

Neuropsychology of Epilepsy

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Introduction

With a prevalence of 1% , a cumulative incidence of 2-4 % and more than 40 million affected persons worldwide, epilepsy is one of the most common diseases affecting the central nervous system (¹). Epilepsy is defined by the repetitive and unprovoked occurrence of epileptic seizures (i.e. by the occurrence of internal or external behavioural changes, which go along with pathological paroxysmal hypersynchronous rhythmic electric discharges in larger neuronal networks). In most patients, these electrophysiological changes can be assessed during seizures (ictally) via electroencephalographic (EEG) recordings from the surface of the head. However, epileptic activity, which in and of itself does not attest to epilepsy, can also be observed interictally in the time between seizures. The risk of a relapse after the first unprovoked seizure is 37%. This relapse risk decreases as the seizure-free time increments increase. However, the relapse rate can increase up to 73% after a second unprovoked seizure occurs (²). Epilepsy can be successfully treated in most cases, but apart from seizures, the cognitive, psychiatric, and psychosocial consequences must also be considered with this disease. Epilepsy is a disease at the edge between neurology and psychiatry. Because of this and because multiple disciplines (neuro-physiology, -pathology, -radiology, -surgery, and -psychology) are concerned with this disease, research in epileptology was interdisciplinary from the very beginning of the understanding that the source of epilepsy must be the brain. Since the early beginnings of epilepsy surgery back in the 1930s in Montreal, Canada, neuropsychology, cognitive neuroscience and clinical epileptology have all been found to be strongly interwoven and they still stimulate each other. Some of the milestones in epilepsy research include Jasper and Penfield's electrocortical functional mapping which represents a valuable tool in epilepsy surgery even today (^{3,4}); This is also the case for Scoville and Milner's lessons about memory from bilateral temporomesial resections for seizure control (⁵). From Sperry's split brain studies or June Wada's intracarotid amobarbital procedure we were able to learn about hemisphere dominance and plasticity (^{6,7}). The introduction of chronic invasive EEG recordings and structural and functional MRI allowed for quantitative and qualitative structure function correlations with high spatial and temporal resolution. Going along with this selective and superselective epilepsy surgery for seizure control allowed for cross-sectional and longitudinal lesional neuropsychology (⁸).

Finally, recent attempts to apply deep brain stimulation for seizure control must be mentioned, even though effects of this procedure on behaviour cannot yet be determined (⁹). Within the context of epilepsy surgery there is hardly a diagnostic tool which has not yet been systematically applied in order to improve patient selection, the surgical approach, or outcome prediction, and which did not allow for the correlation of the brain and its functions to cognition and behaviour. Quantitative and qualitative structural and functional MRI, PET, SPECT, MEG, intracranial EEG and ERPs, belong to the diagnostic repertoire in epileptology.

Traditionally, neuropsychology in epilepsy is localisation diagnostics in terms of the lateralisation and intrahemispheric localisation of impairments. Because of improved imaging and electroencephalographic techniques, questions of outcome and quality control of medical and surgical treatment of epilepsy are currently of major interest (¹⁰). This development is in full accordance with a qualitative change in the treatment of epilepsy which not only aims at seizure control, but also at the preservation or even improvement of the patient's cognitive performance and his psychosocial situation and subjectively experienced quality of life.

The neurocognitive and behavioural findings in epilepsy will be outlined along with the different types of epilepsies. The disease and treatment effects on cognition in epilepsy will be considered as well as the question of how epilepsy and its treatment can interact with mental development and mental decline. The question addressing the extent by which the findings of the respective areas serve for modelling normal brain functions will be of secondary interest.

Classification

In general, seizures are categorized as either generalised or focal (partial) seizures. This is based on whether the pathological hypersynchronous EEG activity is recorded widely distributed or focally over the cortical surface. Seizures are secondarily generalised when they have a focal origin. Focal seizures can coincide with loss of consciousness (= complex partial seizure) or without loss of consciousness (= simple partial seizure). This seizure classification is strongly influenced by the classification of epilepsies, which follows their aetiology and localisation. Accordingly, idiopathic and symptomatic or cryptogenic focal epilepsies are differentiated. The first has a strong genetic component with no underpinning lesions and the latter is due to a definitive pathology or to an assumed and not yet known pathology. Most, but not all,

idiopathic epilepsies are characterized by generalised seizures idiopathic epilepsies are present which show a preference for certain frontal or centrottemporal locations (¹¹). It is important to note that with progress being made in imaging, electroencephalography, neuropsychology, and genetics technology, the definitions and classifications of generalised vs. focal; partial vs. complex partial; or idiopathic vs. symptomatic are constantly changing (¹²). Recognition of autosomal dominant frontal lobe epilepsy for example contradicts the separation of focal symptomatic versus idiopathic generalized epilepsies. Other example is that with invasive EEG recordings there is evidence that behaviourally generalized seizures do not necessarily have a generalized electrophysiological correlate. Also the definition of complex partial seizures as being seizures with a loss of consciousness must be questioned. Active testing during seizures shows that complex partial seizures can go along with selective impairment of language functions which can be misunderstood as a loss of consciousness.

Aetiology

In contrast to most other central nervous diseases, epilepsy is characterised by the fact that not only structural morphological lesions, but also dynamic epileptic dysfunction, affect cognition and behaviour. Treatment affects epilepsy and, in the case of surgery, it also affects the structure. In contrast to lesions and surgical defects, the influence of epilepsy and its medication is potentially reversible. Psychiatric comorbidity must be considered as the third dynamic factor in epilepsy (¹³). Thus, the cognitive condition in a patient with epilepsy is the result of the complex interaction of more stable and dynamic factors. With this, we must also consider that epilepsy not only results from altered brain structures or functions, but that epilepsy itself can also exert an influence upon brain maturation and functional organisation. Many patients with early onset epilepsies show atypical hemispheric dominance patterns which appear to be not genuine, but rather lesion and epilepsy driven (¹⁴). Because of this, and since epilepsy has its natural peak in childhood and later on in adulthood, the constant and dynamic determinants of cognitive impairments must be set into a developmental neuropsychological framework which considers the interactions of epilepsy with the maturing and aging brain.

Types of epilepsy

Idiopathic epilepsies

Idiopathic epilepsies are most notably characterized by a genetic predisposition and the absence of significant brain lesions. Idiopathic generalised epilepsies are additionally characterised by generalised EEG patterns which cover the whole cortex. In contrast, Idiopathic partial epilepsies show preferences of epileptic activity over certain brain regions (i.e. centrotemporal in rolandic epilepsy). It is a commonly held assumption that idiopathic epilepsies are easier to treat and that they are associated with less severe cognitive impairments. This is true in many respects, but this could result in an underestimation of the cognitive and behavioural problems found with idiopathic epilepsies.

Idiopathic generalised epilepsy

Traditionally, epilepsies are divided into two major groups. The first group consists of idiopathic epilepsies which include the generalised epilepsies (IGE) (e.g. epilepsies with tonic clonic seizures, juvenile absence epilepsy or myoclonic epilepsy) and the benign partial epilepsies (e.g. benign epilepsy with centrotemporal spikes BECTS). The second group is comprised of the symptomatic or probably symptomatic focal epilepsies (e.g. mesial temporal lobe epilepsy and neocortical epilepsies). The term generalised epilepsy and the fact that in these epilepsies, generalised epileptic activity can be recorded over cortical areas may be misleadingly suggest that also cognitive impairments must be generalised. In contrast, patients with IGE show only minor problems with respect to global intelligence, but display rather significant problems in the areas of attention, psychomotor speed, visual-spatial skills, and nonverbal memory. Language and verbal memory appear to be unaffected (^{15, 16, 17}). The close relationship between epileptic discharges and cognitive dysfunction is fundamental for the understanding of cognitive impairment in IGE. Because no underlying lesion can be discerned in idiopathic epilepsies, IGE has been thought to be the best model for studying the relationship of epilepsy and cognition. Interestingly enough, cognition and epilepsy in IGE appear to be related in both directions. Impairments become evident as a function of epileptic activity but activities can also activate epileptic discharges and even seizures. In a large study, Matsuoka et al. (2000) showed such activation during cognitive tasks involving motor (e.g. writing) or higher cognitive functions (e.g. calculation, reading) (¹⁸). Comparable observations

have also been made in those patients with symptomatic temporal lobe epilepsy where seizures occurring particularly during memory evaluations indicated activation of the temporal lobe epileptic focus ⁽¹⁹⁾. However, in the Matsuoka study, patients with IGE appeared to be much more prone to showing neuropsychological EEG activation than those patients with focal epilepsies.

In IGE, the negative effects of spike-wave bursts on sensory and executive functions can be noted. Therefore, visual and auditory continuous performance tasks that require sustained attention appear best suited to diagnose the specific dysfunctions for this group of patients ⁽¹⁶⁾. In this type of epilepsy, it appears more likely that impairment in these latter functions secondarily affects other functions of intelligence rather than that mental retardation is a primary feature of the disease. This however does not exclude the possibility of developmental delay and retardation when IGE interferes with basal cognitive functions over a long period of time. Earlier absence epilepsies with an onset in early childhood or at school age are at greater risk for a worse outcome than juvenile absence epilepsies.

Benign childhood epilepsy with centrotemporal spikes

Benign childhood epilepsy with centrotemporal spikes (BECTS) is a frequently diagnosed epilepsy (10-15%), which starts between the age five and nine and extends into adolescence. It has a comparably good prognosis in that most patients become seizure free after puberty. However, with regard to cognitive functioning, the benign nature of this type of epilepsy must be doubted. Particularly during its active phase, neuropsychological deficits have been reported in various domains including attention, motor functions, short-term memory, visual and perceptive abilities. However, language problems relating to the interhemispheric dysfunction of perisylvian language areas appear to be a major characteristic of BECTS ⁽¹⁷⁾. Abnormality of auditory evoked potentials (P85-120) and the absence of mismatch negativity raise evidence that patients with BECTS have abnormal processing of auditory information at a sensory level ipsilateral to the hemisphere evoking spikes during sleep ⁽²⁰⁾. According to a recent study, educational problems are met in about half of the patients, most of them with neuropsychological and language problems suggestive of a developmental learning disability ⁽²¹⁾. This study also supports an earlier observation made in a very large population; the absence of temporo-frontal dipole discharges can be taken as an indicator for a learning disability ⁽²²⁾. BECTS does not

appear to be progressive. In contrast, with the remission of epilepsy, children catch up and develop normally. Minor persisting problems in executive functions and verbal comprehension in children in remission suggest possible long-term effects (^{23,24}). A complete absence of seizures and complete remission of epileptic activity appear essential for a good cognitive outcome.

As with language problems in patients with centrottemporal spikes, visual information processing appears particularly affected in benign partial epilepsy with occipital located discharges (²⁵).

Very special conditions are met in the Landau Kleffner Syndrome (LKS) or the “continuous spikes and waves during slow wave sleep” syndrome (CSWS) ²⁶. Particularly with respect BECTS it might be of interest that these conditions are also associated with language problems. However here a progressive loss and decline of already acquired functions is observed, which can result in severe mental retardation. Children with CSWS show autistic features as well as features of a frontal lobe syndrome, and the mental retardation in these children is believed to result from extensive and continuing epileptic dysfunction affecting the frontal lobes (^{26,27}). It should be mentioned that vice versa epilepsy or epileptic activity is frequently found in children with autistic spectrum disorders. Gabis et al. found that 40% of the 56 autistic children were diagnosed with epilepsy (²⁸). Thus, EEG should be performed in such children and recordings taken during the night should also be included. Very recent findings suggest a significant role of early thalamic lesions in the aetiology of CSWS (²⁹). In contrast to BECTS, wherein the first line expressive language functions appear affected, the Landau Kleffner syndrome is characterized by a sequential and sometimes hierarchical loss of language functions beginning with sensory aphasia, followed by auditory agnosia and finally word deafness as the disease progresses (³⁰). A dissociation between the discrimination of environmental sounds and phonological auditory discrimination indicates problems particularly in auditory phonological discrimination (³¹). Characteristic and presumably also predictive for mental decline is the phenomenon of the nonconvulsive “electrical status epilepticus in sleep” (ESES). Since there is an overlap between BECTS, LKS and CSWS, transitions between the more benign condition in BECTS and the severe encephalopathic conditions in LKS and CSWS seem possible (³²).

Juvenile myoclonus epilepsy

Juvenile myoclonus epilepsy (JME) starts predominantly between the age of 12 and 18 years and is characterized by neuropsychological and behavioural features suggesting the presence of a frontal dysexecutive syndrome (^{33,34,17}). This is indicated by neuropsychological findings which suggest problems with reasoning, concept formation, mental speed and flexibility, or problems in visual working memory (^{35, 36, 37}). However, frontal lobe dysfunction does not appear to be specific to JME. It can be observed in other patients with IGE as well and it is also a common feature of symptomatic frontal lobe epilepsies (³⁸). Whether frontal lobe cognitive dysfunction together with personality change (e.g. limited self-control, suggestibility, indifference, rapid mood changes), form a syndrome characteristic of JME needs to be proven (³³). It should be noted that the aetiological model of “generalized” epilepsy is weakening, provided that partial rather than global impairments are found in IGE. In accordance with the neuropsychological findings there is evidence from EEG and from histological, structural and functional imaging studies, supporting a particular involvement of the frontal lobes, the thalamus, and thalamo-cortical loops in IGE (^{39, 40, 41, 42, 43}).

By summarising the findings in idiopathic epilepsies a wide range of rather mild impairments can be discerned in idiopathic generalised and partial epilepsies. The conditions represented in encephalopathies LKS and CSWS are the exception. In addition to diffuse impairment and learning disorders, characteristic impairments have been observed and can be related to the brain sites involved in the respective syndrome. The impairments can be best understood on the basis of the close relationship between active epileptic processes interfering with cognitive networks of more basal activating, perceptive and executive functions. Within a developmental framework the time during which epilepsy interferes with critical periods of cognitive development is of major importance (i.e. before, at, or after language acquisition, or at the time before or when frontal executive functions develop). Frontal executive functions develop last and may therefore represent a common endpoint of the impairments seen in the idiopathic generalised or partial epilepsies. With remission of epilepsy, recovery from acute epilepsy-driven impairment can be observed, but some long-term residual deficits cannot be excluded, particularly when epilepsy has previously interfered with mental development to a significant degree. Because no

morphological cortical damage could be demonstrated with BECTS, LKS or CSWS until now, these epilepsies provide very interesting insight into cognitive development. Previously acquired skills can be irreversibly lost without damage if the disease starts early, if it affects significant brain areas and if it lasts long enough. “Use it or lose it” is obviously only one scenario of mental retardation; the loss of cortical functions due to the continuous reception of erratic non-sense input is probably another. Aetiologically, the thalamus and thalamo-cortical networks come into focus and future research will show whether focal lesions will also become evident in these epilepsies.

Focal symptomatic epilepsies

In contrast to idiopathic epilepsies in which the impact of epilepsy on cognition is the prevailing factor, the nature of focal symptomatic epilepsies is more decisively determined by the location and aetiology of epilepsy. As for the location of the epilepsy, the International Classification of Epilepsies differentiates localisation related epilepsies according to the cerebral lobes (frontal, temporal, parietal, occipital). However, the temporal lobes and the temporo-mesial structures represent particularly vulnerable structures, which are susceptible to becoming epileptogenic.

Temporal lobe epilepsies

With a diagnosis rate of 70%, temporal lobe epilepsy (TLE) represents the majority of the chronic symptomatic epilepsies; about half of these epilepsies show hippocampal sclerosis and/or atrophy. Whether mesial TLE represents a nosological entity or a syndrome is still a matter of debate ⁽⁴⁴⁾. Neuropsychologically, mesial temporal lobe epilepsy is characterized by impaired declarative memory and often accompanied with low levels of global intelligence ⁽⁴⁵⁾. The latter finding requires special attention since poor intelligence in TLE is often associated with an early onset of epilepsy and thus can be indicative of mental retardation ^(46,47). Consideration of the course of cognitive development and the educational level of the siblings or parents can support this diagnosis. Memory impairment is different from poor intelligence in that it is evident in TLE independent of the age at the onset of epilepsy ⁽⁴⁶⁾.

The technical facilities of the presurgical evaluation of epilepsy patients significantly contributed to our understanding of the close relationship between the morphological

and functional integrity of the temporal lobe structures and declarative episodic memory (i.e. the acquisition and later recall of time and context dependent information). This has been demonstrated by correlating memory function to intracranially recorded evoked potentials, which were then assessed in a N400 word recognition paradigm in which new and old words are differentiated. The better the mesial structures can be recruited during such a memory task, the better the memory will also be in memory tasks outside of the experimental setting (^{48, 49}). With the same procedure, it was also possible to demonstrate the relevance of NMDA-receptor activity for memory formation. Application of ketamin, an NMDA-receptor antagonist that is most likely seen within hippocampal CA1 subregion, completely suppressed memory formation and the respective electrophysiological correlates within the hippocampal proper (⁵⁰). This strong relation has also been demonstrated by correlation of cell counts (i.e. neuron loss in certain hippocampal subregions to memory performance) (^{51, 52}) and even by correlation of memory with long-term potentiation as assessed on a cellular level in human hippocampal slices (⁵³). With electrophysiological coherence measures from depth electrodes, it is possible to directly relate cortico-mesial phase synchronisation between the rhinal cortex and the hippocampus to the formation of declarative memories in the awake state and even during sleep (^{54, 55}).

Since episodic memory is largely a function of the language dominant hemisphere, left temporal and left temporo-mesial epilepsies are very often associated with material specific impairment of verbal learning and memory. Mesial and neocortical structures differentially contribute to verbal memory in that mesial structures serve consolidation and retrieval, while neocortical structures process the content. Therefore, impaired performance in delayed recall measures is highly indicative for left mesial pathology (⁴⁹). Impairment of verbal learning, verbal short-term memory and semantic memory are less specific markers, which can be indicative of left infero-temporal or temporo-lateral lesions or foci (^{56, 57, 58, 59, 60}). Category specific impairments in semantic word fluency have been suggested in lateralized temporal lobe epilepsies, but this is still a matter of debate (^{61, 62}). Different from left TLE, in right TLE only a quantitatively but not a qualitatively different performance in figural memory has been observed dependent on the presence/absence of hippocampal sclerosis (⁶³). Furthermore, the relation between figural visual spatial memory

impairment and right temporal lobe epilepsy is far less consistent than that between verbal memory and the left temporal lobe. While there are studies which clearly indicate such a relation by showing specific deficits in design learning (⁶³), in spatial memory (⁶⁴), in the identification of famous faces (⁶⁵), or the recognition of emotional facial expression (⁶⁶), false lateralizing figural memory deficits are nevertheless very common. In right temporal lobe epilepsy, lack of impairment has been attributed to a more bilateral cerebral organisation of nonverbal memory networks, covert verbalisation, or the type of the test and test materials (e.g. abstractness, complexity) (^{67, 68}). False lateralizing figural memory impairment in left TLE is rather due to atypical language dominance and gender differences (⁶⁹). Frontal lobe dysfunctions are also common in TLE, particularly when generalised tonic clonic seizures are reported (⁷⁰). There is a tight interaction between temporal and prefrontal areas in memory processes (^{71, 72}) and frontal impairments in TLE appear due to irradiating epileptic dysfunction or diachisis phenomena, which can be controlled after successful seizure control. After successful TLE surgery in patients with PET signs of prefrontal hypometabolism, functional neuroimaging may show normalisation of metabolism. This parallels the improvement seen in non-temporal functions after successful surgery (^{73, 74}).

Frontal lobe epilepsies

With a rate of approximately 10-20%, frontal lobe epilepsies (FLE) represent the second largest group of symptomatic epilepsies (⁷⁵). They form a much less consistent neuropsychological entity than temporal lobe epilepsy. In contrast to TLE in which hippocampal sclerosis is a predominant and quite homogeneous morphological feature, more heterogeneous aetiological factors are involved in frontal lobe epilepsy. The frontal lobes are comprised of regions which are involved in various functions. These functions include working memory (prefrontal), social and moral behaviour (orbitofrontal), initiation and organisation of behaviour (prefrontal and supplementary motor area), processing of emotions and reward (basal forebrain and cingulum), language (Broca's area) or motor control (precentral). There are multiple connections of the frontal lobes to other brain areas, but whether epileptic dysfunction in FLE has a distant effect on nonfrontal areas as it is seen in TLE with respect to frontal areas needs to be established. For example, postoperative recovery in temporal lobe functions does not appear as impressive as the recovery of

frontal functions after temporal lobe surgery (^{76,77}). In any case, frontal lobe executive functions reach into other most cognitive functions. Diffuse and non-specific impairments can be the consequence. Therefore, frontal lobe dysfunction in FLE is rarely diagnosed by a single dysfunction or test, but rather in terms of a cognitive profile (^{38,78}). Cognitive impairments which are characteristic for FLE largely resemble those described within the lesion-related literature, but in this respect it is important to note that most literature on patients with FLE also refers to patients with lesions. Neuropsychological differences between lesional and nonlesional (cryptogenic) FLE have not yet been described. An important technical aspect of the evaluation of patients with FLE is that, independent on the presence absence of lesions, impairments might be missed because test situations are mostly clearly structured with clear cut demands. This reduces the level of freedom for the patient and can help him to overcome his particular problems associated with behavioural control. Patients may nevertheless appear normal or they may primarily suffer from behavioural and emotional problems. Most consistent are problems with attention, short term or working memory, mental flexibility, response inhibition, anticipation, or planning and decision-making. Motor coordination test have been found to be particularly sensitive with respect to frontal lobe epilepsy.

On a superior level, one can summarise the various cognitive and behavioural problems in FLE by suggesting a “frontal dysexecutive syndrome” with problems in the selection, initiation, execution and inhibition of responses in different domains (e.g. attention, motor, emotion, reasoning, language). No systematic problems have yet been described as dependent on the lateralisation of FLE, nor have special neurocognitive problems been associated with frontal subregions. (^{38,79,80,81})

Parietal and occipital lobe epilepsies

Posterior epilepsies are rare with a 10% rate and the neuropsychological characteristics of parietal and occipital lobe epilepsies have thus not yet been described with larger groups of patients. Test batteries for epilepsy patients may cover visual attention, language or praxia, but rarely do the tests address somatosensory processes, astereognosis, perceptual thresholds or on transmodal functions (size colour matching) tapping functions of the posterior cortices (⁸²). This makes one wonder since acute parietal or occipital neuropsychological symptoms

mostly become manifest only in seizure semiology or in postictal states but not in chronic epilepsies. Most patients have epilepsies on the basis of early lesions or malformations and the classic posterior symptoms of aphasia, alexia, agraphia, akalkulia, agnosia, optic ataxia, neglect etc., are very rare. Primary or secondary perceptive and sensory problems often appear well compensated on a behavioural level because epilepsy and lesions fall into a time window during which the brain is still functionally plastic and able to cope with the lesions. The resulting impairments are mostly diffuse and mental retardation is seen quite often in parietal epilepsies, presumably because early epilepsy interferes with functions of the input system⁽⁸³⁾. The brain matures from posterior to anterior and negative effects of early damage of posterior functions can well be suggested to influence maturation and functional development of structures and functions which become fully developed later on. Furthermore, as it has also been described for seizure semiology and EEG, the cognitive impairments in posterior epilepsies often mimic those of frontal or temporal lobe epilepsies^(83, 84). Whether this reflects distant effects of posterior foci on frontal and temporal lobe functions by irradiation of epileptic dysfunction via the ventral and dorsal stream needs to be shown. For the neuropsychological diagnosis of parietal epilepsies, tests of stereognosis or haptic search appear to be sensitive tests^(85, 86).

Lesions

Aetiologically, no specific causes for cognitive impairments can be discerned in focal symptomatic epilepsy. Major lesions in focal epilepsies are mostly stationary defects such as, developmental malformations, hippocampal sclerosis or atrophy, head trauma or vascular malformations. Potentially progressive defects such as neoplastic and paraneoplastic tumours, CNS infections, inflammatory and autoimmunological processes appear to be less common. These aetiologies alone can lead to cognitive impairments ranging from mild impairment in circumscribed domains to severe mental retardation or mental decline. In this respect, it is important to know that the cognitive impairments in symptomatic epilepsies are not lesion specific, but that they differ due to differences in age at the onset of the lesion (early onset lesions interfere with brain maturation); differences in functionality of the affected tissues (epileptogenic regions can also be functional); differences in the course and

dynamics of the underlying disease (neoplastic, encephalitis); and finally because of a different lateralisation and localisation (⁸⁷). Lesions normally are not involved in function, but this cannot always be excluded as it has been demonstrated for dysplasias, glioneural tumours, or heterotopic grey matter in an intracranial ERP study or in fMRI activation studies (^{88, 89, 90}).

Epileptic activity and seizures

As for epileptic activity and epileptic dysfunction, seizures, pre- and postictal states and interictal epileptic activity/dysfunction are differentiated. Ictal, peri- and interictal dysfunction can add to the impairments, which are already present due to morphological/structural pathology in symptomatic epilepsies. Cognitive impairment becomes most evident during a seizure. Seizures not only produce positive symptoms (e.g. staring, automatisms, dystonic posturing, etc.) which are subsumed under the term “seizure semiology”, but also negative symptoms in terms of impaired functions (e.g. language consciousness motor control, memory, etc.). Both symptoms can provide valuable clues about localisation and lateralisation of the involved brain structures. However, in contrast to seizure semiology which can be observed, negative symptoms only become evident with testing (^{91, 92}). A more direct relation between the localisation of the seizure activity and behaviour is given when primary sensory or motor areas are affected. This relation is lost when seizures originate or spread into in secondary or tertiary association areas, mesial fronto-limbic or midbrain structures. Then, seizure semiology appears less as a direct correlate of excitatory activity in the respective areas but rather the expression of a disinhibition of atavistic and, by part, very complex templates of behaviour. Very special neuropsychological conditions are met during nonconvulsive status epilepticus, which means ongoing, electrophysiologically-assessed, seizure-like epileptic activity without loss of consciousness and without the overt motor signs of a simple partial or complex partial seizure. A nonconvulsive status may become manifest in a psychiatric condition but in a condition with predominantly cognitive dysfunctions as well. However, with invasive depth electrode recordings quite asymptomatic states can also be observed. Systematic observations are rare (⁹³). EEG monitored bedside testing of consciousness, responsitivity, reactivity memory and higher functions in a verbal and nonverbal mode can be helpful to diagnose this condition, particularly

when repeated testing after medical cessation of the assumed status indicates recovery. One might get a picture about such states by observing frontal lobe nonconvulsive seizures as they occur. Patients in such states showed largely preserved, low-level reactive and reflexive behaviour; strongly varying attention levels; severe impairment of self-initiated planned behaviour; behavioural loops with stereotyped and perseverative responses; ideomotoric apraxia and generally impaired higher cognitive functions (reasoning, calculation) ⁽³⁸⁾. Behaviourally, the patients appear irritated and dysphoric. They may react in a repulsive manner, but not with directed aggression. Other special conditions are short lasting amnesic attacks, which may be recurrent; which are mainly observed in temporal lobe epilepsy and which appear due to circumscribed bilateral temporo-mesial dysfunction. These can be correlates of ictal or postictal states. Periods may last from minutes up to an hour. Consciousness and purposeful behaviour are preserved but the patients may be irritated about the disturbance ^(94, 95).

Depending on the severity of the seizure, postictal impairments can last for hours. The impaired functions reconstitute hierarchically with the distance to the most affected structures and the type of continuing impairment can be indicative of the site of the seizure origin ⁽⁹⁶⁾. A very interesting recent development is concerned with online seizure prediction. This is based on particular EEG characteristics which appear indicative of a seizure and which, by part, can be observed long before a seizure occurs ⁽⁹⁷⁾. Neuropsychologically, one may thus raise the question as to whether there are cognitive changes or mood changes going along with such phases of an increased readiness to seizures. As for interictal epileptic activity in symptomatic focal epilepsies, an impact on cognition and behaviour is assumed similar as it has been discussed with the idiopathic epilepsies. However, the relation between epileptic activity and behavioural change appears much less reliable than in idiopathic epilepsies. At present it we do not know under which conditions interictal epileptic activity will or will not have an effect on cognition or behaviour ⁽⁹⁸⁾. The existence of a sustained, rather than acute, impact of active epilepsy on cognition in focal epilepsies can be estimated with functional recovery of cognitive functions, behavioural disorders, and mood after successful epilepsy surgery ^(74,99, 100).

In summing up so far the findings in focal symptomatic epilepsies, their cognitive and behavioural consequences depend to a lesser degree on the type of underlying lesion (developmental malformation, hippocampal sclerosis, tumor, etc.) than on localization and lateralization of the epileptogenic region and the age at the lesion/epilepsy onset. Structure function relations commonly known from the lesion literature do not apply for early onset focal epilepsies. Dependent on localization and lateralization, early onset focal epilepsies interfere with brain maturation on the one hand and they are effective on the interhemispheric organization of dominance patterns on the other hand. Diffuse and non-specific or atypical patterns of cognitive impairment are the consequence. Severe seizures can additionally lead to irreversible damage but the effect of seizures on cognition is mostly dynamic and reversible as it is the impact of the medical treatment on cognition and behaviour.

Treatment

Medical Treatment

Ictogenesis in focal epilepsy decisively depends on the intrinsic paroxysmal depolarisation of the nerve cell. Therefore, antiepileptic drugs (AEDs) aim at the prevention of repetitive action potentials by blocking the sodium flow at the cell membrane; by augmentation of deficient GABAergic inhibitory processes; or by reduction of pathological glutamatergic excitation. In idiopathic generalised epilepsies, AEDs aim at receptors and ion-channels (e.g. T-calcium channels, GABA A/B receptors), which are causative for synchronized bursts.

According to community-based studies, the majority of people with newly diagnosed epilepsy enter long-term remission. However, for about 40% of the patients the seizures will remain resistant to treatment. The success of the medical treatment depends on the number of seizures before treatment. This may reflect the severity of the disease on aetiology (idiopathic vs. symptomatic and developmental or not), on the response on the first drug applied and on psychiatric comorbidity (^{101, 102}). The selection of the AED depends on the seizure type, syndrome diagnosis, half time and the effect of the AED on metabolism.

Antiepileptic drugs control seizures and seizure reduction may have beneficial effects on cognition. Antiepileptic treatment in and of itself however may have positive or

negative psychotropic effects on cognition and behaviour. Cognitive side effects of AEDs depend on the substance, the number of AEDs, the dose, the titration speed and their efficacy with regard to seizure control. Therefore, neurocognitive evaluations should be preferentially performed when patients are on stable medication and within a steady state. Withdrawal of an AED can cause unwanted dynamics in this steady state, particularly when there are interactions between different AEDs. Withdrawal can furthermore negatively change the epileptic situation in terms of a provocation of (generalised-) seizures. As for cognitive and behavioural side effects of AEDs, these can be idiosyncratic; this means that they are part of the action of the substance or they depend on titration speed and/or dose (blood serum concentration). Most of the AEDs induce dose-dependent diffuse signs of intoxication, which becomes evident with sedation, somnolence, dizziness, psychomotor slowing, ataxia and ocular symptoms. Greater risks of dose dependent adverse effects are given with polytherapy, and particularly when hepatic enzyme inducing or inhibiting drugs cause unwanted metabolic changes (¹⁰³).

The adverse effects of AEDs on cognitive functions may be due to the suppression of neuronal excitability or the enhancement of inhibitory neurotransmission in certain brain areas. Theoretically, this may be different in epileptogenic or nonepileptogenic tissues (^{104, 105}). Furthermore, AEDs may exert a different action depending on the degree of pre-existing morphological damage (¹⁰⁶). As for the AEDs in use, there is converging evidence that the so-called older AEDs (phenobarbital, phenytoin, carbamezepine and valproate) are more problematic than the so-called newer AEDs (lamotrigine, gabapentine, levetiracetam, topiramate, zonisgran, etc.) with respect to cognition and behaviour (^{107, 108}). However, one should keep in mind that the older drugs have been in use for a much longer period of time. Certain aspects of AEDs often become evident a long time after their introduction.

In general, no particular pattern of impairment is observed with different AEDs. With Ketter et al. 1999, one can differentiate sedating effects that are evident in AEDs with a potentiation of gamma-aminobutyric acid (GABA) inhibitory neurotransmission (e.g. barbiturates, benzodiazepines, valproate, gabapentin, tiagabine and vigabatrin) and stimulating and possibly anxiogenic effects with AED which attenuate glutamate excitatory neurotransmission (e.g. felbamate and lamotrigine) (¹⁰⁹). This scheme however is an oversimplification and does not apply for all AEDs equally well (¹¹⁰). Preferential targets of AEDs include the attention and executive functions but

memory and language functions can also be affected (¹¹¹). From behavioural evaluations alone, it is difficult to determine which aspects of cognitive processing are particularly affected and which sites of action can be discerned. This can be demonstrated with the negative cognitive side effects of one of the newer generation of AEDs: Topiramate (TPM). This drug attracted attention when significant language problems were first seen in patients and then later in healthy control subjects (¹¹²). This raised the question as to whether TPM might specifically affect the language system in the left hemisphere. These language problems were mainly seen with respect to verbal fluency and later studies indicated that verbal fluency in this context represents only a striking and easily recognized marker for a more global frontal lobe dysfunction (¹¹³). Side effects of AEDs may also result from interactive effects between mood and cognition. Lamotrigine (LTG) was thought to have had a positive effect on cognition. This presumably results from its strong mood stabilizing effect which eventually led to its successful application in the treatment of patients with major depression (^{114, 115}). Levitiracetam (LEV), another new AED, has arousal activating effects which can result in better cognitive performance, but can also negatively affect behavioural control (e.g. aggression) (¹¹⁶). Presumably, pharmacofMRI will become a useful tool in evaluating such hypotheses. Jokeit et al. showed reduction of temporo-mesial activation patterns during a memory task in patients with temporal lobe epilepsy under carbamazepine (VBZ) (¹⁰⁵).

Two studies recently gained interest in the epileptological community. They showed the negative effects of valproic acid on the verbal IQ of children who were exposed to this drug in utero (^{117, 118}). It is well known that developmental malformations (e.g. spina bifida and fetal antiepileptic syndromes) can result from intrauterine exposition to antiepileptic drugs (^{119, 120}). This can be treated with counselling, folic acid prophylaxis and early prenatal diagnostics. With intellectual impairment or mental retardation, the situation becomes more difficult although a certain overlap between malformations and intellectual retardation can be assumed. It is important to note that almost all studies stress the significant impact of the mother's IQ on the outcome and that impairments become less obvious in the presence of more intelligent mothers (¹²¹). The pathomechanism by which the verbal IQ in particular becomes affected under VPA is not yet known. It is important to note that the current discussion leans toward VPA but that there are other drugs that we do not know much about. Further research in this area is critically needed. Effects of in utero exposition to AED are not

uniform and we neither know the mechanism of damage nor which processes of brain maturation become affected.

Surgery

Surgery can be a very successful treatment option for patients with focal symptomatic epilepsies. Surgery is recommended when patients are pharmaco-resistant, when they have a resectable epileptogenic region, and when surgery in the affected brain structures will not lead to any serious negative side effects (¹²²). In such cases, surgery can be curative. Surgery is resective in most cases, but when the epilepsy originates in eloquent cortex subpial transections, it is an option to prevent the horizontal transmission of epileptic activity between neighbouring parts of the brain without seriously harming the language or motor functions. Another option is palliative surgery which does not strive for complete seizure control, but rather for seizure reduction or for the control of drop attacks. This is the case in patients with multiple foci or in patients in whom rapid interhemispheric seizure spread is controlled by transections of the corpus callosum.

According to a first randomized trial of surgical versus medical treatment, surgery was successful in 58% of operated versus 8% of medically treated patients (¹²³). This outcome parallels what was reported in a recent longitudinal study on medical versus surgical treatment, in which large and homogeneous groups of patients with temporal lobe epilepsy were evaluated (⁷⁴). Seizure outcome can vary with different baseline conditions (temporal/extratemporal localisation, presence and type of a lesion, onset/duration of epilepsy, electroencephalographic focus consistent with lesion and seizure semiology, consistent neuropsychology, seizure severity, psychiatric comorbidity, etc). Successful seizure control improves the quality of life and coincides with a reduction of behavioural problems and improvement of mood (^{74, 100, 124}). However, apart from seizure control, brain surgery can have both positive and negative effects on cognition and behaviour. This requires a careful preoperative evaluation of the site from where seizures take their origin and the functionality of the affected and nonaffected tissues (^{125, 126}). Methods of achieving this include EEG (extracranial/intracranial, interictal/ictal) (¹²⁷); structural and functional imaging techniques (¹²⁸); angiography optional with intracarotid application of amobarbital or methohexital (brevital) (^{129, 130}); and electrocortical stimulation (¹³¹).

From temporal lobe surgery on the language dominant side, one can propose an outcome prediction model which includes three main factors. These factors might also apply to other types of surgery. Thereafter, the outcome is determined: (1) by the functional adequacy of the tissue to be resected. This is reflected by the fact that the resection of unimpaired tissue leads to greater losses and by the fact that greater losses in specific functions are observed in those patients with a better baseline performance (^{49, 132, 133, 134}); (2) by the patient's mental reserve capacities. These are reflected by the fact that the outcome is better for those patients with a better baseline performance, IQ, educational status. The age at the time of surgery is very important (e.g. whether or not the surgery is done within periods critical for plasticity or mental decline) (^{74, 124, 135, 136, 137, 138, 139}); (3) by seizure control. This can lead to the aforementioned release effects and long-term recovery (⁴⁶). In summarising these findings, a poorer cognitive outcome becomes more likely with persistent seizures; with good preoperative memory performance; with an older age at onset of epilepsy, with an older age at the time of surgery; with a larger extent of the resection; with greater collateral brain damage due to surgery; and with lower reserve capacities.

Because postoperative cognitive loss is a function of the damage of functional tissues due to surgery, radiosurgery and gamma knife surgery (GKS) in particular have been suggested an alternative to resective surgery. GKS does not require craniotomy and structural damage and subsequent necrosis are believed to be restricted to small target areas. This method has been applied in patients with hypothalamic hamartomas. The first results of a prospective but not randomized multicenter study of 21 patients with mesial TLE are now available. They indicate that 65% of the patients are seizure free after two years with no neuropsychological deterioration (^{140, 141}). However, categorical neuropsychological data have been used in this study and categorical data are often subject of a bottom effect (i.e. the patients could hardly become significantly worse). A recent report shows three cases which point in another direction (¹⁴²). A randomized controlled trial with elaborate neuropsychology would be necessary in order to compare the outcomes of resective surgery versus radiosurgery.

For the sake of completeness deep brain stimulation for seizure control in patients with refractory epilepsy must be mentioned. If resective surgery cannot be performed because the epileptogenic zone is within eloquent cortex and when significant neuropsychological consequences must be expected, then deep brain stimulation via

an implanted pulsgenerator may be an option. High frequent electric stimulation of thalamic nuclei obviously modulates neuronal excitability and can lead to significant seizure reduction and decrease of interictal epileptiform activity. Comparable results have been obtained with unilateral hippocampal stimulation with refractory mesial TLE. Up to now it has not yet been evaluated, as to whether stimulation indeed preserves function or whether it interferes with the functionality of the stimulated area (^{143, 144, 145}). The ultimate goal of such an approach is the development of devices which combine seizure prediction and stimulation methods and allows for EEG triggered suppression of epileptic activity by deep brain stimulation. (¹⁴⁶)

Vagal Nerve Stimulation

In recent years, the electrical stimulation of the vagal nerve (VNS) has turned out to be something like a “third way” for treating pharmaco-resistant epilepsies (other than medical and surgical treatment) (¹⁴⁷).

Since its approval in 1997, this cardiac pacemaker-like impulse generator was implanted in more than 25,000 patients worldwide. The device stimulates the vagal nerve via a spiral electrode and has also been approved for the treatment of very severe depression. Depending on the individual settings, the intermittent electrical pulses are applied to the vagal nerve (current: 0,25 - 3,00 mA; pulsewidth: 200-300 μ s; pulse frequency: 20-30 Hz; cycles: ON-duration 7-30 s, OFF-duration: 15-300 s). With regard to efficacy and the suggested influence on cognitive functioning, it is important to know that the afferent projections of the vagal nerve either directly or indirectly approach brain areas which are also relevant to epilepsy (e.g. locus coeruleus, thalamus, hippocampus and amygdale). The clinical efficacy of the vagus nerve stimulator has been demonstrated with double blind, dose controlled studies. In about 40-50% of the patients, a seizure reduction of at least 50% can be obtained. The efficacy appears to increase with the duration of the treatment, but absolute seizure control is rare. From a neuropsychological standpoint, this instrument is of major interest since it's intermittent and programmable stimulation condition allows for an experimental evaluation of the modulatory effects of peripheral vagal stimulation on central nervous functions. Indeed, positive psychotropic effects in terms of attention improvement and decision-making word recognition have been reported in addition to a negative effect on figural memory (^{148, 149, 150, 151}). Apart from

its acute effects, no persisting changes as assessed with a neuropsychological test battery have yet been demonstrated (¹⁵²).

Behavioural therapy

Behaviour modification and neurofeedback are treatment options, which mainly arose from three observations: 1. Seizures in reflex epilepsies can be suppressed by sensory stimulation; 2. Seizures often start with an aura as a first sign of an evolving seizure. This can be taken as a warning sign; 3. The EEG can be taken to visualize pathological and nonpathological brain activity (^{153, 154, 155, 156}).

On a superordinate level, a reduction of seizure supporting behaviour (e.g. sleep deprivation and alcohol) and an increase of health related behaviour (e.g. compliance) could also have a positive effect on seizure frequency. A good example of how compliance can be improved has been demonstrated with the introduction of an electronic pill box (¹⁵⁷).

More interesting from a neuropsychological point of view is the self-control of seizures by counteracting measures in the presence of an aura or by interictal training of conditions that are incompatible with seizures via EEG biofeedback. Both approaches might find a common explanation in the principal of „recruitment and availability“. This means that a spread of epileptic activity is most likely when focus surrounding tissues have a medium activity level and functional occupation of nonaffected brain tissues as well as their inactivation prevents their recruitment by epilepsy (¹⁵⁸). In a patient with an occipital focus and a fixation-off epilepsy (repetitive spike activity occurring with eye closure), a linear relation could be shown between epileptic spike activity and graded variations of the visual input (¹⁵⁹). Control mechanisms aim at weak- or non-epileptic tissues rather than strong epileptic tissues. This has been demonstrated with the evaluation of the effects of attending behaviour on seizure activity in the alumina-gel monkey model of focal epilepsy (¹⁶⁰). The strong local interrelation between activation and epilepsy can also be shown with nonlinear analyses of electroencephalographic intrahippocampal depth recordings during memory and non-memory tasks which involve the mesial temporal lobe structures or not (¹⁶¹).

Taking this as the background, both the behavioural and the EEG feedback approach probably do very much the same. The EEG biofeedback seems more effective in

patients with an aura. It explicitly or implicitly relies on the individual's cognitive, emotional and imaginative processes, by which the patients try to modify their EEG activity (e.g. slow DC shifts, sensorimotor rhythm).

Although the principal possibility of self-control has long since been known, the boom was in the '70s and '80s. Even though the incredible effects on seizure frequency (up to 70% seizure reduction) and responder rates (up to 82%) have been described, these methods remained largely experimental and did not become a clinical standard. A critical point with regard to feedback and self-control techniques may be that, from a theoretical point of view, cerebral activation can not only suppress but also elicit seizures (^{18,19}). However, a recent study which used the feedback of galvanic skin response in order to increase the tonic level of peripheral sympathetic arousal, achieved a 49% seizure reduction (median 59%). This shows that the issue of self-control via feedback is still under evaluation (¹⁶²). Prospective randomized and placebo controlled studies of homogeneous patient groups which evaluate the sustained efficacy of behavioural interventions in epilepsy would be highly valued.

At present, educational modular programs for patients and their relatives or caregivers, which include teachings about epilepsy appear much more promising than applying self-control techniques alone. Such consider also diagnostic issues, treatment, psychosocial aspects, and coping with epilepsy. Such teaching programs improve quality of life and they can also lead to a reduction of seizure frequency (^{163,164}).

Chronic epilepsy and cognitive development

Mental decline?

A point of major importance with regard to the impact of seizures and the impact of seizure activity on cognition in epilepsy is whether or not chronic epilepsy damages the brain (¹⁶⁵). As already described within the epilepsy seizure section, seizures and severe seizures in particular can result in irreversible damage. However, this appears to be an individual condition rather than the rule. According to a recent review on this issue, the cumulative effect of seizures on cognition appears less severe than might be expected (¹⁶⁶). Cross-sectional studies in chronic, uncontrolled temporal lobe epilepsy indicate a significant decline in intelligence after intervals

greater than three decades (¹⁶⁷). However, those studies which cross-sectionally correlate cognitive performance with duration of epilepsy suffer from a shortcoming: since most epilepsies start early, their duration is largely synonymous with chronological age. A comparison of age regressions of performance in healthy subjects and patients puts such findings into perspective (¹⁶⁸). Verbal memory decline, which is indicated by age regression in left mesial TLE, runs largely in parallel to the age regression observed in controls. Nevertheless, there is a memory decline in chronic uncontrolled TLE when patients are evaluated in a longitudinal study design. In summary, a very slow and individually progressing cognitive decline can be suggested (^{169, 74}). Presumably this applies to chronic focal epilepsies in general, but this remains to be seen. It also remains to be demonstrated whether different domains are affected in other epilepsies or whether such a decline is specific or non-specific. Most of the impairment met in patients with symptomatic focal epilepsies seems to exist at, or even prior to, the onset of epilepsy and cognitive problems due to the interference of lesions/epilepsy with brain maturation and mental development. The impact of additional, later acquired lesions and their interaction with processes of aging appear to be much more relevant for the individual mental development than for the accumulation of seizures (^{87, 46}). This view would be in line with recent cross-sectional and longitudinal MRI volumetric evaluations in patients with chronic epilepsy, which do not suggest accelerated atrophy or volume loss with longer lasting epilepsies (¹⁷⁰).

No longitudinal studies are available which span time intervals longer than ten years. Therefore, the impact of epilepsy on cognitive development must thus be deduced from a mixture of findings regarding epilepsies in children versus adults; retrospective evaluations of patients with early versus late onset of epilepsy; and an evaluation of patients who underwent epilepsy surgery at a younger versus older age. When epilepsy hits the maturing brain, then the underlying lesion, epileptic dysfunction or negative treatment effects can cause developmental delay or retardation, even if the latter two factors are controlled. Global intellectual retardation is often the consequence. This is reflected by the fact that mental retardation is more likely to occur in early childhood epilepsies than in those epilepsies with an onset in adolescence or later. The more deleterious effect of earlier onset epilepsies on cognitive development is also indicated when evaluated in a mostly homogeneous group of patients with temporal lobe epilepsies. Childhood TLE displays more diffuse

impairment than adult TLE. In particular, language functions are impaired more often in children, but material-specific memory deficits are similar in both groups (^{83,171,172}). Retrospective evaluations in adult patients with TLE reveal that patients with earlier onset (>15 yrs.) show memory plus intellectual impairment, whereas patients with later onset epilepsies show primarily memory impairment. Comparably intellectual impairment is a rare condition in patients with untreated late diagnosed epilepsies (⁴⁶).

Functional plasticity and reserve capacities



Early onset epilepsy

The fact that early onset epilepsies lead to more severe and diffuse impairment than late onset epilepsies makes one wonder, particularly given the fact that childhood also represents a period during which the brain can be assumed to be still highly and functionally plastic. Indeed, there are astonishing cases of formerly left-hemisphere, language-dominant patients who underwent a left-sided hemispherectomy for seizure control (mostly patients with Rasmussen's encephalitis). Later on, they displayed at least partial contralateral language reorganisation if the surgery was performed early enough. Such reorganisation has been observed even in older children of up to nine years of age (^{173 174 175 176}). However, as impressive as such case reports may be, it is a myth to believe that the loss of a total hemisphere can be completely compensated. The children will not achieve the performance level they would have shown had both hemispheres been fully functional and intact, even if the surgery had been realized at a very early age (¹⁷⁷). This is consistent with the general finding in atypical language dominant patients with left hemisphere epilepsies; right hemisphere language restitution is not synonymous with better language functions (¹⁴). Moreover, right hemisphere preservation and restitution of language is often achieved only at the cost of functions normally mediated by the right hemisphere (^{178 179 180}). This negative effect of language restitution at the cost of nonlanguage functions has been called the "crowding" or "suppression" effect. It becomes most obvious with respect to material-specific memory and should be understood in terms of an incompatibility of different modes of information processing rather than a struggle of functions about space (¹⁸¹). Studies based on results from separate unilateral short-term anaesthesia

(WADA test ⁶) of the hemispheres suggest that more than one third of the patients with focal symptomatic epilepsies show patterns of atypical hemispheric language dominance. The presence and the degree of right-hemispheric participation in language are significantly correlated with an earlier age at onset of left-hemisphere epilepsy (^{14, 182}). Apart from an early onset of epilepsy, children and adults with atypical language dominance are often left-handed; show lesions close by or within language relevant structures; and display neuropsychological "crowding effects" with distinct nonverbal memory deficits (^{14, 183}). Atypical hemisphere dominance, however, is not an "all or nothing" phenomenon and graded patterns of right hemisphere dominance as well as distinctive patterns of interhemispheric dissociations of expressive and receptive language or handedness and language (^{184, 185, 186}). Dissociation of memory and language can also be found (^{187, 188}). In contrast with widespread left-hemispheric damage which leads to contralateral reorganisation, circumscribed epileptogenic lesions can lead to ipsilateral perilesional language reorganisation (¹⁸⁹). The question of whether ipsilateral reorganisation depends on the type of lesion or on lesion onset is a matter of discussion (^{190, 191, 192}). The presence of atypical dominance is not necessarily fixed to the presence of lesions close to or within the cortex normally relevant for language. It is observed as well with circumscribed lesions or foci not overlapping with language areas, indicating distant effects of focal epilepsies on regions outside the epileptogenic area (¹⁸²). That atypical dominance in epilepsy is not only lesion driven but also epilepsy driven has recently been shown by correlating atypical language dominance in TLE with left hemisphere epileptic activity (¹⁹³).

It is important to note that there is a clinical bias in lateralisation research, which focuses on left hemisphere epilepsies and considers right hemisphere epilepsies only when the seizure semiology indicates right hemisphere language or when the patients are left handed. Evaluation of larger series of consecutive, nonselected patients with left and right epilepsies first indicates that 24% of patients with right hemispheric epilepsies also show a pattern of atypical language dominance and that second the possibility of a transfer of language functions from the right to the left hemisphere can be suggested (¹⁴). The findings in right hemisphere epilepsies mirror those in left epilepsies in that atypical language dominance occurs more frequently in late-onset, right-sided epilepsies than in early-onset, right hemisphere epilepsies. This indicates that in the early-onset group, right-sided epilepsy forced predisposed

right-sided language functions to be „transferred“ to the left hemisphere, or that early right-sided epilepsy prevented the establishment of language representation in that hemisphere (¹⁹⁴).

Later onset epilepsy

If epilepsy affects the mature brain, greater partial impairment is observed. When compared to adults, children show a greater functional plasticity and reserve capacity (⁸³). This can be demonstrated for example with recovery from epilepsy surgery (¹⁹⁵). Patients with adult onset epilepsy experience irreversible impairment of fully acquired functions rather than retarded development. This can also be demonstrated within the context of epilepsy surgery. In this case surgery stands for an acquired lesion, which is very similar in children and adults and which allows for the evaluation of compensation and restitution capacities at different ages. In left TLE patients, there is a clear relationship between increased risks of postoperative verbal memory decline following anterior temporal lobectomy and increasing age at the onset of epilepsy (¹³⁷). When compared to adult TLE patients, TLE children below the age of 16 show a lower risk of postsurgical memory deterioration (¹³⁷¹⁹⁶), and within a three to twelve month follow-up, the postoperative memory decline appears to be more reversible in children than in adults (¹³⁶). Although additionally acquired damage can add to the pre-existing damage and this might result in an accelerated mental decline (¹⁹⁷), there is nevertheless evidence for processes of plasticity also in the adult brain. Again, the respective knowledge mostly stems from TLE. With fMRI, for example, it could be demonstrated that verbal memory involves the right temporal lobe in left TLE (¹⁹⁸), and intracranially recorded, event-related potentials within the right hippocampus predict verbal memory outcome after left temporal surgery (¹⁹⁹). There is also clinical evidence of adult memory reorganisation from observations showing that in preoperatively atypically dominant patients the so-called suppression or crowding effect was reversed after surgery (²⁰⁰).



The question of whether patients with chronic epilepsy are at a greater risk for becoming demented as they age has rarely been addressed. A recent study on older patients found cognitive impairments comparable to those patients with mild cognitive impairment (MCI). Patients with epilepsy on AED polytherapy displayed the worst performance (²⁰¹). Even when the epilepsy does not turn out to be a progressively dementing disease, the fact that the starting condition for physiological mental aging

is much worse than in healthy subjects suggests a larger portion of demented patients and a much earlier onset of dementia in patients with epilepsy (^{168,138}). For intelligence, a postponed decline in patients with a better education versus patients with a poorer education has been found. This indicates greater reserve capacities for those with a better education (¹⁶⁷). Future research must address the question as to whether certain types of epilepsy (e.g. temporal lobe epilepsy with memory impairment or frontal lobe epilepsy with impaired executive functions, psychiatric comorbidity, and genetic predispositions for accelerated mental decline) are risk factors. These factors can be considered in patient counselling, particularly when surgical interventions are planned and bear the risk of additional cognitive impairment.

In conclusion it was a major aim of this section to show that a developmental neuropsychological approach is essential for the understanding of the impact of epilepsy and its treatment on cognition and behaviour. In so far epilepsy can serve to model neurodevelopmental impairments in childhood, the interaction of a chronic disease with physiological processes of aging, and the brains capacities to reconstitute and compensate with early versus late lesions. Finally epilepsy provides a model to study the differential impact of lesions versus epileptic dysfunction on cognition.

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