disrupt sleep, thereby indirectly affecting learning. For example, benzodiazepines and barbiturates may reduce sleep latency but are also known to reduce slow-wave and REM sleep. Studies of gabapentin, pregabalin, and tiagabine have shown increased slow-wave sleep [58–60]. Most of these studies have not looked at memory; however, in one study, increased slow-wave sleep appeared to correlate with improved attention in subjects with epilepsy and insomnia [61]. Further study is clearly needed to see whether certain types of learning can be improved with anticonvulsants independent of their effects on seizures and interictal discharges.

3.1.4. Summary

There is growing evidence that quality sleep is required for most, if not all, types of long-term memory consolidation. Most studies to date have studied implicit learning; some of these suggest that slow-wave sleep may be particularly important in memory consolidation. Sleep deprivation has been shown to adversely affect short-term memory and declarative memory tasks (word pairs). In patients with epilepsy, control of nocturnal seizures is essential for memory. However, other factors, including sleep disorders and possibly particular anticonvulsant drugs, may be important in improving the sleep of patients with epilepsy and, thereby, improving their learning and memory.

3.2. Epilepsy and criminality

Ilo E. Leppik

The commonly held belief that persons with epilepsy may be particularly prone to criminality was first proposed by Lombroso in the 19th century. In addition, the epilepsy defense, by which a person who has committed a crime may be found to have “diminished legal responsibility,” has received wide attention in the news media because of some highly publicized cases. One that captured the public imagination was the case of Jack Ruby, the killer of Lee Harvey Oswald, who was implicated in the killing of President John F. Kennedy [62]. The defense asserted that he had carried a pistol into the police station, confronted Lee Harvey Oswald, and shot him at point blank range during an epileptic seizure and that he had no memory of the event.

Because amnesia is a component of a complex partial seizure, clever attorneys and persons accused of a crime saw the epilepsy defense as a useful tactic, and therefore, it became more widely used. In 1979 alone, five cases of murder went to court using this defense [63]. In some cases of murder, juries found the person not guilty of criminal behavior and only short periods of confinement in psychiatric facilities were ordered. In some of these cases, later medical examinations failed to find evidence for epilepsy.

News articles found through an internet search illustrate the variability of verdicts. In Los Angeles, a 35-year-old man with known epilepsy had killed his girlfriend by strangulation. The defense argued, with the support of a prominent epileptologist, that if provoked during a seizure, a person with epilepsy could “carry out simple reactive behaviors”. However, other experts testified that strangulation was too complex an act, and the jury found the man guilty. In Canada, a person with epilepsy murdered a nun in the halfway house in which

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he was a tenant, apparently during a seizure. The court found him "not criminally guilty" because the act occurred in the context of a seizure but sentenced him to live in a secluded home and to follow a strict regimen of taking his medications regularly. In India, a person with epilepsy hurled a stone at a temple priest of an opposing faith, resulting in death. The court found him not guilty of murder because of epilepsy. In Zimbabwe, a woman used an ax to kill a neighbor she accused of having an affair with her boyfriend and secretly buried the body, but the court found her not guilty of murder once they discovered that she had epilepsy.

Increasing concern regarding the misuse of medical evidence in criminal cases led to an International Workshop on Aggression and Epilepsy in 1980 [63]. The panel concurred that aggression may occur in a person with epilepsy in the following circumstances: prodromal irritability may enhance aggressive behaviors, aggression may occur during altered brain function during a seizure, postictal psychosis may be associated with aggressive behavior, and a person with epilepsy may have alterations in limbic activity leading to aggression. Of these states, murder during a seizure is the most interesting condition because the actions are performed during an altered state of mind. To clarify the issue of the epilepsy defense, the panel made the following recommendations [63]:

- The diagnosis of epilepsy in such a person should be established by at least one neurologist with special competence in epilepsy.
- The presence of epileptic automatisms should be documented by history and by closed-circuit television and electroencephalographic biotelemetry.
- The presence of aggression during epileptic automatisms should be verified in a videotape-recorded seizure in which ictal epileptiform patterns are also recorded on the electroencephalogram.
- The aggressive or violent act should be characteristic of the patient's habitual seizures, as elicited in the history.
- A clinical judgment should be made by the neurologist, attesting to the possibility that the act (the alleged crime) was part of a seizure.

A few studies have addressed the issue of criminal behavior in persons with epilepsy. A 35-year population-based study in Sweden used the population registry to examine the association of epilepsy (n = 22,947) and traumatic brain injury (n = 22,914) with convictions for violent crimes. Overall, 973 (4.2%) individuals with epilepsy committed a violent crime, significantly higher than in the control population. However, this association disappeared when individuals with epilepsy were compared to their siblings without epilepsy, suggesting that epilepsy was not associated with increased risk but rather with familial factors [64].

Another approach to addressing the issue of criminality and epilepsy is to determine the prevalence of epilepsy in prison populations. An analysis of seven surveys of 3111 prisoners found the prevalence to be 0.7%, as compared to approximately 1% for men aged 25–35 years in the general population, and, therefore, comparable to the prisoners [65].

Persons with epilepsy face a number of difficulties in society resulting from misunderstanding of the effects of a seizure on the mind while the brain is in the process of a seizure. This prejudice has been reinforced by news media coverage of the rare crimes committed by persons with epilepsy or cases in which attorneys have used the epilepsy defense in an effort to absolve the accused individual of responsibility. Today, extended evaluations of seizures with video-EEG recordings provide much better documentation of what actions are possible during complex partial seizures. It is the consensus of most epileptologists that complex, directed activities with an intended outcome are not possible in the context of ictal behaviors. However, violent aggressive acts with resultant physical injuries are possible during a seizure, especially if the individual is provoked during the seizure. Overall, there is no evidence that a person with epilepsy without other contributing environmental factors is more prone to criminal behavior than the general population. Although the Lombrosian hypothesis enjoyed a great deal of support from the medical community in the past, there is little support for it at the present time [66].

3.3. Unveiling the mystery of déjà vu

Milan Brázdil

Déjà vu is a fascinating and mysterious human experience that is characterized by the recognition of a situation concurrent with the awareness that this recognition is inappropriate. This strange feeling of irrelevant familiarity is a widespread phenomenon occurring both in clinical (mainly in persons with epilepsy) and nonclinical populations. About 60–85% of healthy respondents reported having experienced déjà vu in recent relevant epidemiological studies. By its nature, this phenomenon has attracted the attention of psychologists and neuroscientists for more than a century. Yet despite numerous theories about what nonpathological déjà vu is and what causes it, until now, no ultimate explanation has been generally accepted. On the other hand, clinically oriented modern neuroscience has provided us with a number of tools for studying the brain processes underlying déjà vu.

There is accumulating evidence that a neural network connecting mesiotemporal regions, specifically the hippocampus and entorhinal cortex, is involved in the generation of déjà vu in patients with epilepsy [67]. It can be assumed that functional alteration of limbic-temporal network physiology fundamentally contributes to this illusion of familiarity. If nonpathological déjà vu experiences are qualitatively the same as pathological (e.g., seizure-related) déjà vu phenomena (an idea attributed to Wilder Penfield more than 50 years ago), then different functional modes of the corresponding limbic-temporal network and perhaps even its distinct morphological features should differentiate between healthy subjects with déjà vu experiences (DV) and subjects without them (nonDV). Therefore, we recently investigated potential differences in brain morphology between DV and nonDV healthy subjects [68].

In this study, we used a novel multivariate technique – source-based morphometry (SBM) – which is more sensitive to subtle differences in local gray matter volume (GMV) than previously used univariate parametric methods. One hundred and thirteen healthy subjects underwent high-resolution MRI investigation of the brain and completed the Inventory for Déjà Vu Experiences Assessment (IDEA). Subsequently, subjects were divided into two subgroups according to their answer to the critical question: 'Have you ever had the feeling of having experienced a sensation or situation before in exactly the same way when in fact you are experiencing it for the first time?' All respondents who answered 'yes' were categorized as DV subjects (N = 87), and the respondents who answered 'never' represented nonDV subjects (N = 26).

The statistical analysis of structural MRI data revealed a set of cortical (predominantly mesiotemporal) and subcortical regions in which there was significantly less gray matter volume in DV subjects compared to nonDV subjects. Importantly, gray matter volume within depicted regions significantly decreased with increasing frequency of déjà vu experiences in individuals. Hence, in this study, we demonstrated, for the very first time, a clear structural correlate of nonpathological déjà vu experience.

Interestingly, the set of brain regions with different structural properties in DV and nonDV subjects resembles a pattern of GMV changes seen in subjects with mesial temporal lobe epilepsy (MTLE). In these patients, previous morphometric studies repeatedly disclosed a significant loss of volume in hippocampal as well as extrahippocampal gray matter, including parahippocampal regions, amygdala, entorhinal and perirhinal cortices, lateral temporal neocortex, thalamic and striatal nuclei, cingulate gyrus, insula, and cerebellum. All these structures belong to a clinically relevant limbic-temporal network that seems to play a crucial role in the pathogenesis of MTLE. On the other

Please cite this article as: Rektor I, et al, Epilepsy, behavior, and art (Epilepsy, Brain, and Mind, part 1), Epilepsy Behav (2013), http://dx.doi.org/10.1016/j.yebeh.2013.03.011

hand, the most extensive GMV differences in healthy subjects with and without DV experiences were observed within the hippocampal regions, where the patterns of GMV differences differ between DV subjects and subjects with MTLE. An anterior–posterior volume reduction gradient, known from studies to be associated with MTLE/HS, was not observed in DV subjects; instead, the hippocampus was affected comparably in both its anterior and posterior parts, and the parahippocampal cortex was affected only in the posterior portion of the temporal lobe.

In summary, our results point to similarities in the anatomical structures involved in patients with MTLE and DV subjects. But there remain many questions — in particular, what does a smaller hippocampus infer in DV subjects, and how closely does the physiological basis of nonpathological déjà vu resemble an ictal event? It is known that the hippocampal formation is especially plastic and exceptionally vulnerable not only to the effects of a variety of insults (including seizures, ischemia, and inflammation) but also to the effects of environmental and physiological influences such as early-life psychosocial stress and sleep deprivation. All these factors, especially when occurring early in development, have been repeatedly linked to hippocampal atrophy, alterations of prenatal/postnatal neurogenesis in the dentate gyrus, and neuronal hyperexcitability.

Thus, we can speculate that the negative effects of diverse, and even mild, early-life insults on hippocampal internal structure with dendritic atrophy of CA3 pyramidal neurons and altered postnatal neurogenesis with increasing neuronal excitability in the region are present in DV subjects. Recently a series of experimental in vitro studies of epileptiform discharges showed that CA3 damage results in loss of hippocampal control over the entorhinal cortex. In such a case, some erratic or perhaps physiological spontaneous discharges from the entorhinal cortex might propagate and interact in an abnormal manner through the hippocampal–entorhinal as well as extrahippocampal circuits, giving rise to higher-order erroneous 'cognitive feelings'. Remote volume changes in the insular, lateral temporal, and subcortical regions seen in DV subjects then probably results from altered anatomical connectivity of the altered hippocampal formation.

Given our anatomical findings, the paroxysmal character of déjà vu, and the possible impact of environmental and molecular factors on hippocampal neurogenesis and excitability, the role of "small seizures" in the genesis of nonpathological déjà vu experiences deserves consideration.

3.4. How to detect and diagnose self-induction behavior

Dorothée G. A. Kasteleijn-Nolst Trenité

Although other methods of self-induction of epileptiform discharges and seizures have been described such as hand clapping [69], music [70], cheirogenic movements [70], and touch [71], most (96%) self-induction behavior is noticed in photosensitive patients [71,72]. Nevertheless, self-induction in photosensitive patients is still a relatively rare and intriguing phenomenon. Most patients with reflex epilepsy want to have their seizures suppressed and avoid provocative stimuli, but some patients, surprisingly, make use of their reflex epilepsy and deliberately seek out the provocative stimulus.

The first case history of self-induced seizures by using sunlight was published in 1932 by Radovici [73], describing compulsory blinking in strong sunlight in a 20-year-old mentally retarded man: "rapid myoclonic movements of the eyelids while looking into bright sunlight are the trigger of a tonic–clonic convulsion". Although mentally handicapped patients are mentioned often, by no means do they represent the majority of those who self-induce seizures [72]. Mentally handicapped patients show the self-inducing behavior more bluntly, and it is also more "accepted" as such.

The hallmark of self-induction is abnormal behavior, and parents recognize that their children are "drawn like a magnet" to sunshine, the TV, or striped patterns of high contrast and seem to be in "trance". Stress and tiredness generally increase the frequency of self-induction. This, together with the fact that correction of this behavior is extremely difficult, is quite shocking for parents.

Whether the blinking and hand waving should be considered as part of the seizure itself (eyelid myoclonus with absences) or as the preceding act to evoke epileptiform discharges has been debated up to the present day [74]. The discrimination between the two is easy when the child or adult admits that he evokes the discharges and seizures deliberately for pleasure or relaxation [71,72]. However, many persons feel ashamed to admit this to others [75].

The method of self-induction can be very elaborate, like in the adolescent farmer boy who discovered that he could obtain certain sensations from standing in front of a snow fence when the sun was low and rocking back and forth so as to produce a flicker. He could also run back and forth under trees using the interruption of the sunlight by the branches [76]. Most patients, however, use more convenient methods like eye blinking [72], and a change from hand waving to blinking is often noticed as the child gets older. Interestingly, patients can even change from pattern self-induction to sunlight blinking.

Regardless of their favorite visual stimulus, all such patients are photosensitive and can be diagnosed when a proper photic stimulation methodology is used [77]. Detection of self-induction during an EEG depends largely on the duration of the study, intensity of surrounding light (preferably sunlight), being seated (the eyes can be turned upwards toward the flashing source of light), and especially feeling at ease with the doctors and EEG technicians. When a patient is not feeling observed, the self-induction behavior is more likely to occur. Therefore, observation of the patient during preparation of the EEG or while the patient is walking in the corridor can help as well.

Lack of any complaint about visual stimuli is very typical for these patients, even if they are exceedingly photosensitive in the laboratory. Another characteristic is the apparent resistance of seizures to AEDs, which is usually based on noncompliance.

Many such patients are seen by psychiatrists for treatment of their compulsive disorder. It differs though from most tics in that self-induction has a constant form and occurs only in sunlight or when the patient is exposed to other strong visual stimuli, such as TV or patterns.

In summary, the typical aspect of self-induction behavior is an irresistible, compulsive attraction to a (visual) stimulus frequently associated with pleasure that interferes with school and social activities. Most children have behavioral disturbances that are difficult to manage, especially for the parents. Compliance with AED treatment or other practical measures is generally poor. Standardized photic stimulation and long-term video-EEG monitoring can reveal that blinking and slow eye closures precede epileptiform discharges.

3.5. Preictal psychiatric symptoms

Marco Mula

Patients with epilepsy may experience a number of psychiatric and cognitive symptoms or behavioral manifestations during the period around the ictus. They are obviously unique to patients with epilepsy and are referred to as periictal symptoms [78]. These include symptoms preceding (preictal) or following (postictal) the seizure or occurring as an expression of the seizure activity (ictal).

The practicality of classifying behavioral symptoms according to their temporal relation to seizure occurrence has been recognized for a long time. These phenomena were well-described by Gowers [79] and Jackson [80], but also Kraepelin [81] and Bleuler [82]. However, among all behavioral manifestations, periictal behavioral symptoms still remain the least recognized by clinicians and the least investigated in systematic research studies. Such paucity of data probably reflects the attention of clinicians to manifestations strictly connected to cortical EEG epileptic abnormalities, considering all clinical manifestations occurring during

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an apparently "normal" or nonspecifically abnormal segment of EEG as clinically irrelevant. Consequently, ictal psychopathology has been better defined and described than periictal phenomena. Nonetheless, periictal psychiatric symptoms contribute substantially to disability and distress among people with epilepsy [83].

Preictal psychiatric symptoms usually consist of a cluster of symptoms preceding seizures by a few minutes up to three days. Such symptoms, although not characterized by any detectable surface EEG change, probably represent the expression of underlying epileptic activity. Around one-third of patients with partial seizures report premonitory symptoms, usually before secondary generalized tonic–clonic seizures [84]. Prodromal depression or irritability may occur hours to days before a seizure and is often relieved by the convulsion. Blanchet and Frommer [85] investigated the presence of preictal psychiatric symptoms in 27 consecutive patients who were asked to rate their mood on a daily basis for a period of 1 month. Rating scales identified the presence of dysphoric symptoms, consisting of irritability and mood changes, approximately 3 days before the seizures. These symptoms worsened in severity closer to the time of the seizure and remitted approximately 1 day after the seizure, although in some cases, symptoms persisted for up to 3 days after the seizure. A recently published study pointed out that behavioral changes are the most frequently reported preictal symptoms, being characterized by irritability or decreased tolerance and lasting several hours [86]. Another recent study found that approximately 13% of patients experienced irritability, dysphoria, or depressed mood preceding seizures [87]. Such feelings are almost indistinguishable from interictal ones, apart from duration and close relation with seizure occurrence. It seems, therefore, important for clinicians to inquire about these phenomena because these cannot be detected by rating scales or questionnaires [88].

The relationships between interictal psychopathology and periictal behavioral manifestations are poorly specified. However, emerging evidence clearly suggests that these variables are intimately related, with the majority of supportive data coming from the literature about psychoses of epilepsy. On the one hand, interictal symptoms represent a risk factor for the development of periictal psychiatric symptoms. In fact, a previous personal history or a family history of any psychiatric disorder is associated with the development of a postictal psychotic episode [89]. On the other hand, postictal psychopathology seems to be connected with the development of a chronic psychiatric disorder. It has been estimated that around 13.9% of patients with a history of postictal psychosis may subsequently develop an interictal psychosis [90].

Another interesting issue is that of periictal exacerbation of interictal symptoms. A U.S. study reported exacerbation in the postictal period in 94% of patients and de novo postictal symptoms with different psychopathological features in 83%. Interestingly, the authors pointed out that antidepressant drug treatment did not prevent the development of postictal mood symptoms but was shown to be effective for interictal symptoms [91]. Notably, it has been suggested that antiepileptic drugs with negative psychotropic properties (e.g., barbiturates and benzodiazepines) may yield a trend toward a greater likelihood of developing postictal exacerbation of interictal symptoms [91].

The presented data illustrate the relatively high prevalence of periictal psychiatric symptoms and their very close relationship with interictal symptoms. Without doubt, the recognition of these symptoms requires a thorough appreciation of psychiatric phenomena in patients with epilepsy, including insights to guide the interpretation of treatment response. In fact, failure to identify such conditions has several practical implications in terms of prognosis and therapeutic strategies.

3.6. Presence, self and other

Shahar Arzy

Feeling-of-a-presence (FOP) refers to the illusion that somebody is close by although nobody is around (Fig. 7) [92–99]. This experience

Fig. 7. Illustration of feeling-of-a-presence.
Courtesy: M. Boyer.

is sometimes described by patients with epilepsy or schizophrenia, yet it is frequently experienced by healthy people in solitude or darkness. In both cases, it is mostly a transient experience, which often disappears when the patient tries to ascertain himself that there is "nobody there" by looking toward the felt location of the "presence". Although such people did not see the "presence", they are convinced that it is a "real" presence [92,97].

Presence recently became not only a clinical phenomenon but also an important term in technology and psychology. Indeed, reading a book, seeing a movie, or speaking to somebody over the phone all involve some level of FOP [100]. Virtual reality games, robotics, and video conferences also endeavor to produce a tangible experience of "presence" through putting one's self in the virtual reality as well as of images and characters of the virtual reality in the self's own mind [101].

Case descriptions of FOP (Box 1) show a high affinity between the patient's own self and that of the "presence" [97]. The "presence" is almost always experienced on one side of the patient's body, in the peripersonal space. Some patients may also mention a psychological or physiological affinity to the "presence" or a sharing of actions (echopraxia). Other patients describe that the "presence" assumes the same body position as themselves or shares their physical characteristics such as height or gender. In addition, despite the fact that patients often refer to the presence as an "other", it is often described as a "shadow" or as a "black man" at the brink of vision, which makes it difficult to identify it as "another".

The phenomenon of FOP has been associated with many neurological disturbances, mostly epilepsy [92–94,98,99,102–104], but also migraine [93,105], neoplasm [92,106,107], head injury [108], acute hypoxia, and intoxication [109]. In psychiatry, FOP has been described in patients with schizophrenia [95], depression [108], and organic psychosis [107]. However, it may also present in healthy subjects, especially during long periods of loneliness and exhaustion, periods that may be experienced by mountaineers, explorers, sailors, and castaways [93,102,110].

The appearance of FOP during various neurological and psychiatric conditions, as well as in healthy subjects, hints to a possible hidden role of FOP in the functional self [111]. Such a role may be also related to the dichotomy of FOP as a projection of one's own self (as illustrated by the above-mentioned affinities of the FOP to the experiencer), and on the other hand, its perception by the experiencer as "another person" or a "shadow". This is indeed the case in perceiving other people. While others are perceived as distinguished from one's own self, in the extrapersonal space, having separated bodies and desires, they are simulated by the experiencer by projection of his/her own thoughts about the world. The distinction between self–other is therefore difficult; can one set the distinction between the 'other' as a separate entity and the projection or simulation of his own self? This distinction may also be simulated by the FOP — a projection of one's own body and/or self, which is perceived as another person.

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Box 1

A 32-year-old right-handed woman suffered from epilepsy since the age of 18. The patient described the bizarre sensation of a "shadow" nearby, always to her right and slightly behind her. This sensation repeated approximately 2–3 times a week. Without seeing it, she felt that this "shadow" is black, accompanies her, and always assumes the same position as she does. It was always very close to her own self-location yet distinguished from her own body. She estimated the "shadow's" height to be identical to hers. The shadow did not speak nor move unless she had moved herself. It seemed to always be the same shadow. She reported that "while looking at this shadow I see nothing, yet I am sure he is there". Another hallucination reported by the patient included a face of a person located in front of her. She identified this person to be a male, having the same age and ethnicity as her, as well as similar hair and eye color as hers. Moreover, he spoke to her in a similar manner as she does. He was always located the same distance from her, that is, as close as possible to her own self-location, yet distinguished from her own body. She felt a close affinity to this person who was "mocking her" frequently.

Neurological examination was found to be within normal limits. The neuropsychological examination revealed mild deficits in memory. Interictal EEG showed right temporo-parietal slowing. Magnetic resonance imaging demonstrated mild right ventricular enlargement, and FDG-PET of her brain (Fig. 8) demonstrated marked right temporo-parietal hypometabolism.

The above-mentioned hypothesis is supported by the neuroanatomical basis of FOP. In most patients with circumscribed lesions, FOP has been associated with posterior parietal damage, especially at the temporo-parietal junction [93,97,98,103,106,107,110], though several patients with temporal lobe epilepsy and FOP have been described [92]. Some cases were right-hemispheric predominant [94,102], while others showed left-hemispheric predominance [97,104,106].

The parietal lobe and the temporo-parietal junction are known to be involved in self-processing, self–other distinction, the integration of multisensory body-related information, and other illusory own-body perceptions [112]. In particular, the temporo-parietal junction was found to be involved in theory of mind [113], or the ability to attribute mental states to others [114]. This region was also found to be implicated in self–other distinction [115,116] and in perspective taking, which is a necessary condition for distinguishing self from other [117].

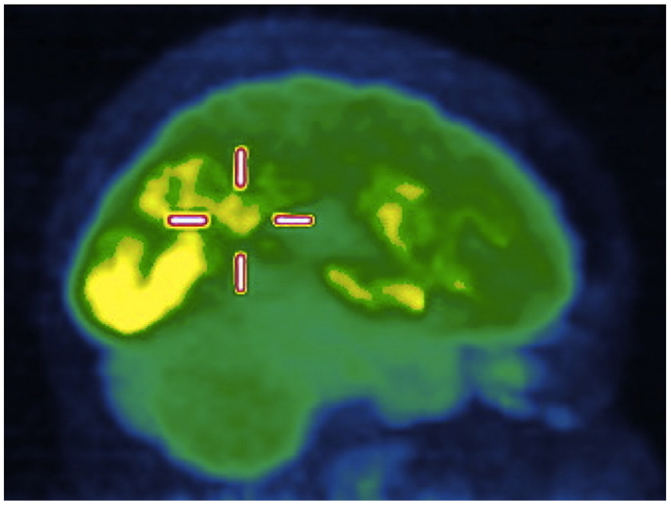

Fig. 8. FDG-PET study showing hypometabolism in the right temporo-parietal junction of a patient with feeling-of-a-presence.

In addition, FOP may be important with respect to its relation to schizophrenia — not only is it found in patients with schizophrenia but the feeling of somebody nearby who does not exist may also resemble schizophrenic symptoms such as paranoia. The implication of own self in FOP may also hint to the relation of own body and self to images of others, hallucinations, and control delusions as seen in schizophrenia [118]. Like in FOP, it may be hypothesized that patients with schizophrenia may refer their thoughts to others, while they were originally directed to their own self. Indeed, neuroimaging studies showed the temporo-parietal junction to be related to the schizophrenia spectrum [119–122].

In conclusion, FOP, found in healthy subject as well as in patients with various neuropsychiatric disorders, combines aspects related to one's own self with the representations of others. As such, FOP may serve as a model for physiological mental activities such as theory of mind, mentalizing others, and self–other distinction. It may also help in understanding pathological conditions of self and other, such as those found along the schizophrenia spectrum or in body image disturbances.

3.7. Antagonism and the concept of forced normalization

Michael Trimble

Classification of the psychiatric comorbidities of epilepsy has often led to conceptual confusions. One way to classify them is in relation to the seizure itself. Ictal (periictal) disorders are directly related to the seizure, while interictal disorders are unrelated in time to the seizure. A third category is of disorders which, due to brain damage or disease, lead to both seizures and psychiatric illness. The concept of forced normalization as a seizure-related disorder refers, in effect, to an interictal disorder but with some features of a postictal disorder. It remained unacknowledged by two generations of neurologists, even though it was recognized in the 19th-century literature and was only rediscovered in the middle of the 20th century. The latter was due to the introduction of the EEG into clinical practice and the ability to record EEGs in patients on a daily basis.

Heinrich Landolt (1917–1951), at the Swiss Epilepsy Centre in Zürich, had the opportunity to carry out serial EEGs on residents, and he was able to record EEG changes in relationship to alteration of their behavior. He obtained EEG recordings during preseizure dysphoric episodes and during limited periods of frank psychosis lasting days or weeks in patients with epilepsy. He noted improvement in EEG activity during such psychotic episodes and referred to this as 'forced normalization' (Forcierte Normalizierung). He defined forced normalization as the following: "Forced normalization is the phenomenon characterized by the fact that, with the recurrence of psychotic states, the EEG becomes more normal, or entirely normal, as compared with previous and subsequent EEG findings" [123].

Forced normalization was thus essentially an EEG phenomenon. Landolt noted that similar changes could be provoked by anticonvulsant drugs, and that at the end of a psychotic episode, the EEG returned to being abnormal. Although initially he discussed this in relation to temporal lobe epilepsy, later he drew attention to its occurrence with generalized epilepsies, in particular the precipitation of psychosis in patients with generalized absence seizures by ethosuximide. Although the psychiatric presentation of forced normalization is generally associated with psychoses, variant forms include prepsychotic dysphorias, and depressive, manic, hypochondriacal, and twilight states [124].

A preferable term, perhaps, is paradoxical normalization, introduced by Wolf. As a general rule in epilepsy, if the behavior deteriorates, so does the EEG. Thus, in nonconvulsive status epilepticus or in

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encephalopathies, the EEG will not only give diagnostic clues but may also be used to trace the progression of the alterations of the mental state. By contrast, in forced normalization, the EEG improves, but the behavior becomes worse.

The clinical counterpart of forced normalization is referred to as alternative psychosis, in which less attention is paid to the EEG and more to the presence or absence of seizures, in association with the psychoses. Thus, one problem in diagnosing forced normalization is often a lack of EEG during the phase of abnormal behavior and available comparisons before and after.

Although the classical clinical picture of forced normalization is that of a psychosis, which can resemble schizophrenia with delusions and hallucinations appearing in a state of unconfused consciousness, often a mixed picture is seen, with marked affective components. Often, it appears as a paranoid or even manic psychosis. In lesser forms, the clinical picture may merely present as an exacerbation or precipitation of previously observed behavioral problems as seizures remit. Thus, the clinical presentation has overlaps with the presentation of postictal behaviors, at which times the EEG can also appear "normalized".

Detection of the psychosis is very difficult in those with a learning disability, and episodes of paranoid aggression mixed with dysphoria may be mistaken for more straightforward behavioral problems unrelated to epilepsy. The disturbed behavior may last days or weeks. It is often terminated by a seizure, and the EEG abnormalities then return.

The importance of forced normalization has again become apparent with the introduction of new generations of AEDs in the past 20 years. Many of these are given to patients with persistent seizures, and some have strong antiseizure properties. Observations of forced normalization have thus been reported with several such agents, including levetiracetam, tiagabine, topiramate, vigabatrin, and zonisamide. It was earlier observed with ethosuximide and can be precipitated by drugs such as benzodiazepines and barbiturates [125,126].

Although many patients with temporal lobe epilepsy become seizure-free after surgery, few develop psychoses, and the forced normalization picture is rarely seen. However, there are cases reported in association with vagus nerve stimulation [127].

The mechanisms underlying the switch from seizures to a floridly abnormal mental state are unclear, yet the observations raise important questions about the biological relevance of seizures and the seizure threshold and the close link between cerebral energetic distributions and underlying neuroanatomical circuitry. Thus, in a brain that has learned to have seizures beginning in certain defined areas of the cortex, the effects of quite suddenly altering the flow of electrochemical forces by the introduction of a compound that alters the local neurochemical environment must be taken into account. There are few intracranial recordings of patients in the transition from one phase of forced normalization to another, so what is happening, for example, at the medial temporal cortex when the clinical picture changes is unknown. It is known that the surface EEG changes, i.e., "normalizes". But it is also known that a "limbic status" can last several days without any expression in the surface EEG, and there is at least one case documented in whom a short-lived psychosis developed with disappearance of the surface EEG changes, following electrical DC polarization of medial temporal structures [128].

The most important thing about forced normalization is to recognize it. Many of those dealing with epilepsy are reluctant to accept that stopping seizures, which must be the main aim of treatments, could, in and of itself, lead to alternative clinical expressions of the underlying neuropathology and neurophysiology that also result in epileptic seizures. Given that medial temporal structures are involved in many cases of intractable epilepsy and in disorders such as schizophrenia and mania, it is hardly surprising that such alternating clinical pictures can be observed. Yet, there is still a hesitation to accept the Landolt phenomenon, especially in the clinical setting.

Assessment requires careful attention to the timing of the mental state changes to drug prescriptions or dosage changes, to the drugs themselves (the ones most implicated but are not exclusively those that are GABAergic), and to the EEGs if they are available. Confirmation of the diagnosis comes with lowering the dose of the AED and allowing seizures to return but hopefully, with a lesser frequency. One factor in the precipitation of these syndromes is a rapid change of seizure frequency. Starting these drugs at a slower pace and increasing slowly is one way to minimize the onset of the psychopathology.

Finally, some patients can be treated with a combination of psychotropic and antiepileptic agents, maintaining their seizure freedom while taking, for example, an antipsychotic or an antidepressant drug. However, the balance with regards to longer-term complications and the monitoring of progress over time requires considerable expertise and understanding of the neuropsychiatric syndromes of epilepsy. As Jan Stevens pointed out many years ago, "All that spikes is not fits" [129].

Recommended reading: Trimble MR, Schmitz B. Forced normalisation and alternative psychoses of epilepsy. Wrightson Biomedical Publishing Ltd, Petersfield, UK. Copies are available from the author.

3.8. Can neuroimaging solve the mind–body problem?

Amos D. Korczyn

The psychophysical problem has haunted neuroscientists, psychologists, and philosophers for centuries, and until recently, it was primarily a domain only for theoretical work. The new technologies which have been introduced into neuroscience, particularly functional magnetic resonance imaging (fMRI), provide a new angle from which to look at this problem and may help to delineate the outstanding issues.

While we all understand what is meant by the brain, the concept of "mind" is more evasive. For the present discussion, the "mind" refers to mental processes which differ qualitatively from the physical body. By contrast, "physical" refers to molecules, cells, organs, and processes, all of which obey the basic laws of physics, whereas "mental" refers to emotions, sensory perceptions, empathy, etc., which do not obey the above laws.

All physiological processes, including those of the brain, such as metabolism, action potentials, and neurotransmitter release and interaction with receptors, function on the basis of physico-chemical rules. They can be recorded and measured and influenced by physical factors. Mental processes are seemingly independent of those rules. There is an onerous correlation between mental processes and physiological activities in the brain. Since the latter can be recorded and measured, they are objective. On the other hand, mental processes are subjective and as such, should be interpreted with caution. Several attempts have been made to correlate mental processes (e.g., anxiety) and objective changes (such as activation of the amygdala). However, as is well known, the existence of a correlation between two variables does not mean that they are the same.

Among philosophers, there is a distinct separation between monists, who believe that mental processes are just a reflection of the underlying physiological processes, and the dualists, who do not accept that, although they too mostly agree that mental processes depend on brain activity. There are many examples of an interaction between mental and physical processes. However, the mechanisms underlying this interaction are obscure. Examples of the interaction include pain, where physical stimuli cause mental suffering, and the placebo effect, where the mere expectation of a change (i.e., a mental process) will induce physical change in the body. Psychosomatic diseases, somatoform disorders, and hypnosis are other examples of how mental activities affect the body.

Please cite this article as: Rektor I, et al, Epilepsy, behavior, and art (Epilepsy, Brain, and Mind, part 1), Epilepsy Behav (2013), http://dx.doi.org/10.1016/j.yebeh.2013.03.011

The ultimate goal of neuroscience is to achieve total understanding of the brain. The relevant question for our discussion is whether such a model, if fully developed into a working robot, will result in something having mental activities, values, emotions, and self-consciousness.

This issue is critical. The question of whether a complete wiring diagram of the human brain can be achieved can probably be answered affirmatively. If it can be done for *Drosophila* and *Aplysia*, there is no theoretical reason why it cannot be achieved for higher creatures, including humans. Thus, while this goal may be science fiction at present, it may potentially materialize in the future.

But even if a model of the brain can be manufactured, the really important issues then only emerge. Would the model be able to think? Or to plan? This of course depends on our definition of thinking or of planning. The same can be said about creativity. A computer can invent certain things. The chess-playing computer does not only retain and play back previously played games stored in its huge memory, it can also "invent" new moves it never played before and outwit human champions. But can it have artistic creativity? Can it write Shakespeare's tragedies or sonnets? Will it have an intuition or develop a sense of guilt? Will it be able to introspect, be self-aware, and have meta-awareness, i.e., be able to know that it is self-aware? And if it does something evil, can it be judged (by its peers, of course) and be punished? What would constitute a proper punishment for such a deed? Temporary disruption of its energy source, perhaps.

New neuroimaging methods, like fMRI and positron-emission tomography (PET), have been exceptionally useful in localizing cerebral functions. In this regard, they supplant and complement previous methods like autopsy. However, the search for localization is based on the unproven assumption that mental processes are necessarily localized. Is it necessary so that higher mental processes, for example, love or introspection, have unique areas of the brain where they reside? This assumption may not be correct. Nonetheless, neuroimaging methods, such as fMRI, can detect the physiological processes underlying mental activities and demonstrate their existence and brain localization. These techniques are widely available, relatively cheap, noninvasive, and can be used repeatedly in healthy individuals as well as in those suffering from brain diseases. However, again, the existence of a correlation between reported mental activities (e.g., anxiety) and brain activation (e.g., in the amygdala) does not, and cannot, prove that the two are identical.

4. Stress, epilepsy, and aging

4.1. Epidemiology of stress and epilepsy

Dale C. Hesdorffer

People with epilepsy often report that stress increases their seizure frequency, although the underlying mechanisms have not been elucidated in human populations. Jackson [130] postulated theoretical pathways through which chronic stress and impaired coping behaviors may influence health. Although developed within the context of health disparities, this model may also be useful for describing how different stressors or psychiatric disorders may influence the occurrence or worsening of seizures (Fig. 9). The occurrence or worsening of seizures can occur through environmental or personal stressors that influence poor health behaviors (i.e., lack of sleep, overeating), which in turn may be associated with chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis, leading directly to the occurrence or worsening of seizures or leading to this outcome via intervening psychiatric disorders.

There is no doubt that stress can cause seizures in individuals. In a case study of a 9-year-old girl with seizures monitored in an epilepsy monitoring unit (EMU), seizures occurred in response to stressful situations involving her mother [131]. During her EMU stay, 95% of her seizures occurred while her mother was by her side, whereas no seizures were experienced when her father stayed with her, though seizures returned when her mother returned.

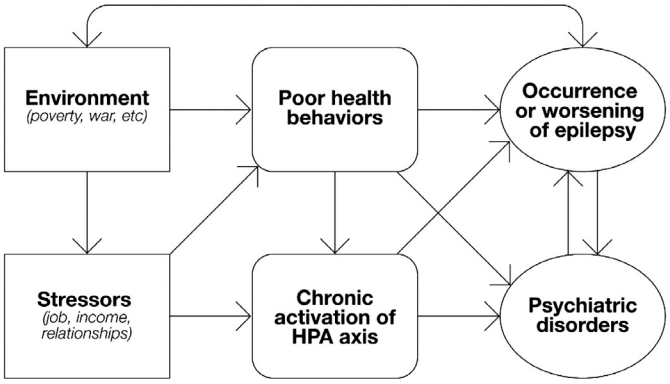

Fig. 9. Theoretical model of environment, stressors, and poor health outcomes in epilepsy. Adapted from [130].

4.1.1. Stressful life events

The question is whether there is an association between markers of stress and epilepsy on a population level. The strongest evidence comes from a population-based Danish study of the risk for new-onset epilepsy in parents who lost a child [132]. In this study of 21,026 parents who had lost a child and 293,745 parents who had not lost a child, there was a 1.5-fold increased odds of developing epilepsy (95% CI: 1.2–1.9) after adjusting for age, gender, education, residence, and number of parents and children in the family. The increased odds of epilepsy was greater in mothers (OR = 2.2; 95% CI: 1.7–2.9) than in fathers (OR = 09; 95% CI: −.7–1.3), although fathers experienced a 1.9-fold increased odds of developing epilepsy in the first three months after the child's death. It is possible that some of these seizures were nonepileptic seizures.

Low socioeconomic status (SES) represents a persistent stressful life event that may lead to the occurrence of seizures or to seizure exacerbation in people with epilepsy. In an Icelandic study [133], low SES (indexed by income) was associated with a 2.8-fold increased odds of developing epilepsy in adults with epilepsy of unknown cause, but the association was not found in children. Similar findings have been seen in southeast England [134], where the lowest SES group had a 2.3-fold increased odds of epilepsy (95% CI: 1.5–3.7) compared to the least deprived after adjusting for age and gender. However, a Swedish study failed to find an association [135].

4.1.2. Anxiety and depression as stressors

Anxiety and depression are associated with an increased risk of developing epilepsy [136,137] even for epilepsy of unknown cause. In a cross-sectional study [138], depression, but not stress or anxiety, predicted time of last seizure before enrollment and change in seizure frequency. Lifetime history of depression is associated with continued seizures after anterior temporal lobectomy, that is, after the putative seizure focus has been removed. Together, these data suggest an underlying biological susceptibility to seizures in association with a lifetime history of depression and of anxiety because these disorders increase the risk for newly diagnosed epilepsy, and they increase the risk for continued seizures after anterior temporal lobectomy [139].

4.1.3. War and natural disasters

War and natural disasters are profound stressors to all those living in the affected areas. Such stressors may have specific effects on people with epilepsy, resulting in increased seizure frequency.

During the Croatian war of 1991–1995, some regions of the country were profoundly affected while others were not. In a study of

Please cite this article as: Rektor I, et al, Epilepsy, behavior, and art (Epilepsy, Brain, and Mind, part 1), Epilepsy Behav (2013), http://dx.doi.org/10.1016/j.yebeh.2013.03.011

outcomes of epilepsy [140], 81 children living in war zones were compared to 63 children not residing in war zones. After 10 years of follow-up, 52 (64.2%) children were followed from the war zone area and 34 (54.0%) in a zone unaffected by war, representing low follow-up rates. Children with epilepsy living in war zones were less likely to have regular check-ups during war (42% vs 94%; $p < 0.01$), and less likely to have stable epilepsy after the war (58% vs 85%; $p < 0.001$), although there was no difference in stable epilepsy before the war (90% vs 94%, ns). The lack of regular check-ups during the war may have influenced postwar seizure outcomes.

Stress and epilepsy were examined during the 1991 Gulf War. In less than a month, 39 missiles landed in 18 separate attacks on Israel, mostly at night. Shortly after the war ended, 100 Israeli patients with prevalent epilepsy from outpatient facilities were interviewed about their seizure frequency in the past and during the missile attacks [141]. An increased seizure frequency was reported after the attacks by people with epilepsy. Seizure frequency increased in 7.2% of those living in the target area, and in 27% with past anxiety, 40% with sleep deprivation, and 22% with severe anxiety during the war compared to none with mild anxiety and 7% with moderate anxiety. However, recall bias may be a consideration when studies enroll patients after a war and ask about information before and after the war.

In a natural disaster in 1995, 250,000 people residing in an area where the Rhine enters the Netherlands were evacuated to escape floods that submerged large tracts of cities. After the flood, evacuated individuals with epilepsy were compared to controls from the same clinics matched by age, average seizure frequency, gender, and type of epilepsy [142]. Evacuees were more likely to report more frequent seizures than controls (27% vs 3%; $p < 0.05$) after the flood, but they were also more likely to report fewer seizures (3% vs 0%; <0.05) and no difference in seizure frequency (80% vs 7%; $p < 0.05$).

4.1.4. Conclusions

Population-based studies provide the best evidence for the association between stressful life events and the development of epilepsy or exacerbation in the number of seizures in persons with established epilepsy. Psychiatric disorders, particularly anxiety and depression, can index stress, and these disorders are associated with an increased risk of developing seizures in population-based studies. They are also associated with increased seizure frequency. Studies, particularly those during war and natural disasters, have usually been affected by small sample size, large attrition, and recall bias, although results have been similar to the population-based data.

That stress can cause seizures in individuals is without doubt as evidenced by the N-of-1 study recounted earlier in which physicians used an elegant challenge–dechallenge–rechallenge approach to elucidate the association. Studies are needed to better understand the mechanism by which stress leads to seizures in human populations.

4.2. Psychological and pharmacological treatments of stress in epilepsy

Marco Mula

In general terms, treatments available for stress-related disorders span a variety of psychological and pharmacological domains when used both separately and in combination with one another. Both approaches appear to be mainstays of treatment, and practical considerations or patient preferences may guide the choice of treatments. The selection of an initial treatment plan may depend largely on whom a patient sees for treatment. A patient presenting to a nonphysician mental health provider is more likely to receive a form of psychotherapy, while presentation to a physician provider could result in either psychotherapy or pharmacological therapy, or both. Subsequently, the selection of specific psychotherapies or specific pharmacological interventions may depend to a large degree on the clinician's training.

Specific psychological interventions that have been studied for the treatment of stress-related disorders include the following: cognitive-behavioral therapy such as cognitive restructuring, cognitive processing therapy, exposure-based therapies, and coping skills therapy (including stress inoculation therapy); psychodynamic therapy; eye movement desensitization and reprocessing (EMDR); interpersonal therapy; group therapy; hypnosis/hypnotherapy; eclectic psychotherapy; and brainwave neurofeedback. These therapies are designed to minimize intrusions, avoidance, and hyperarousal symptoms. Pharmacotherapies, including the use of selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors, other second-generation antidepressants, atypical antipsychotics, anticonvulsants/mood stabilizers, adrenergic agents, benzodiazepines, and other treatments such as naltrexone, cycloserine, and inositol, have also been used [143].

In epilepsy, data regarding treatment of stress-related factors are fairly scanty. Preliminary studies pointed out the role of sympathetic arousal modulation on the pathophysiology of seizures [144,145]. Along the same line, some authors conducted clinical studies on the use of relaxation techniques as a treatment for seizures [146]. Further studies in this area are more than warranted in order to clarify the potential impact of behavioral therapies on seizure control.

4.3. Brain maturation and epilepsy

Vladimír Komárek

Even though prenatal development of cerebral cytoarchitecture plays an important role in the natural development of the human mind, postnatal interactive optimization of cerebral connectomics is the main determinant (Fig. 10).

Structural and functional cortical networks share some of the same characteristics, although their relationship is complex and nonlinear ("Small World Network"). Studies of the human connectome expand our knowledge of network topology and dynamics in the healthy, developing, aging, and diseased brain. Atypical development of structural and functional connectomes is also present in neurodevelopmental disorders associated with epilepsy. Recent studies using models of temporal lobe epilepsy have shown loss of small-world topology in cellular networks during bursting and have shown that variations of small-world topological and synaptic properties of a computational model can cause transitions between normal, bursting, and seizing behaviors [147–149].

A developing brain is intrinsically more prone to epileptic seizures and, vice versa, an epileptic process in an immature brain might lead to an intractable epileptic encephalopathy, such as West syndrome. Epileptic and nonepileptic neurodevelopmental syndromes associated with the hereditary impairment of brain maturation (HIBM) concept, combining genetic and electrographic traits in atypical Rolandic syndromes or in Landau–Kleffner syndrome, represent a relatively benign alternative.

An interaction between the developing cerebral web for speech processing and a dysplasia-associated epileptic process is yet another example. In these patients, functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) tractography provide specific information on the actual development of the dorsal (fasciculus arcuatus) as well as ventral interconnections between speech centers and on their relationship with the epileptogenic zone and/or lesion [150]. In our recent study of children with developmental dysphasia, we found age- and disorder-dependent characteristics of functional as well as structural brain connectomes (Fig. 11).

We suggest that early identification of potential sources of epileptogenesis (e.g., focal cortical dysplasia and/or tubers) followed by an appropriate intervention, respecting developmental connectomics, might offer a better prognosis for successful completion of cerebral development and thus normal development of the human mind.

Please cite this article as: Rektor I, et al, Epilepsy, behavior, and art (Epilepsy, Brain, and Mind, part 1), Epilepsy Behav (2013), http://dx.doi.org/10.1016/j.yebeh.2013.03.011

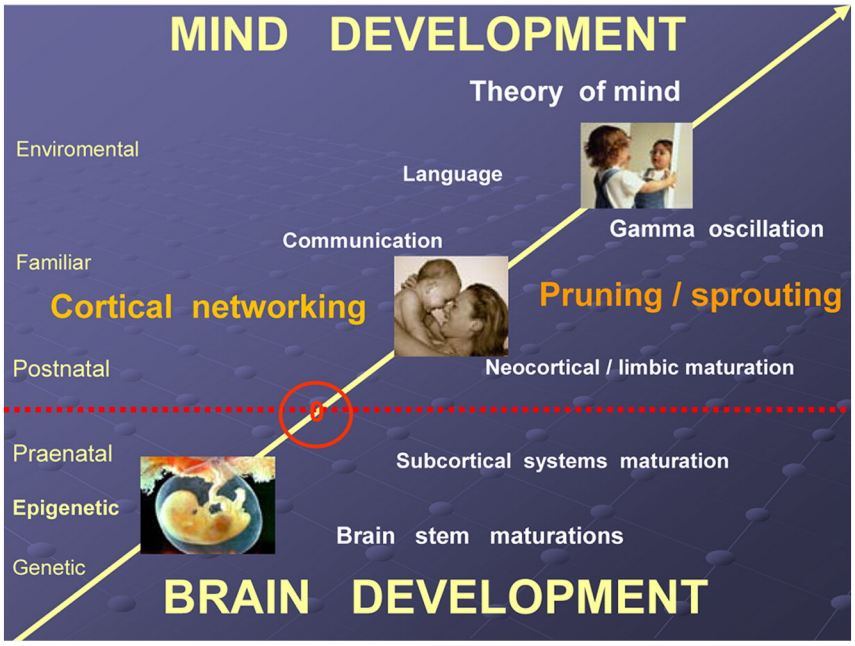

Fig. 10. Schematic illustration of the relationship between development of the mind and the brain.

Another important consideration in deciding the timing for surgery in children is developmental cerebral cortical plasticity. The pediatric brain is capable of significant reorganization of neurological function, including language, after insult and surgery. In most children, developmental cerebral cortical plasticity reduces the anticipated neurological deficits following resective surgery, and these factors are important when evaluating pediatric patients for surgery.

This study is supported in part by IGA MZ ČR grant NT-11443 and by MH CZ – DRO, University Hospital Motol, Prague, Czech Republic 00064203.

4.4. Is the risk of postsurgical memory decline after temporal lobe surgery age dependent?

Ivana Tyrliková, Zuzana Hummelova, Radka Kubiková, Sabina Telecká, Mojmír Tyrlík, Ivan Rektor

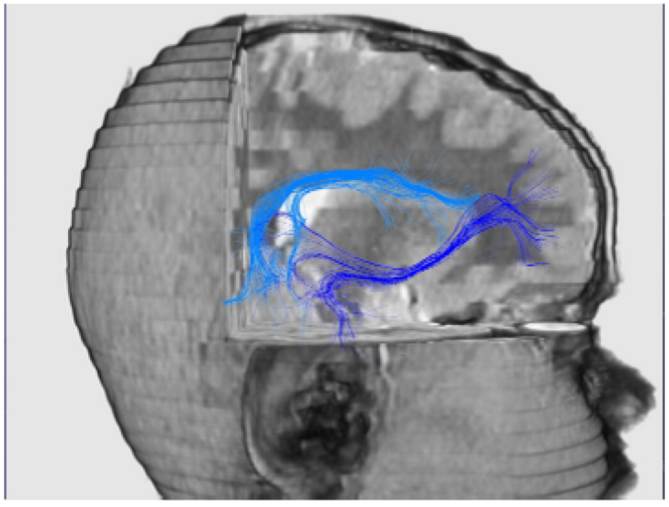

Fig. 11. Image showing connectomes from a study of children with developmental dysphasia.

Temporal lobe surgery is an accepted treatment for pharmacoresistant epilepsy. Most patients undergo surgery during their childhood or early adulthood, but in general, increasing age at surgery is associated with worse seizure outcome as well as more peri- and postoperative complications.

One of the widely discussed risks of temporal lobe surgery is memory decline. The relationship between age at time of surgery and postoperative memory in published studies is ambiguous, however. Therefore, we conducted a long-term follow-up of our sample of patients who underwent TLE surgery. We compared patients less than 30 years old with patients over 45, with respect to impact on memory and its predictors.

4.4.1. Methods and sample

Our sample consisted of 81 patients with pharmacoresistant epilepsy (52 males and 29 females) who underwent temporal lobe surgery in our center from 1999 to 2006. The patients were divided according to age into the following three categories: 30 years old and below ($n = 34$), from 31 to 44 ($n = 16$), and over 45 ($n = 31$).

We utilized the Wechsler Memory Test III to evaluate memory before surgery, and at one year and three years after surgery. Some patients were evaluated again five or ten years after surgery, respectively. We used the last available evaluation in the period of three to ten years after surgery for the analysis of long-term memory.

4.4.2. Results

We found in the long-term follow-up that memory worsened in 41.7% of patients over 45 years old, compared to 55.6% of patients in the middle-age group and 32.4% of patients in the group aged 30 years and below. We also found a significantly higher presurgical memory quotient (MQ) (105.5) in patients whose memory worsened when compared to unchanged patients ($p = 0.002$), regardless of their age category or whether the etiology of their epilepsy was mesial temporal sclerosis (MTS) or not.

When patients with MTS were analyzed separately, the presurgical MQ in the group of patients over the age of 45 was significantly lower (86.6) than in both younger groups (group aged 30 years and below — mean = 97.9; group aged between 30 and 44 — mean = 102.2; $p < 0.001$). The same results were displayed in the postsurgical

evaluations up to 1 year and 3 years after surgery. Analyses at further timepoints could not be performed.

We found a difference between the group of patients with MTS and the group with other causes of TLE with respect to postsurgical memory. Whereas there was no decrease of MQ from pre- to postsurgical evaluation with the MTS group, there was a significant decrease of MQ between the first and third postsurgical years ($p < 0.001$). The pre/post surgical memory change and the change from the first to the third year after surgery were negatively correlated ($p = 0.001$).

Contrary to this, we found a considerable decrease of MQ in both periods in the group of patients without MTS, which, when compared with the MTS group, was statistically significant ($p = 0.038$). We did not find any differences with respect to age groups.

With respect to hemisphere dominance, the memory decline of patients undergoing surgery of the dominant hemisphere did not differ from that of patients with surgery of the nondominant hemisphere. Further, we did not find any differences with age groups. However, we did observe a change when recent and delayed memory scores were analyzed separately. Delayed verbal memory declined and delayed visual memory did not change in patients undergoing surgery in the dominant hemisphere, while delayed verbal memory did not change and delayed visual memory declined in patients undergoing surgery in the nondominant hemisphere ($p = 0.03$).

Finally, the presurgical MQ was independent of presurgical seizure frequency, and the postsurgical MQ did not significantly vary with surgery outcome (Engel classification).

4.4.3. Discussion

A considerable decline of MQ in older patients after TLE surgery is frequently reported in the literature [151], and many studies report a low risk of postsurgical memory decline in patients with MTS [152]. Our results show a stability of MQ in the group of older patients. On the other hand, the MQ data in the younger patients point to heterogeneous outcomes of postsurgical memory decline associated with factors other than whether the etiology is MTS. This finding is in concordance with the study of LoGalbo et al. [153], who found significant verbal memory decline in patients with left-sided MTS and mediocre presurgical MQ. Since a drop of one standard deviation of MQ over 30 years was recorded in patients with epilepsy due to MTS, our older group of patients showed a significantly lower mean MQ when compared to the younger groups.

We found out that the MQ of patients with etiologies other than MTS decreased immediately after surgery, whereas the decrease in MQ in patients with MTS etiology occurred later, between the first and third year after surgery. We further found that this effect is age-independent. The influence of preoperative functional status of temporal structures on the dynamics of postoperative memory decline is widely accepted. The functional integrity of left-sided mesial and cortical temporal structures is especially important for adequate verbal memory functioning. We hypothesize that presurgical damage of these structures in patients with MTS, whose memory is already deficient preoperatively, reduces the possibility of functional compensation by homologous contralateral structures as hypothesized by Helmstaedter and Elger [154]. Later postsurgical memory decline is probably influenced also by subsequent atrophy in tissue which was spared during surgery or a collapse of compensatory processes.

On the other hand, we hypothesize that the drop in memory immediately after surgery probably results from the resection itself in patients with TLE due to etiologies other than MTS, who have less functional impairment of mesial and temporal structures and, therefore, more often have normal presurgical memory.

4.4.4. Conclusion

Our data showed that almost 2/3 of patients after TLE surgery did not suffer from memory decline. An older age at the time of surgery did not increase the risk for postsurgical memory decline. The study

was supported by CEITEC - Central European Institute of Technology, CZ.1.05/1.1.00/02.0068).

4.5. Effects of long-term epilepsy and of temporal lobe resection on cognitive aging

Marilyn Jones-Gotman, Sarah J. Banks

Healthy adults can expect to experience some cognitive decline as they age. People with temporal lobe epilepsy (TLE) demonstrate specific deficits, especially memory deficits, related to their epilepsy, and those who undergo surgical treatment can be expected to show further impairment. We investigated whether the effect of aging on memory is greater in patients with TLE than in healthy individuals, and in particular, we explored how resective surgery for TLE impacts cognition as the patient ages. The study was supported by CEITEC - Central European Institute of Technology, CZ.1.05/1.1.00/02.0068).

4.5.1. Methods

We administered cognitive tests to patients with unilateral TLE who had undergone resection from the epileptogenic temporal lobe at least 20 years prior to the study and who were 55 years old or older. A smaller group of unoperated patients was also studied — they too were 55 years old or older and had been diagnosed with TLE at least 20 years prior to the study. We included a control group of 20 healthy subjects who were matched to the patients on age and years of education. The tests that we administered focused on memory, but we also sampled all major cognitive domains (general intellectual function, attention, language, and executive function). We also included questionnaires concerning independence and quality of life. All patients and control subjects underwent a 3-Tesla structural MRI, allowing us to assess the extent of removal in operated patients and any age-related atrophy.

4.5.2. Results

To date we have tested 45 subjects (9 left-operated, 10 right-operated, 6 left-unoperated, and 20 healthy control subjects). Among those who had undergone operations, one patient with left temporal lobe resection (TLR) and 2 with right-sided TLR continue to have significant seizures. Most continue to take antiepileptic medication, but some are seizure-free and not taking medication. Four of the unoperated patients (all with left TLE) still have seizures and take antiepileptic medication.

Results of cognitive tests show that the left-operated patients differed significantly from the healthy control group on several verbal measures, including word finding and reading and, notably, verbal memory. The left-unoperated group also differed from the healthy control group on word finding and reading and on one of the verbal memory measures; in addition, they differed from the control group on a test of verbal comprehension and word fluency. However, we note that the unoperated group is still very small, so their results may not hold up when the group is larger. The right-operated patients differed from the healthy control group on four measures, all but one of which qualify as nonverbal, and notably, they differed on a measure of nonverbal memory but not on any verbal memory measure. The verbal test on which they performed poorly was reading: all three patient groups differed from the healthy control group on that test.

4.5.3. Conclusions

These results show that the specific deficits related to resection from the left or right temporal lobe continue to exist 20 years or more after surgery. This means that certain cognitive skills of aged patients who have undergone temporal lobe resection remain significantly impaired compared to those of their age-matched peers, but it also means that the patterns of strengths and weaknesses of patients with TLR remain stable over time. The data suggest that the rate of age-related memory

Please cite this article as: Rektor I, et al, Epilepsy, behavior, and art (Epilepsy, Brain, and Mind, part 1), Epilepsy Behav (2013), http://dx.doi.org/10.1016/j.yebeh.2013.03.011

decline is not greater in people who have undergone surgical treatment of TLE than in the healthy aging population; they retain their material-specific deficits, but the magnitude of the difference between these older patients compared to their age-matched controls is not obviously greater than that commonly seen in younger patients and their matched controls. Our group of unoperated patients is very small and consists only of patients with left TLE, but the findings for these few patients suggest that those who have not undergone surgical treatment may show cognitive deficits at least as great as those who were operated.

4.6. The aging brain and epilepsy: what do we know?

Gail L. Risse

Little is known about age-related changes in the brain associated with chronic epileptic seizures. While it is generally accepted that repeated seizures can have a damaging effect on the developing brain, the relationship between normal aging and poorly controlled seizures has not been clearly established. Is the older epileptic brain more vulnerable to an accelerated rate of normal aging, or is it more likely to develop neurodegenerative disease? What is the impact of long-term treatment with antiepileptic drugs or resective surgery on the aging brain? Before these and related questions can be addressed, a basic understanding of brain changes in normal aging is essential. This summary reviews structural and functional changes in the brain associated with normal aging, explores the evidence of cognitive decline in older patients with ongoing seizures, and recommends key areas for future research to determine the impact of epilepsy on the aging brain.

Recent decades have seen a dramatic increase in research dedicated to understanding age-related structural and functional changes in the normal human brain. The development of CT and MRI in the 1970s enabled measurement of brain volume in vivo for the first time, and researchers soon described brain volume loss of both gray and white matter associated with advancing age. After age 60, brain volume may decrease by as much as 5% per year because of both shrinkage of cells and actual cell death. Volume loss is not uniform, with the greatest decreases in gray matter noted in the orbital and inferior frontal cortices, the cingulate gyrus and insular cortex, as well as the inferior parietal and mesial temporal regions [155]. Brain volume is greater in the right hemisphere of healthy adults, and atrophy may occur earlier in men than in women [156].

A logical extension of this research has been the application of these age-related changes to our understanding of neurodegenerative processes that occur in the later decades. It has been reported that disproportionate atrophy in the temporal lobe (TL) has more often been associated with the onset of dementia, and longitudinal decreases in TL volume, including the hippocampus, have been found to be greater among individuals diagnosed with mild cognitive impairment (MCI) [157].

Cognitive decline appears to reflect known patterns of brain atrophy in healthy elderly persons and those with early dementia. Atrophy of prefrontal cortex has been associated with lower scores on executive function measures in healthy elderly subjects [158], while progression of hippocampal atrophy has been shown to correlate with declining mental status in patients diagnosed with MCI and AD [159]. These and other studies have led to the frontal lobe hypothesis of cognitive aging [160], which postulates relatively greater atrophy in the frontal lobes concomitant with a decline in executive functions in the normal aging brain.

This pattern of normal aging is consistent with the "last in–first out" theory in which the most recently developed brain areas, both phylogenetically and ontogenetically, are the first to be affected by the normal aging process. In contrast, pathological aging, for example, in Alzheimer's disease, may involve early structural changes primarily in the temporal lobes in association with memory loss.

Functional neuroimaging of cognitive test performance has offered support for these theories with reduced activation in the frontal lobes of older subjects during performance of executive function tasks [161]. Neuroimaging studies have also reported similar findings during memory tasks that specifically have an "executive function" component such as retrieval tasks [162] and have further supported the theory of asymmetric involvement of frontal lobe functioning. Young subjects show a prominent activation of the right prefrontal cortex during memory retrieval, whereas high-performing older subjects demonstrate a bilateral activation pattern. This phenomenon has been called "HAROLD" or hemispheric asymmetry reduction in old adults [163]. It seems to suggest that less-lateralized cognitive processing in older individuals may represent a possible compensation strategy in the healthy aging brain. Interestingly, older subjects with a performance deficit demonstrate activation patterns similar to those of the younger subjects.

There is little evidence of progressive cognitive decline over the lifespan of patients with chronic epilepsy, although this has remained a controversial topic in our field. A recent cross-sectional study examined the cognitive profiles of patients with temporal lobe epilepsy with unilateral hippocampal sclerosis in 3 age cohorts [164]. No significant differences in cognitive performance were identified based on age alone. Rather, patterns of cognitive impairment were identified in younger subjects with no suggestion of relatively greater impairment in the older age cohorts. It is worth noting that the oldest subjects in this study were 65 years of age, and no measures of executive function were described. The possibility that cognitive decline after age 65 may be accelerated in patients with chronic epilepsy requires further study in a longitudinal research design.

Anecdotal observations of cognitive decline among aging patients with epilepsy are not uncommon in the clinic, especially in the 7th decade and beyond. These cases should always be evaluated further to rule out a possible independent neuropathological process. In addition, prospective studies examining the relationship of these findings to seizure frequency, duration and dosage of antiepileptic medications, and other variables should be undertaken. Original research with the epilepsy population might also include measurement of regional brain atrophy in relation to specific areas of the epileptogenic cortex, functional neuroimaging of cognitive processing in elderly patients with epilepsy, and comparison of frontal and temporal neuropsychological test performance over time, controlling for baseline impairment, seizure focus, medication, and surgical procedures. In the meantime, continued study of the aging brain in healthy individuals will facilitate informed decision-making and treatment considerations in elderly patients with epilepsy.

Acknowledgments (for other authors)

Sarah J. Banks, Milan Brázdil, Zuzana Hummelova, Robert Kuba, Radka Kubiková, Sabina Telecká, and Mojmír Tyrlík.

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Please cite this article as: Rektor I, et al, Epilepsy, behavior, and art (Epilepsy, Brain, and Mind, part 1), Epilepsy Behav (2013), http://dx.doi.org/10.1016/j.yebeh.2013.03.011

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Please cite this article as: Rektor I, et al, Epilepsy, behavior, and art (Epilepsy, Brain, and Mind, part 1), Epilepsy Behav (2013), http://dx.doi.org/10.1016/j.yebeh.2013.03.011