

**Clinical Neuropsychology in Epilepsy**  
- Theoretical and Practical Issues -

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## **Abstract**

For the understanding of cognitive impairment in epilepsy, it is essential to appreciate that static and dynamic factors affect brain function in this disease. Whereas morphological lesions or structural changes are associated with more or less irreversible deficits, epileptic activity, seizures, and the treatment of epilepsy can cause dynamic and principally reversible impairments. The contribution of these factors varies depending on the type of epilepsy, the age at lesion/epilepsy onset, the localisation and lateralization of epilepsy and individual demographic patient characteristics. Altered brain structure and function can result in epilepsy, but epilepsy can as well alter the functional cerebral organisation of the brain. Thus epilepsy-related cognitive impairment must be seen within a developmental neuropsychological framework. From a neuropsychological point of view, it is essential as to whether epilepsy hits the maturing versus mature or aging brain. Epilepsy can result in retardation, loss of acquired functions, or accelerated mental decline. Cognitive impairments in epilepsy often exist from the beginning of epilepsy, early onset lesions/epilepsy interfere with mental development, and a progressive aetiology, severe seizures, and lesions secondary to epilepsy can accelerate mental decline. Uncontrolled epilepsy and epileptic activity as well as the treatment of epilepsy may reversibly and irreversibly affect cognition. Within this framework neuropsychology has become an essential diagnostic tool for the early detection and monitoring of cognitive impairment and its determinants in beginning and chronic epilepsies. Neuropsychology serves as a valuable tool for quality and outcome control of the treatment of epilepsy and helps to improve the individual medical care of patients with epilepsy.

## **Introduction**

Neuropsychology in epilepsy is characterized by its close connection to neurophysiology, neuropathology and neuroradiology, and neuropharmacology. The synergy of these faculties has decisively been stimulated by epilepsy surgery. Neuropsychology traditionally is synonymous with the detection, lateralisation, and localisation of brain dysfunctions and associated behaviours. However, today in the presence of powerful high resolution brain imaging techniques and in the presence of sophisticated electroencephalographic evaluation tools, the role of neuropsychology is changing (Baxendale and Thompson, 2010). Apart from revealing cerebral dysfunctions related to epilepsy, neuropsychology is more and more becoming a tool for the monitoring of epilepsy outcome and for quality control of the treatment of epilepsy (Elger et al., 2004a; Helmstaedter, 2009a). Standardized neuropsychological evaluation has become an integrated and essential tool in the diagnostic and clinical evaluation of surgical patients with epilepsy and from there it is going to expand to a critical role in the routine care of patients with epilepsy on a more general level. This change of the diagnostic focus, however, does not supersede the examination of specific brain dysfunctions. In contrary, if cognitive effects of epilepsies and underlying pathologies are to be detected or if the cognitive consequences of the pharmacological or surgical treatment are in the focus of interest, then it is essential to have sensitive und specific measures, which respond to the etiological factors involved and which reflect focal and systemic changes in affected brain regions and functional networks (Hoppe and Helmstaedter, 2010). There is a diversity of different test instruments available leaving the examiner spoilt for choice (Jones-Gotman et al., 2010). After 20-30 years of intensive research on the neuropsychology of epilepsy, PubMed (<http://www.ncbi.nlm.nih.gov/sites/entrez>) lists over 3000 publications when searching for the terms “epilepsy and cognition”. Test selection should be evidence based and oriented to predefined criteria and clinically relevant questions. Going along with diagnostic and therapeutic improvements in epilepsy, neuropsychological instruments themselves should become a subject of ongoing quality control. The specific role of neuropsychology in epilepsy and the diagnostic options for clinicians are best illustrated on the basis of the following aetiological model of the cognitive impairments in epilepsy.

### **1. Aetiology of cognitive impairments in epilepsy**

Epilepsies are classified according to their aetiology, topography, and seizure characteristics. The traditional classification system differentiates idiopathic, symptomatic, and cryptogenic epilepsies, the major differential criteria being the presence, suggestion or absence of a cerebral lesion, and the degree of genetic determination. Classifications of the epilepsies change with the number of aetiological factors revealed (Berg et al., 2010). For the neuropsychology of

the epilepsy, however, all factors are of interest, which may affect cognition along with the course of the disease and its treatment.

For cognitive impairments in epilepsy an aetiological model can be suggested, according to which dysfunctions may result from more stable and irreversible structural morphological cerebral changes on the one hand and from more dynamic and principally reversible epilepsy and treatment related dysfunctions on the other hand (**Figure 1**). The relative contribution of these factors may differ dependent on subject variables, the localisation and lateralisation of the epilepsy, and variables like age, age at the onset, and the duration of epilepsy, which comprehend the impairments within a neuro-developmental framework (Elger et al., 2004b). In addition to lesions, epilepsy, and treatment related factors, the influence of psychiatric comorbidity on cognition needs to be taken into consideration.

Taking this model as the basic, the practical clinical questions to neuropsychology are at hand (see **Table 1**).

## **2. Neuropsychological assessment**

### **Mental status examination and evaluation of change**

As for the neuropsychological examination of patients with epilepsy a principal distinction to be made is whether the neuropsychological status is to be evaluated or whether the evaluation aims at performance change due to changes in epilepsy or treatment. Cognitive status evaluations should at best be performed in an adequate distance to the last seizure, when the seizure situation is stable, and when the patient is on an antiepileptic medication which can be rated as harmless for cognition. This must be taken into account in advance in order to prevent hours of invalid testing. This is particularly relevant when the test routine considers application of comprehensive standard batteries. Because of the dynamic impairments that are characteristic of epilepsy and since neuropsychology in epilepsy also means outcome and quality control, assessing cognitive change is an essential part of patient care in epilepsy. Evaluation of change along with the course of epilepsy or treatment requires knowledge about the reliability (stability) of the applied instruments (i.e. are parallel versions available, is the same test repeated, which practice effects can be expected, does the instrument provide reliable change indices (RCI)?). Many tests are not standardized for repeated application and this needs to be considered when interpreting changes in cognitive measures (Hermann et al., 1996).

### **Individual versus standardized evaluations**

A second important differentiation is whether to approach the patient individually by eclectic test selection or by use of a standard test battery. Individual diagnostics reveal more information about a given patient, but particularly in research oriented epilepsy centres a standardized diagnostic approach might be preferable in order to learn across patients and to

modify the approach dependent on diagnostic outcomes. Most epilepsy centres use test batteries and while there is at least some agreement on which domains need to be assessed there appears to be great heterogeneity in regard to individual test selection. This is indicated by the international overview over commonly used tests in 1993 (Jones-Gotman et al., 1993) and this is also indicated by a recent evaluation which assessed the question of evidence based diagnostics in 14 epilepsy centres in German speaking countries (Witt and Helmstaedter, 2009). This evaluation counted more than 200 different test instruments in use, only 25% of the tests were selected evidence based, about 30% of the tests were selected due to subjective and pragmatic reasons, and for the rest of the tests no explicit rationale for selection was provided. Different tests provide different outcomes and in order to overcome this Babylonian diversity some paediatric and adult epilepsy centres in Germany now use the same core test battery (Helmstaedter, 2009a; Witt and Helmstaedter, 2009). In the US the same issue is followed by the National Institute of Neurological Disorders and Stroke (NINDS) common data elements project which provides detailed recommendations for neuropsychology in patients with epilepsy (<http://www.commondataelements.ninds.nih.gov/Epilepsy.aspx>). Such agreements are required to facilitate communication of neuropsychological results (on scientific issues as well as on individual patients) across different centres.

Most centres assess intelligence (IQ). Testing of IQ is very time consuming and does only in part aim at basic neuropsychological functions. It can, however, be indicative for mental retardation and developmental hindrance, particularly when compared to the performance levels of parents and siblings. In children, IQ is still the best predictor for school performance. However, because the majority of epilepsies start early, and because this often results in lower IQ, the intelligence level as assessed by full scale IQ's should not be considered as a reference or correction to identify partial impairments in specific cognitive domains. This would lead to an underestimation of the patients impairments. The interpretation of neuropsychological results in consideration of the IQ should only be applied in case of later acquired epilepsy/lesions.

For the diagnosis of partial impairments in the different cognitive domains, e.g. in order to lateralise or localise impairments or in order to isolate the major reason for dysfunctional behaviour, specific and well validated measures should be chosen according to evidence in the epilepsy literature. This information, however, is not necessarily provided by common compendia of neuropsychological test instruments for adults or children (Baron, 2004; Lezak et al., 2004; Strauss et al., 2006).

The experience and agreement on which tests to use for the diagnostics of partial impairments covary with the prevalence of the different epilepsies. For temporal lobe epilepsy tests on verbal and figural memory list learning tests are preferred, for frontal lobe epilepsy tests on motor coordination, attention, planning, mental flexibility and response

inhibition. Posterior parietal or occipital epilepsies have hardly been systematically evaluated but here tests on sensory tactile discrimination appear to be valid.

In general the same tests may be used for localisation diagnostics, which have been proven to be valid in regard to progressive, traumatic, or vascular lesions in the respective brain regions. Syndrome oriented tests like aphasia examinations, however, may turn out insensitive in regard to the often mild to moderate impairments in epilepsy. A very important issue is that tests which claim to assess the same cognitive domain (for memory for example the Auditory Verbal Learning Test, the California Verbal Learning Test, Wechsler Memory Scale) may have different sensitivity and specificity to localized lesions and dysfunctions in epilepsy. Different outcomes are the result which cannot be directly compared (Helmstaedter et al., 2009; Loring et al., 2008).

### **Neurodevelopmental aspects**

In younger children developmental aspects in regard to motor and language development need to be considered and one may not forget that, dependent on the time of injury/epilepsy onset, there are potentials for reorganisation, and with progressing brain maturation symptoms may change and children may grow into impairments not seen before (Gleissner and Helmstaedter, 2008). Tests and structured developmental interviews which are commonly used for the presurgical evaluation of children and mentally retarded adults with epilepsy have been listed by Gleissner and Helmstaedter (2008). Since developing children represent a “moving target” and since often, dependent on age, different tests must be used, a standardized evaluation of children across ages and mental capabilities can be difficult. For orientation normalized and standardized questionnaires for parents of children with epilepsy may provide information about cognitive and behavioural dysfunctions (Gleissner et al., 2006). In children the direct monitoring of adaptive behaviours is essential since motivational and attentional problems may lead to an underestimation of the child’s performance (performance-competence discrepancy).

### **Hemispheric organisation, plasticity, reserve capacity**

Questions regarding the localisation and hemispheric lateralisation of an impairment and questions regarding postoperative outcomes and reserve capacities require knowledge about the hemispheric dominance for the performance in question. This information is mainly needed in the context of epilepsy surgery and mainly aims at the prevention of aphasia or amnesia. In hemispherectomy and callosotomy information on motor or visual organisation are of additional interest.

Left handedness and ambidexterity are good markers of atypical language dominance, particularly in early onset left hemisphere epilepsies. In addition neuropsychological test profiles with comparably well preserved language and unexpectedly affected non-language functions can be indicative for atypical language dominance in left hemisphere epilepsies. Traditional neuropsychological techniques like tachistoscopia or dichotic listening which assess ear or visual field dominance may serve as a gross orientation but for clinical decision making such tests do not suffice.

The most reliable tool to determine hemispheric dominance is still the intracarotid application of amobarbital for anaesthesia of the individual hemispheres that was first described by Juhn Atsushi Wada and therefore is also known as the Wada test. The intracarotid amobarbital test (IAT) is invasive and its indication is fixed to brain surgery. It was first initially invented to prevent postoperative aphasia, later it was used also for prevention of global amnesia due to temporal lobe surgery. The IAT provides the unique possibility to assess functions of one isolated hemisphere by temporarily deactivating the contralateral hemisphere i.e. it discloses deficits and compensatory capabilities of the isolated hemispheres. For a long time the IAT was obligatory before epilepsy surgery but now its indication became rare (Baxendale 2008, Helmstaedter 2008) mainly because of more selective surgical procedures and alternative non-invasive tools for the assessment of cerebral dominance. Alternatives to the IAT that provide the determination of language dominance in the individual patient comprise functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), positron emission tomography (PET), single photon emission computed tomography (SPECT), near-infrared spectroscopy (NIRS) and functional transcranial Doppler sonography (fTCD) (Abou-Khalil 2007). The vast majority of these non-invasive techniques registers hemodynamic responses to language paradigms. A problem with nearly all these approaches is the lack of normative data and the different protocols/paradigms across different centres (Dodrill 1997, Haag 2008). Additionally almost all alternatives to the WADA bear the risk of false positive and negative findings. If resections in or close to suggested eloquent cortex is planned, electrocorticographic functional mapping via implanted electrodes or during awake surgery is used to delineate the exact resection borders (Baxendale, 2002; Baxendale et al., 2008; Gaillard, 2004; Haag et al., 2008; Helmstaedter, 2008c; Helmstaedter and Kurthen, 2002).

### **Modular testing**

Taking the time constraints for neuropsychologists and the need for evidence based neuropsychological evaluation in epilepsy into account a modular neuropsychological assessment can be proposed which directly aims at the questions to neuropsychology posed in **Table 1**. **Table 2** provides the schedule and rationale of such a modular diagnostic approach,

which may just be taken as an example without claiming exclusivity of what can be done for and around epilepsy patients.

### **3. Neuropsychological findings in epilepsies**

This section reviews the neuropsychological features of different types of epilepsy that are listed in **Table 3** including information about the manifestation age, the precipitating conditions, and the suggested course of cognitive development.

#### **Idiopathic epilepsies**

Idiopathic epilepsies in the first line are traditionally defined as having a genetic predisposition in the absence of brain lesions. Whereas idiopathic generalized epilepsies (IGE) are characterized by generalized EEG patterns which cover the whole cortex, idiopathic partial epilepsies show epileptic activity limited to certain brain regions.

Idiopathic epilepsies generally appear to be more easy-to-treat and because of the lack of lesions they are reported to be associated with the less severe cognitive impairments than focal symptomatic epilepsies. This however must not hide the fact that there are cognitive and behavioural problems in idiopathic epilepsies. In idiopathic epilepsies there is a stronger relation between epileptic activity and cognition than in symptomatic focal epilepsy. To which degree epileptic activity in these epilepsies marks dysfunctional brain development which goes along with cognitive impairment and to which degree it directly affects cognition is difficult to separate. Different from what would be expected from the term “generalized epilepsy” a wide range of partial rather than generalized impairments can be discerned in generalized and partial idiopathic epilepsy. EEG, histological findings, and findings from structural and functional imaging studies support an involvement of the frontal lobes, the thalamus, and thalamo-cortical loops in IGE (Aghakhani et al., 2004; Meencke and Janz, 1985; Salek-Haddadi et al., 2003; Woermann et al., 1999). The cognitive impairments in the idiopathic epilepsies differ dependent on whether epilepsy interferes with critical periods or so called spurts of cognitive development, e.g. before, at, or after language acquisition, or at the time before or when frontal executive functions develop. Frontal executive dysfunctions are seen in both partial and generalized idiopathic epilepsies and appear to mark a common endpoint of a neurodevelopmental hindrance. Despite the mostly good prognosis long term residual deficits cannot be excluded.



**Patients with IGE** make up about 6-12% of the children with epilepsy. It appears to have peaks with early childhood, 5-8 years, and 9-12 years (see table 3). Patients with IGE show only minor problems with respect to global intelligence but they experience problems in attention, psychomotor speed, visuo-spatial skills, and nonverbal memory. Language and verbal memory appear unaffected (Hommet et al., 2006; Mirsky et al., 2001; Pavone et al., 2001). In IGE impairments become evident as a function of epileptic activity, but cognitive processes can also induce epileptic discharges and seizures (Matsuoka et al., 2000). It may be of interest that such a relation can sometimes be noticed also in focal symptomatic epilepsies (Helmstaedter et al., 1992). Epileptic spike-wave activity in IGE specifically affects sensory and executive functions and tests requiring sustained attention in continuous visual and auditory tasks seem to be suited to identify epilepsy related dysfunctions in this group of patients (Jambaque et al., 2001). Continuing epileptic activity experienced over a long period of time interferes with brain development. Consequently early onset absence epilepsies starting in early childhood or at school age are at greater risk of a poor outcome than juvenile absence epilepsies.

**Benign partial epilepsies and related syndromes.** Benign childhood epilepsy with centrotemporal spikes (BECTS) is a frequent epilepsy (10-15% of epileptic children), with an onset between age 3 and 13 (most between 5 and 10). BECTS has a good prognosis since most patients become seizure free after puberty. It should be noted that rolandic discharges which are typically seen in this type of epilepsy, are also frequently seen in healthy children as well as in non-epileptic children with cognitive or behavioural disorders, with headaches and some genetic disorders (Stephani and Carlsson, 2006). Language problems are a major characteristic of BECTS (Liasis et al., 2006; Papavasiliou et al., 2005). In this context it may be of interest that rolandic discharges have been reported for 10% of 300 dyslexic children (Stephani and Carlsson, 2006). In the active phase of BECTS neuropsychological deficits comprise attention, motor functions, short-term memory, visual and perceptive abilities. Despite normal IQ, most patients have neuropsychological and language problems suggestive of a developmental learning disability, and problems appear more severe with complex partial seizures (Giordani et al., 2006; Stephani and Carlsson, 2006; Vinayan et al., 2005). With seizure remission children can catch up with normal development but minor persisting problems can still be found in executive functions and verbal comprehension (Lindgren et al., 2004; Monjauze et al., 2005). Thus, absence of seizures and complete remission of epileptic activity appear to be essential for a good cognitive outcome.

According to its localisation, benign partial epilepsy with occipital located discharges appears to affect visual information processing (Wolff et al., 2005), but patients score worse than normal controls also in intellectual functions, memory, and attention (Gulgonen et al., 2000).

The very special conditions of Landau Kleffner Syndrome (LKS), continuous spike-wave during sleep (CSWS) and electric status epilepticus during sleep (ESES) (Van Hirtum-Das et al., 2006) are also associated with language problems. Strong parallels and transitions from LKS to ESES as well as from partial generalized epilepsy to ESES are discussed (Rossi et al., 1999; Saltik et al., 2005; Van Hirtum-Das et al., 2006). Different from BECTS, however, patients with LKS, CSWS, ESES experience a progressive loss and decline of already acquired functions which can result in severe mental retardation (Debiais et al., 2007). An early age at onset and a longer duration of these conditions appear essential for poorer mental outcome. As with BECTS more frequent epileptic discharges and generalized epileptic activity seem to be related to greater cognitive problems (Van Hirtum-Das et al., 2006).

**Juvenile myoclonus epilepsy (JME)** starts predominantly between 12 and 18 years, and it is characterized by neuropsychological and behavioural features of a frontal dysexecutive syndrome (Janz, 2002). This is indicated by neuropsychological findings of problems in reasoning, concept formation, mental speed and cognitive flexibility, or problems in visual working memory as assessed in an experimental 18FDG-PET study (Devinsky et al., 1997; Sonmez et al., 2004; Swartz et al., 1996). According to Trinkla (2006), 35% of 43 patients with JME showed one or more Axis I or II disorders. Twenty three percent of this sample showed a personality disorder which would be supportive for the suggestion by Janz (2002) that frontal lobe cognitive dysfunction together with personality change (e.g. limited self-control, suggestibility, indifference, rapid mood changes) form a syndrome characteristic of JME.

### **Focal symptomatic epilepsies**

#### **Epileptic encephalopathies (West- and Lennox-Gastaut-Syndrome, Dravet Syndrome)**

After having already dealt with the Landau Kleffner Syndrome in the context of BECTS, the severe epilepsy syndromes, West-Syndrome (catastrophic epilepsy with infantile spasms) and Lennox-Gastaut-Syndrome with predominant atypical absences and tonic seizures are characterised by diffuse and multifocal epileptic activity due to diverse, diffuse and multifocal lesions (Crumrine, 2002; Shields, 2002). The West-Syndrome is often accompanied by mental deterioration, behavioral regression with visual unresponsiveness, and reduction of social interaction with autistic features. The majority of patients will not achieve normal intelligence in adulthood (Jambaque et al., 2001). About 40% of Lennox-Gastaut patients evolve from West-Syndrome and this group also shows rapid progressive intellectual decline

(Jambaque et al., 2001). As with most other epilepsies, cognitive outcome is worse with an earlier onset which interferes with brain maturation and hinders cognitive development. Standardised neuropsychological testing can hardly be performed since IQ ranges below 50 in the majority of cases. Behaviourally, impairment of motor speed, apraxia, autistic or psychotic traits, hyperkinesia, spatial disorientation, and perseveration can be observed and the long-term outcome is generally poor (Besag, 2004). While the West- and the Lennox-Gastaut Syndrome are aetiologically and clinically very heterogeneous, 35% of patients with a Dravet Syndrome (severe myoclonic epilepsy of infancy) have a dominantly inherited sodium channel related gene defect (SCN1A) (Oguni et al., 2005). This syndrome is characterized by myoclonic seizures, absence and focal seizures. Developmental hindrance ranges from mild to severe, most children suffer from behavioural problems in terms of hyperactivity and autistic traits. According to a recent longitudinal study mental retardation, psychotic or autistic traits and hyperactivity were very common between the ages one and four, going over into stabilization on a level below normal (Caraballo and Fejerman, 2006; Jambaque et al., 2001; Wolff et al., 2006).

### **Localisation related epilepsies**

**Temporal lobe epilepsies (TLE)** represent with about 70% the majority of the chronic symptomatic epilepsies, about half of them show hippocampal sclerosis and/or atrophy. Because of its high prevalence and because the temporal lobe structures represent morphologically distinct and well defined brain structures the functional correlates of temporal lobe epilepsies are yet the best evaluated. Whether mesial TLE represents a nosological entity or a syndrome is a matter of debate (Wieser, 2004). The temporal lobe structures are involved in memory processing and impairment of declarative episodic memory (knowledge fixed in space and time) represents the major cognitive impairment in this group of epilepsies. Semantic memory (context free world knowledge) is also found to be impaired in TLE but this appears more related to temporo-lateral neocortical dysfunction as compared to episodic memory which appears directly related to hippocampal pathology and dysfunction (Helmstaedter, 2002). Correlations between test performance and mesial structures in TLE have for example been demonstrated for hippocampal volumes (Sawrie et al., 2001), hippocampal cell loss in distinct subfields (Pauli et al., 2006), event related potentials (Fernandez et al., 2002; Vannucci et al., 2008), rhinal-hippocampal gamma band coupling (Fell et al., 2001), long-term potentiation (Beck et al., 2000) and functional MRI (Bonelli et al., 2010). For clinical practice this means that memory assessment in TLE can be taken as a good marker of temporo-mesial pathology/dysfunction.

Episodic memory impairment in TLE tends to be material specific (verbal/nonverbal) according to whether the left (language dominant) or right hemisphere is affected. Whereas the relation between verbal memory and the left

temporal lobe is a quite consistent feature of left TLE, the relation between the right temporal lobe and figural visuo-spatial memory appears inconsistent. Major reasons for erroneous lateralisation of material specific memory impairment are age (material specificity develops with brain maturation), sex differences (females show advantages in verbal and disadvantages in figural memory), atypical language dominance (verbal memory is often preserved at the cost of figural memory, and this is also related to gender), verbalization strategies (this accounts for figural memory), and test materials (figural: abstractness, allocentric vs. egocentric; verbal: load on working memory, semantic processing, organisation, IQ). Hermann (1997), in his definition of the neuropsychological characteristics of mesial TLE already stated that these patients often suffer from low IQ. In this respect some authors suggest mental decline with a longer duration of epilepsy (Jokeit and Ebner, 2002). However such studies rarely take education levels into account. Poor intelligence in chronic TLE is mostly related to poorer education levels and poor education can hardly be interpreted in terms of a loss of previously acquired functions due to longer duration of epilepsy (Kaaden and Helmstaedter, 2009). As discussed before, the impairments seen in TLE appear to be present from the beginning of the disease and active epilepsy does not necessarily add to this. Secondary acquired traumata or progressive pathologies (e.g. tumours, encephalitis) are an exception (Malter et al., 2010). As discussed for other epilepsies early onset TLE interferes with cognitive and brain development and patients fail in building up an adequate performance when compared to healthy. Early onset TLE impairs functions of directly affected structures (temporal) but also interferes with the development of structures (mainly frontal) which mature later [on](#) (Helmstaedter and Elger, 2009; Kaaden et al., 2009; Weber et al., 2007). Apart from memory problems patients with TLE also show impairments in frontal lobe associated executive functions. This can in part be explained by in the just discussed neurodevelopmental context but in part also by reversible effects of irradiating epileptic dysfunction or diaschisis phenomena on distant brain areas (Hermann et al., 1988; Jokeit et al., 1997).

Temporo-mesial pathology not only affects memory but also emotion processing and reward learning. Accordingly patients with TLE often show comorbid depression, impaired social cognition and preference learning (Frisch et al., 2009a; Johnsrude et al., 2000; Schacher et al., 2006). An extreme may be seen in autism which appears a special characteristic of tuberous sclerosis patients with temporal lobe tubers (Bolton et al., 2002). Comparing TLE patients with frontal lobe patients, introversion, neuroticism, cognitive (memory) impairment and social limitations are the prominent behavioural feature of temporal lobe epilepsy (Helmstaedter and Witt, 2011). In this context the old literature referred to the so called temporal lobe personality which comprised of a mixture of behaviours that from a today's point of view would better be psychiatrically or neuropsychologically explained (Blumer et al., 2004; Devinsky and Schachter, 2009).

**Frontal lobe epilepsies (FLE)** represent the second most common group of symptomatic epilepsies. In contrast to TLE in which hippocampal sclerosis is a predominant and quite homogeneous morphological feature, very heterogeneous aetiological factors are involved in frontal lobe epilepsy. Frontal lobe executive functions are involved in most other cognitive domains which results in diffuse and comparably non-specific impairments. However, the cognitive and behavioural impairments characteristic for FLE largely resemble those described in the lesion-related literature. On a superordinate level they can best be described as a dysexecutive syndrome with impairment of response selection, initiation, execution and inhibition. In particular patients have been demonstrated to show attention problems, problems with short-term or working memory, mental flexibility, response selection, response inhibition, planning, and motor coordination (Exner et al., 2002; Helmstaedter et al., 1996b; Upton and Thompson, 1996). Frontal lobe epilepsies also affect memory performance but in another way than temporal lobe epilepsies (Centeno et al., 2010). In keeping with the frontal dysexecutive functions, discriminative elements in verbal learning memory as assessed with the Auditory Verbal Learning Test are for example: irregular learning curves across subsequent learning trials (ups and downs instead of steady increase), perseverations due to monitoring problems, interference phenomena in terms of proactive interference, problems with source memory since two lists had to be learned, distractibility in recognition memory, and comparably well preserved long term retention of what had been learned (Helmstaedter et al., 2001b). As with TLE, the neuropsychology of frontal lobe epilepsy can hardly be appreciated without taking behavioural changes into consideration. The frontal lobe is traditionally referred to as the “social brain” and as with TLE, dysfunctional behaviours can be discerned in FLE which characteristically correspond to the affected brain region. Compared to TLE patients, FLE is more likely associated with hyperactivity, impulsivity, conscientiousness, obsession and behaviours, which one could traditionally term as organic psycho-syndrome (Helmstaedter and Witt, 2011).

**Posterior, parietal- and occipital epilepsies (PLE)** represent a very small proportion of symptomatic epilepsies. Consequently studies focusing on cognition in patients with parietal or occipital lesions are rare. Different from patients with cerebrovascular or traumatic lesions, in posterior epilepsies symptoms like aphasia, apraxia, neglect or anopsia are a rare phenomenon (Busch, in press). These typically posterior symptoms are if at all seen as a correlate of late and acquired brain lesions or in the context of ictal and postictal seizure semiology. Instead the impairments seen in PLE rather resemble those seen in temporal or frontal lobe epilepsy. Neuropsychological data of paediatric patients with parietal lobe epilepsy (PLE) indicate subaverage intelligence and domain over spanning impairments in memory, attention and executive functions (Gleissner et al., 2008). Similarly a corresponding evaluation in adult patients with PLE demonstrated deficits in almost all cognitive domains (Witt et al., 2008a) including frontal and temporal lobe

functions. Comparing the cognitive profiles of TLE, FLE and PLE in a large series of surgical patients reveals the generally poorest performance levels in PLE (Helmstaedter et al., 2007). Two explanations may hold for this observation. First of all developmental hindrance can be suggested as in most other early onset epilepsies and an impaired input system can be suggested to have greater negative effects on downstream functions than an impaired memory or executive system. Second a negative impact of epileptic dysfunction irradiating along the axis of dorsolateral and frontomedian long fiber tracts may serve as an explanation for the impairment pattern. This at least would mirror the conditions seen with the spread of seizures in posterior epilepsies which often mimic temporal or frontal lobe seizures (Akimura et al., 2003).

### **Differential diagnostics of neuropsychological impairment in epilepsy**

As already mentioned above, cognitive impairments in epilepsy result from the epilepsy, its medical treatment, and the underpinning morphological structural change or damage. Whilst the impact of each of these factors can well be proven, the way in which these factors interact is largely unknown. In the individual patient repeated testing along with changes in therapy or the seizure situation is the only way to disentangle the relative contribution of these factors. Neuropsychological monitoring of the treatment of patients with limbic encephalitis may serve as an example (Malter et al., 2010).

### **Epileptic dysfunction and seizures**

In regard to the factor „epilepsy“, type of epilepsy (idiopathic, symptomatic), intra- and interhemispheric localisation and spread of epileptic activity, the age at the onset, the duration and severity of the epilepsy (seizure type and frequency) are relevant for the cognitive outcome.

Evidence of a direct relation between electroencephalographic epileptic potentials and cognitive impairments can be assessed only under controlled conditions, that is by running neuropsychological assessments in parallel to the EEG, or by the monitoring of cognition along with “treatment of the EEG” (Binnie, 2003). Whereas, in animal models, a relation of epileptic activity and behaviour can well be demonstrated the establishment of such relations in humans provides difficulties (Holmes, 2010; Zhou et al., 2007). As already mentioned, a close relation between epileptic activity and cognition is discussed for the idiopathic focal or generalized epilepsies. However, despite the high relevance particularly for the developing child (Austin and Dunn, 2002), it takes wonder that up to now no EEG-locked standardised assessment or test procedure has become routine (Aldenkamp et al., 2004). In addition it is important to

note that the negative impact of epileptic activity or the positive effect of controlling epileptic activity on cognition cannot be generalized over all patients.

In focal symptomatic epilepsies a relation between epileptic activity and cognitive impairments may exist in individual patients but in this type of epilepsy the correlation appears different and weaker than in idiopathic focal or generalized epilepsies. Most evident, however is the relation in „subclinical“ or „emotional“ seizures, which proceed without the involvement of the motor system. Apart from more acute effects of epileptic activity on behaviour there are indirect indicators which can be taken as evidence that interictal epileptic dysfunction additionally affects cognition and behaviour in a more chronic fashion. Positive cognitive and behavioural changes in the time after successful epilepsy surgery for example indicate a slowly progressing system reset and release of functions which had been suppressed or hindered before surgery (Helmstaedter et al., 2003; Lendt et al., 2000; Witt et al., 2008b). The cognitive effects of epileptic activity during sleep and awake states in childhood epilepsies may be taken as another example (Nicolai et al., 2006). Furthermore, an impact of epilepsy on the acute and chronic functional organisation of the brain has been demonstrated by correlating interictal activity with hemisphere dominance patterns (Helmstaedter et al., 2006; Janszky et al., 2003). The issue of epileptic activity and its treatment gains increasing interest independent of epilepsy, since epileptic activity without the manifestation of seizures can be observed in autistic spectrum disorders, in dyslexia, ADHD etc. (Dunn, in press).

Symptoms within as well as after the seizure have diagnostic relevance. Seizure semiology often allows already a suggestion which hemisphere and which brain regions become primarily and secondarily involved (Jordan, 2007; So, 2006). Apart from seizure semiology in terms of a *positive symptomatology* there are additional cognitive deficits in terms of a *negative symptomatology* during seizures. However, impairment in contrast to semiology requires active testing of the patient during the seizure (Lux et al., 2002). After the seizure, the time needed to become reoriented as well as type, degree, and duration of postictal impairment are related to the seizure. Postictal aphasia, disorientation, and pareses for example can indicate the lateralisation of the seizure origin. Seizure propagation determines the duration of the seizure, ictal consciousness and postictal recovery. Even when patients appear completely reoriented, partial impairments in individual performances may persist for hours. Postictal impairments reflect the lateralisation and localisation of the seizure. Recovery is hierarchical in that cognitive functions distant to the primary focus recover earlier than functions associated with the area of the focus (Helmstaedter et al., 1994a). It may be of interest that functional release/recovery after successful epilepsy surgery shows parallels to recovery from seizures.

A highly relevant and in regard to epileptic dysfunctions essential question is whether chronic epilepsy progressively damages the brain (Sutula and Pitkänen, 2002). To bring it to the point, will chronic uncontrolled epilepsy

result in dementia? According to studies in animals there is evidence for a negative effect of seizures on the brain and on the maturing brain in particular. However, very different effects can be demonstrated dependent on the animal/epilepsy model and age at damage. In humans it is difficult to disentangle the differential influence of initial precipitating lesions, seizures, and the consequences of seizures (e.g. hypoxia). Here seizures normally cause reversible impairment. In single cases with severe seizure conditions (series of generalized seizures, convulsive or nonconvulsive status epilepticus) permanent damage can be the result, but even here the differential impact of the seizure/epileptic activity and the often severe underlying pathology is not self evident (Dietl et al., 2004; Dodrill, 2004; Helmstaedter, 2007).

Cross sectional studies indicate some very slow decline (> 30 years) with chronic uncontrolled epilepsy. Longitudinal studies indicate some impact of continuing seizure and seizure control on cognition but hardly indicate continuous decline as a function of time. However, as already discussed before in the context of temporal lobe epilepsies, duration of epilepsy can hardly be separated from age in early onset epilepsy (Jokeit et al., 2000). There now is evidence from newly diagnosed children and adults that cognitive impairments often is already present at the time of epilepsy onset (Helmstaedter and Witt, 2010; Hermann et al., 2006; Taylor et al., 2010). Between 40 and 60% of newly diagnosed patients exhibit cognitive impairments. Thus in chronic epilepsy the factor “epilepsy” more likely hinders mental development than that it causes mental decline. Accordingly the onset of epilepsy and its underpinnings appear to be the decisive factors for cognition and cognitive development and call for early and consequent epilepsy and cognition related interventions. Nevertheless in older patients with chronic epilepsy an increased number of severely impaired subjects must be suggested. If patients become impaired early in the course of the disease, and if mental decline with “normal” ageing runs in parallel but on a lower level as compared to the course of cognition in healthy subjects, patients must end up earlier at very poor levels than healthy subjects (Helmstaedter and Elger, 1999).

### **Antiepileptic drug treatment**

Pharmacological treatment of epileptic seizures carries the risk of cognitive side effects that may affect daily functioning and quality of life. Efficacy and tolerability of the treatment are decisive for compliance and the long term retention of the therapy (Bootsma et al., 2009). On the one hand antiepileptic drugs (AEDs) may induce or aggravate cognitive impairments in different cognitive domains. On the other hand one should know that effective seizure control can lead to improvements in cognition and behaviour. Consequently seizure control can mask adverse cognitive side effects or falsely suggest positive side effects of the AED in use.

The risk of cognitive side effects increases with (1) rapid titration, (2) higher doses, and (3) a higher overall drug load in the case of polytherapy. This at least accounts to the so called older AED which have more interaction



potentials (e.g. enzyme induction /inhibition) than the so called newer AED. Titration speed, dose, and number of AED also represent the points of action to control cognitive and behavioural side effects. For clinical practice it might be useful to know that a recent cross sectional evaluation in a large series of 1430 patients indicates that, independent on which drugs are used, cognitive problems are present but acceptable with monotherapy and two AED when compared to controls or an off drug condition, whereas impairment become significant with three and more AED (Witt and Helmstaedter, 2010).

The individual antiepileptic agents in part differentially affect cognition. A first very gross differentiation considers that the AEDs of the first generation had sedative properties and affected global (intellectual) performance, that the second generation was primarily associated with impairments in psychomotor speed and memory function, whereas the newest generation rather seems to have psychotropic side effects. Among the classical AEDs bromide, benzodiazepines and phenobarbital (PB) are more frequently associated with cognitive side effects than phenytoin (PHT), valproic acid (VPA) or carbamazepine (CBZ) (Ortinski and Meador, 2004). With the exception of topiramate (TPM) and perhaps also zonisamide (ZNS) (Park and Kwon, 2008) the so called newer AEDs seem to have superior cognitive profiles than the former generations (French et al., 2004).

**Table 4** provides an overview over the cognitive side effects of AEDs reported in recent reviews for children (Loring and Meador, 2004) and adults (Aldenkamp et al., 2003; Kwan and Brodie, 2001; Ortinski and Meador, 2004; Park and Kwon, 2008). Preferential targets of AEDs include the attention and executive functions, but memory and language functions can also be affected. However, even when specific impacts on memory (PHB, CBZ) or language (TPM) are assumed, attention and executive functions are almost always affected. Thus when monitoring of cognitive side effects in the individual patient is required one may rely on computerized or paper pencil screening tests which focus on these functions (Aldenkamp et al., 2005; Helmstaedter et al., 2010; Hessen et al., 2006; Lutz and Helmstaedter, 2005).

AEDs also have indications for other neurological conditions (e.g. migraine or neuralgia) and psychiatric disturbances (Spina and Perugi, 2004) and AEDs with psychotropic side effects can also help to encounter psychiatric comorbidity in epilepsy (Hermann et al., 2008). In this regard Ketter's hypothesis can be taken into account, according to which AEDs with a potentiation of gamma-aminobutyric acid (GABA) inhibitory neurotransmission (e.g. barbiturates, benzodiazepines, valproate, gabapentin, tiagabine and vigabatrin) have a sedating, and AED which attenuate glutamate excitatory neurotransmission (e.g. felbamate and lamotrigine) a stimulating effect (Ketter et al., 1999). However, Ketter's assumptions are an oversimplification and do not apply for all AEDs equally well (Roberts et al., 2005).

Dependent on behavioural traits one should prevent their amplification as it has been suggested for the stimulating effect of levetiracetam (LEV) in patients predisposed to be more extraverted, irritable and impulsive (Helmstaedter et al., 2008a). One should nevertheless keep in mind that positive psychotropic effects of AEDs, be it secondary via mood (e.g. lamotrigine; LTG) or directly via arousal (e.g. LEV), can also improve cognition. Severe psychiatric conditions require treatment (Kanner, 2008) and in case of success this can also have a positive effect on neuropsychological functions.

Cognitive side effects of AEDs are principally reversible after withdrawal, but there are few important exceptions. Treatment with vigabatrin (VGB) can lead to irreversible visual field defects (Gonzalez et al., 2009; Krauss, 2009) and is therefore mainly reserved for severe infantile epileptic encephalopathies (West-Syndrome). Irreversible effects of antiepileptic drug treatment are of particular importance in the case of pregnancy and lactation and also in the case of paediatric patients with epilepsy. In utero as well as early childhood exposure to antiepileptic medication may chronically affect the maturing and developing brain (Frisch et al., 2009b; Harden et al., 2009; Holmes, 1997; Meador et al., 2009).

### **Lesions, pathology, and surgery**

The cognitive capabilities in focal symptomatic epilepsies are determined by the localisation, lateralisation, the extent, and the type of the lesion which underpins epilepsy. The cognitive profile of a temporal lobe epilepsy with hippocampal sclerosis differs for example from that found in temporal lobe epilepsy with temporo-mesial or temporo-lateral tumours (Helmstaedter et al., 1997a). As already mentioned in section about TLE, structural-functional relationships have also been demonstrated for different degrees of mesial pathology in terms of neuronal loss in hippocampal subregions. (Pauli et al., 2006) or between other brain volumetric measures and memory (Butler et al., 2009).

Pathology is decisive for cognition because the type of pathology is correlated to the age at lesion/epilepsy onset. With early congenital, acquired or developmental lesions (e.g. cortical dysplasia) the brain is still functional plastic and it has more capacities for compensation than the mature brain (e.g. traumatic, inflammatory, neoplastic lesions). Despite greater plasticity early lesions and dysfunctions hinder mental development. Accordingly early onset lesions/epilepsies are often characterized by non-specifically rather globally reduced intellectual capabilities whereas late acquired lesions/late onset epilepsies rather show partial impairments with largely unimpaired intelligence (see the discussion above).

## **Epilepsy surgery**

Surgery can be a very successful treatment option for patients with focal symptomatic epilepsies. A randomized trial of surgical versus medical treatment indicated successful seizure control in 58% of operated versus 8% of medically treated patients (Wiebe et al., 2001). Successful seizure control reduces behavioural and mood problems and improves overall quality of life. However, apart from seizure control, brain surgery can have negative effects on cognition and behaviour which quantitatively and qualitatively exceed those seen before surgery (Elger et al., 2004a; Helmstaedter et al., 2007).

There is now some common sense that three factors determine the cognitive outcome of epilepsy and its treatment. The first and probably most predictive factor is the question of the “functionality” of the affected and non-affected brain regions (Chelune, 1995; Stroup et al., 2003). Functionality of the brain even appears to be related to some degree to seizure control (Helmstaedter, 2009b). Closely connected to the question of “functionality” is the second factor, which is the patient’s “mental reserve capacity” (Helmstaedter, 1999). The third factor is “seizure control” (Helmstaedter et al., 2003).

Both, functional integrity of the affected and to be resected tissues and reserve capacity are reflected by baseline performance. On the one hand those with a better baseline performance will also be those with the better outcomes (reserve), on the other hand those with a better baseline performance are at greater risk to lose after surgery (functionality). Functionality is expressed by baseline performance in directly affected brain areas. Both functionality and reserve capacity depend on the patient’s age at the time of surgery. The critical phases of cerebral functional plasticity are about in the time of puberty, the time when reserve capacities and capabilities for compensation start to decline with ageing is about age thirty (Helmstaedter, 1999). Methods to estimate functional adequacy and reserve capacity in addition to neuropsychological assessment are EEG recordings (extracranial/intracranial, interictal/ictal) (Rosenow and Lüders, 2004), structural and functional imaging techniques (Koepp and Woermann, 2005), angiography with intracarotid application of amobarbital, methohexital (Brevital) or etomidate (Amidate) (Banks et al., 2010; Buchtel et al., 2002), and last but not least electrocortical stimulation (Wellmer et al., 2009).

### *Temporal lobe surgery*

The logical consequences for epilepsy surgery from these findings would be to remove what is necessary to control seizures, and to leave as much as possible functional tissues in order to preserve the patient’s cognitive functions. This is best illustrated by the findings regarding temporal lobe epilepsy surgery. TLE is frequently associated with memory impairment already before surgery, and surgery can significantly add to this. In the Bonn series 898 patients operated and neuropsychologically evaluated between 1988 and 2003 cognitive impairments in the 732 patients with temporal

lobe epilepsy were clearly dominated by memory impairments (46-69%) followed by problems in language, motor functions, attention and visuo-construction. Memory in addition was the domain of major postoperative change (losses in between 27-40%). Left temporal lobe resected patients in particular are at a high risk to experience verbal memory decline. However, at the same time cognitive improvements mainly in frontal lobe associated functions can be observed after temporal lobe surgery (**Table 5**) (Helmstaedter et al., 2007). These changes are consistent with what is reported in the literature (Lee et al., 2002).

A recent review on the quest for the most successful surgical approach in temporal lobe surgery came to the conclusion, that different surgical approaches in temporal lobe epilepsy do not result in different seizure outcomes (Schramm, 2008). From a neuropsychological point of view there is, however, converging evidence that in patients with mesial TLE, the cognitive outcome of more selective surgery is superior to that of standard anterior 2/3 temporal lobe resections (Alpherts et al., 2007; Clusmann et al., 2002; Helmstaedter et al., 1996a; Helmstaedter et al., 2008c; Morino et al., 2006; Paglioli et al., 2006; Renowden et al., 1995; Sindou et al., 2006). However, selectivity of TLE surgery has its limits in that collateral neocortical damage and dissection of fibre tracts (e.g. temporal stem) due to the surgical approach can negatively affect memory outcome (Helmstaedter et al., 2008c; Helmstaedter et al., 2004b). Another limitation is that preservation of function and sparing of mesial tissue conflicts with the position that the total resection of the hippocampus is essential for the achievement of seizure freedom (Olivier, 1996). A randomized trial on mesial resection length indicated superior seizure outcome but no different neuropsychological outcome after total as compared to partial hippocampectomy in standard anterior temporal lobectomy (Wyler et al., 1995). The functional relevance particularly of the more posterior parts of the hippocampus for memory outcome has been indicated by several studies (Baxendale et al., 2000; Bonelli et al., 2010). In this regard the question of preservation of functional tissue which can be obtained with radiosurgery may be of interest which claims to be non-destructive and which aims at the change of the intrinsic epileptic characteristics of the radiated tissue (Barbaro et al., 2009; Bartolomei et al., 2008). Comparably the future cognitive outcomes of deep brain stimulation will be of interest, but it still needs to be established, as to whether stimulation indeed preserves function or whether it interferes with the functionality of the stimulated area (Benabid et al., 2002; Boon et al., 2007); (Velasco et al., 2007). In addition the eventual effects of chronic implantation of depth electrodes needs to be evaluated. After right sided selective TLE surgery for example some lasting negative effect of bilateral depth electrode implantation on verbal memory has been described (Gleissner et al., 2002).

#### *Extratemporal lobe surgery*

What can be stated for temporal lobe epilepsy seems to be true also for the cognitive outcome of extratemporal lobe surgery. That is to say, additional impairments due to surgery should be less likely if surgery is restricted to pre-damaged and epileptogenic tissue and if surgery does not affect eloquent areas still involved in function. Frontal lobe resections with subpial transections (dissection of horizontal cortico-cortical connections) can have negative cognitive consequences on motor function, speed, response inhibition and language, when the intervention includes the supplementary motor areas, the central region or the motor language area. As seen after temporal lobe surgery extra-frontal performances may improve (Altenmuller and Schulze-Bonhage, 2007; Helmstaedter et al., 1998; Lendt et al., 2002). More historical studies only report the patient's postoperative condition and do not allow conclusions on changes due to surgery (Elger et al., 2004a). Reports on epilepsy surgery in the posterior cortex do not indicate additional cognitive deterioration (Gleissner et al., 2008; Witt et al., 2008a), but resections carry the risk of visual field defects (Luerding et al., 2004), contralateral sensory deficits (two point discrimination, stereognosis; (Salanova et al., 1995)) and a transient partial Gerstmann syndrome (Binder et al., 2009). Since release effects due to postoperative seizure freedom are observed in attention (Gleissner et al., 2008) and executive function (Witt et al., 2008a) only, most of the preoperative impairment appears to be rather static and not the result of a dynamic and reversible secondary epileptogenic involvement of temporal and frontal structures.

### *Callosotomy*

The main objective of callosotomy, i.e. the more or less complete dissection of the hemispheres, is less a curative treatment than a palliative treatment for the control of drop attacks and generalized tonic-clonic seizures due to rapid interhemispheric seizure spread. Patients undergoing callosotomy mostly suffer from severe epilepsies, they are often mentally retarded, and they often show atypically organised hemisphere dominance. Wada testing of these patients (see next section) is essential in order to prevent disconnection syndromes. Lassonde and Sauerwein (1997) published a series of 25 paediatric patients who underwent callosotomy and who all benefited from surgery. The greatest improvements were observed in social adjustment. Younger patients showed greater gains than older patients. No negative cognitive change but positive social development have also been reported by Provinciali et al. (1990). Sass et al. (1990) in contrast observed impairments after total and partial callosotomy and raised concerns with respect to motor function and language particularly in those patients with a dissociation of hand and language dominance. One year after surgery, in a series of 15 mostly anterior callosotomies (Elger et al., 2004a), there was a trend of deterioration in language functions (N=10), significant worsening in figural memory (n =11), but stable performance in attention, verbal memory and visuo-construction. Apart from mutism which was reversible in all cases (Quattrini et al., 1997), persisting

alien hand syndromes in three patients with mixed dominance were observed after anterior callosotomy. Another study did not find an increased risk of neuropsychological impairments in the presence of mixed dominance patterns (Mamelak et al., 1993).

### *Hemispherectomy*

Hemispherectomy is the ultimo ratio in the presence of severe catastrophic epilepsies that are confined to one hemisphere (mostly Rasmussen's encephalitis, Sturge Weber syndrome, hemimegalencephaly). In these patients the neuropsychologically most relevant question is to which degree the contralateral non-affected hemisphere is going to take over functions of the affected hemisphere. However, despite undoubtful efficacy in controlling seizures in 65-80% of the patients there is no place for excessive optimism in regard to plasticity. Although functional cerebral plasticity extends into puberty, Bayard and Lassonde in a review of studies between 1972 and 1997 (Jambaque et al., 2001) report that postoperative IQ was not related to age at surgery and that even in early surgery the right hemisphere obviously cannot take over all linguistic features normally carried out by the left hemisphere. This would be in line with findings from intracarotid amobarbital testing (IAT or Wada see next section) that atypical dominance and even complete right hemisphere language dominance does not guarantee better language functions postoperatively (Helmstaedter et al., 1997c). Motor functions seem to improve, but attention and memory generally appear to be deficient after surgery (Jambaque et al., 2001). Later studies largely confirm that the outcome of hemispherectomy is mostly determined by the presurgical condition and that no major positive cognitive change can be expected after surgery (Basheer et al., 2007; Battaglia et al., 2006; Devlin et al., 2003; Lettori et al., 2008; Pulsifer et al., 2004). However, parents nevertheless report significant individual improvements and positive behavioural change. This is confirmed by a recent longer term follow-up evaluation of the academic and psychosocial achievements of 57 patients (Buddewig et al., 2009). This study indicated that early operated patients (< age 7) had the best seizure outcome, that patients with surgery between age 7 and 16 had the best pre- to postoperative cognitive and behavioural change and that the best overall psychosocial outcome was observed in the group operated later than age 16. This latter group, however, also had the best baseline conditions. Overall, 23% of 57 patients passed a regular school, 21% of 33 patients older than 20 years were employed on a low level, and less than half of the patients (42%) was rated as being able to lead an independent life, 15% have or had a partnership (Buddewig et al., 2009).

### *Vagal nerve stimulation*

From a neuropsychological standpoint, vagal nerve stimulation for seizure control is of particular interest since its 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 improved attention, decision-making, or word recognition have been reported, but negative effects have also been described (Clark et al., 1999; Hassert et al., 2004; Helmstaedter et al., 2001a; Martin et al., 2004). Apart from its acute effects, no persisting changes as assessed with a neuropsychological test battery have yet been demonstrated (Hoppe et al., 2001a; b).

#### *Weighting memory against seizure outcome*

A very important and superordinate question for surgical patients is whether they would be willing to risk additional cognitive impairment in the prospect of seizure control. In this respect seizure outcome appears to have priority. (Helmstaedter, 2008a; Langfitt et al., 2007). The respective findings in addition call for increased attention to prevent the so called „double loser“, i.e. the coincidence of not becoming seizure free plus a postoperative additional loss in cognitive functions. These patients show deterioration in quality of life in the long run. For seizure free patients one cannot, however exclude, that additional impairments due to surgery provide the basis for later accelerated mental decline with ageing (Helmstaedter et al., 2002).

Finally it should be mentioned that cognitive rehabilitation programs may be helpful to counteract losses due to surgery. Training of affected but even more training of compensatory functions can in part reverse deficits (Helmstaedter et al., 2008b). Unfortunately such interventions are mostly fixed to surgery and this means in most cases after a long history of suffering from epilepsy and concomitant impairment. According to what has been reported so far about the negative effects of an early onset of epilepsy on cognitive development such support would be appreciated much earlier in the course of the disease.

#### **Hemispheric dominance and functional plasticity**

Most epilepsies start early in life and the maturing and developing brain has the capacities for functional reorganisation, restitution and replacement in response to the lesion/dysfunction. This process is generally referred to as functional cerebral plasticity.

In early onset epilepsies affecting the left hemisphere the brain lesion and the epileptic dysfunction represent two factors which, taken alone but also in combination, may drive an intra- or interhemispheric cerebral reorganisation of language functions. This compensatory plastic process promotes and supports the preservation of at least basic

language-based communication skills. Intrahemispheric reorganisation comprises recruitment of unaffected adjacent brain regions (Ojemann, 1993). In this case the precise topography of language function may be determined by electrical stimulation mapping (ESM) (Wellmer et al., 2009). Interhemispheric reorganisation involves contralateral homologue brain structures. Here it is important to note that reorganisation of language dominance does not follow an all or none principle. Instead it is highly economic for individual functions. Dissociation of handedness, expressive and receptive language, or verbal memory are common (Kurthen et al., 1992). The transfer can for example be limited to expressive language functions if the presence of a left frontal lobe lesion/dysfunction or to receptive language functions in case of a left temporo-posterior lesion/dysfunction.

Whereas lesions are assumed to have a chronic and irreversible effect on cerebral hemispheric organisation, epilepsy as a potentially controllable condition is assumed to have a more dynamic and eventually reversible impact on hemispheric dominance (Helmstaedter et al., 2006; Janszky et al., 2003; Janszky et al., 2004; Regard et al., 1985; Taylor and Regard, 2003).

An overview (**Table 6**) over 595 IATs performed between 1997 and 2006 in Bonn indicate atypical language dominance in 35% of presurgical patients (43% in left, 24% in right hemispheric epilepsies) (Fritz, 2009; Helmstaedter, 2010). Dependent on WADA protocol, cohort, and patient selection bias, the respective numbers in the literature vary between 17% atypically dominant out of 90 patients (Mateer and Dodrill, 1983) to 38% out of 73 patients (Rey et al., 1988). Möddel et al. (2009) report 22% atypical dominant out of 445 patients. The time window for plastic changes of language functions expires with the completion of language development and reaches into puberty (Helmstaedter et al., 1997c). In left hemisphere epilepsies with an onset before age 15, 51% were atypically dominant in contrast to 28% of those with a later onset (Helmstaedter, 2010). The degree of a right hemispheric involvement in language functions correlates with the onset of the disease and the extent of structural or functional damage, i.e. the earlier the onset, the more language can be found in the right hemisphere, and the pattern of complete right dominance is seen more frequently in extratemporal lobe epilepsy (E-TLE) directly affecting language areas (29%) than in left temporal lobe epilepsy (13%). Furthermore women benefit more from atypical language dominance than men in regard to material specific cognitive functions (Helmstaedter et al., 2004a; Helmstaedter et al., 1999). As already mentioned, left handedness in combination with an early onset of the disease is a good indicator for atypical language dominance (left handed: 91%; right handed: 24%) but not vice versa.

Atypical language dominance is often associated with a constellation of material-specific cognitive deficits that contradicts the lateralisation of the epileptic focus or lesion. A patient with left hemispheric epilepsy and atypical language dominance may show deficits in visual spatial tasks, whereas language related functions and verbal memory



are preserved. This effect is termed “crowding” or “suppression” and indicates a transfer of language to the right hemisphere at the cost of original right-hemispheric functions (Strauss et al., 1990). The findings are in keeping with a theoretical concept which suggests an incompatibility of basic aspects of verbal vs. non-verbal information processing within the same (unaffected) hemisphere rather than a struggling for space (Helmstaedter et al., 1994b).

The prevalence of atypical language dominance in right hemispheric epilepsies is more than 20% (Helmstaedter, 2010; Helmstaedter et al., 1997c). Language within an epileptic right hemisphere rather seems genuine than a consequence of the epilepsy. In this regard is remarkable, that right hemispheric language in right hemisphere epilepsy is less likely in early than later onset epilepsies, this being a finding which raised the idea of a language dominance shift from the right to left hemisphere due to an early affected right hemisphere (Helmstaedter et al., 1997b). This however appears to occur “silently”, that is to say, without a specific effect on the patients neuropsychological profile.

## **Conclusion**

It was the explicit aim of this chapter to provide the reader with an overview of what neuropsychology in epilepsy can do for the diagnostics and differential diagnostics of cognitive impairment associated with epilepsy and which options arise from neuropsychological diagnostics for quality and outcome control. Today this can be performed time economic and evidence based.

The major emphasis was laid on

- (1.) the differentiation of static and irreversible versus dynamic and reversible impairments and their determinants
- (2.) the fact that, with the exception of epilepsies with progressive aetiology, early onset chronic epilepsy is more a developmental hindering than progressively dementing disease
- (3.) the finding that impairments establish early in the course of epilepsy calling for early interventions which take into account that outcomes depend on the functionality of the affected brain, its reserve capacities and the control of seizures and epileptic dysfunction.

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## Tables

Table 1

<b>Questions to neuropsychology</b>	
<b>General practice</b>	
<ul style="list-style-type: none"><li>▪ Can cognitive impairments be discerned (global vs. partial)?</li><li>▪ Can these impairments be related in a plausible way to the epilepsy and the underpinning structural/morphological lesions?</li><li>▪ What do the impairments tell us about neurodevelopment (mental retardation vs. loss of acquired functions)</li><li>▪ In case of repeated measures, what do the impairments tell us about the course of the disease (accelerated decline, recovery/release, developmental hindrance or catch-up)?</li><li>▪ Which impairments can be observed in the context of seizures, i.e. ictal (during the seizures), postictal (after the seizure)? How long do these impairments persist, is permanent damage the result?</li><li>▪ Is there a behavioural correlate of epileptic activity as indicated by EEG during waking states and sleep (paroxysmal or continuous activity, spike-wave complexes etc.)?</li><li>▪ Does the antiepileptic medication taken alone or via its impact on seizures or mood have a positive/negative impact on cognition?</li></ul>	
<b>Epilepsy surgery</b>	
<ul style="list-style-type: none"><li>▪ Are the impairments consistent with known lesions, the type of lesion (AHS, tumour, developmental, dysplasia) and the localisation of the lesion/epilepsy?</li><li>▪ Is there evidence for impairments exceeding what would be expected from MRI and type of epilepsy?</li><li>▪ Is there evidence for cerebral plasticity (dominance patterns, hemispheric reorganisation)?</li><li>▪ Which are the direct and longer term consequences of invasive treatments (surgery, radio therapy, deep brain stimulation, vagal nerve stimulation)?</li><li>▪ Which are the patients' resources to compensate additional damage (plasticity, reserve capacity, compensation)?</li></ul>	
<b>Superordinate</b>	
<ul style="list-style-type: none"><li>▪ Which are the consequences for every day life, school, occupational achievement, interpersonal relations, quality of life?</li><li>▪ Suggestions for interventions (ergotherapy, logopedics, neuropsychological rehabilitation etc.)?</li></ul>	

Table 2

<b>Question guided modular evaluations</b>
<ul style="list-style-type: none"> <li>▪ Evaluation and screening of major impairments is performed using computerised testing (Hoppe et al., 2009) which includes attention, reaction times, memory and executive functions and which can be applied repeatedly if required. (~ 25 Minutes)</li> </ul>
<ul style="list-style-type: none"> <li>▪ The question of developmental hindrance, delay, retardation, catch-up is assessed by testing of IQ and/or application of standardized neurodevelopmental interviews (Gleissner et al., 2008).</li> </ul>
<ul style="list-style-type: none"> <li>▪ Aura, seizure semiology, ictal and/or postictal testing provide information about which cognitive functions are positively (semiology) or negatively (testing) affected in the context of seizures (Helmstaedter et al., 1994a; Jordan, 2007; Lux et al., 2002). (up to 5 Minutes) *</li> </ul>
<ul style="list-style-type: none"> <li>▪ Before performing extended testing, patients are screened for cognitive antiepileptic side effects (Helmstaedter, 2008b; Helmstaedter et al., 2010; Lutz and Helmstaedter, 2005). If the drug regimen is critical and if this test indicates serious impairment of executive functions, further testing is postponed until AED have been changed. (about 10-15 minutes)</li> </ul>
<ul style="list-style-type: none"> <li>▪ In case of presurgical evaluations or for differential diagnosis a localisation or lateralisation diagnostics is required, a battery of frontal executive and of verbal and figural memory functions is applied (Gleissner et al., 1998; Helmstaedter and Durwen, 1990; Helmstaedter et al., 1998; Helmstaedter et al., 1996b; Helmstaedter et al., 2001b; Helmstaedter et al., 1991; Muller et al., 1997). (about 1 - 1½ hour)</li> </ul>
<ul style="list-style-type: none"> <li>▪ In case of a decision for surgery this is extended by assessing IQ (short version based on 5 subtests), motor, language, visuo-constructive, visual-spatial, and semantic memory functions (total test-battery including the tests mentioned before ~3 ½ hours). The overall information is assumed to have greater external validity than single tests and the results for example may be provided to therapeutic training or rehabilitation services if this is indicated.</li> </ul>
<ul style="list-style-type: none"> <li>▪ Language/memory lateralisation is noninvasively assessed via fMRI, language in younger children by functional transcranial Doppler sonography (fTCD).</li> <li>▪ In rare cases additionally the WADA test is performed, in case of surgery in suggested eloquent cortex electrocortical stimulation (Deppe et al., 2004; Fernandez et al., 2003; Kurthen et al., 1994; Weber et al., 2006; Wellmer et al., 2009).</li> </ul>
<ul style="list-style-type: none"> <li>▪ Cognitive evaluation is accompanied by assessment of depression (Beck Depression Inventory), anxiety (Zung Self-Rating Anxiety Scale), personality (FPZ), and a measure on quality of life in epilepsy (QOLIE 10) (Helmstaedter and Witt, 2011).</li> </ul>

\* [EEG locked continuous performance testing in order to assess the impact of epileptic activity is not included since in this regard no standards are yet in sight.]

Table 3

<b>Cognition as function of different types of epilepsy</b>			
<b>Type of epilepsy</b>	<b>Manifestation</b>	<b>Precipitating condition</b>	<b>Course of cognitive development</b>
<b>Idiopathic Epilepsies</b>			
Early childhood epilepsy with GTCS and hemi grand mal	age 5-15	normal	unfavourable/dementia
Benign myoclonic. epilepsy	until age 3.	normal	positive/retardation possible
Severe myoclonic. epilepsy (mitochondrial defects)	age 1	normal	unfavourable/dementia
Myoclonic-astatic epilepsy	until age 5	mostly normal	ranges course dependent from partial deficits to dementia
Absence epilepsy			
- early onset	age 1-4	normal	partial deficits possible
- pyknolepsia	age 5-8	normal	partial deficits possible
- juvenile	age 9-12	normal	partial deficits possible
Juvenile myoclonic epilepsy	age 12-18	normal	frontal lobe partial deficits
Juvenile epilepsy with GTCS	age 12-18	normal	partial deficits (frontal?)
<b>Symptomatic or cryptogenic epilepsies</b>			
Focal epilepsies	every age	normal or impaired	onset and localisation dependent partial deficits and low IQ
- frontal lobe	every age	normal or impaired	predominant impairment of executive functions
- temporal lobe	every age often early	normal or impaired	predominant episodic memory impairment (material-specific)
- parieto-occipital	every age often early	normal or impaired	frontal or temporal like rather than classic parietal dysfunctions
- E. partialis continua Rasmussen encephalitis	every age	mostly impaired	often one hemisphere affected unfavourable/dementia
<b>Encephalopathy /catastrophic epilepsies</b>			
West-Syndrome	age 1	mostly impaired	unfavourable/retardation
Lennox Gastaut syndrome	age 2-7	mostly impaired	unfavourable/retardation
<b>Benign partial epilepsies and related syndromes</b>			
Rolando-epilepsy	age 2-12	maturation disorder (hereditary)	partial deficits
Pseudo Lennox syndrome	age 2-7	maturation disorder (hereditary)	impaired language development and other partial deficits
CSWS / ESES- (continuous spike wave)	age 2-10	maturation disorder (hereditary)	onset and course dependent retardation and dementia
Landau Kleffner Syndrome (LKS)	age 4-10	maturation disorder (hereditary)	auditory agnosia and aphasia predominant / retardation



**Table 4**

<b>Overview over the cognitive effects of common antiepileptic drugs</b>									
	<b>Attention</b>		<b>Memory</b>		<b>Language</b>		<b>Psychotropic</b>		
	ad	ch	ad	ch	ad	ch	ad	ch	
Levetiracetam (LEV)	0	↑	0					↑	
Lamotrigine (LTG)	0	↑	0		0			↓/↑	
Tiagabine (TGB)	0		0		0			0	
Vigabatrin (VGB)	0		0		0				
Felbamate (FBM)	(↓)								
Zonisamide (ZNS)	(↓)								
Oxcarbazepine (OXC)	↓/↑		0						
Gabapentin (GBP)	↓	↓	0		0			(↑)	
Clobazam (CLB)	↓	↓	0					↓	
Valproic Acid (VPA)	↓		↓		0			↑	↑
Carbamazepine (CBZ)	↓		↓	(↓)					
Phenytoin (PHT)	↓		↓	(↓)					
Phenobarbital (PB)	↓		↓			(↓)			
Topiramate (TPM)	↓	↓	↓		↓	↓		(↓)	

↓: negative effect ; ↑ positive effect; ( ): possible effect;  
 0: no effect; blank: no evidence; ad: adults; ch: children

Table 5

Cognition before and after temporal lobe surgery								
Domain	% preoperative impairments <sup>a</sup>			n	% postoperative changes (1 year) <sup>b</sup>			
	N	L TLE	R TLE		L TLE		R TLE	
		[x < m-1.5 SD]			↓	↑	↓	↑
verbal memory	732	69	46 ***	732	40	14***	27	29
figural memory	732	49	59 **	707	31	27 n.s.	28	23 n.s.
attention	717	21	29 *	709	11	36***	11	40***
language	653	39	32 n.s.	618	21	27	14	32***
motor function	717	30	40 n.s.	449	16	34***	16	37***
visuo-construction	602	19	21 n.s.	554	10	35***	13	31***
vocabulary - IQ	591	8	11 n.s.	n.a.				
WADA atyp. dom.	320	41%	22% ***	n.a.				

L TLE/R TLE left/right temporal lobe epilepsy, m: mean, SD: standard deviation; n.s.: not significant, n.a.: not available, \* p<0.05, \*\* p<0.01, p<0.001;

<sup>a</sup> chi<sup>2</sup>, <sup>b</sup> Wilcoxon Signed Ranks Test

Table 6

<b>Wada test results in 595 presurgical patients with epilepsy</b>	
Atypical dominance in 35%	
<b>side</b>	left (43%) > right (24%)
<b>366 left hemispheric epilepsies (62%)</b>	
<b>handedness</b>	left (91%) > right (31%)
<b>sex</b>	Female (46%) > male (38%)
<b>onset</b>	early (51%) > late [14+yrs.] (28%)
<b>complete right hemispheric language dominance</b>	
<b>site</b>	E-TLE (29%) > TLE (13%)

E-TLE: extratemporal lobe epilepsy, TLE = temporal lobe epilepsy

Figure caption

Figure 1: Aetiological model of cognitive dysfunction in epilepsy