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Third International Congress on Epilepsy, Brain and Mind: Part 1

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Abstract

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Conflict of interest

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Epilepsy is both a disease of the brain and the mind. Here, we present the first of two papers with extended summaries of selected presentations of the Third International Congress on Epilepsy, Brain and Mind (April 3–5, 2014; Brno, Czech Republic). Epilepsy in history and the arts and its relationships with religion were discussed, as were overviews of epilepsy and relevant aspects of social cognition, handedness, accelerated forgetting and autobiographical amnesia, and large-scale brain networks.

Keywords

Epilepsy; Cognition; Social cognition; Religion; Music; Handedness; Accelerated forgetting; Networks

1. Introduction

The Third International Congress on Epilepsy, Brain and Mind (EBM3) took place in Brno, Czech Republic, on April 3–5, 2014. Being the third in a series of these biannual congresses, it maintained successfully the wide dimensions and high level of presentations and debate. While discussions about epilepsy and the brain, and specifically epilepsy as a brain disease, are the basis of all epilepsy congresses, during this and previous EBM congresses, we tried to look at issues within the triangle of epilepsy, brain, and mind.

There is no question today that epilepsy is a disease of the brain, rather than of the mind. Back in history, this has not always been clear, and it is interesting why for a long time it was thought, on the one hand, to be a disease of the body (rather than the head...), whereas oppositely, it was considered a disease of the mind, i.e., a mental disorder. Of course, this debate (which has been discussed in previous EBM meetings and again in EBM3) has been terminated by the clear-cut electrophysiological data, proving epilepsy to be a functional brain disease.

All scientists today accept that the brain is the organ of the mind, although differences exist along the monism–dualism spectrum. However, it is clearly beneficial and interesting to look at how the mind is affected by brain diseases, as exemplified by dementia, where the mind is being slowly eroded, or by Parkinson's disease, which is commonly accompanied by depression. By contrast, epilepsy is significantly much more heterogeneous in its mental manifestations, and unlike other diseases, here, the relationship is bidirectional. Not only do seizures cause mental aberrations, but the mind, in turn, can also induce psychogenic seizures during which we cannot see electrical discharges (though the movements constituting the episodes are triggered by the activity of some neurons, i.e., these neurons discharge electrically).

The mental affection in epilepsy relates, in many cases, to transient electric discharges. However, many mental phenomena are not brief but rather continue for prolonged periods of time, when current physiological techniques fail to show abnormal activity, especially paroxysmal abnormalities. The existence of such phenomena, manifested as mood changes or psychosis, are clearly a fertile ground for investigation of the brain and mind, and several

aspects of these were investigated and discussed in the EBM3 congress as reflected by the extended abstracts which follow.

Across the time domain, we explored the history of our understanding. Along the cultural domain, we were impressed by the effect that epilepsy could have on artistic production, mainly in literature and music. Developmentally, we discussed the effects of antiepileptic drugs on cognition and behavior, as well as on electrical changes in the brain, some of which were recently explored for the first time.

The relationship of epilepsy with religious experiences has always attracted attention and is definitely an endless source of debates. It is perhaps not surprising that a “seizure” is interpreted by observers (and sometimes by patients themselves) as being of divine origin, leading at times to affected persons being crowned as leaders, such as Jeanne (Joan) d’Arc, but which may also confine such poor patients to mental asylums. Another interesting and unexplained aspect is the manifestation of hyperreligiosity which is well described in patients suffering from temporal lobe epilepsy.

Memory complaints are extremely common among persons with epilepsy, and can theoretically be due to brain damage, the epileptic activity itself, as well as the antiepileptic drugs. However, very frequently, the complaints are not fully corroborated by neuropsychological tests, leading to the important issue of metamemory, an understudied area in the field of epilepsy. In some cases, it may reflect the existence of depression, in others the limitation of the neuropsychological tests, but importantly may also be due to the way in which persons with epilepsy, as well as people in general, view themselves and their strengths and limitations. A better understanding of this complex and important field is clearly needed.

2. Epilepsy, history, and the arts

2.1. Epilepsy in Italian literature from Dante onward

Marco Mula—Since ancient times, epilepsy — the sacred disease — has been surrounded by an aura of mystery, superstition, and magic. Over the centuries, epilepsy has also been a frequently occurring neurological disorder due to lack of effective treatments, the high prevalence of traumatic brain injuries occurring from wars, and high rates of CNS infections and early birth problems. It is, therefore, plausible that many writers actually witnessed epileptic seizures, and these experiences may have been important sources of inspiration for their literary characters, whose features and stories may have been also influenced by common beliefs.

In the Divine Comedy, while relating the punishment of the thief Vanni Fucci in Canto 24 of the Hell, Dante described the paroxysmal features of an epileptic seizure, including the sudden changes in the physical aspects of the thief during the seizure and his gradual recovery from the attack, with postictal confusion and a deep sensation of fear and anguish. In this episode, the reference to epilepsy is quite clear as Dante uses the word “opillazio”. This word, from the Latin “opillatio”, was used only in the medical context and represented a type of obstruction of the pneuma caused by phlegma, which since the era of the

Hippocratic Corpus was viewed as the main cause of epileptic seizures. It is also interesting that the character having a seizure is in hell and is a thief who stole something from a church. Some authors speculated that Dante himself might have had epilepsy [1], although there are no data supporting this hypothesis.

In “La storia”, Elsa Morante describes two characters with epilepsy, namely Ida and her son Usepe. Ida’s disease is quite mysterious in the novel and nicely couples with her need to hide her Jewish origin during World War II in Nazi-occupied Italy. Her son, Usepe, is the result of Ida being raped by a Nazi soldier. Interestingly enough, Usepe’s character is quite peculiar. He is sometimes considered a “special” child because of his ability to be in contact with nature. In this case, epilepsy is not totally surrounded by a negative aura, although it still remains magical and mysterious.

Between these two examples there are not only six centuries of history but also, importantly, Cesare Lombroso’s theories. According to Lombroso, epilepsy, degeneration, and geniality shared a number of similarities, such as genetics, the tendency to commit suicide, religious fervor, and mental rambling [2]. The way epilepsy was perceived and described in literature definitely changed after Lombroso introduced his theories, thereby further establishing him as one of the most famous and at the same time controversial figures in the history of neuropsychiatry.

2.2. Epilepsy in popular music

Jerome Engel, Jr—It was previously commented that, in contrast to creators of graphic art and literature, there appear to be no prominent classical composers with epilepsy. But this is not the case with popular music [3]. At this meeting two years ago, it was concluded that it was impossible to know what percentage of popular musicians might have epilepsy or the types of seizures they have or their causes, let alone the contribution of epilepsy to their music [3]. Furthermore, most popular musicians, including rap and hip-hop artists, are predominantly poets, so any contribution of epilepsy to their creative process would pertain as much to their literary output as to their musical compositions [3].

Perhaps the most famous popular musician with epilepsy is Neil Young, who has acknowledged his condition publicly and also mentioned it in his recent autobiography, *Waging Heavy Peace* [4]. He has not, however, commented on how his epilepsy might have influenced his enormous body of work, although particular songs such as *Helpless* and *She’s Lost Control* would seem to reflect the predicament of someone with epileptic seizures that occur without warning. His performance of *The Hitchhiker* is particularly explosive, if not convulsive, and contains the refrain:

They took us by surprise
The doctor gave me Valium
But I still couldn’t close my eyes
I still couldn’t close my eyes

However, the song refers to drug effects and not epileptic seizures.

Other prominent popular musicians who have acknowledged their epilepsy include Prince, Lil Wayne, Chris Knox, Adam Horowitz of the Beastie Boys, and Lindsey Buckingham. Chris Knox produced an album titled *Seizure*, which included the song *Grand Mal*, and also wrote another called *Lapse*, where he refers to screams and falls. Prince referred to his epilepsy in *The Sacrifice of Victor*:

I was born on a blood-soaked table
Cord wrapped around my neck
Epileptic to the age of seven
I was sure heaven marked the deck.

Artists without epilepsy commonly use epileptic seizures and epilepsy as a metaphor for various purposes, particularly in hip-hop and rap music. In her review of the topic, Baxendale observed: "... the language of epilepsy has also been appropriated by some musical artists to represent a state of sexual ecstasy and dance abandon. The reference to these states as 'epilepsy' or 'seizure' in numerous songs suggests that this shorthand is widely recognized, certainly within the hip-hop culture. .. The appropriation of the language of epilepsy to represent sexual orgasm in dance trance represents a contemporary departure in the artistic representation of epilepsy-related images and associations in the 21st century" [5].

In other works, epilepsy and seizures are used to represent nonsense and rhyme, are descriptions of others who are having seizures, and imply madness or retardation. Madness is particularly popular in the pop horror genre, and the Black Eyed Peas recorded an infamous song titled *Let's Get Retarded*:

Bob your head like epilepsy, up inside your club or in your Bentley
Get messy, loud and sick.
Y'all pass slo mo in another head trip.

After considerable objection, the title of the song was changed to "Let's get started", and references to epilepsy were removed.

Some hip-hop and rock groups have actually used epilepsy or epilepsy-related terms as names for their bands, including: Epilepsy, Seizure, Aura, Déjà Vu, Status, The Limbic System, Hippocampus Boom, and The Falling Sickness. Most of these groups are regional and not well-known.

In summary, references to seizures and epilepsy appear in modern popular music, particularly rock and hip-hop, as both positive (e.g., sex) and negative (e.g., madness) metaphors, but also apparently due to the desire to be provocative and shocking. A few prominent popular musicians are known to have epilepsy, but this has not appeared to influence their work to any appreciable degree. In any event, the influence of epilepsy on popular music is manifested in the lyrics, and not the music, and therefore, the creative output of these musicians is better considered as poetry rather than musical composition.

2.3. Epilepsy in classical antiquity

William Theodore—Greco-Roman medicine lasted for 1000 years, from the 5th century BCE to the 5th or 6th CE. Most medical writers whose work from that time has survived belonged to a small educated and economically comfortable class with strong philosophical and literary interests. For example, Plato attributes to Hippocrates the opinion that disease can only be understood in the context of a universal world view [6]. In a less specialized world, medicine was an avocation for wealthy intellectuals as well as a profession. Available evidence for ancient views of epilepsy depends on texts, surviving perhaps as much by chance as perceived value, not necessarily reflecting an accurate view of contemporary popular disease constructs or medical practice. Familiar words, such as ‘hysteria’, may have had a different meaning than those in vogue today.

Society, predominately agricultural, only had a few large cities, such as Rome and Alexandria. Athens at its height may have had 150–300,000 inhabitants [7]. Physicians, like artists, tended to travel; Greek experts were popular at the Achaemenid court. Ancient Near Eastern and Greco-Roman art and science influenced each other, but the impact of Near Eastern and Egyptian medicine on Greco-Roman practice is unclear [6].

Three general ‘schools’ of ancient medicine are recognized [6]. ‘Rationalists’ or ‘dogmatists’, the oldest, thought that the identification of underlying pathology, and, often, specific environmental characteristics, was key for proper medical practice. Herodotus (485–425 BCE?) mentions approvingly that Egyptian physicians included specialists in ‘unseen’ diseases as well as for more obvious afflictions of eyes or teeth (2.84.1). ‘Empiricists’, a school developing from about 200 BCE, thought that underlying pathology was unknowable and practice should be based on experience. ‘Methodists’, from about the first century CE, thought that treatment depended on knowledge of the generalizable features of each disease. Differences among schools were less marked in their practice than texts.

Early possible mentions of epilepsy underline ambiguities. Heraclitus (ca 500 BCE) called false opinion a ‘sacred disease’ (Diehls 46 = Diog Laert IX 7). Herodotus, attempting to explain the seemingly irrational behavior of the Persian King Cambyses, suggests either divine retribution for mistreatment of the Apis Bull or a childhood disease ‘some call sacred’, that would likely affect his mind as well as body (III.33). However, his somatic symptoms are not described, and ‘sacred disease’ was used for different things, including leprosy, at different times [8].

Though Alcmaeon of Croton and Democritus of Abdera may have written earlier works, the first surviving text devoted to epilepsy, *On the Sacred Disease*, usually dated 450–400 BCE, is one of the most remarkable [8–10]. The author contends that epilepsy (the actual term is used only once or twice) is no more sacred than any other disease and has a hereditary component, frequent childhood onset, and a physiologic basis related to excess brain phlegm blocking the downward flow of air, and further states that it should be treated mainly by diet and exercise. Pathologic evidence supporting this theory came from an examination of the brains of epileptic goats, which were said to be “moist”. *Airs, Waters and Places*, from the same period, emphasizes the effect of climate: children living in a city exposed to hot southern winds will suffer from spasms, asthma, and a “sacred disease” due to moist heads

full of phlegm disturbing other organs [11]. *Wounds in the Head* describes spasms contralateral to an injury [12]. A fascinating passage in Aphorisms 2.26 notes that the combination of fever and spasms was less dangerous in children younger than seven years than in older patients.

More than likely, there was a well-known physician called Hippocrates, said to come from the island of Cos, where a ‘school’ of medicine was part of the late 6th to 5th century BCE Ionian and wider Greek ‘enlightenment’, who may well have been the author of *On the Sacred Disease* and several other contemporary ‘Hippocratic’ works [9]. Epilepsy was distinguished clearly from ‘mania’, but an association with ‘melancholy’ and stigma are clearly described in the Corpus [13].

Fifth-century poets, philosophers, and physicians participated in a common cultural milieu. Herodotus, for example, uses illness as a metaphor for social and political disorder (5.28.1). However, suggestions that seizures and postictal psychoses may be depicted in several Greek Tragedies, particularly Herakles and Iphigenia in Tauris of Euripides, are not supported by close analysis [14].

A retreat from rationalism in the Hellenistic and Early Christian eras was associated with the rise of mysterious cults and magical thinking. Physicians were not necessarily opposed to invoking the aid of the gods: for example, by referring patients to the shrines of Asklepios [15, 16]. Traditionalists such as Aretaeus of Cappadocia (1 CE) considered treatments such as hippopotamus testicles, vulture brain, or human liver beyond the bounds of medical practice, instead recommending diet and drugs designed to combat the excessive brain cold and humidity that caused seizures, bleeding, or, in extreme cases, trephination [8]. Celsus (1 CE) recommended avoiding stress, light diet, hellebore, purges, and bleeding or cautery below the neck [17]. He described successful treatment by drinking fresh hot blood drawn from the neck of a gladiator — “miserum auxilium tolerabile miserius malum fecit”. Throughout antiquity, pharmacologic practice mixed ‘physiologic’ and ‘magical’ drugs [8]. The Latin name for epilepsy, ‘morbus comitialis’, reflected superstition that assembly meetings had to be stopped if someone had a seizure.

Galen of Pergamon (2 CE), the most prominent Roman physician, developed the humoral theory implied initially in the Hippocratic corpus [8]. He gives perhaps the first clear description of an aura, as well as a ‘Jacksonian’ seizure (De Locis Affectus 3). Galen thought psychic pneuma receives sensations and carries the brain’s commands to muscles through the spinal cord and nerves [18]. Cutting into an animal’s lateral ventricle but not cortex caused death due to escaping pneuma. In addition to focal mechanisms, thick phlegm accumulating in brain cavities could prevent the free flow of psychic pneuma and cause seizures. Treatment should promote phlegm evacuation by purging, bleeding, diet, and moderate exercise [8].

Later writers generally reprised existing tradition. The Latin translation by Caelius Aurelianus (5CE?) of Soranus of Ephesus (1–2 CE?) provides a valuable summary of several centuries of practice [19]. Ancient physicians wrote cogent descriptions of seizures and epilepsy, challenging views of divine origin, recognizing genetic predispositions, and

prescribing ‘rational’ treatment based on physiologic concepts. The tradition faded in late antiquity in concert with the collapse of the Roman Empire and rise of Judeo-Christian theology with its emphasis on eschatology, and denigration of the physical world and the human body. Nevertheless, ‘Hippocratic’ medicine was one of the most important forces in the origins of the Western intellectual tradition.

2.4. Science and superstition in the history of epilepsy

P. Wolf—Rather than reflecting steady progress from ignorance to enlightenment, the history of epilepsy can be described as a never-ending antagonism between beliefs in supernatural powers and scientific approaches.

Prehistoric artifacts of survived trephinations probably provide the earliest indications of a rational approach to epilepsy based on deduction from observation. When they performed trephinations to treat skull fractures, the prehistoric surgeons in many instances could observe that acute traumatic seizures disappeared when they successfully cleaned and mended the wound, taking out the bone fragments. The majority of trephinations, however, were done on intact skulls, and only a small logical step was required to translate the experience with brain traumas into treatment of people with nontraumatic seizures. In historical times, trephination was accepted as a treatment for epilepsy; an early proponent was Aretaeus the Cappadocian [8].

The written history of epilepsy in the Western world begins with the Babylonian codex of the late 2nd millennium BC, which has been analyzed by Kinnier Wilson & Reynolds [20]. Various well-described seizure types were attributed to the influence or “hand” of name-given evil spirits (Lilû, Urtilli, Ishtar etc). It is difficult for us to know if this was a natural or supernatural explanation and if such a distinction even existed at the time. How different was the concept of an invisible force producing seizures in somebody from the experience of a lightning which comes out of the air and can kill, or of a wind which is invisible but real enough to drive one’s boat or capsize it? Winds to this day also are given names by seafaring peoples. We must be careful not to jump to conclusions.

However, some 600 years later, Hippocrates drew up the lines sharply when he argued for natural causes against the widespread belief that epilepsy was sent by gods [21]. The Hippocratic surgeons knew contralateral seizures caused by brain wounds, and this may have been important for their understanding that the seat of epilepsy is in the brain. Hippocrates’ principle of treatment for epilepsy (like for other diseases) is remarkably “modern”: to do what is opposed to it and to avoid what favors it — bearing witness to a concept in which seizures resulted from an interaction of a set of antagonistic influences, one facilitating and the other preventing seizures.

Hippocrates’ rejection of supernatural explanations of epilepsy by no means settled the matter in the minds of the public. Christian doctrine considered epilepsy as a possession by evil spirits, and patients were treated with exorcism. How evil spirits could obtain such official recognition in a monotheistic religion is not easy to understand. The natural causes of ancient Greek medicine included influences of the celestial bodies, and reference of epilepsy to the moon (presumably derived from the periodic recurrence of seizures, e.g.,

catamenial epilepsy) was considered a natural explanation. For Church Father Origenes, it was, therefore, a problem that Matthew, in his version of the boy with epilepsy in the synoptic gospels, calls him σεληνιαζόμενος (moon sick), which is theologically incorrect, and yet a gospel could not be wrong. John Chrystosomos († 407) found the solution: “don’t get confused. It is the father of the boy who uses such language” [22].

Whereas numerous paintings over hundreds of years of Christian Saints performing exorcisms document this position of the church [23], an ex-voto of 1501 [24] presents a different aspect of belief: pilgrimages undertaken by pious sufferers of intractable diseases and their caretakers in the hope of receiving cure by God’s mercy. The ex-voto reports a critical event in the history of a boy with epilepsy (either absence status or post-status stupor) which ended by the intervention of the Holy Virgin. The votive gift of a waxen head shows that no superstitious theories are involved but the family is perfectly aware that epilepsy is a disease of the brain. Specific epilepsy pilgrimages came into existence even more recently, and head models to this day are recommended to the pilgrim as suitable votive gifts in case of epilepsy [23].

However, even in our age of great breakthroughs in the scientific understanding of epilepsy, superstitious views are by no means extinct. In 1976, the German public was shocked by the case of Anneliese Michel, a young woman with temporal lobe epilepsy and psychosis who stopped medical treatment and died from exhaustion and starvation during a series of exorcisms undertaken by two Catholic priests. At trial, the priests asserted that the girl was possessed by demons who, like in the Babylonian text, even had names: Osman, Tarik, Judas, Laima, Patait, and Hitler. Surprisingly, even today on the internet, there is a vivid discussion of the correct view of this case, whether from the medical or the supernatural perspective, and astrologists have even joined in as defenders, as they see it, of natural causes, i.e., the influence of stars.

Are supernatural explanations always an expression of ignorance and superstition? According to British writer Margiad Evans’ own experience, “the old idea of demoniac possession ... arose not from the onlookers of sufferers in fits but from the sufferers themselves. Because in the violent attacks one feels as though the body has been entered by a terrific alien power; and that that power is trying, after entrance, to push its way out again.” Likewise, German writer Monika Maron, a declared atheist, reports that after her first seizure, she was “obsessed with the idea that an alien force had simply switched me off for fifteen minutes... and ... slightly altered the way my brain functions. I didn’t really believe that, but it corresponded well with the state in which this inexplicable incident had left me” [25].

Thus, the fundamental aspects of a scientific understanding of epilepsy, presumably based upon the observations of prehistoric surgeons, were expressly formulated 2500 years ago, but superstitions are great survivors. For the rational mind, they are difficult to understand, but some may be based upon unusual subjective seizure experiences.

3. Epilepsy and religion

3.1. Spiritual and religious symptoms in epilepsy

Eylert Brodtkorb—Throughout history, epilepsy has been perceived as a mysterious and supernatural disorder with a religious dimension. A number of mystics, including prophets, saints, and founders of sects, may have had epilepsy [26]. Epilepsy was once referred to as the Sacred Disease [27]. Many cultures still view seizures as the result of demonic or divine influences.

Religious and spiritual symptoms in epilepsy have received relatively little clinical and scientific attention. Misinterpretations of these manifestations may have contributed to prejudice and isolation of people with epilepsy. It is important to come to terms with these phenomena; they should indeed be “brought out of the shadows”. A new and scientific approach to this topic is emerging. A PubMed search with the keywords Epilepsy and Religion provides 240 hits since 1960, 100 of them from the last decade. Religious phenomena in epilepsy can be related to seizures in three ways: ictal, postictal, and interictal [26].

3.1.1. Ictal religious symptoms: Various studies indicate that hyperactivation of networks involving the deep-seated structures of the temporal lobes and insula can evoke religious and spiritual experiences. Involvement of the anterior part of the insula has recently been suggested as the neural basis for ecstatic seizures with heightened self-awareness [28,29]. Picard et al. have recently demonstrated that stimulation of the anterior-dorsal insula induced the habitual ictal symptoms of intense bliss in one patient [30].

Approximately 1% of people with temporal lobe epilepsy report religious or metaphysical semiological components [26], sometimes strong and distinct, or as a vague background. This frequency may be underestimated, as these experiences may be considered weird and private, beyond what can be expressed in words and without counterparts in real life. There may be ecstasy or perfect harmony and a sensed presence of God or of contact with eternity. Some may have a perception of receiving divine messages, whereas others may have stereotyped visual or acoustic hallucinations with religious content. Combinations of these phenomena are common.

Of 11 consecutive patients with ecstatic or pleasant seizures seen at our epilepsy outpatient clinic, five had religious/spiritual experiences [31]. One reported a sort of vague cosmic sensation, perceived to come from outside this world, which could not be described in words. Another described a feeling of contact with a divine power accompanied by an erotic sensation, without distinct sexual character. He said he could sense the color orange, like a beautiful sunset, but without seeing it. When in the presence of someone else, he could feel a peculiar unification with that person. A middle-aged woman had vocal hallucinations accompanied by an intense teenage feeling of being in love. A deep bass was interpreted as God’s voice. She could never grasp the meaning of the words. Another two also felt they were receiving messages; one reported a prophetic communication giving life a new dimension. She had an intense urge to keep the sensation going in order to understand it, and had the feeling that she did, but could not recall it. Several others also had a strong wish to

stop the auras from fading away; they tried to keep the pleasant and ecstatic sensations for a longer time, albeit endeavoring to avoid a generalized seizure. One patient initially refused to have a low grade glioma resected. Some others admitted trying to titrate their medication down to a level permitting only the auras to occur, a brittle balance which was often not successful.

3.1.2. Postictal religious symptoms: Some individuals have postictal religious psychoses lasting for several days, often with a sense of selection and great personal significance with obsessive ideas on how to serve God [26,32]. Postictal psychoses occur after a lucid interval following a cluster of seizures, and the psychosis usually lasts a few days to a week, often after a cluster of seizures. They build rapidly up and terminate gradually after a mean duration of 9–10 days, but may last for months. They are characterized by delusions in clear consciousness, often with a strong spiritual content [33], and as an “acute religious fever” sometimes even manifesting as a religious conversion [34]. As a rule they develop after long-standing uncontrolled epilepsy; bilateral epileptic foci are common. Personality change with aggressive and suicidal behavior may occur. Adequate treatment with antiepileptic and antipsychotic drugs is mandatory [26].

3.1.3. Interictal religiosity: A subgroup of people with temporal lobe epilepsy may develop a preoccupation with philosophical or religious questions without psychotic traits. The interictal behavior syndrome (Geschwind syndrome) is thought to occur to a variable degree in about 7% of patients with temporal lobe epilepsy [35]. Lateralization of seizure onset to the right is common. Eighteen typical interictal personality traits have been reported to occur with increased frequency in temporal lobe epilepsy (Table 3.1.1) [36–38]. A number of these characteristics may be recognized in patients with long-standing temporal lobe epilepsy. In people with a secular upbringing, a strong philosophical and metaphysical spirituality may be devoid of faith. Hypergraphia may manifest as strikingly detailed and copious writings, often concerned with religious or moral issues [39], reminiscent of various historical religious texts.

3.1.4. Conclusion: Enhanced religiosity in epilepsy may be ictal, interictal or postictal. It is important to recognize these phenomena as either related to or distinct from psychiatric complications of epilepsy. Ictal religious and ecstatic symptoms may be enjoyed and desired. Any ambivalence to treatment should be addressed. Nonadherence to drug treatment may occur.

Interictal religious symptoms as part of the interictal behavior syndrome require insight, understanding, and patience. Postictal religious psychoses may be very dangerous and should not be ignored. Any sign of acute religious delusions should be taken seriously. Obsessive, paranoid, and suicidal behavior may need vigorous treatment.

A part of the literature on epilepsy and religiosity concerns historical cases and is anecdotal and controversial. However, similar experiences occur in patients of today and are usually interpreted differently than in cultures of the past. One thing can hardly be disputed: the role of epilepsy in the history of religions has not been fully acknowledged.

3.2. Joan of Arc: saint, witch or person with epilepsy?

Fabienne Picard—Whether Joan of Arc had epilepsy is controversial, with proponents of the affirmative answer assuming that her sense of mission (and success in getting thousands of people help her to chase away the English out of France) came from her experiences of seizures.

The documentation of her trial for Condemnation in 1431 provides a description of her episodes of experienced visions and voices. From the age of thirteen, she experienced frequent episodes of auditory hallucinations associated with elementary or complex visual hallucinations (a great light or human faces). These attacks had a sudden onset, lasted seconds or minutes at most, and could occur when awake, or if during sleep would arouse her. Some could be triggered by an auditory stimulus. She had no disorganized thought between the episodes.

This semiology of the episodes is very suggestive of epileptic seizures, which have been considered as ecstatic by some authors (including recently by Oliver Sacks), or as a partial epilepsy with auditory features by others, which seems more concordant with the ictal symptoms. The visual and auditory hallucinations could have had a religious content because she was immersed in religiosity during her childhood and adolescence. We can suppose that such hallucinations, without the knowledge of their medical origin, gave her a sense of divine mission and, hence, significant strength to try to accomplish the orders she heard during the episodes.

Her role during the Hundred Years war and her narration of her strange episodes led Joan of Arc to be burned for heresy at the age of nineteen. Yet she was rehabilitated 25 years later and, in 1920, was beatified as a “Saint” for her achievement.

3.3. Wise-Knut — a Norwegian clairvoyant with epilepsy

Karl O. Nakken—Knut Rasmussen Nordgarden (1792–1876) is one of the most remarkable persons to have ever lived in Norway. His special abilities made him renowned all over the country, and many considered him to be a new prophet. Owing to his supernatural power, he was named Wise-Knut or Miracle-Knut.

He has been the subject of several biographies [40–43] (Fig. 3.3.1). I have speculated about what kind of epilepsy he might have had and the role the epilepsy may have played in his extraordinary life.

3.3.1. Adolescence: He was born and brought up at a small farm in a rural area named Svatsund in Gausdal, a poor mountain district. His mother was a sincere Christian, and so was his school teacher. Due to his illness he was often absent from school, and he learned to read and write by his own effort. He spent most of his time at home with his mother because he had seizures as soon as he tried to do hard work at the farm.

3.3.2. Odd appearance: He had a somewhat odd and “ugly” appearance. “While having a seizure he was still more frightful to look at” [42]. He was large-limbed and tall, and he limped. He had unusually long raven-black and coarse hair hanging down to his shoulders

like flapping wings. He had big sparkling and strongly squinted eyes. His whole appearance created both surprise and respect.

3.3.3. The epilepsy: He had the onset of epilepsy when he was about 6 months old. He often fell to the ground with “spasms”. During some of the seizures, his head was dragged toward one side [42]. On other occasions, people lost contact with him “as if he was dreaming” [41]. He could hear a voice in his ear, often in a commanding way. He also had convulsions with “grinding his teeth and foaming at the mouth” [41].

His seizures gradually abated throughout childhood, and by the time he reached his teens, he was seizure-free. However, when he was 16 years of age, his father died. His seizures relapsed, and he had recurrent seizures the rest of his life.

3.3.4. A revelation: When 26 years old, he became so violently ill that he had to stay in bed for weeks. After days of seizures, he eventually became calmer. He could then hear harps playing in the air and the singing of hymns. Later, he heard music played on violins and clarinets sweeping along the floor as though it came from the earth itself, accompanied by a choir of heavenly voices. Finally, the music rose up toward the skies and faded into silence [41].

Later on he was able to recall a few words of the hymns: throw away all witchcraft and trust in the medicine of God, i.e., “the flesh and blood of our Lord” [41].

3.3.5. Healer, missionary, and clairvoyant: After the revelation, he dedicated his life to God. He became a revivalist preacher. He often gave prayers, and he sang a many of those hymns he had heard. Moreover, he became a healer and a clairvoyant. “He could heal people by the mere imposition of hands. Furthermore, he could positively tell where lost things were to be found, and he could tell what people living far away were doing or talking about” [42]. Farmers consulted him about where to dig for water.

He believed that his strange abilities were given to him as a gift from God, and that God in every case used him as a tool. “The prophets have had it like myself” [41]. He could not touch gold, silver, or copper without having spasms, and thus, he never accepted payment. “I’ve got the gift for nothing, and I shall give it away for nothing” [41].

3.3.6. Conflicts with the authorities: The legal authorities accused him of quackery and for unlawful religious teaching. Once, he was arrested by the local sheriff. However, Knut got such violent spells that he was hurled out of the sleigh and thrown with weird force far away from the road. “Knut’s moans were unspeakably heart-rending” [41]. He never complained or defended himself. According to Bjørnson “it was his beautiful and wonderful mildness that made them hate him” [41].

3.3.7. What was his epilepsy type, and what role did the epilepsy play in his odd life?: In retrospect, it is difficult to make a firm diagnosis. However, there is no doubt that he had epilepsy, though the etiology is not known. Nevertheless, he possibly had febrile seizures as a child, then a lucid interval with seizure freedom, and seizure relapse in the

teens. As the seizure semiology is consistent with temporal lobe epilepsy, it is tempting to believe that he might have had mesial temporal sclerosis. On the other hand, ictal auditory symptoms of a spiritual nature may indicate seizures of neocortical temporal origin. His religious awakening with the revelation was presumably part of a postictal psychosis. Unfortunately, the description of his seizures in the biographies is not very precise. However, he may have had both simple and complex partial seizures with or without secondary generalization. Whether he, in addition to epileptic seizures, also had psychogenic, nonepileptic seizures, remains uncertain.

Interictally, he was indeed preoccupied with religious matters. He wrote so extensively that he could have been hypergraphic. Thus, it is tempting to speculate that he had an interictal behavior disorder (Geschwind syndrome) [44].

Through the ages, people with epilepsy have either been demonized or considered to be holy persons. In Norway, Wise-Knut is an example of the latter. In many ways, his life was a mystery. Among his contemporaries, he created great sensations. According to Bjørnson, he was “truly a blessing not only to people within his reach but to many a sick and unhappy man and woman living far away in other lands” [41] (Fig. 3.3.2).

3.4. Epilepsy in the Bible, Talmud, and Jewish tradition

Meir Bialer—The Bible (Old Testament; “*Tanach*”) represents the essential foundation of the Jewish religion, and the Talmud contains canonized writings of a historical, religious, and legal character assembled over many generations, from 14th century BCE to 6th century CE. This summary reviews occurrences of symptoms in the Bible and Talmud that might resemble epileptic phenomena.

A few seizure-like episodes are depicted in the Bible, and, oddly, all involved prophets [45,46]. One of them pertains to the Hebrew term “*Nefilat Appayim*” (falling on one’s face). In several instances, a person fell on his face during an epiphany, prophecy, or while receiving a message from God (e.g., Abraham, Moses). However, one cannot assume that the phrase “falling on his face” definitely signifies epilepsy, since it has a common alternative religious significance (“*Tahanun*”) that is even in use today. The Hebrew term “*Nefilat Appayim*” (falling on your face) is part of the morning and afternoon Jewish prayer called “*Tahanun*” (entreaty). Originally, Jews lied down completely on their faces to do what is called a “*Tehinah*”, a prayer that involves a special personal request that is not deserved. It is an occasion when the person asks a “favor” even if the person does not feel worthy.

In the Bible, the Midianite prophet Bileam (Fig. 3.4.1) was described as “falling into a trance down (“*nophel*”) but having his eyes open” (Numbers 24:16). The term “falling down” was also used in relation to King Saul; “and he fell down naked whole day and whole night while joining a group of prophets” (Samuel I 19:24). While the term “falling down” may imply that King Saul and Bileam might have had epilepsy [45], there are alternative explanations, the issue being one of translation and interpretation. The expression “falling on his face” could reflect an unsuccessful attempt to translate a Hebrew idiom that signifies humility before a superior while bowing. In the case of Bileam, the words “into a trance” do not appear in the Hebrew Bible but are an addition of the translators. The King Saul episodes

seem like a form of mass hysteria. King Saul may have experienced extreme ecstasy, but not necessarily status epilepticus [45].

Altschuler suggested that the prophet Ezekiel, who prophesized during the destruction of Solomon's Temple from the years 593-577 BC, had temporal lobe epilepsy. He based his opinion on the presence of the following necessary ingredients for the diagnosis [47]:

- a. Extreme religiosity coupled with aggressive and pedantic prophecies
- b. Concern with minute details of the temple
- c. Repetitive hypergraphia (the book of Ezekiel is the fourth longest book in the Bible)
- d. Criticism of women's sexual behavior
- e. Multiple fainting spells and sticky personality

For many centuries, epilepsy was closely linked to demonology in ancient Jewish sources. It is not certain that the Sages of the Talmud still believed in the demonic origin of the disease, although the wording (to be seized) and the magical incantations or amulets used against it raise that issue. Here also, there is an issue of Hebrew translation and interpretation. During the time of the Talmud (2–5th century BCE), the Jews referred to a person with epilepsy as a *"nikhpe"*, meaning "one of writhes", perhaps also "one who is bent or forced over (by the demon)". Epilepsy was considered by the Talmudists as a serious disease which may be hereditary or even contagious. The Hebrew *"nikhpe"* (from the noun *"kefia"*) actually has the same meaning as the original Greek term epilambano, meaning to seize or to attack. The *"nikhpe"* (person with epilepsy) of the Talmud was nevertheless considered to have normal humanity, being unable to assume responsibility at times, but normal most of the time. Preventive and curative aspects, according to the period, included empirical as well as other less rational means [45].

Later, the term *"holi nophel"* was used as an equivalent to the Latin term for "falling sickness". The following are Talmudic examples of the etiology of epilepsy [45]:

- a. "If one stands nude to the light of a candle, he will be *nikhpe*" (person with epilepsy).
- b. "If one stands nude to the light of a candle or the moon, he endangers himself seriously".
- c. Sexual intercourse in immodest and indecent conditions was considered an etiological factor. The child born under these conditions will be *"nikhpe"*.
- d. Several Talmudic and midrashic sources consider epilepsy as the attack of a demon *"shed"* or spirit (*"ruah"*) [45].

In the Talmud, there are some hints that epilepsy could possibly be induced by a froth that appears during the attack, which would render the patient's breath dangerous. The Talmud calls this syndrome *"ra'atan"*, since epilepsy was considered a serious disease. Rabbi Judah the President (2nd century CE) considered epilepsy as a dangerous internal disease such that the patient was exempt from responsibility for all commandments (except three). One of the

reasons given was that during a seizure, there is a danger that a patient might fall into fire or water. Modern rabbinical scholars maintained epilepsy in this category because of the dangers incurred during seizures.

There is no detailed description of an epileptic seizure in the Talmud. A priest is unfit to serve in the Temple if he has seizures, “even if it occurs only once in days”, meaning even if the seizure can be foretold. According to the Talmud, epilepsy may appear for the first time at any age. It may be congenital; epilepsy is counted with other “defects that one may be born with”. It is mentioned that severe forms of epilepsy may affect the patient’s psychological state, while mild seizures that occur rarely may even be concealed. Genetic and eugenic aspects are also mentioned in the Talmud, possibly after Hippocrates who said that epilepsy is hereditary, “like other diseases”. The following are specific citations from the Talmud concerning epilepsy [45]:

- a. “A man should not marry a woman coming either from a family of persons with epilepsy, or from a family of lepers”.
- b. “A person with epilepsy is sometimes in full conscience and sometimes like an insane person”.
- c. “A woman with epilepsy may conceal this defect from her environment, if the seizures occur at regular times”.
- d. “Persons with epilepsy (*“nikhpim”*) are those with 3 reported cases”.

No antiepileptic drugs are mentioned in the Talmud. In later Jewish texts of medieval times, there are references to: saffron (crocus), clove (*“tsiporn ha-bosem”*), oxymel, and several herbs (e.g., *Artemisia*, *Valeriana*, and *Arnika*). Magical (nonmedication) acute and preventive means include an amulet (*“kame’a”*) that was worn by persons with epilepsy [45].

Moses Maimonides (“Rambam” — 1138–1204) was a famous doctor and an eminent scholar (his uniqueness is exemplified by the proverb: “From Moses to Moses there has never been another Moses” (Fig. 3.4.2)). According to Maimonides, an epileptic seizure is accompanied by “confusion of the senses”, and consequently, epileptic symptoms are attributed to a filling of the chambers of the brain. Maimonides used the term “kordiakos” to refer to a form of epilepsy and considered the affected person to be delirious even after the seizure occurred. Some persons have their minds deranged even when they have no attacks; thus, the validity of their testimony is questionable. Maimonides draws a comparison between epilepsy and several other syndromes in the Talmud, where a patient is “sometimes in full conscience, sometime like insane” [45], and this affects their degree of legal responsibility. Similarly, Talmudic commentaries have raised the supernatural aspect of epilepsy.

While many symptoms described in the Talmud relate to the clinical examination of patients with epilepsy, medical practice was not the object of the Talmudists’ intellectual pursuits, and so epilepsy was mainly considered with regard to its legal implications [48]. The legal status of patients with epileptic seizures may help understand why the sages (*“chazal’s”*)

considered King Saul a righteous person (“*tzadik*”) despite his unjust behavior toward David.

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3.5. Hyperreligiosity in epilepsy: a sociohistorical epiphenomenon?

Walter van Emde Boas—In the medical and social approaches to the person with epilepsy, much has changed for the better during the last several decades. Yet while we, in our “enlightened” Western society, no longer automatically consider the person with epilepsy as cursed, degenerate, or feeble minded, some vestigial remains of centuries of prejudice are still manifest.

A typical example of this persisting discriminatory attitude, even among doctors working in the field, is the continued use of the concept of the so-called “epileptic personality”, or preferably, the “personality disorder of epilepsy”, suggesting that the patient with epilepsy is “different” and characterized by the disorder rather than to be suffering from its consequences. This concept dates back to the early 20th century work of Emil Kraepelin (1856–1926), but it was further “methodologically” studied, adapted by, and named after Norman Geschwind (1926–1984) and his followers [49].

Where more up-to-date studies try to provide quantitative assessment and comparison of personality traits according to DSM standards between various patient populations, including patients with epilepsy, the Geschwind Syndrome reads as an ill-conceived mix of personality traits, negative social characteristics, and pseudoquantified “abnormal” behavioral patterns. Among the latter, hyperreligiosity and hypergraphia feature among the often “reported” features as highly typical.

My personal experience in more than 30 years of epilepsy care, however, has provided little evidence of hyperreligiosity, and then only to a limited extent in a few of the older permanent residents in our institution at the time of my arrival there in 1982, all of whom are since deceased. Again, with some individual exceptions, the same is true for hypergraphia. An informal poll among my colleague neurologists involved in the care of over 5000 outpatients with epilepsy seemed to confirm the current extreme rarity of these features, even in the traditionally Christian-fundamentalist areas of the Netherlands, some of which were and still are among the catchment areas of our clinics.

A more formal questionnaire survey assessing epilepsy and religion, reported by Devinsky [50], also yielded very mixed results, and a repeated PubMed search covering the period 1987–2014 seems to corroborate this finding, despite the growing interest in the relation between religion and epilepsy. An earlier search on Religion and Epilepsy in PubMed, covering the period 1987–2003, resulted in 132 hits, almost exclusively dealing with case histories of patients with perictal or postictal religious feelings or visionary experiences or with pathohistoriography of religious figures, suspected of having been suffering from epilepsy. A repeated search, covering the period January 2013–March 2014 yielded another

108 hits, almost doubling the average per year, and now also including subjects like the (positive) effects of religion (or meditation, yoga, etc.) on seizure frequency or quality of life or “religious” ictal signs and symptoms, such as the sign of the cross. Some studies provide evidence of some biologic and anatomic correlates of “altered” religiosity in some subjects with temporal lobe epilepsy [38,51], but these are selected patients, not representative for the population as a whole.

A search on Hyperreligiosity and Epilepsy in 2003 had yielded only three hits; one case history, one on postictal phenomena, and only one study actually assessing the phenomenon in a somewhat larger population with epilepsy and that one with negative results [52]. A repeated search in March 2014 provided only four additional references, again including some single case histories but otherwise providing little evidence.

Thus, while it is clear that in some patients with (temporal lobe) epilepsy, religion and/or religious or mystical experiences play a role in their interictal, periictal or postictal conditions, the concept of hyperreligiosity in epilepsy remains controversial at best [26] and with little convincing evidence that it really is an intrinsic phenomenon of (temporal lobe) epilepsy as such.

Why then does this improvable concept, based on “true observations” from the past, persist? It is not too difficult to hypothesize that this observed “abnormal” hyperreligiosity was, in fact, “induced”, not by the epilepsy but by the circumstances in which the persons with epilepsy were taken care of and observed.

Of course, there are true personality traits that set persons with epilepsy, as a group, apart from the population at large, predominantly DSM-IV Cluster C traits such as Avoidance, Dependency and Obsessive Compulsive Behavior [53]. But at the time that Kraepelin made his observations, even the main (University) hospitals were largely staffed with religiously motivated nurses, and all the institutions, actually rather asylums, that were founded at the end of the 19th century or early 20th century, and which followed the example of Friedrich von Bodelschwing d.Ä (1831–1919) in Bielefeld with the specific purpose to take care of the “epileptics” and other derelict subjects, were run by religious organizations. Looking at the pictures of day to day life in Bethel (Bielefeld, Germany), Meer & Bosch (Heemstede, the Netherlands), Philadelphia (Dianalund, Denmark) and other institutions from the period 1890–1920, there is hardly a picture that does not show the patient or patients under the supervision, care, or guidance of religious persons, deaconesses, nuns, ministers, and priests, and with religious images on all the walls in every room, day and night.

Apart from the fact that, in that period, religion was more actively prevalent and practiced than today and that for some of the institutions, the religious background of the clients played a role in their eligibility for admittance, it is clear that, as in some religious schools well into the 1960s and sometimes even today, religious behavior was mandatory for the clients. And they, the persons with epilepsy, being avoidant and dependent on their caregivers, the religiously motivated nurses and directors (doctors would only come in later), complied, and being obsessive compulsive, they complied extra.

In the setting of the institution, relatively excessive religious behavior would not only be acceptable, but would also make you a good patient in the eyes of your caregivers. This was the case even if the behavior would be noted as “hyperreligious” and, thus, “abnormal” by the occasionally attending “Nervenarzt” who, being there to examine the derelicts, the epileptics, the alcoholics, and other “subnormals” in an era of subjective and unquantified observations, was primed to identify “abnormal characteristics” in these “abnormal” subjects.

Now in the secularized 21st century, at least in the Western world and in the settings where we take care of our persons with epilepsy, this emphasis on religion has vanished and, apparently, so has the “hyperreligiosity” of persons with epilepsy.

We hypothesize, therefore, that these beautifully described hyperreligious patients with epilepsy from bygone times were in fact just compulsive obsessive proselytes, reflecting the characteristics of their wardens and their society rather than of their affliction.

Observing another obsessive compulsive behavior can illustrate this further. Hypergraphia is another traditional hallmark of the “epileptic personality”, represented by long lists of physical signs and symptoms, elaborate seizure journals, medication schemes, etc. Certainly, this has been observed in some (but never statistically assessed in how many) subjects with epilepsy. Also, there are the literary or pseudoliterary writers, reported to have been suffering from epilepsy, in whom, contrary to their unaffected colleagues, their activity is suggested to be driven by their condition rather than their drive.

To what extent this behavior is spontaneous or induced by the society demands or the doctor’s interest and practice of requesting or even providing the patients with seizure diaries is not clear. The shift from handwriting to elaborate computer data sheets and graphics, as well as joining the general blogging community and endlessly spewing out mostly irrelevant information to the worldwide network of “friends”, however, indicates that the visible manifestations of this compulsive behavior in subjects with epilepsy follow general changes in society and, thus, in their eventual expression, are not typical for epilepsy, but as far as present, just an expression of an underlying personality trait.

Thus, the excessive obsessive compulsory traits, observed in some subjects with epilepsy, appear as at least partly adaptive and/or compensatory behaviors, the expression of which will change over time, depending on the demands and characteristics of the society in which the person is living.

The so called “Specific Personality Characteristics” such as “hyperreligiosity” or “hypergraphia” as observed a century ago, therefore, should not be interpreted as intrinsic characteristics of the person with epilepsy but as secondary expressions, i.e., epiphenomena of disproportionate adaptive behavior, induced by the surrounds of society.

Certainly, “hypergraphia” in a more modernized version still exists in society in general and, thus, also in persons with epilepsy. Epilepsy-associated religious experiences, however, appear to remain limited to a small minority of patients with epilepsy, and in our more

secular modern society, “hyperreligiosity” as a specific behavioral trait of epilepsy seems to have disappeared, representing an epiphenomenon of adaptive behavior in the past.

Epilepsy, after all, is what you have, not what you are.

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4. Epilepsy, social cognition, and handedness

4.1. How much does this face alert you? The role of arousal from facial expression in medial temporal lobe epilepsy

Stefano Meletti—The study of the perception and recognition of emotions (ER) in medial temporal lobe epilepsy (MTLE) has demonstrated that patients with chronic medial temporal lobe damage present deficits in the recognition of multiple emotions and that these deficits are not specific for one sensory modality [54,55]. Indeed, patients with MTLE perform worse than control populations when they have to judge facial expressions, emotional prosody, or even the emotional content of music. Several patient-related variables can impact the severity of ER, including extent of amygdala damage, bilateral temporal lobe dysfunction, age of epilepsy onset, and disease duration [56]. However, the exact nature of the ER impairment has not been elucidated so far. Considering that patients with MTLE who show ER impairments display a normal knowledge of the conceptual meaning of the different emotions (i.e., the semantic significance of fear), one possibility to explain ER deficits can be that MTLE disrupts the arousal reaction that is normally induced by the presentation of emotionally charged stimuli (either with positive or negative valence).

A few investigators have studied the role of temporal structures in the evaluation of the arousal dimension of faces [57,58]. The role of the amygdala in arousal and valence attribution has, thus, recently been considered. Whereby the amygdala has been associated with both autonomic (skin conductance response) and cognitive aspects (rating) of emotional arousal, its role in valence evaluation is less consistent [57,58]. Low arousal response to emotional stimuli could have several consequences on behavior, such as decreased attention to relevant biological stimuli, impairment in the judgment of emotions in others, and less engagement in social activities and social networks.

To test this hypothesis, we recently investigated the rating of arousal from facial expression in a group of seizure-free patients after anterior temporal lobectomy [59]. We observed that these patients showed lower arousal ratings for neutral as well as several negative facial expressions as compared with controls. Moreover, duration of epilepsy before surgery showed an association with lower ratings of arousal for angry and fearful faces. These findings are consistent with previous reports of impairment in arousal processing for faces, emotional pictures, or music in patients with selective amygdala damage. Moreover, we are currently testing arousal from facial expressions in patients with chronic drug-resistant MTLE before surgery. Preliminary results showed that patients with unilateral and bilateral MTLE were subjectively less aroused than control populations from facial expressions

(either from fearful or happy faces). Patients with bilateral MTLE maximally expressed this deficit.

We suggest that arousal from emotional stimuli is altered in MTLE and that this deficit could be one of the mechanisms underlying or predisposing patients to social cognition impairments.

4.2. Epilepsy surgery and changes in social cognition

Jana Amlerova, Petr Marusic—Emotion recognition from another person's face and empathy to others' mental states are important domains of social cognition. Those abilities are frequently impaired in patients with temporal lobe epilepsy (TLE) [56,60–63]. Though patients with TLE are frequent candidates for epilepsy surgery, the effects of resection within temporal lobes on social cognition are still not fully established. Recent studies showed that right-sided temporal lobe surgery could be a risk factor for impairment in both aspects [64–66].

Considering the emotion recognition from faces, Adolphs et al. suggested that following temporal lobectomy, patients with right TLE performed significantly worse, especially in recognizing fear, whereas patients with left TLE were not affected. Moreover, there was no significant correlation between the extent of amygdala damage and facial emotion recognition performance [65]. On the other hand, Shaw et al. showed the neutral effect of epilepsy surgery on facial emotion discrimination. This study also found improved performance in fear detection tasks, predominantly after left-sided surgery [67]. Benuzzi et al. demonstrated possible mechanisms of brain plasticity allowing improvement in emotion recognition after temporal lobectomy [68].

The nondominant temporal lobe seems to play a pivotal role in empathy and judgment about mental states. But the influence of epilepsy surgery appears to be more neutral than in emotion recognition. No significant differences were found between the preoperative and postoperative groups with MTLE in the study of Schacher et al. [66]. Patients with right-sided MTLE performed only slightly worse than the left-sided group. Similarly, Shaw et al. did not find an effect of temporal resection on faux pas detection [67].

Studies mentioned above were mostly cross-sectional and included only postoperative patients, with the exception of the study of Shaw et al. [67]. In our own study, an experimental neuropsychological protocol including the Emotion Recognition Test (ERT) and Faux Pas Test (FPT) was used to evaluate emotion recognition and social cognition in a group of patients with unilateral refractory TLE [69]. Our aim was to investigate the influence of epilepsy surgery on those abilities in patients with TLE in a cross-sectional and longitudinal study and to identify the main risk factors for the emotion recognition and social cognition impairment. We found that epilepsy surgery within the temporal lobe seems to have a neutral effect on patients' performances in both domains. But there were individuals who improved or declined after temporal lobe resection. The changes were not associated with any clinical or demographic variables, including age, seizure frequency, age at epilepsy onset, duration of epilepsy, or intelligence level. Therefore, we suggest that a degree of individual variability with possible postoperative deterioration should be taken into

account for decision-making on the management of patients with refractory TLE. Research on larger series should be conducted to identify the clinical characteristics of the patients who are at risk for postoperative deterioration in social cognition.

4.3. Handedness: language location in multilingual persons

Ilo E. Leppik—Precise language localization is an important factor in planning for epilepsy surgery, and handedness is often a surrogate marker for speech lateralization. There are many varieties of language capabilities (Table 4.3.1) and also differences in handedness. A number of questions arise.

4.3.1. Does atypical language lateralization affect mastery of foreign languages, academic achievement, artistic talent, or intelligence?: In one study, language lateralization was identified by transcranial Doppler ultrasound during which hemispheric perfusion differences were measured during a word generation task [70]. A strong correlation between right handed–left language and vice versa was found. There was no difference between persons who had left ($n = 264$), right ($n = 31$), or bilateral ($n = 31$) hemisphere language representation in academic achievement, artistic talent, verbal fluency, and linguistic processing, demonstrating that atypical hemispheric representation is not associated with any impairments.

4.3.2. What is the localization of languages in a particular trilingual person with language in the right hemisphere?: Positron emission tomography (PET) was used with word-generation tasks to identify speech localization in a right-handed person [71]. Language had been lateralized to the right hemisphere by intracarotid sodium amobarbital testing. Cerebral blood flow patterns were similar for all three languages (French, Spanish, and English; two acquired early, one late) using synonym generation compared with a silent resting baseline. Several regions in the right inferior frontal cortex (corresponding to those observed in the left hemisphere in healthy right-handed volunteers) were activated by single word analysis. This unusual person demonstrates that in spite of unusual presentation, organization of simple vocabulary appears to use the same relative anatomical structures in the opposite hemisphere.

4.3.3. What is the cerebral organization of language in bilinguals of Western and Asian language speakers?: To investigate cerebral organization, Klein et al. used PET in subjects ($n=7$) who had Mandarin Chinese as their first language (L1) and subjects ($n = 7$) who learned English (L2) later in life [72]. When activation from word repetition was subtracted from verb generation in L1 and L2, increases of cerebral activity were observed in left inferior frontal, dorsolateral frontal, temporal, and parietal cortices, and right cerebellum for both languages. There was no spatial separation of cerebral blood flow peaks in the frontal lobe during this test. This study demonstrated that there are shared neural substrates for contrasting languages such as Mandarin and English.

4.3.4. Is age of language acquisition able to influence cortical shape?: Klein et al. used MRI to measure cortical thickness “CIVET” processing at over 80,000 points to determine the effects on brain structure of learning a second language (L2) [73]. The study included 22

monolinguals and 66 bilinguals. The bilingual subjects had learned languages at different ages: some (n = 12) had learned both languages early (0–3 years), some (n = 25) had learned L2 after achieving proficiency in their first language early (4–7 years), and some (n = 29) in late childhood (8–13 years). The subjects were from 23 to 28 years of age at the time of the MRI study. The monolinguals and simultaneous bilinguals did not differ in cortical thickness in any region. Persons who were monolinguals did not differ in cortical thickness in any region from those who were simultaneous bilinguals. Significantly thicker cortex in the left inferior frontal gyrus (IFG) and thinner cortex in the right IFG was seen with acquisition of L2. There were significant correlations between age of acquisition of L2 and cortical thickness regions: cortical thickness correlated with age of acquisition positively in the left IFG and negatively in the right IFG. Their results showed that learning a second language modifies brain structure in an age-dependent manner, whereas simultaneous early acquisition of two languages has no additional effect on brain development.

4.3.5. Are there differences in white matter structures between mono- and bilingual children?: Mohades et al. [74] used magnetic resonance diffusion tensor imaging (MR-DTI) to study the impact of bilingualism on the microstructure of the white matter pathways used for language processing in 40 children aged 8 to 11 years. Of these, 15 were simultaneous bilingual, 15 sequential, and 10 monolingual. The mean fractional anisotropy (FA) was obtained for four major white matter pathways in each subject. There were no differences among the 3 groups in left arcuate fasciculus/superior longitudinal fasciculus (Broca's to posterior language zone). In simultaneous bilinguals, left inferior occipitofrontal (anterior frontal regions/posterior temporal occipital) pathways had higher density than monolingual or sequential bilinguals. However, compared to monolinguals, simultaneous bilinguals had lower density of bundles running from anterior corpus callosum projecting to the orbital lobe. This study demonstrates that white matter structures adapt to bilingualism.

4.3.6. Can structural changes occur in adults?: Hosoda et al. used multimodal imaging studies of 67 young adult Japanese speakers (mean age 20.1 years; 31 men, 36 women) who were enrolled in a four-month intensive English training class [75]. All were considered to be right-handed by the Edinburgh Handedness Inventory. Imaging was done before and after the intensive course, and changes in the gray matter, white matter, and connectivity were compared to the final score on the English Vocabulary Test. Brain structure before the four-month training did not predict gain in L2 ability. After training, gray matter volume increased in the inferior frontal gyrus, and connectivity with the caudate nucleus and superior temporal gyrus, predominantly on the right, was correlated with L2 vocabulary competence. With learning a second language vocabulary, young adult speakers can induce bidirectional changes in the mirror-reverse of the traditional language areas. These changes were correlated with the gain in L2 ability in the trained group but were not observed in the control group. From this study, it appears that the right hemispheric network can be reorganized into language-related areas through use-dependent plasticity in young adults.

4.4. Handedness in patients with mesial temporal lobe epilepsy and hippocampal sclerosis (MTLE/HS)

Milan Brázdil—The impact of “epileptic activity” on the organization of some crucial brain functions (e.g., language and memory) is currently widely accepted. “Hardware” modifications related to neural plasticity were repeatedly observed over the past decade in studies of patients suffering from mesial temporal lobe epilepsy (MTLE). The relationship between MTLE with hippocampal sclerosis (HS) and hand dominance, however, has not yet been studied in detail.

Based on empirical data and recent literature on the significant reorganization of speech and memory in patients with left-sided MTLE/HS, we tested the hypothesis that left-sided MTLE/HS has a significant impact on the organization of motor cortex and handedness [76–82]. To investigate hand dominance in subgroups of patients with right- and left-sided MTLE/HS, 73 subjects with a diagnosis of unilateral MTLE/HS were prospectively included in the analysis. We investigated 31 patients with right and 42 patients with left MTLE/HS, 41 females and 32 males. All of our patients had MRI evidence of unilateral HS concordant with the results of at least one of the following investigations — interictal or ictal EEG, interictal PET, ictal SPECT, or neuropsychological testing. Subjects with discordant data were not included into the study. Hand dominance was assessed in each subject using the standard Edinburgh Handedness Inventory.

In the subgroup of patients with left-sided MTLE/HS, 33.3% were left-handed. In the subgroup of patients with right-sided MTLE/HS, 12% were left-handed. Subsequent statistical analysis confirmed a significantly higher rate of left-handedness in subjects with left-sided epilepsy (Fisher $P = 0.0399$, chi-square = 0.0453). In addition, within the subgroup of patients with left-sided MTLE/HS, the age of seizure onset was significantly lower in the group of left-handers than in the group of right-handers (t-test $P = 0.032$, Mann-Whitney U test $P = 0.017$) (Fig. 4.4.1).

The higher rate of left-handedness in subjects suffering from left-sided TLE as well as the earlier age of seizure onset in the left-handers support our hypothesis of a clinically important impact of the disease on the organization of the motor cortex. Importantly, Kim et al. observed a fourfold increase in the rate of left-handedness in subjects with left-sided epilepsy among a voluminous and heterogeneous group of patients with unilateral MTLE [81]. In our study, we showed that the earlier the age of seizure onset, the higher the likelihood of remote effect of the disease. Keeping in mind the modern view of MTLE/HS as a network disease, theoretically, either disturbance of the network or the spread of epileptic activity through the network from the epileptic focus to the frontal lobe in early childhood might produce a “pathological lefthander”.

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5. Memory complaints in epilepsy

5.1. Flashbulb memories in epilepsy

Birgitta Metternich, Andreas Schulze-Bonhage—Flashbulb Memories (FM) are autobiographical memories associated with receiving unexpected news of high emotional impact (e.g., 9/11). Flashbulb Memories are not memories for the actual event itself, but for the circumstances of hearing about it (reception event, RE) [82]. To date, FB have been investigated in patients with epilepsy in a few behavioral studies [82.1,82.2]. Here, we present preliminary results of an fMRI study regarding FM performance in patients with epilepsy and healthy controls.

We have studied 13 healthy controls (CG) and, to date, 5 patients with LTLE. We plan to include 12 patients with LTLE and 12 with RTLE. The fMRI paradigm is a block design with 3 conditions: 1. FM: Subjects are asked to recall the reception events for a number of potential FM events with the help of cues pertaining to the canonical categories. 2. FM-control: The same procedure for control events which lack the features of typical FM events (i.e., high emotional impact, unexpectedness). 3. Implicit baseline. A postscan questionnaire including a rating of the emotional reaction is completed and then completed again after eight weeks. The consistency of the answers between both questionnaires is assessed. Emotional reaction (EMO) is included in the SPM analytical model as a modulating parameter.

Preliminary results show a strong trend toward lower FM consistency for LTLE vs. CG. For the control group, the contrast FM > FM-control showed activations corresponding with the autobiographical memory network [82.3]. The same contrast for CG > LTLE showed an activation in the left insula.

Activations associated with EMO regarding the FM events in the control group were not predominantly left-sided and involved the right and left amygdala.

Emotional reaction in CG > LTLE showed activations in the left medial TL, right insula, right superior TL, left HC and left amygdala, left medial FL, right HC, and smaller activations in the right TL pole and left cerebellum. The inverse contrast (EMO LTLE > CG) showed activations in the right superior TL and right inferior parietal lobe as well as right cerebellum.

5.1.1. Discussion: These preliminary results suggest that in healthy controls, activations for FM > FMC correspond with the network of episodic autobiographical memory. Analyses with the parameter emotional reaction in the CG group indicate that FM may be different from ordinary autobiographical memories, as we have not found predominantly left-sided activations, and furthermore limbic activations including the amygdalae. The stronger right-sided activations in the group with LTLE on emotional reaction might reflect a compensatory mechanism.

5.2. The not-so-strange sensation of déjà vu in epilepsy

Chris J.A. Moulin, Jonathan Fortier—In healthy people, déjà vu is an infrequent mental experience, defined as “the phenomenological experience of recognizing a current situation and the awareness that this feeling of recognition is inappropriate” [83]. This feeling is perhaps more frequent in temporal lobe epilepsy (TLE) where it is reported as an ictal symptom (for review, see [84]). In fact, although patients with TLE who experience déjà vu may do so many times a month [85], the proportion who experience déjà vu is smaller than the proportion of people without epilepsy who experience it (controls 76.1%, TLE 63.1%) [86].

The current thinking is that déjà vu arises from ‘decoupled familiarity’ due to a brief perturbation of the temporal lobe, which generates an erroneous feeling of familiarity [84]. This hypothesis derives from a work studying TLE. It has been shown that the déjà vu experiences of people with and without TLE are phenomenologically similar [85]. This account of déjà vu resonates with historical views of its relation with memory retrieval and consciousness in the temporal lobe (e.g., [87]). It also fits well with contemporary views of memory function, which posit that the medial temporal lobe is responsible for the recognition of prior occurrence, and that two processes govern memory: recollection and familiarity. People act metacognitively on a feeling of familiarity (thought to be parahippocampally mediated) and initiate a retrieval search (involving adjacent recollection networks in the hippocampus). The interplay between familiarity and recollection in the temporal lobe memory system coordinates retrieval from memory, with a low-level automatic feeling of familiarity leading to a more effortful top-down recovery of contextual information [88].

In déjà vu, we propose that activation of the familiarity circuitry, independent of an appropriate stimulus, generates a feeling of familiarity, but the resulting search of memory returns nothing. The awareness that the familiarity is inappropriate, driven by top-down evaluations of the memory system and the failure to retrieve any memory to support the feeling of familiarity, generates the conflict that is at the heart of this sensation.

Thus, we arrive at a view of déjà vu that fits well with existing knowledge of the temporal lobe memory system and its disruption in TLE [89]. If déjà vu per se is the same in TLE, what clinical features that are associated with it are of relevance? Warren-Gash and Zeman [85] neatly summarized this issue by discussing déjà vu and ‘the company it keeps’. We have developed this idea in Fig. 5.2.1. In short, clinical déjà vu may be differentiated from healthy déjà vu only in terms of associated symptoms, experiences, and metacognitions. In TLE, déjà vu is likely to be associated with headache, gustatory sensations, emotional states, and depersonalization and derealization. Warren-Gash and Zeman [85] (p.147) report one description: “At work I was on the phone and a colleague asked ‘are you ok?’ The conversation seemed familiar; I felt warm and had a metallic taste in my mouth. I had to sit down.” This account includes familiarity but also features other sensations and phenomena (a metallic taste, warmth) which would be very unusual in a healthy person’s déjà vu experience.

As shown in Fig. 5.2.1, we propose that some of these associated phenomena are neural in their origin, based on the discharge from and into temporal regions and wider networks. These may involve gustatory illusions and other types of perceptual disturbances, but also the retrieval of information and prior scenes and physiological sensations and emotions (for a discussion of temporal lobe phenomena and the ‘dreamy states’, see [90]). The right side of the figure presents metacognitive evaluations of the phenomenon. These contain beliefs and thoughts associated with déjà vu, and the attribution and explanation of the experience, such as the possible anxiety associated with déjà vu. In TLE, it is possible that déjà vu signals a possible seizure or other epileptiform event, and so the experience is not as ‘meaningless’ as it is in controls.

The decoupled familiarity hypothesis and the role and nature of the associated phenomena in déjà vu in TLE warrant a closer examination. One limitation of previous research is that most measurement of déjà vu occurs after-the-fact, based on retrospective reports of prior experiences. Given that déjà vu is a fleeting and infrequent experience, this means that reports of déjà vu may be unreliable or lacking in detail. The most commonly used inventory of déjà vu (the IDEA; [91]) does not reflect recent advances in the characterization of déjà vu or our knowledge of the memory system. To further investigate déjà vu, we will need new measurement methods, such as on-the-spot recording of experiences on smart phones and questionnaires designed around theoretical concerns. If we can isolate déjà vu in the laboratory in healthy participants, we will need to examine it in patients with TLE. For the moment, however, the growing number of studies of déjà vu in TLE point to it being a memory glitch which exposes the nature of the memory system, and something which is not quite so strange after all.

5.3. Accelerated long-term forgetting in epilepsy

Nils Muhlert—Reports of memory problems are common in epilepsy clinics, but corresponding abnormalities are not always identified on standard clinical memory tests. An increasing number of studies point to the existence of accelerated long-term forgetting (ALF) in people with epilepsy, in which memory is near normal over short delays, but impaired over days or weeks. This form of memory loss has now been frequently documented in people with epilepsy (for a review, see [92]). Examining the prevalence of ALF and understanding its causes are of crucial importance both clinically, as it helps to explain why many people with epilepsy report poor memory despite performing within normal levels on standardized neuropsychological tests [93], and theoretically, since it may shed light on normal long-term memory processes.

Despite many studies reporting ALF in people with temporal lobe epilepsy (TLE), some studies document null findings (e.g., [94–96]). These difficulties in replicating ALF, or at least in separating it from forgetting over shorter, 30-minute delays, cast doubt on whether ALF is genuinely separable from more ‘typical’ patterns of accelerated forgetting (i.e., those that can be detected over immediate or 30-minute delays). Indeed, if ALF and ‘typical’ accelerated forgetting patterns are not distinguishable, then clinicians may avoid going to the lengths of organizing additional, very long-term testing sessions. This, therefore, has implications for resources, as well as for an understanding of the mechanisms underlying

ALF. Here, I present evidence to suggest that ALF studies with negative findings may not have fully accounted for factors that can influence rate of forgetting, and then summarize the evidence regarding the mechanisms underlying ALF.

5.3.1. Factors affecting rate of forgetting and their consideration in studies of ALF in epilepsy: Careful review of the broader literature on interindividual differences that influence forgetting has revealed that forgetting may be influenced by aging, by the method of learning information (and its vulnerability to ceiling and floor effects), the level of initial learning, overlearning of information, and potentially, general intellectual function [92]. Table 5.3.1 lists studies of ALF in people with epilepsy and considers whether they have accounted for these factors in their design, ranking them so that those toward the top have accounted for the highest number of these factors. The last column in the table also indicates whether each study reported evidence for ALF in people with epilepsy. From this, it can be seen that studies which failed to demonstrate ALF in TLE are among those that have accounted for the fewest factors.

These findings do not prove that studies which failed to show ALF in epilepsy would have done so had they used a different design. Indeed, current evidence suggests that ALF may be more prevalent in those with some forms of epilepsy, such as TLE, than others, such as idiopathic generalized epilepsy [97]. In addition, ALF has not been shown to be present in all people with TLE [97,98]. Given the inconsistent findings in this area, there is a need for further well-designed studies to probe the distinction between standard and nonstandard forms of forgetting in patients with epilepsy, which may provide insight into their separate or shared mechanisms.

5.3.2. Possible mechanisms for ALF: Accelerated long-term forgetting has typically been attributed to a failure of normal long-term memory processes, such as consolidation (as hypothesized by the ‘Standard Model’ of long-term memory, [99]) or stabilization (as hypothesized by the ‘Multiple Trace Theory’ of long-term memory, [100]). These models converge in predicting that processes which impede or compromise learning or early consolidation/stabilization of memories would prevent later retrieval of that information. Accelerated long-term forgetting studies have generally assumed that these processes must be those associated with epilepsy, particularly TLE, such as damage within temporal lobe structures or epileptiform activity. The evidence, however, only partially supports this view. Magnetic resonance imaging studies of people with ALF display multiple forms of structural damage, which indicate loss of volume [101,102], gliosis [102], and reduced neuronal density/mitochondrial function [103] of the hippocampus. Yet crucially, these studies failed to show any correlation between ALF and the extent of pathology, and so further information is needed to establish a causative role.

Neurophysiological studies have investigated links between ALF and clinical or subclinical epileptiform activity. One study reported greater forgetting over a four-week period in those with previous evidence of interictal discharges compared with those with normal EEG [104]. Similarly, forgetting over a four-day delay has been found to be greater in those with epileptiform discharges during that time period than those with normal EEG [105]. One question that arises from this work is whether activity during sleep accounts for ALF,

particularly since impaired memory in people with epilepsy has been identified following 24-hour delays [106], sleep complaints are common in people with simple and complex partial seizures [107], people with Transient Epileptic Amnesia (who commonly display ALF) often experience amnesic episodes upon awakening prior to treatment [108], and people with TLE and bilateral mesial temporal sclerosis show reduced strengthening of memories during sleep [109].

This view is in the process of being overturned, as recent research instead demonstrates that forgetting is greater during 12-hour periods of wakefulness than 12-hour periods of sleep [110]. This is in line with an earlier pilot study of forgetting in epilepsy [111] and further supported by animal studies, as rat models of TLE show normal replay of behavior-driven sequences of single cell hippocampal activity during sleep [112]. In contrast, these three studies suggest that activity during periods of wakefulness following learning, possibly within the first few hours [113], may be more closely linked to ALF, as would be predicted by interference-based models of amnesia (e.g., [114,115]). These exciting findings now require further carefully designed studies to examine which specific processes cause ALF. This information may reveal potential avenues for its treatment, in order to ameliorate a memory disorder that can have a serious negative impact upon independence, employment, education, social relationships, and quality of life in people with epilepsy.

5.4. Epilepsy and autobiographical memory

Adam Zeman—Autobiographical memory (AM) allows us to access memories about our own lives [116,117]. These include memories for facts, such as where we lived when we were five or which year we left school, and memories for episodes, like a first date or a nerve-wracking public performance. Episodic AM calls on our remarkable capacity for ‘mental time travel’ or ‘autonoetic consciousness’, the ability to ‘relive’ or ‘re-experience’ events from the past, sometimes in vivid sensory detail. In William James’ words, such memories have the ‘warmth and intimacy’ that attends experiences ‘appropriated by the thinker as his own’. They call upon a distributed network of brain regions substantially overlapping with those of the ‘default mode network’, the set of brain areas especially active in the resting brain which is often deactivated by externally imposed cognitive tasks [118,119]. Proposed functions for AM include an important role in interpersonal relationships, including the mediation of social emotions such as pride or shame, and a contribution to imaginative thinking, ‘future thinking’, and problem-solving.

Episodic AM is a late developing and vulnerable form of memory. Impairment of episodic AM, out of proportion to impairment of other subtypes of memory, has been described in association with diffuse cerebral pathology [120], following damage to the right frontotemporal region [121,122], damage to visual cortices [123], and in association with temporal lobe epilepsy (TLE) [124–126]. In the context of temporal lobe epilepsy (TLE), it occurs in refractory TLE [125,127,128], among patients who have undergone temporal lobectomy [128–130], in patients with adult-onset drug-sensitive TLE [103], as the predominant feature of TLE in patients with subtle TL seizures [131], and as a prodromal presentation of TLE [132].

Transient Epileptic Amnesia (TEA) is a recently described subtype of TLE presenting with predominantly amnesic symptoms, usually in middle aged or elderly individuals [108,133,134]. The seizures of TEA often occur on waking and typically involve periods of anterograde and/or retrograde amnesia lasting for around 30 min. The sufferer may question his or her companions repetitively. Retrograde amnesia sometimes predominates so that patients may 'remember not being able to remember'. Two-thirds of patients with TEA will have more classical manifestations of epilepsy in at least some attacks. These include olfactory hallucinations in almost half, automatisms, and brief periods of unresponsiveness. Transient Epileptic Amnesia is associated with subtle hippocampal, perirhinal, and orbitofrontal cortical volume loss [101,135].

The seizures of TEA generally respond promptly to modest doses of standard anticonvulsant drugs. However, the majority of patients also report interictal memory difficulties developing at around the same time as their seizures, but persisting — at least to some degree — despite successful treatment of the seizures. Autobiographical memory loss is the most frequent of these symptoms, occurring in around three-quarters of patients [136,137]. Half of the affected patients complain of accelerated long-term forgetting (ALF), the loss of information over hours to days which appears to have been successfully acquired at shorter intervals [97,106]. A third of the patients describe difficulties with topographical memory, manifesting in problems navigating previously familiar routes or in recognizing previously familiar landmarks. The combination of amnesic seizures occurring in midlife, often on waking, olfactory hallucinations, and persistent AM loss, ALF, and topographical amnesia is distinctive and 'syndromic' [138]. The underlying cause of TEA remains unknown — cerebrovascular disease, neurodegenerative disorder, and autoimmune encephalitis are all plausible candidates, but there is no clear evidence for these in the majority of cases.

We have recently encountered two patients whose cases illustrate the strikingly disproportionate AM loss, associated with symptomatic ALF, occasionally seen among people with TLE:

- i. ST is a 47-year-old scientist with a successful academic career. He has a history of subtle TLE, starting in childhood when it was treated for around 6 years, but persisting into adulthood, untreated until recently. Despite normal performance on standard memory tests, and reassurance that his memory was 'normal' following neuropsychological evaluation, ST has no ability to reexperience autobiographical memories older than about 2 months.
- ii. MB is a 74-year-old man who had three temporal lobe seizures in the 1980s, with several episodes suggestive of TEA in recent years. He also has two episodes of major depression, treated with psychotropic drugs. In 2007, he noticed a profound amnesia for autobiographical events, erasing his memory for highly salient events such as his two weddings, the births of children, and family holidays. Like ST, despite this striking autobiographical amnesia, he was reassured that his memory was normal following standard neuropsychological evaluation.

ST and MB give strikingly similar accounts of the nature and impact of their memory disorder. Both speak of their past in terms of an impenetrable ‘void’. Both have functioned successfully in professional capacities largely on the basis of ‘factual’ as opposed to episodic knowledge, though the relative preservation of their episodic memory for recent events has undoubtedly been helpful. Both describe a sense of estrangement from their past selves, due to their inability to recollect so many important events from their past, difficulties in sustaining friendships due to the loss of shared history, a pervasive sense of isolation due to their difficulty in explaining their situation to others, and difficulties with future thinking and open-ended problem solving. Both have developed a range of strategies to help them deal with their disorder and have contemplated the creation of a full-blown ‘prosthetic memory’.

Thus, episodic autobiographical memory is an important and vulnerable aspect of human memory. It is often affected by TLE and can occasionally be its presenting features. It is particularly prominent and frequent in TEA, a subtype of TLE characterized by recurrent episodes of amnesia in middle-aged people, often occurring on waking. A range of questions remain unanswered: which phase or phases of memory processing are disturbed in patients with disproportionate autobiographical amnesia due to epilepsy? What are the contributions of functional and structural pathology? Finally, of greatest interest to our patients, to what extent can anticonvulsant therapy prevent or ameliorate this disabling form of memory disorder?

6. Large scale brain networks in epileptic brain and mind

6.1. Interactions between epileptic discharges and the Default Mode Network

Jean Gotman—Interictal epileptic discharges (IEDs) are brief events visible in the EEG of many patients with epilepsy. In generalized epilepsy, IEDs are widespread and believed to involve thalamocortical circuits. They are not usually accompanied by any visible behavioral manifestations but have been shown to cause short delays or occasional errors in answers to brief stimuli occurring at the time of the IED. In focal epilepsy, IEDs are focal and believed to involve a small part of the brain, typically a fraction of a lobe. They have been associated with errors or lack of responses in tasks directly involving the region of the IED, at the time of the IED. For example, an IED in the occipital cortex may alter response to a visually presented stimulus [139,140].

6.1.1. EEG-fMRI of IEDs: A relatively recent method, EEG-fMRI, allows the investigation of metabolic changes in the whole brain at the time of IEDs. The method consists in recording the scalp EEG while performing an fMRI scan. It is then possible to measure the BOLD (blood oxygenation level dependent) changes in the whole brain at the time of IEDs observed in the EEG. This allows us to evaluate if regions other than the regions involved in the direct generation of the IEDs are also affected at the time of the IED. For instance, one can ask if an EEG spike generated in the temporal lobe affects only the temporal lobe, or has consequences in other brain regions. The EEG-fMRI studies have demonstrated increases in BOLD signal in the regions thought to be the primary generators of IEDs. This provides a

valuable tool for the evaluation of the source of epileptic discharges, which is important in the presurgical evaluation of patients with medically intractable epilepsy [141].

6.1.2. The Default Mode Network: The fMRI studies performed in healthy subjects during a variety of cognitive tasks revealed that a network of brain regions becomes deactivated at the time of many tasks. Whereas the region directly involved in a task (for instance the left central cortex for a task involving movement of the right hand) is *activated* (increase in BOLD signal), at the same time, the Default Mode Network (DMN) is deactivated (decrease in BOLD). The DMN consists primarily of the posterior cingulate and inferior parietal and anterior frontal cortices bilaterally (Fig. 6.1.1). It was found that this group of regions is deactivated with many tasks, independently of the nature of the task [142]. Because fMRI only makes measurements of BOLD changes between two conditions (it does not make absolute measurements), it was hypothesized that the regions of the DMN are actually active between tasks and become inactive or less active at the time of a task. This activity at the time of presumed rest (between task) has been considered as representing the fact that during rest, the brain is involved in monitoring the internal and external environments, whereas at the time of the task, this monitoring decreases while the brain concentrates on the task itself.

6.1.3. IEDs and the Default Mode Network: It was observed in a group study of patients with idiopathic generalized epilepsy [143] that, at the time of generalized spike and wave discharges, the largest activation was in the thalamus; other regions with increased BOLD included the mesial frontal regions, the cerebellum, and regions that were interpreted as being in the insulae but that may have been in the putamen in light of recent findings [144]. There was also an unexpected reduction in BOLD activity in the DMN. This reduction, in a network presumed to be involved in monitoring the environment, was thought to possibly contribute to the decreased awareness of the environment observed during spike and wave discharges. The neurophysiological mechanisms linking the thalamocortical discharges and the DMN are not known. The fMRI measurements only have a time resolution of 2 or 3 s, and it is not certain if the deactivation of the DMN comes before, after, or at the same time as the thalamocortical activity. Results in this respect have been contradictory.

Surprisingly, it was also found that focal IEDs result in partial deactivation of the DMN. Group studies of patients with temporal lobe epilepsy [145,146] and patients with frontal lobe epilepsy [145] show that some nodes of the DMN, sometimes ipsilaterally and sometimes contralaterally to the focus, are deactivated (Fig. 6.1.2). It may be presumed that, at the time of focal IEDs, there is a reduction in activity of the DMN, possibly resulting in a brief and partial reduction in ability to monitor the environment.

The above results, therefore, indicate that at the time of focal or generalized IEDs, regions distant from the generators are also involved. Whereas the generating regions show an increase in BOLD signal reflecting the intense neuronal activity of the epileptic discharge, these distant regions show a decrease in BOLD signal, reflecting a decrease in neuronal activity in a region normally active at rest.

6.2. The subcortical structures in partial epilepsy: fMRI and intracerebral recording studies of basal ganglia in epilepsy

Ivan Rektor, Robert Kuba, Milan Brázdil, Jan Chrastina, Irena Rektorová, Eva Bujnošková, Radek Marek—The growing knowledge of brain functional changes related to partial epilepsies has led to the hypothesis that epilepsy affects large neural networks involved in normal brain function. Brain impairment distant from the epileptic focus and not revealed by damage of underlying neuronal substrate, e.g., cognitive decline, could be explained by a disturbance of brain network connectivity. The epileptic activity could lead to the modulation of widespread physiological networks via subcortical structures [146–148]. We have tested the hypothesis that the modulation of cortical functional connectivity (FC) via the basal ganglia (BG) is affected in partial epilepsy.

In the first fMRI study, the impact of epilepsy on the (FC) of the BG in two large-scale resting state networks (RSN), the default mode network (DMN) and somatomotor network (SMN), was studied in 10 healthy control subjects (HC) and 24 patients with epilepsy — 14 patients with extratemporal epilepsy and 10 patients with temporal epilepsy (TLE).

Resting state fMRI data were obtained using the 1.5 T Siemens Symphony scanner. The Group ICA of fMRI Toolbox (GIFT) program was used for independent component analysis. The component representing the DMN was chosen according to a spatial correlation with a mask typical for DMN. The FC between the putamen and the primary somatomotor cortex was studied to assess the connectivity of the putamen within the BG-RSN. A second-level analysis was calculated to evaluate differences among the groups using SPM software.

In HC, the BG were functionally negatively correlated with typical DMN regions, such as the posterior medial and prefrontal cortices. In patients with epilepsy as compared to HC, the magnitude of anticorrelation between the putamen and brain regions engaged in the DMN was significantly lower. The disturbed FC of the BG in patients with epilepsy as compared with HC was further illustrated by a significant decrease in connectivity between the left/right putamen and the left/right somatomotor cortex, i.e., between regions that are engaged in the BG-RSN [149].

In the second fMRI study, the mutual correlation of 90 cerebral areas was calculated in 20 healthy controls, 22 patients with TLE (left 9, right 13), and 22 patients with extratemporal epilepsy (left in 9, right in 13). We used a partial least square method applied to the group-specific correlation matrices to find intergroup differences in overall brain functional connectivity. The whole brain was parceled to the 90 regions according to the AAL atlas. The representative time-series of each ROI were cross-correlated to form subject-specific 90×90 correlation matrices, which were averaged to form the group-specific correlation matrices.

We found decreased FC of the BG and the rest of the brain for each of the patient groups, except those with right-sided temporal lobe epilepsy. Using the graphical theory approach, the loss of connectivity strength of the BG was observed in patients with epilepsy; the effect was found in low correlation coefficients. Further, we found that the significance of the

putamen and pallidum for overall brain connectivity differed between the healthy controls and the patient groups.

In addition, we have performed stereoelectroencephalography (SEEG) recordings in eight candidates for epilepsy surgery as treatment for intractable TLE. Diagonal multilead electrodes were targeted into the amygdalohippocampal complex via the frontal approach and passed through the BG with their several leads. The BG activity was studied interictally and ictally during 16 complex partial and 4 secondarily generalized seizures.

The human striatum and pallidum did not generate specific epileptic EEG activity, neither interictal nor ictal, not even when the seizures were generalized. The visually observed slowing and amplitude increase in the BG was found with the spread of the epileptic activity from the hippocampus to other areas [150]. In five patients, the time frequency analysis and the power spectral analysis were used to analyze the preictal and ictal EEG. Significant frequency components of 2–10 Hz, with the maximum in the 5- to 10-Hz range, were constantly observed in the BG [151]. The frequency of this component slowed by around 2 Hz during seizures. There was a significant ictal increase of power spectral density in all frequency ranges. The changes in the BG were consistent while the seizure activity spread over the cortex, and they partially persisted after the clinical seizure ended. They were inconsistently present in the first period after the seizure onset.

6.2.1. Discussion and conclusion: Unlike in HC, the BG in TLE are not correlated with a DMN component, and the FC of the BG is decreased with SMN. When studying the intergroup differences in the overall brain of functional connectivity using specific correlation matrices, we found decreased functional connectivity of the BG and the rest of the brain for each of the patient groups, except the group with right-temporal lobe epilepsy. The graphical theory approach confirmed the distributed impairment of cortical connectivity in epilepsy and also that the significance of the putamen and pallidum for overall brain connectivity differs between the healthy controls and the groups with epilepsy. Based on our SEEG studies, the time course of the oscillatory activities together with the absence of the epileptiform EEG activities in the BG lead us to suggest an inhibitory role of the BG in temporal lobe seizures [152]. This “filtering effect” of the BG may act as an obstacle to the spread of ictal activity.

The BG may modulate cortical large scale networks, and this modulation is affected by partial epilepsy. The epileptic process reduces the FC between the BG and large-scale brain networks. This may reflect an altered function of the BG in epilepsy. The BG should be seriously considered as a potential target for neuromodulatory and pharmacological treatments of epilepsy.

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6.3. Mapping language and epilepsy networks in the developing brain

Vladmir Komárek, M. Kyn I, J. Šanda, M. Vránová, R. Vydrová—Recent research showed the importance of language-associated pathways during brain development as well as in the presurgical assessment of children with refractory epilepsy, namely with epileptogenic zone in language-related regions [153–156]. Currently, language studies agree on the concept of two interacting pathways connecting the language-relevant regions in the temporal and the frontal cortices. Within this dual stream model, the ventral pathway connects the temporal cortex with the pars orbitalis and triangularis via the inferior frontooccipital fascicle (IFOF), uncinate fascicle (UF) and inferior longitudinalis fascicle (ILF). The arcuate fascicle (AF) is the main constituent of the dorsal pathway. Imaging studies have suggested that bilateral processing of language is more common than previously thought, for example, when semantic processing is involved. magnetic resonance diffusion tensor imaging that delineates white matter tracts, characterizing connectivity patterns over large areas of the whole brain, has identified not only physiological changes during brain development, but also abnormalities associated with epilepsy.

We studied dorsal and ventral streams as identified by diffusion tensor imaging (DTI). We performed DTI in 38 children with developmental dysphasia (DD), in 39 healthy children, and in 30 children with intractable epilepsy (see Table 6.3.1).

With tractography, bilateral clusters of AF were detected manually from MR data; ventral streams were identified using regions of interest (Fig. 6.3.1). Additionally, pyramidal tract and optic radiation were most commonly examined in the group with epilepsy (Fig. 6.3.2).

Diffusion tensor imaging parameters such as fractional anisotropy (FA), apparent diffusion coefficient (ADC), volume, and count of fibers were established. Statistical analysis was performed using tests as appropriate.

The results show insufficient arcuate fascicle and ventral streams in children with DD. In the group with epilepsy, a significant decrease of long-term permanent deficits (especially hemiparesis, but also visual field and language impairments) has been seen.

Our findings show the importance of ventral streams, namely IFOF, in the language development, and indicate their importance in pediatric patients undergoing epilepsy surgery to preserve their specific language skills.

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References

1. Dante Santagata, M. Il romanzo della sua vita. Milano: Mondadori; 2012.
2. Monaco F, Mula M. Cesare Lombroso and epilepsy 100 years later: an unabridged report of his original transactions. *Epilepsia*. 2011; 52(4):679–688. [PubMed: 21320108]

3. Engle J Jr. Popular music in epilepsy Neil Perceval Young. *Epilepsy Behav.* 2013; 28:266–267.
4. Young, N. *Waging heavy peace: a hippie dream.* London: Blue Rider Press, Penguin Group; 2012.
5. Baxendale S. The representation of epilepsy in popular music. *Epilepsy Behav.* 2008; 12:165–169. [PubMed: 17980673]
6. Nutton, V. *Ancient medicine.* London: Routledge; 2004.
7. Ober, J. *Mass and elite in democratic Athens.* Princeton: Princeton University Press; 1991.
8. Temkin, O. *The falling sickness.* Baltimore: Johns Hopkins University Press; 1971.
9. Jouanna, J. *Hippocrates.* Baltimore: Johns Hopkins University; 1999.
10. Jones, WHS., editor. *Hippocrates. The sacred disease.* Cambridge, MA: Harvard University Press; 1923. [and trans]
11. Jones, WHS., editor. *Hippocrates. Airs, waters, places.* Cambridge, MA: Harvard University Press; 1923. [and trans]
12. Witherington, ET., editor. *Hippocrates. On wounds in the head.* Cambridge, MA: Harvard University Press; 1928. [and trans]
13. Hippocrates. *Epidemics VI.* In: Littré, E., editor. *Oeuvres complètes.* Vol. 5. Paris: J.-B. Baillière; 1846. [and trans]
14. Holmes B. Euripides in the flesh. *Class Antiq.* 2008; 27:231–281.
15. Dodds, ER. *The Greeks and the irrational.* Berkeley: University of California Press; 1962.
16. Edelstein, EJ. *Edelstein L Asclepius II: interpretation.* Baltimore: Johns Hopkins University Press; 1945.
17. Spencer, WG., editor. *Celsus. De medicina I.* Cambridge, MA: Harvard University Press; 1935. [and trans]
18. Siegel, RE. *Galen on psychology, psychopathology and function and diseases of the nervous system.* Basel: Karger; 1973.
19. Drabkin, IE., editor. *Aurelianus Caelius. On acute disease and on chronic diseases.* Chicago: University of Chicago Press; 1950. [and trans]
20. Kinnier Wilson JV, Reynolds EH. Translation and analysis of a cuneiform text forming part of a Babylonian treatise on epilepsy. *Med Hist.* 1990; 34:185–198. [PubMed: 2187129]
21. Adams, F., editor. *Hippocrates. On the sacred disease.* <http://classics.mit.edu/Hippocrates/sacred.html>
22. Dölger F. Der Einfluss des Origenes auf die Beurteilung der Epilepsie und Mondsucht im christlichen Altertum. *Antike Christentum.* 1934; 4:95–110.
23. Wolf, P. Sociocultural history of epilepsy. In: Panayiotopoulos, CP., editor. *Atlas of epilepsies.* London: Springer; 2010. p. 35–43.[part 2.]
24. Wolf P, Trinka E, Bauer G. Absence status epilepticus: the first documented case? *Epilepsia.* 2007; 48(Suppl. 8):4–5.
25. Wolf P. Descriptions of clinical semiology of seizures in literature. *Epileptic Disord.* 2006; 8:3–10. [PubMed: 16567320]
26. Devinsky O, Lai G. Spirituality and religion in epilepsy. *Epilepsy Behav.* 2008; 12:636–643. [PubMed: 18171635]
27. Diamantis A, Sidiropoulou K, Magiorkinis K. Epilepsy during the Middle Ages, the Renaissance and the Enlightenment. *J Neurol.* 2010; 257:691–698. [PubMed: 20037763]
28. Picard F, Craig AD. Ecstatic epileptic seizures: a potential window on the neural basis for human self-awareness. *Epilepsy Behav.* 2009; 16:539–546. [PubMed: 19836310]
29. Landtblom AM, Lindehammar H, Karlsson H, Craig AD. Insular cortex activation in a patient with “sensed presence”/ecstatic seizures. *Epilepsy Behav.* 2011; 20:714–718. [PubMed: 21440512]
30. Picard F, Scavarda D, Bartolomei F. Induction of a sense of bliss by electrical stimulation of the anterior insula. *Cortex.* 2013; 49:2935–2937. [PubMed: 24074887]
31. Hansen BA, Brodtkorb E. Partial epilepsy with “ecstatic” seizures. *Epilepsy Behav.* 2003; 4:667–673. [PubMed: 14698700]
32. Kanemoto K, Kawasaki J, Kawai I. Post-ictal psychosis: a comparison with acute interictal and chronic psychosis. *Epilepsia.* 1996; 37:551–556. [PubMed: 8641232]

33. Nadkarni S, Arnedo V, Devinsky O. Psychosis in epilepsy patients. *Epilepsia*. 2007; 48(Suppl. 9): 17–19. [PubMed: 18047594]
34. Dewhurst K, Beard AW. Sudden religious conversions in temporal lobe epilepsy. *Br J Psychiatry*. 1970; 117:497–507. [PubMed: 5480697]
35. Benson DF. The Geschwind syndrome. *Adv Neurol*. 1991; 55:411–421. [PubMed: 2003418]
36. Bear DM, Fedio P. Quantitative analysis of interictal behavior in temporal lobe epilepsy. *Arch Neurol*. 1977; 34:454–467. [PubMed: 889477]
37. Devinsky, O., Vorkas, C., Barr, WB., Hermann, BP. Personality disorders in epilepsy. In: Engel, J., Pedley, TA., editors. *Epilepsy: a comprehensive textbook*. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 2105–2112.
38. Trimble M, Freeman A. An investigation of religiosity and the Gastaut-Geschwind syndrome in patients with temporal lobe epilepsy. *Epilepsy Behav*. 2006; 9:407–414. [PubMed: 16919503]
39. Waxman SG, Geschwind N. Hypergraphia in temporal lobe epilepsy. *Neurology*. 1974; 24:629–636. [PubMed: 4209727]
40. Skar J. Knut Rasmusson Nordgarden eller Visknut. *Det norske samlage*. 1898
41. Bjørnson, B. Wise-Knut. New York: The Premier Press; 1909.
42. Fosse I. Vis-Knut Den framsynte fra Gausdal Vis-Knut-heimens venner. 1983
43. Møller A. Vis-Knut JW Cappelen Forlag. 1980
44. Devinsky J, Schachter S. Norman Geschwind's contribution to the understanding of behavioral changes in temporal lobe epilepsy: the February 1974 lecture. *Epilepsy Behav*. 2009; 15:417–424. [PubMed: 19640791]
45. Kottek SS. From history of the medicine: epilepsy in ancient Jewish sources. *Isr J Psychiatry Relat Sci*. 1988; 25:3–11. [PubMed: 3075204]
46. Feinsod M. Neurology in the Bible and the Talmud. *Handb Clin Neurol Hist Neurol*. 2009; 95:37–47.
47. Altschuler EL. Did Ezekiel have temporal lobe epilepsy? *Arch Gen Psychiatry*. 2002; 59:561–562. [PubMed: 12044200]
48. Wizman S. Epilepsy in the Talmud. *Derech Hateva*. 2001:37–39.
49. Bear DM. Temporal lobe epilepsy—a syndrome of sensory-limbic hyperconnection. *Cortex*. 1979; 15:357–384. [PubMed: 540509]
50. Devinsky O. Religious experiences and epilepsy. *Epilepsy Behav*. 2003; 4:76–77. [PubMed: 12609231]
51. Wuerfel J, Krishnamoorthy ES, Brown RJ, Lemieux L, Koepp M, Tebartz van Elst L, et al. Religiosity is associated with hippocampal but not amygdala volumes in patients with refractory epilepsy. *J Neurol Neurosurg Psychiatry*. 2004; 75:640–642. [PubMed: 15026516]
52. Tucker DM, Novelly RA, Walker PJ. Hyperreligiosity in temporal lobe epilepsy: redefining the relationship. *J Nerv Ment Dis*. 1987; 175:181–184. [PubMed: 3819715]
53. Swinkels WAM, van Emde Boas W, Kuyk Y, van Dyck R, Spinhoven P. Interictal depression, anxiety, personality traits and psychological dissociation in patients with temporal lobe epilepsy (TLE) and extra-TLE. *Epilepsia*. 2006; 47:2092–2103. [PubMed: 17201709]
54. Gosselin N, Peretz I, Noulhiane M, Hasboun D, Beckett C, Baulac M, et al. Impaired recognition of scary music following unilateral temporal lobe excision. *Brain*. 2005; 128:628–640. [PubMed: 15699060]
55. Bonora A, Benuzzi F, Monti G, Mirandola L, Pugnaghi M, Nichelli P, et al. Recognition of emotions from faces and voices in medial temporal lobe epilepsy. *Epilepsy Behav*. 2011; 20:648–654. [PubMed: 21459049]
56. Meletti S, Benuzzi F, Cantalupo G, Rubboli G, Tassinari CA, Nichelli P. Facial emotion recognition impairment in chronic temporal lobe epilepsy. *Epilepsia*. 2009; 50:1547–1559. [PubMed: 19175397]
57. Adolphs R, Russel JA, Tranel D. A role for the human amygdala in recognizing emotional arousal from unpleasant stimuli. *Psychol Sci*. 1999; 10:167–171.
58. Berntson GG, Bechara A, Damasio H, Tranel D, Cacioppo JT. Amygdala contribution to selective dimensions of emotion. *Soc Cogn Affect Neurosci*. 2007; 2:123–129. [PubMed: 18414599]

59. Meletti S, Picardi A, De Risi M, Monti G, Esposito V, Grammaldo LG, et al. The affective value of faces in patients achieving long-term seizure freedom after temporal lobectomy. *Epilepsy Behav.* 2014; 36C:97–101.
60. van der Meer L, Groenewold NA, Nolen WA, Pijnenborg M, Aleman A. Inhibit yourself and understand the other: neural basis of distinct processes underlying Theory of Mind. *NeuroImage.* 2011; 56:2364–2374. [PubMed: 21440642]
61. Anderson AK, Spencer DD, Fulbright RK, Phelps EA. Contribution of the anteromedial temporal lobes to the evaluation of facial emotion. *Neuropsychology.* 2000; 14:526–536. [PubMed: 11055255]
62. Meletti S, Benuzzi F, Rubboli G, Cantalupo G, Stanzani Maserati M, Nichelli P, et al. Impaired facial emotion recognition in early-onset right mesial temporal lobe epilepsy. *Neurology.* 2003; 60(3):426–431. [PubMed: 12578923]
63. Olson IR, Plotzker A, Ezzyat Y. The enigmatic temporal pole: a review of findings on social and emotional processing. *Brain.* 2007; 130(Pt 7):1718–1731. [PubMed: 17392317]
64. Adolphs R, Tranel D, Damasio H. Emotion recognition from faces and prosody following temporal lobectomy. *Neuropsychology.* 2001; 15(3):396–404. [PubMed: 11499994]
65. McClelland S III, Garcia RE, Peraza DM, Shih TT, Hirsch LJ, Hirsch J, et al. Facial emotion recognition after curative nondominant temporal lobectomy in patients with mesial temporal sclerosis. *Epilepsia.* 2006; 47(8):1337–1342. [PubMed: 16922878]
66. Schacher M, Winkler R, Grunwald T, Kraemer G, Kurthen M, Reed V, et al. Mesial temporal lobe epilepsy impairs advanced social cognition. *Epilepsia.* 2006; 47:2141–2146. [PubMed: 17201715]
67. Shaw P, Lawrence E, Bramham J, Brierley B, Radbourne C, David AS. A prospective study of the effects of anterior temporal lobectomy on emotion recognition and theory of mind. *Neuropsychologia.* 2007; 45:2783–2790. [PubMed: 17568631]
68. Benuzzi F, Zamboni G, Meletti S, Serafini M, Lui F, Baraldi P, et al. Recovery from emotion recognition impairment after temporal lobectomy. *Front Neurol.* 2014; 5:92. [PubMed: 24936197]
69. Amlerova J, Cavanna AE, Bradac O, Javurkova A, Raudenska J, Marusic P. Emotion recognition and social cognition in temporal lobe epilepsy and the effect of epilepsy surgery. *Epilepsy Behav.* 2014; 36:86–89. [PubMed: 24892754]
70. Knecht S, Dräger B, Flöel A, Lohmann H, Breitenstein C, Deppe M, et al. Behavioural relevance of atypical language lateralization in healthy subjects. *Brain.* 2001; 124:1657–1665. [PubMed: 11459756]
71. Klein D, Milner B, Zatorre RJ, Visca R, Olivier A. Cerebral organization in a right-handed trilingual patient with right-hemisphere speech: a positron emission tomography. *Neurocase.* 2002; 8:369–375. [PubMed: 12499411]
72. Klein D, Milner B, Zatorre RJ, Zhao V, Nikelski J. Cerebral organization in bilinguals: a PET study of Chinese-English verb generation. *Neuroreport.* 1999; 9:2841–2846.
73. Klein D, Mok K, Chen JK, Watkins KE. Age of language learning shapes brain structure: a cortical thickness study of bilingual and monolingual individuals. *Brain Lang.* 2014; 131:20–24. [PubMed: 23819901]
74. Mohades SG, Struys E, Van Schuerbeek P, Mondt K, Van De Craen P, Luypaert R. DTI reveals structural differences in white matter tracts between bilingual and monolingual children. *Brain Res.* 2012; 1435:72–80. [PubMed: 22197702]
75. Hosoda C, Tanaka K, Nariyai T, Honda M, Hanakawa T. Dynamic neural network reorganization associated with second language vocabulary acquisition: a multimodal imaging study. *J Neurosci.* 2013; 33:13663–13672. [PubMed: 23966688]
76. Alessio A, Pereira FRS, Sercheli MS, Rondina JM, Ozelo HB, Bilevicius E, et al. Brain plasticity for verbal and visual memories in patients with mesial temporal lobe epilepsy and hippocampal sclerosis: an fMRI study. *Hum Brain Mapp.* 2013; 34:186–199. [PubMed: 22038783]
77. Brázdil M, Zákopán J, Kuba R, Fanfrdlová Z, Rektor I. Atypical hemispheric language dominance in left temporal lobe epilepsy as a result of the reorganization of language functions. *Epilepsy Behav.* 2003; 4:414–419. [PubMed: 12899862]

78. Brázdil M, Chlebus P, Mikl M, Pažourková M, Krupa P, Rektor I. Reorganization of language-related neuronal networks in patients with left temporal lobe epilepsy — an fMRI study. *Eur J Neurol*. 2005; 12:268–275. [PubMed: 15804243]
79. Chlebus P, Brázdil M, Hlušík P, Mikl M, Pažourková M, Krupa P, et al. Handedness shift as the consequence of motor cortex reorganization after early functional impairment in left temporal lobe epilepsy — an fMRI case report. *Neurocase*. 2004; 4:326–329.
80. Janszky J, Jokeit H, Heinemann D, Schulz R, Woermann FG, Ebner A. Epileptic activity influences the speech organization in medial temporal lobe epilepsy. *Brain*. 2003; 126:2043–2051. [PubMed: 12821521]
81. Kim H, Kim J, Yi S, Son EI. Evidence for the pathological right-handedness hypothesis. *Neuropsychology*. 2001; 15:510–515. [PubMed: 11761040]
82. Brewer, WF. The theoretical and empirical status of the flashbulb memory hypothesis. In: Winograd, E., Neisser, U., editors. *Affect and accuracy in recall*. Cambridge: Cambridge University Press; 1992. p. 274-305.
821. Kapur, N., Abbott, P., Graham, KS., Simons, JS. The neuropsychology of human flashbulb memory. In: Schroeder, J., Brecht, FG., editors. *Das autobiographische Gedächtnis*. Heidelberg: AKA GmbH; 2009. p. 75-99.
822. Metternich B, Wagner K, Schulze-Bonhage A, Buschmann F, McCarthy RA. Flashbulb memories in patients with temporal lobe epilepsy. *Epilepsy Behav*. 1992; 28(1):71–77.
823. Maguire EA. Neuroimaging studies of autobiographical event memory. *Philos Trans R Soc Lond B Biol Sci*. 1992; 356(1413):1441–1451.
83. O'Connor AR, Moulin CJA. Recognition without identification, erroneous familiarity, and déjà vu. *Curr Psychiatry Rep*. 2010; 12:165–173. [PubMed: 20425276]
84. Illman NA, Butler CR, Souchay C, Moulin CJA. Déjà experiences in temporal lobe epilepsy. *Epilepsy Res Treat*. 2012; 2012:539567. <http://dx.doi.org/10.1155/2012/539567>. [PubMed: 22957231]
85. Warren-Gash C, Zeman A. Is there anything distinctive about epileptic déjà vu? *J Neurol Neurosurg Psychiatry*. 2014; 85:143–147. [PubMed: 23315620]
86. Adachi N, Akanuma N, Ito M, Adachi T, Takekawa Y, Adachi Y, et al. Two forms of déjà vu experiences in patients with epilepsy. *Epilepsy Behav*. 2010; 18:218–222. [PubMed: 20494621]
87. Penfield W, Perot P. The brain's record of auditory and visual experience. *Brain*. 1963; 86:595–696. [PubMed: 14090522]
88. Moulin CJA, Souchay C, Morris RG. The cognitive neuropsychology of recollection. *Cortex*. 2013; 9:1445–1451.
89. Martin CB, Mirsattari SM, Pruessner JC, Pietrantonio S, Burneo JG, Hayman-Abello B, et al. Déjà vu in unilateral temporal-lobe epilepsy is associated with selective familiarity impairments on experimental tasks of recognition memory. *Neuropsychologia*. 2012; 50:2981–2991. [PubMed: 22841992]
90. Bartolomei F, Barbeau E, Gavaret M, Guye M, McGonigal A. Cortical stimulation study of the role of rhinal cortex in déjà vu and reminiscence of memories. *Neurology*. 2004; 63:858–864. [PubMed: 15365137]
91. Sno HN, Linszen DH. The déjà vu experience: remembrance of things past? *Am J Psychiatry*. 1990; 147:1587–1595. [PubMed: 2244635]
92. Elliott G, Isaac CL, Muhlert N. Measuring forgetting: a critical review of accelerated long-term forgetting studies. *Cortex*. 2014; 54c:16–32.
93. Witt JA, Glockner C, Helmstaedter C. Extended retention intervals can help to bridge the gap between subjective and objective memory impairment. *Seizure*. 2012; 21:134–140. [PubMed: 22119172]
94. Giovagnoli AR, Casazza M, Avanzini G. Visual learning on a selective reminding procedure and delayed recall in patients with temporal lobe epilepsy. *Epilepsia*. 1995; 3:704–711.
95. Bell BD. WMS-III logical memory performance after a two-week delay in temporal lobe epilepsy and control groups. *J Clin Exp Neuropsychol*. 2006; 28:1435–1443. [PubMed: 17050268]

96. Bell BD, Fine J, Dow C, Seidenberg M, Hermann BP. Temporal lobe epilepsy and the selective reminding test: the conventional 30-minute delay suffices. *Psychol Assess.* 2005; 17:103–109. [PubMed: 15769231]
97. Muhler N, Grunewald RA, Hunkin NM, Reuber M, Howell S, Reynders H, et al. Accelerated long-term forgetting in temporal lobe but not idiopathic generalised epilepsy. *Neuropsychologia.* 2001; 49:2417–2426.
98. Gascoigne MB, Smith ML, Barton B, Webster R, Gill D, Lah S. Accelerated long-term forgetting in children with temporal lobe epilepsy. *Neuropsychologia.* 2014; 59:93–102. [PubMed: 24784007]
99. Alvarez P, Squire LR. Memory consolidation and the medial temporal lobe: a simple network model. *Proc Natl Acad Sci U S A.* 1994; 91:7041–7045. [PubMed: 8041742]
100. Nadel L, Moscovitch M. Memory consolidation, retrograde amnesia and the hippocampal complex. *Curr Opin Neurobiol.* 1997; 7:217–227. [PubMed: 9142752]
101. Butler CR, Bhaduri A, Acosta-Cabronero J, Nestor PJ, Kapur N, Graham KS, et al. Transient epileptic amnesia: regional brain atrophy and its relationship to memory deficits. *Brain.* 2009; 132:357–368. [PubMed: 19073652]
102. Wilkinson H, Holdstock JS, Baker G, Herbert A, Clague F, Downes JJ. Long-term accelerated forgetting of verbal and non-verbal information in temporal lobe epilepsy. *Cortex.* 2012; 48:317–332. <http://dx.doi.org/10.1016/j.cortex.2011.01.002>. [PubMed: 21397222]
103. Tramon E, Felician O, Barbeau EJ, Guedj E, Guye M, Bartolomei F, et al. Long-term consolidation of declarative memory: insight from temporal lobe epilepsy. *Brain.* 2011; 134:816–831. [PubMed: 21354976]
104. Mameniskiene R, Jatuzis D, Kaubrys G, Budrys V. The decay of memory between delayed and long-term recall in patients with temporal lobe epilepsy. *Epilepsy Behav.* 2006; 8:278–288. [PubMed: 16359927]
105. Fitzgerald Z, Thayer Z, Mohamed A, Miller LA. Examining factors related to accelerated long-term forgetting in epilepsy using ambulatory EEG monitoring. *Epilepsia.* 2013; 54:819–827. [PubMed: 23360077]
106. Muhler N, Milton F, Butler CR, Kapur N, Zeman AZ. Accelerated forgetting of real-life events in transient epileptic amnesia. *Neuropsychologia.* 2010; 48:3235–3244. [PubMed: 20620156]
107. de Weerd A, de Haas S, Otte A, Trenite DK, van Erp G, Cohen A, et al. Subjective sleep disturbance in patients with partial epilepsy: a questionnaire-based study on prevalence and impact on quality of life. *Epilepsia.* 2004; 45:1397–1404. [PubMed: 15509241]
108. Butler CR, Graham KS, Hodges JR, Kapur N, Wardlaw JM, Zeman AZ. The syndrome of transient epileptic amnesia. *Ann Neurol.* 2007; 61:587–598. [PubMed: 17444534]
109. Fuentemilla L, Miro J, Ripolles P, Vila-Ballo A, Juncadella M, Castaner S, et al. Hippocampus-dependent strengthening of targeted memories via reactivation during sleep in humans. *Curr Biol.* 2013; 23:1769–1775. [PubMed: 24012316]
110. Atherton KE, Nobre AC, Zeman AZ, Butler CR. Sleep-dependent memory consolidation and accelerated forgetting. *Cortex.* 2014; 54:92–105. [PubMed: 24657478]
111. Deak MC, Stickgold R, Pietras AC, Nelson AP, Bubrick EJ. The role of sleep in forgetting in temporal lobe epilepsy: a pilot study. *Epilepsy Behav.* 2011; 21:462–466. [PubMed: 21715230]
112. Titiz AS, Mahoney JM, Testorf ME, Holmes GL, Scott RC. Cognitive impairment in temporal lobe epilepsy: role of online and offline processing of single cell information. *Hippocampus.* 2014; 24:1129–1145. [PubMed: 24799359]
113. Hoefelijzers, S., Dewar, M., Della Sala, S., Butler, C., Zeman, A. Accelerated long-term forgetting can become apparent within 3–8 hours of wakefulness in patients with transient epileptic amnesia. *Neuropsychology.* 2014. <http://dx.doi.org/10.1037/neu0000114>
114. Bartko SJ, Cowell RA, Winters BD, Bussey TJ, Saksida LM. Heightened susceptibility to interference in an animal model of amnesia: impairment in encoding, storage, retrieval—or all three? *Neuropsychologia.* 2010; 48:2987–2997. [PubMed: 20561536]
115. Dewar M, Garcia YF, Cowan N, Della Sala S. Delaying interference enhances memory consolidation in amnesic patients. *Neuropsychology.* 2009; 23:627–634. [PubMed: 19702416]

116. Berntsen, D., Rubin, DC., editors. Understanding autobiographical memory. Cambridge: Cambridge University Press; 2012.
117. Piolino P, Desgranges B, Eustache F. Episodic autobiographical memories over the course of time: cognitive, neuropsychological and neuroimaging findings. *Neuropsychologia*. 2009; 47:2314–2329. [PubMed: 19524095]
118. Svoboda E, McKinnon MC, Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia*. 2006; 44:2189–2208. [PubMed: 16806314]
119. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci*. 2008; 1124:1–38. [PubMed: 18400922]
120. Evans JJ, Graham KS, Pratt KH, Hodges JR. The impact of disrupted cortico-cortico connectivity: a long-term follow up of a case of focal retrograde amnesia. *Cortex*. 2003; 39:767–790. [PubMed: 14584552]
121. Levine B, Black SE, Cabeza R, Sinden M, McIntosh AR, Toth JP, et al. Episodic memory and the self in a case of isolated retrograde amnesia. *Brain*. 1998; 121:1951–1973. [PubMed: 9798749]
122. Levine B, Svoboda E, Turner GR, Mandic M, Mackey A. Behavioral and functional neuroanatomical correlates of anterograde autobiographical memory in isolated retrograde amnesic patient M.L. *Neuropsychologia*. 2009; 47:2188–2196. [PubMed: 19154750]
123. Rubin DC, Greenberg DL. Visual memory-deficit amnesia: a distinct amnesic presentation and etiology. *Proc Natl Acad Sci U S A*. 1998; 95:5413–5416. [PubMed: 9560290]
124. Butler CR, Zeman AZ. Recent insights into the impairment of memory in epilepsy: transient epileptic amnesia, accelerated long-term forgetting and remote memory impairment. *Brain*. 2008; 131:2243–2263. [PubMed: 18669495]
125. Lah S, Lee T, Grayson S, Miller L. Effects of temporal lobe epilepsy on retrograde memory. *Epilepsia*. 2006; 47:615–625. [PubMed: 16529630]
126. McAndrews, MP. Remote memory and temporal lobe epilepsy. In: Zeman, A. Kapur, N., Jones-Gotman, M., editors. *Epilepsy and memory*. Oxford: Oxford University Press; 2012. p. 227–243.
127. Addis DR, Moscovitch M, McAndrews MP. Consequences of hippocampal damage across the autobiographical memory network in left temporal lobe epilepsy. *Brain*. 2007; 130:2327–2342. [PubMed: 17681983]
128. Viskontas IV, McAndrews MP, Moscovitch M. Remote episodic memory deficits in patients with unilateral temporal lobe epilepsy and excisions. *J Neurosci*. 2000; 20:5853–5857. [PubMed: 10908628]
129. Lah S, Grayson S, Lee T, Miller L. Memory for the past after temporal lobectomy: impact of epilepsy and cognitive variables. *Neuropsychologia*. 2004; 42:1666–1679. [PubMed: 15327933]
130. Noulhiane M, Piolino P, Hasboun D, Clemenceau S, Baulac M, Samson S. Autobiographical memory after temporal lobe resection: neuropsychological and MRI volumetric findings. *Brain*. 2007; 130:3184–3199. [PubMed: 17986479]
131. Jansari AS, Davis K, McGibbon T, Firminger S, Kapur N. When “long-term memory” no longer means “forever”: analysis of accelerated long-term forgetting in a patient with temporal lobe epilepsy. *Neuropsychologia*. 2010; 48:1707–1715. [PubMed: 20178808]
132. Hornberger M, Mohamed A, Miller L, Watson J, Thayer Z, Hodges JR. Focal retrograde amnesia: extending the clinical syndrome of transient epileptic amnesia. *J Clin Neurosci*. 2010; 17:1319–1321. [PubMed: 20598890]
133. Zeman AZ, Boniface SJ, Hodges JR. Transient epileptic amnesia: a description of the clinical and neuropsychological features in 10 cases and a review of the literature. *J Neurol Neurosurg Psychiatry*. 1998; 64:435–443. [PubMed: 9576532]
134. Mosbah A, Tramoni E, Guedj E, Aubert E, Daquin G, Ceccaldi M, et al. Clinical, neuropsychological and metabolic characteristics of transient epileptic amnesic syndrome. *Epilepsia*. 2014; 55:699–706. [PubMed: 24580051]
135. Butler C, van Erp W, Bhaduri A, Hammers A, Heckemann R, Zeman A. Magnetic resonance volumetry reveals focal brain atrophy in transient epileptic amnesia. *Epilepsy Behav*. 2013; 28:363–369. [PubMed: 23832133]

136. Milton F, Butler CR, Benattayallah A, Zeman AZ. The neural basis of autobiographical memory deficits in transient epileptic amnesia. *Neuropsychologia*. 2012; 50:3528–3541. [PubMed: 23036282]
137. Milton F, Muhler N, Pindus DM, Butler CR, Kapur N, Graham KS, et al. Remote memory deficits in transient epileptic amnesia. *Brain*. 2010; 133:1368–1379. [PubMed: 20360051]
138. Zeman A, Butler C. Transient epileptic amnesia. *Curr Opin Neurol*. 2010; 23:610–616. [PubMed: 20885322]
139. Shewmon DA, Erwin RJ. The effect of focal interictal spikes on perception and reaction time. I. General considerations. *Electroencephalogr Clin Neurophysiol*. 1988; 69:319–337. [PubMed: 2450731]
140. Shewmon DA, Erwin RJ. Focal spike-induced cerebral dysfunction is related to the after-coming slow wave. *Ann Neurol*. 1988; 23:131–137. [PubMed: 3377436]
141. An D, Fahoum F, Hall J, Olivier A, Gotman J, Dubeau F. Electroencephalography/ functional magnetic resonance imaging responses help predict surgical outcome in focal epilepsy. *Epilepsia*. 2013; 54:2184–2194. [PubMed: 24304438]
142. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. *Proc Natl Acad Sci U S A*. 2001; 98:676–682.
143. Gotman J, Grova C, Bagshaw AP, Kobayashi E, Aghakhani Y, Dubeau F. Generalized epileptic discharges: thalamocortical activation and suspension of the default state of the brain. *Proc Natl Acad Sci U S A*. 2005; 102:15236–15240. [PubMed: 16217042]
144. Moeller F, Groening K, Moehring J, Muhle H, Wolff S, Jansen O, et al. EEG-fMRI in myoclonic astatic epilepsy (Doose syndrome). *Neurology*. 2014; 82:1508–1513. [PubMed: 24696509]
145. Fahoum F, Lopes R, Pittau F, Dubeau F, Gotman J. Widespread epileptic networks in focal epilepsies: EEG-fMRI study. *Epilepsia*. 2012; 53:1618–1627. [PubMed: 22691174]
146. Laufs H, Hamandi K, Salek-Haddadi A, Kleinschmidt AK, Duncan JS, Lemieux L. Temporal lobe interictal epileptic discharges affect cerebral activity in “default mode” brain regions. *Hum Brain Mapp*. 2007; 28:1023–1032. [PubMed: 17133385]
147. Blumenfeld H. From molecules to networks: cortical/subcortical interactions in the pathophysiology of idiopathic generalized epilepsy. *Epilepsia*. 2003; 44(Suppl. 2):7–15.
148. Federico P, Archer JS, Abbott DF, Jackson GD. Cortical/subcortical BOLD changes associated with epileptic discharges — an EEG-fMRI study at 3 T. *Neurology*. 2005; 64:1125–1130. [PubMed: 15824333]
149. Rektor I, Tom ík J, Mikl M, Mare ek R, Brázdil M, Rektorová I. Association between the basal ganglia and large-scale brain networks in epilepsy. *Brain Topogr*. 2013; 26:355–362. [PubMed: 23400553]
150. Rektor I, Kuba R, Brázdil M. Interictal and ictal EEG activity in the basal ganglia. *Epilepsia*. 2002; 43:253–262. [PubMed: 11906510]
151. Rektor I, Kuba R, Brázdil M, Halámek J, Jurák P. Ictal and peri-ictal oscillations in the human basal ganglia in temporal lobe epilepsy. *Epilepsy Behav*. 2011; 20:512–517. [PubMed: 21345740]
152. Rektor I, Kuba R, Brázdil M, Chrastina J. Do the basal ganglia inhibit seizure activity in temporal lobe epilepsy? *Epilepsy Behav*. 2012; 25:56–59. [PubMed: 22835431]
153. Brauer J, Anwender A, Perani D, Friederici AD. Dorsal and ventral pathways in language development. *Brain Lang*. 2013; 127:289–295. [PubMed: 23643035]
154. Dijkstra KK, Ferrier CH. Patterns and predictors of atypical language representation in epilepsy. *J Neurol Neurosurg Psychiatry*. 2013; 84:379–385. [PubMed: 22942215]
155. Engel P. Connectomics and epilepsy. *Curr Opin Neurol*. 2013; 26:186–194. [PubMed: 23406911]
156. Friederici AD, Gierhan SME. The language network. *Curr Opin Neurobiol*. 2013; 23:250–254. [PubMed: 23146876]

Fig. 3.3.1.
Biography of Knut Rasmussen Nordgarden by Arvid Møller [43]. Reproduced with permission of the publisher.

Fig. 3.3.2.
Grave of Knut Rasmussen Nordgarden. (Photo credit Karl O. Nakken).

Fig. 3.4.1.

Bileam (Balaam) and the angel, painted by Gustav Jager, 1836. (From Wikipedia.org; [http://en.wikipedia.org/wiki/Gustav_J%C3%A4ger_\(painter\)#mediaviewer/File:Gustav_Jaeger_Bileam_Engel.jpg](http://en.wikipedia.org/wiki/Gustav_J%C3%A4ger_(painter)#mediaviewer/File:Gustav_Jaeger_Bileam_Engel.jpg)).

Fig. 3.4.2.

Maimonides — Rabbi Mosheben Maimon (Rambam; 1138-1204). His uniqueness as a famous doctor and an eminent scholar is exemplified by the proverb: “From Moses to Moses there has never been another Moses”.

(Left) Portrait from He.Wikipedia.org (<http://he.wikipedia.org/wiki/%D7%A8%D7%9E%D7%91%22%D7%9D#mediaviewer/File:Maimonides-2.jpg>); (right) statue from Wikimedia Commons (http://he.wikipedia.org/wiki/%D7%A8%D7%9E%D7%91%22%D7%9D#mediaviewer/File:03_Lundi_03_Cordoue_02_Maimonide.JPG).

Fig. 4.4.1.
The age of seizure onset in patients with left-sided MTLE/HS for left-handers and right-handers.

Fig. 5.2.1.

'The company that it keeps'. Déjà vu, the brain, and metacognitive and emotional interpretations.

Fig. 6.1.1.
Regions of the Default Mode Network. (From [119]).

Fig. 6.1.2. Combined EEG-fMRI study of a patient with left temporal spikes. Left temporal activation (red–yellow) is primarily in mesial temporal structures. Deactivation (blue) is visible in regions of the Default Mode Network (posterior cingulate, anterior frontal, bilaterally).

Fig. 6.3.1.
Mapping language networks in the developing brain.

„Multimodality image-guided surgery“

MRI – FCD

SISCOM

DTI – pyr. tr

– fasc. arcuatus

6yrs girl FCD type IIb

Fig. 6.3.2.
Tractography findings.

Table 3.1.1

Selected elements of the interictal behavioral syndrome (Geschwind syndrome). [35–37].

Deepened emotionality
Obsessive behavior
Moralism
Augmented sense of personal destiny
Strong religious interest
Hypergraphia

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Table 4.3.1

Varieties of language abilities.

Monolingual (L1)
Bilingual Simultaneous
Second language learner (L2)
Early childhood 6–8 years
Late childhood 9 to puberty
Adult
Bilingual — European
Bilingual — European and Oriental
Multilingual

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Table 5.3.1

Methodological evaluation of group studies of ALF in people with epilepsy and healthy controls. Colors represent whether studies accounted for each factor, with green representing those that have and orange representing those that have not. The final column indicates whether the study reported evidence for ALF in epilepsy or not.

Authors (year)	Matched patients and controls?	Test material	Ceiling & floor effects avoided?	Initial performance after filled delay?	Matching procedure included?	Initial performance equated?	Evidence of ALF in TLE?
[102]	Age—yes IQ—yes	Verbal Visuo-spatial	Yes	Yes	Yes	Yes	Yes
[106]	Age—yes IQ—yes	Verbal	Yes	Yes	Yes	Yes	Yes
[97]	Age—yes IQ—yes	Verbal Visuo-spatial	Yes	Yes	Yes	Yes	Yes
[116]	Age—yes IQ—yes	Verbal Visuo-spatial	Yes	Yes	Yes	6/8 tests	Yes
[110]	Age—yes IQ—yes	Verbal Visuo-spatial	Yes	No	Yes	Yes	Yes
[117]	Age—yes IQ—yes	Verbal	Yes	No	Yes	Yes	Yes
[101]	Age—yes IQ—yes	Verbal Visuo-spatial	Yes	No	Yes	Yes	Yes
[118]	Age—yes IQ—yes	Verbal Visuo-spatial	Yes	No	Yes	Yes	Yes
[119]	Age—yes IQ—yes	Verbal	No	No	Yes	Yes	Yes
[120]	Age—yes IQ—yes	Verbal Visuo-spatial	No	No	Yes	Yes	Yes
[108]	Age—yes IQ—yes	Verbal Visuo-spatial	No	No	Yes	Yes	Yes
[105]	Age—yes IQ—yes	Verbal Visuo-spatial	No	No	Yes	Yes	Yes

Authors (year)	Matched patients and controls?	Test material	Ceiling & floor effects avoided?	Initial performance after filled delay?	Matching procedure included?	Initial performance equated?	Evidence of ALF in TLE?
[121]	Age—yes IQ—yes	Verbal Visuo-spatial	Yes	No	Yes	No	Yes
[122]	Age—yes IQ—no	Verbal	No	Yes	Yes	Yes	Yes
[123]	Age—no IQ—no	Verbal	Yes	No	Yes	Yes	Yes
[124]	Age—yes IQ—yes	Verbal Visuo-spatial	No	No	No	Yes	Yes
[103]	Age—yes IQ—yes	Verbal Visuo-spatial	No	No	No	Yes	Yes
[96]	Age—yes IQ—no	Verbal Visuo-spatial	Yes	No	Yes	No	No
[94]	Age—yes IQ—no	Visual	Yes	No	Yes	No	No
[125]	Age—yes IQ—no	Verbal Visuo-spatial	Yes	No	No	No	Yes
[104]	Age—yes IQ—no	Verbal Visuo-spatial	Yes	No	No	No	Yes
[95]	Age—yes IQ—no	Verbal	Yes	No	No	No	No

Table 6.3.1

Demographic data.

	Patients N = 38	Controls N = 39	P-value
Boys	68%	48.7%	0.089
Right-handed	84.2%	87.9%	0.743
Age (mean $\pm$ SD)	100.7 $\pm$ 19.5	109.2 $\pm$ 19.3	0.036