A Comparative Approach to Interictal Memory Disturbances in Patients with Epilepsies

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Summary

Memory complaints are the most commonly reported cognitive problems in patients with epilepsy. Perceived forgetfulness, however, is also an issue for up to 50% of neurologically healthy elderly individuals. Moreover, some degree of memory impairment is also a prominent feature in the majority of neurological and psychiatric disorders. Therefore, when considering memory impairment in epilepsies, it is useful to take an epidemiological perspective and take into account not only the base rates of memory impairment in these conditions, but also to recognize the fact that there is a high rate of comorbidity between such disorders and epilepsy. In order to highlight common and divergent pathways of memory impairment, we have compared symptoms of memory deficits and underlying pathology in a representative selection of neurological and psychiatric disorders.

Our comparative analysis reveals that impairments in memory encoding and memory retrieval are a common feature in all selected disorders as well as in normal aging. This suggests that the majority of memory failures in those patients may arise from transient or chronic prefrontal dysfunction. Retention, in contrast, seems to be almost exclusively affected in Alzheimer's dementia and mesial temporal epilepsy (MTLE) as it depends on the functional integrity of the hippocampal formation and anterior diencephalic structures. Due to frequent additional prefrontal disturbances we assume that MTLE is characterized by memory impairment of a fronto-temporal spectrum. In idiopathic generalized epilepsy (IGE) and frontal lobe epilepsy (FLE), a more prefrontal profile characterizes the memory impairments which resemble those seen in non-epileptic disorders such as ADHD.

Epileptologie 2011; 28: 164 – 176

Key words: Memory, epilepsies, aging, frontal lobe, temporal lobe, hippocampus

Interiktuale Gedächtnisbeeinträchtigungen bei Patienten mit Epilepsie im Vergleich zu mnestischen Symptomen ausgewählter neurologischer Erkrankungen und psychiatrischer Störungen

Die von Epilepsiepatienten am häufigsten geäusserte Beeinträchtigung kognitiver Leistungen betrifft das Gedächtnis. Wendet man sich klinisch und wissenschaftlich Fragestellungen des Gedächtnisses bei Menschen mit Epilepsie zu, wird häufig ausser Acht gelassen, dass Vergesslichkeit von mehr als der Hälfte älterer neurologisch gesunder Menschen beklagt wird und zum Symptombild der meisten neurologischen und psychiatrischen Erkrankungen gehört. Die vorliegende Arbeit vergleicht Gedächtnisbeeinträchtigungen von Menschen mit Epilepsie mit denen von gesund alternden sowie einer Reihe ausgewählter neurologischer Erkrankungen und psychiatrischer Störungen. Wir zeigen auf, dass insbesondere Beeinträchtigungen der Gedächtnisenkodierung und des -abrufs ein Merkmal aller beschriebenen Erkrankungen und Störungen wie auch des normalen Alterns sind. Die häufigsten Fehlleistungen des Gedächtnisses resultieren aus transienten oder chronischen Beeinträchtigungen präfrontaler Funktionen. Behaltensleistungen sind dagegen akzentuierter betroffen bei der mesialen Temporallappenepilepsie und der Demenz vom Alzheimertyp. Behaltensleistungen sind insbesondere von der Integrität der hippokampalen Formation und anteriorer dienzephaler Strukturen abhängig. Weil bei Patienten mit hochaktiver mesialer Temporallappenepilepsie frontale Strukturen häufig funktionell beeinträchtigt sind, postulieren wir als häufiges klinisches Bild charakteristische Beeinträchtigungen von Gedächtnisleistungen im Sinne eines Spektrums fronto-temporaler Minderleistungen. Bei idiopathischen Epilepsien und Frontallappenepilepsie weisen die Beeinträchtigungen ein deutlicher frontal ausgeprägtes Muster auf, das eher mit Symptombildern vergleichbar ist, wie wir es auch bei Patienten mit Aufmerksamkeitsstörungen (ADHS) finden.

Schlüsselwörter: Gedächtnis, Epilepsie, Altern, Frontallappen, Temporallappen, Hippokampus

Comparaison des affections interictuelles de la mémoire de patients atteints d'épilepsie avec les symptômes mnésiques d'affections neurologiques et de troubles psychiatriques choisis

La déperdition de la performance cognitive la plus citée par les patients épileptiques concerne la mémoire. Lorsqu'on s'intéresse dans une perspective clinique et scientifique aux questions touchant à la mémoire des personnes atteintes d'épilepsie, on a tendance à oublier que plus de la moitié des personnes âgées sans troubles neurologiques se plaignent d'une mémoire déficiente et que la distraction et l'oubli entrent aussi dans le schéma symptomatique de la plupart des affections neurologiques et psychiatriques. Le présent travail établit une comparaison entre les troubles de la mémoire de personnes atteintes d'épilepsie, de personnes saines vieillissantes, ainsi que d'une série d'affections neurologiques et de troubles psychiatriques. Nous montrons notamment que des „pannes de codage" et de décryptage de la mémoire sont le dénominateur commun de toutes les maladies et des troubles décrits, mais aussi du vieillissement ordinaire. Les ratées les plus fréquentes de la mémoire proviennent de dysfonctionnements passagers ou chroniques des fonctionnalités préfrontales. Les facultés mnésiques sont concernées davantage en cas d'épilepsie des structures mésiales du lobe temporal et de démence du type Alzheimer. Les facultés mnésiques sont avant tout tributaires de l'intégrité de la formation hippocampique et des structures diencéphaliques antérieures. Parce que l'on observe fréquemment des perturbations fonctionnelles des structures frontales chez les patients avec une épilepsie mésiale du lobe temporal hautement active, nous postulons que les affections caractéristiques des facultés mnésiques au sens d'un spectre de déficiences des performances fronto-temporales constituent une manifestation clinique caractéristique. Lors d'épilepsies idiopathiques et d'épilepsies du lobe frontal, les affections affichent un schéma nettement plus frontal avec une symptomatique plutôt comparable à celle que nous trouvons chez les patients avec une déficience d'attention (ADHS).

Mots clés : Mémoire, épilepsie, vieillissement, lobe frontal, lobe temporal, hippocampe

1. Introduction

As far back as Aristotle, ancient philosophers considered memory to be an instrumental function in contrast to traits such as temperament that were held to be more of a core feature of a person. However, the study of the effects of memory impairment and loss has shown us that memory is more than a mere instrumental function. Our personal history is essential in helping us define who we are. Once that history is disturbed or, as in the case of amnesia or dementia, entirely vanishes, one loses an indispensable element in the perception and awareness of selfhood.

Memory impairment can be a significant added burden for patients with epilepsy who are already struggling with a debilitating and chronic disorder. One should be particularly aware of its potential impact on academic achievement in children with epilepsy. The present paper provides a phenomenological and comparative perspective on the epidemiology of memory symptoms and impairment in epilepsies.

When general practitioners question their patients about possible memory impairments, usually every second older patient complains of memory problems [1]. Why are these complaints so frequent in the general population, and why are they more frequent in patients with epilepsies?

With the exception of very rare savants everybody experiences their memory to some degree as fallible. Since long before Sigmund Freud formulated psychoanalysis, forgetting has been part of the "Psychopathology of Everyday Life". Forgetting is probably the most frequently used excuse for things we failed to do or for things we did wrong. The excuse of forgetting is usually socially acceptable because it is much easier to say, "It is not me, it is my memory!"; and it is easier to forgive forgetting than it is to forgive a character flaw. In addition, it appears that having a bad memory is more acceptable and less stigmatising than admitting to other faults such as anhedonia (no longer finding activities pleasurable), depression, or anxiety. Thus, we feel that a thorough understanding of the almost universal memory complaints necessarily integrates the influences of social norms and conventions, folk psychology, and individual experiences of memory decline and failure.

Patients with epilepsy more frequently report memory impairments than individuals without epilepsy. One reason could be that they tend to overestimate their memory problems [2-5], possibly as a result of their commonly low mood and diminished self-esteem. Indeed, various studies have repeatedly reported a stronger correlation between subjective memory complaints and measures of depression and anxiety than between subjective complaints and actual performance in memory tests [6, 7]. **Table 1** provides a summary of common comorbidities seen in patients with epilepsy that may in part explain the increased frequency of memory complaints in this population. Depression and ADHD themselves may have a considerable impact on memory performance, as will be discussed later. The influence of psychiatric comorbidities on memory in epilepsy has been widely neglected.

The absence of a close correlation between subjective memory complaints and objective memory measures can also be explained by the fact that patients usually evaluate their own memory based on the frequency of "tip of the tongue" states and "going back to check" phenomena rather than their ability to learn

a word-list or to reproduce a prose passage [8, 9], the most common objective memory tests. In addition, patients are unable to differentiate between memory impairment and insufficient information processing due to weak or fluctuating attention.

reserve capacity – helps to explain individual differences observed in the expression of symptoms during the course of chronic or progressive disorders.

In focal epilepsies remote functional deficit zones are further sources of inter-individual variability.

Table 1: Estimates of the prevalence of selected psychiatric disorders in epilepsies after Kanner [10].

	Epilepsy	General Population
Depression	11-60%	2-4%
Anxiety	19-45%	2.5-6.5%
Psychosis	2-8%	0.5-0.7%
ADHD	25-30%	2-10%

There are considerable differences in the results of memory tests within samples of aged-matched healthy controls and patients sharing the same pathology. State dependent intra-individual differences as well as inter-individual differences in memory encoding, memory consolidation, and recall are the source of substantial variability in memory performance. Inherited factors such as ApoE genotype, neurochemical and brain metabolic activity, brain maturation, education, and medication are among various additional factors that can influence everyday memory as well as test performance.

It is reasonable to assume that brains develop a functional reserve or have a spare capacity to cope with neuronal loss via efficiency, redundancy, plasticity, and reorganisation [11, 12]. Studies of various degenerative brain disorders (for example, Parkinson's disease, vascular dementia, and Alzheimer's dementia) suggest that a functional decline becomes apparent only if a certain amount of brain tissue is insulted. This means that individual performance differences are related to differences in available reserves and, thus, that the greater the reserve, the more severe the pathology must be in order to cause functional impairment [13]. Epidemiological evidence indeed suggests that individuals with better cognitive abilities, including memory, have a reduced risk of developing Alzheimer's disease (AD) [14]. Various animal models also suggest that enriched environments, a factor that is supposed to enhance brain reserve capacity, may prevent brain disorders. It has been shown that enriched environments provide resilience to hippocampal insults resulting from seizures and excitotoxic injury [15]. In summary, the heuristic concept of brain reserve capacity – including memory

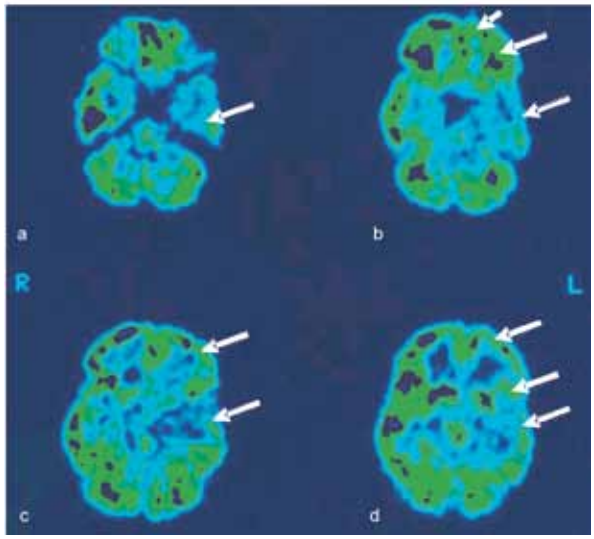

Figure 1. Characteristic metabolic maps (FDG-PET) of a 24-year-old male patient with left-sided medial temporal lobe epilepsy demonstrating the most prominent hypometabolic zones in medial (a) and lateral temporal (b) regions [16]. Note the additional remote metabolic depressions in left fronto-orbital (b), prefrontal (b, c), and fronto-opercular cortex (d). R and L indicate the patient's right and left side.

Figure 1 shows a representative FDG-PET scan of a 24-year-old male patient with left-sided medial temporal lobe epilepsy. It is noteworthy that the patient showed MRI-proven abnormalities exclusively within left-sided mesial temporal lobe structures whereas FDG-PET demonstrated widespread metabolic disturbances within left temporo-lateral structures, left pre-

frontal structures, and within the left thalamus. It is well known that these structures modulate or govern the formation and recollection of new episodic memories. However, there are very few studies that have investigated the influence of remote effects on cognition and especially on memory in patients with focal epilepsies. Functional or structural deafferentation, excitotoxic effects, antiepileptic drugs, and aging act on the functional integrity of mesiotemporal, diencephal, and prefrontal circuits that are critically involved in memory formation and recall.

Various factors like memory reserve capacity, inherited vulnerability of memory functions, localisation and age at lesion, pathological electrical brain activity, and seizures affect memory performance of patients with epilepsies. More than 50 years of neuropsychological examination of patients with epilepsy has shown that one group of patients in particular is especially prone to develop deficits of declarative memory: those with mesial temporal lobe epilepsy. This syndrome, which is usually characterized by febrile convulsions, hippocampal sclerosis, and a seizure onset rarely prior to school age, has the status of being a model disorder for the study of anterograde episodic memory. Moreover, the comprehensive pre-surgical and post-surgical evaluation of many patients with refractory MTLE has provided excellent research opportunities far beyond the diagnostic standards in other disorders. In clinical samples of patients with unilateral MTLE, however, the textbook material-specific deficits and specific deficits in certain memory processes are frequently absent at the individual level and are only represented in group sample statistics by weak to moderate effect sizes [17]. Without question, memory research is indebted to the epilepsies for its temporo-limbic model of episodic memory. However, despite an almost homogenous morphology, MTLE has tremendous intrinsic developmental and seizure-related dynamics that challenge linear and dichotomous memory models such as verbal vs. non-verbal, retrograde vs. anterograde and episodic vs. semantic.

In the following sections we comparatively describe the effects of normal aging, epilepsy as well as selected psychiatric and degenerative disorders. Such a comparative approach should help broaden our understanding of the pathological core processes and characteristics of memory impairment in epilepsies by revealing similarities and differences among disorders that primarily or only incidentally affect memory processes.

2. Conditions and disorders of long-term memory

2.1 Normal aging

We are all probably susceptible to memory loss if we live long enough. From both a neuropsychological as well as a neurophysiological perspective, the frontal lobes are presumed to be the most vulnerable area with regard to normal aging processes. Regarding memory, it has been shown that performance of older adults is especially disrupted in tasks that involve frontal structures. Hence, memory deficits in older adults appear to originate largely from insufficient control strategies during encoding and retrieval, which explains why healthy older adults seem to be more susceptible to false memories and have more difficulties in source memory than younger adults [18]. An analysis of the normative data from the German adaptation of the Auditory Verbal Learning Test (Verbaler Lern- und Merkfähigkeitstest, VLMT [19], and of a Swiss normative sample of the CERAD (The Consortium to Establish a Registry for Alzheimer's Disease [20]), demonstrates that the impact of normal aging on memory processes is moderate (around one standard deviation over 30 years) and affects mainly encoding, retrieval, and recognition, and to a lesser extent retention. The Seattle longitudinal study revealed a comparable decline of roughly two standard deviations from the age of 25 to the age of 81 in episodic memory functions [21]. Whereas episodic memory experiences a gradual decline across the adult lifespan, semantic memory, on the other hand, is stable until late in life [22]. From a clinical point of view it should be noted that memory complaints are more frequent in healthy subjects aged forty and older. Therefore, patients with epilepsies could potentially falsely attribute age-related memory impairments to their epilepsy.

2.2 Epilepsies

As already noted, epilepsy as a chronic illness is associated with various factors that may influence the course of an individual's memory performance. The differences between three major types of epilepsies, idiopathic generalized epilepsies, temporal lobe epilepsy, and frontal lobe epilepsy stress the significance of disease-related pathological pathways and lesions on the nature of memory deficits.

2.2.1 Idiopathic Generalized Epilepsies (IGE)

About one third of all epilepsies are idiopathic generalized epilepsies (IGE). The most prevalent major risk factor for IGE identified to date is the 15q13.3 microdeletion [23]. About 50% of patients with IGE suffer from Juvenile Myoclonic Epilepsy (JME). This syndrome with a complex inheritance is clinically characterized by myoclonic jerks upon awakening, generalized tonic clonic seizures (GTCS) and frequent typical absences [24].

An essential characteristic of IGE is normal morphological MRI-scans. Volumetric MRI-studies, however, provide evidence of smaller thalami and frontal

lobe tissue early in the course of recent-onset JME [25]. Similarly, magnetic resonance spectroscopy (MRS) has revealed reduced N-acetyl aspartate levels in prefrontal areas and reduced choline and myo-inositol levels within the thalamus [26]. Memory test performance has been found to be correlated with MRS-measures of neuronal dysfunction in the temporal lobes [27]. Because the temporal lobes were exclusively measured in this study no conclusion can be drawn as to whether IGE specifically affects memory residing within temporal lobe structures.

A recent positron emission tomography (PET) study suggests that dopamine signalling is impaired in the target regions for dopaminergic neurons, the striatum and frontal lobe, and is apparently related to interictal neuropsychological dysfunctions in JME [28].

Neuropsychological frontal lobe functions in JME have been examined in several studies. Working memory, set shifting, reasoning, planning, verbal fluency, and mental flexibility are frequently found to be mildly impaired in JME [29, 30]. Only a few studies, however, have investigated memory functions in patients with either IGE or JME [27]. Patients with IGE have been reported to exhibit poorer initial learning efficiency than controls, to require a greater number of trials to reach a learning criterion, and to have retrieval rather than retention difficulties [31]. Dickson et al. [27] reported that 85% (26/30) of patients with IGE complained of memory impairments. Neuropsychological testing in this sample revealed poor performance in recall, recognition, visual and verbal memory tests. Unfortunately, the influence of antiepileptic drugs and other epilepsy associated factors was not controlled. The same methodological shortcoming limits the conclusions that can be drawn from the study by Pascalicchio et al. [29] that reported cognitive impairments in patients with JME in various domains including memory.

There are contradictory results as to whether verbal or non-verbal memory is more impaired in IGE [21]. Task difficulty could be partly responsible for inconclusive findings [32]. To summarize, to date we have no clear evidence whether IGE specifically and directly impairs memory or whether verbal or non-verbal memory is more affected. Learning and encoding, rather than retention and recognition, appear to be more affected in IGE. It is reasonable to assume that secondary impairments of episodic and semantic memory processing due to affected executive functions and impaired attention comprise the primary pathological mechanism of memory impairments in patients with IGE.

2.2.2 Focal Epilepsies

In 60-70% of all epilepsies seizures originate from an epileptogenic zone that usually can be localized by ictal EEG and MRI. Early ictal symptoms are usually determined by localisation and not aetiology. A retrospective analysis of more than 3,000 neuropsychological patient files from the Bonn epilepsy surgery program revealed that the majority of patients with focal epilepsies demonstrated severely affected (< 2 sd) performance in various functional domains. Verbal and figural memory were the most frequently impaired functions [33]. It is noteworthy that this sample represents consecutive patients in a Grade IV epilepsy centre that is specialised for epilepsy surgery and is therefore not representative of the majority of epilepsy patients. However, it illustrates that patients with refractory focal epilepsies are prone to suffer from significant memory disturbances.

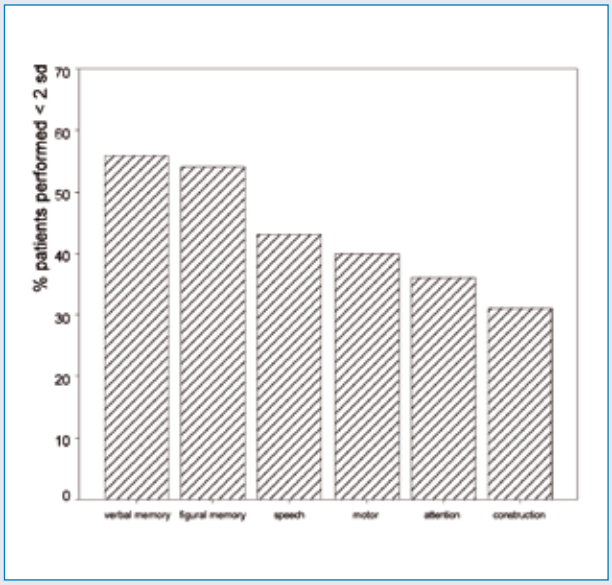

Figure 2. Data by Hoppe et al. [33]. Frequency of patients with focal epilepsies (N = 3,193) who performed below two standard deviations on a range of cognitive tasks. Note it is a sample of consecutive patients from a Grade IV epilepsy centre and epilepsy surgery program in Bonn, Germany.

2.2.2.1 Mesial temporal lobe epilepsy (MTLE)

In 50% of focal epilepsies, seizures originate within the temporal lobes, mostly within the mesial temporal lobe. Not only because of its high prevalence but also because of its potential for drug resistance and its risk of memory impairment, MTLE is the most important focal epilepsy in clinical practice as well as in research.

Since the landmark publications by Brenda Milner 50 years ago on tragic memory losses following bilateral temporal lobectomy MTLE is considered to be a model disorder for anterograde episodic memory disturbances [34]. Although gradual memory impairment can be shown by neuropsychological testing in the majority of patients with MTLE, only a minority suffer from clinically relevant memory disturbances [35]. Nevertheless, memory is considered to be the main neuropsychological impairment in MTLE. Patients with

MTLE typically perform worse than controls in tests assessing the ability to retain new information over a delay of about 30 minutes. Consolidation, retention, and delayed recall are the greatest affected functions in patients with MTLE. The degree and type of impairment depends on the lateralization of TLE. Left-sided TLE is usually associated with more pronounced deficits in verbal memory whereas right-sided TLE is less consistently related to non-verbal memory deficits. The Rey Auditory Verbal Learning test is one of the most frequently used tests to evaluate memory functions in patients with MTLE. Patients with left-sided MTLE usually benefit less from the repeated learning trials, recall fewer words after presentation of an interference list and forget more words after a 30 minute retention interval compared to patients with right-sided temporal lobe epilepsy. The latter commonly perform at a level between that of healthy controls and patients with left-sided MTLE. Age at lesion, duration of epilepsy, degree of pathological abnormalities, seizure frequency and seizure type are correlated with memory performance [36-38]. In patients with MTLE lateralized to the speech dominant hemisphere semantic memory can be as impaired as episodic memory (Giovagnoli et al. 2005) [39]. Semantic memory specifically is more susceptible to structural temporal lateral lesions and an early seizure onset [39, 40].

The frequent propagation of epileptic activity from temporal to frontal structures in complex-partial seizures and secondarily generalized seizures can temporarily or chronically impair the functional integrity of remote symptomatogenic zones [16]. Therefore, it is not surprising that several studies have revealed that patients with MTLE and FLE are impaired in certain aspects of executive and attentional functions [35].

More recently remote memory and accelerated forgetting have been identified as possible additionally affected memory processes in patients with MTLE [41].

2.2.2.2 Frontal lobe epilepsy (FLE)

In about 2% of all epilepsies, seizures originate from a primary epileptogenic focus somewhere within the frontal lobes which cover about 40% of the cerebral cortex [24]. The frontal lobes are anatomically as well as functionally subdivided into motor cortex, premotor cortex, prefrontal cortex, and limbic and paralimbic cortex. Frontal lobe lesions in general, and more specifically frontal lobe epilepsy, do not typically produce the kind of severe memory disturbances that is seen in patients with mesial temporal lobe epilepsy (MTLE) [42]. Consequently, memory studies in patients with FLE are rare [43]. Lesional as well as functional imaging studies in subjects without epilepsy, however, provide sufficient evidence that the prefrontal cortex promotes the formation of episodic long-term memory [44]. It is reasonable to assume that deficits in executive functions combined with attentional and working memory weaknesses may affect encoding as well as retrieval. Indeed, attention and working memory are equally affected in patients with FLE and MTLE [40]. Clinical observations and theoretical considerations favour the assumption that memory deficits in patients with prefrontal disturbances arise from deficits in control processing rather than from a primary deficit in memory retention. A review of the literature finds that patients with prefrontal lesions are impaired in the following memory related processes: free-recall, memory clustering, memory strategies, metamemory, consistency of recall, source memory, memory for temporal order, associative learning and insight into one's own memory problems [44, 45, 46]. Despite these deficits, patients with frontal lobe lesions may perform almost normally under highly structured memory encoding and retrieval conditions. Semantic memory is apparently not specifically affected, with the exception of memory retrieval processes which are vulnerable to frontal lobe pathology [39].

Although determining lateralisation of the epileptogenic zone in frontal lobe epilepsies via neuropsychological tests is rather difficult [40], McDonald et al. [45] described a complex relationship between functional lateralisation within the frontal lobes and aspects of memory processing: Left frontal epileptogenic lesions impaired encoding but not recognition. In contrast, right frontal lesions impaired recognition but not recall.

To summarize, memory symptoms in frontal lobe epilepsies are similar to those frequently reported in patients with IGE but do not resemble the pattern seen in TLE. Memory symptoms in FLE patients are predominantly related to executive and attentional dysfunctions. The lateralisation issue appears to be rather complex due to the more intricate interplay between prefrontal cortices compared to primary motor or sensory cortices. Moreover, epileptic brain electric activity and seizures propagate rapidly into contralateral structures and may cause bilateral functional impairment.

2.3 Psychiatric disorders

2.3.1 Schizophrenia

A large body of evidence has shown memory to be an area of significant cognitive deficit in schizophrenia and more severe than that seen in most other psychiatric disorders [47-50]. Far-reaching and pervasive cognitive deficits have been identified in schizophrenia in a variety of cognitive domains; however, the largest effect sizes have been identified for global verbal memory [51]. A more detailed look at memory was provided in a meta-analysis performed by Aleman et al. [48]. This explored the degree, extent and pattern of memory impairment in schizophrenia as well as studying possible moderator variables (medication, duration of illness,

positive / negative symptoms etc.). Large effect sizes were found for delayed and immediate recall measures and moderate effect sizes for recognition measures. Deficits were also found in short-term memory (digit span, digit span backwards) and in the learning curve. Impairments were independent of the type of material (visual-nonverbal / verbal), a finding replicated by other studies [51]. The impairments seen in immediate recall (and not affected by longer retention intervals) and weaker learning have been interpreted by some authors [46, 52] to be indicative of impairments in encoding, and some researchers hold the deficits in encoding to be a core deficit in schizophrenia [53]. In this light, Gold et al. [49] found their patients with schizophrenia to be less able to benefit from semantic information to aid encoding and Boyer et al. [52] have outlined evidence for impairments in contextual binding.

Patients with unrecognized mesial temporal lobe epilepsy could be misdiagnosed as having schizophrenia because of ictal or interictal psychotic symptoms and pronounced memory deficits. However, MRI- and EEG-diagnostics would disclose the etiology of memory deficits in these patients.

2.3.2 Depression

Deficits in cognitive functions, primarily in the domains of executive functioning and memory have been consistently reported in the literature on cognition in depression [54]. Findings as to exactly which aspects of memory are impaired and the severity of the impairments, as well as associations with disease variables, are less consistent than research findings in schizophrenia. Most often, deficits have been identified in verbal recall and recognition [50, 55] and one meta-analysis of cognitive function found the largest effect sizes for encoding and retrieval [56]. While the main focus of research on memory in major depressive disorder has focussed on verbal memory, deficits have also been found in recall and recognition of visuo-spatial information [53, 57]. The effects of duration of illness and / or number of hospitalizations and symptom severity on memory impairment are unclear. Numerous studies have indicated that first-episode patients are not as impaired as patients with recurrent episodes [58, 59] while other groups have failed to find an association between memory dysfunction and duration of illness [55, 60]. Generally, inpatients have been found to have more severe impairments [50] and two recent studies exploring outpatients with less severe symptomatology (including a majority of first-episode and non-medicated patients) have failed to find significant verbal memory impairments [57, 60]. Further, research groups have found persistent verbal memory impairments after remission of symptoms [61-63]. The persistency of memory impairment after remission as well as the inability of some studies to find a correlation between memory impairment and symptoms [54] have led several authors to argue that the observed memory dysfunctions are a trait rather than state abnormalities or are epiphenomena related solely to depressive symptoms [55, 53, 63].

The high prevalence of depression in patients with epilepsies (**Table 1**) raises the question of whether depressive symptoms are responsible for memory impairments beyond those caused by the epilepsy itself.

2.3.3 Attention deficit / Hyperactivity disorder (ADHD)

The majority of memory research in attention deficit / hyperactivity disorder has focussed on working memory. A meta-analysis by Martinussen et al. [64] revealed moderate to large impairments in working memory with the largest impairments found in spatial storage and spatial central executive (i.e., manipulation of information stored in short-term memory) domains and more moderate impairments in verbal working memory functions. A further study of ADHD subtypes found that poor performance in the central executive domain (regardless of modality) tended to be associated with the inattentive subtype of ADHD [65]. In more classical memory research, a meta-analysis examining overall neuropsychological functioning in adults with ADHD as compared to controls found that verbal memory (along with complex attention variables) was one of the best discriminator variables [66]. A study of verbal memory and learning (a word-list learning task) found that adults with ADHD were able to learn significantly fewer words and to use fewer semantic clusters, but they did not differ from controls in rates of forgetting. The authors interpreted the findings as evidence of deficient encoding or reduced retrieval performance.

The high levels of comorbidity between ADHD-like symptoms and epilepsies (**Table 1**) raises the prospect that ADHD symptoms are an additional factor contributing to memory impairments in a substantial number of patients.

2.4 Degenerative disorders

2.4.1 Alzheimer's disease (AD)

In Alzheimer's Disease (AD) the anterograde episodic memory deficit is profound and pervasive. Depending on the pathology starting in the medial temporal lobe, more specifically the entorhinal cortex, memory impairment is usually the first symptom in the course of the disease [67]. It is the predominant impairment in 71% of patients [68] and accounts for 68% of the measured cognitive deficit [69]. The severe hippocampal dysfunction leads to an inability to store and consolidate

new information. Therefore, all aspects of anterograde episodic memory performance – encoding, retention, retrieval and recognition – are equally disturbed. However, the most sensitive measure with regard to differential diagnosis is rapid forgetting, resulting in poor retention. Moreover, low recognition performance in AD patients generally reflects a profound storage deficit [70]. Since atrophy spreads from the medial temporal lobe to lateral temporal areas, semantic memory is often affected quite early in the disease process as well, although this finding seems to be controversial, and the degree of semantic impairment in patients with AD may be variable in the early stages [69, 71, 72].

Patients with unrecognized mesial temporal lobe epilepsy aged fifty and older could be misdiagnosed as to having AD due to severe memory deficits in their everyday life or due to poor performance in the Mini-Mental State Test [73-75]. However, MRI- and EEG-diagnostics would disclose the etiology of memory deficits in these patients.

2.4.2 Fronto-temporal dementia (FTD, frontal variant)

Compared to other neurodegenerative disorders, episodic memory seems to be relatively well preserved in fronto-temporal dementia [76]. Retention especially has been shown to be fully normal [77]. Nevertheless, on formal neuropsychological testing memory deficits may account for 41.1% of the fronto-temporal dementia (FTD, frontal variant) patients' overall cognitive impairment [69]. In accordance with the restriction of pathology to the frontal lobes at the beginning of the disease, memory is primarily impaired due to executive problems, i.e. inefficient learning strategies or deficient retrieval monitoring. Consequently, qualitative errors such as confabulations or misconstructions have often been found in the performance of FTD patients [77]. Semantic memory is generally found to be unimpaired in early stages of the frontal variant of FTD.

2.4.3 Vascular dementia (VaD)

In contrast to most neurodegenerative disorders, which show relatively intact semantic memory, semantic memory impairment in VaD appears to be common and also more profound than in patients with AD [72]. As in the case of episodic memory, the impairment is moderate with no distinction between different memory processes. However, the individual cognitive profiles of patients with VaD are quite variable: Reed et al. [68] characterized subjects by their neuropsychological profiles and found that only 45% demonstrated a predominant executive impairment, while 18% showed a profile of below-average memory functioning and 36% fit neither pattern. The reason for this variability presumably lies in the heterogeneity of cerebrovascular pathology. Jellinger [78] distinguishes between multifocal (disseminated) lesions and focal disease and points out that episodic memory can be markedly compromised if focal vascular pathology in the hippocampus leads to neuronal damage and necrosis. Yet, Price et al. [79] found no strong relationship between white matter abnormalities (WMAs) as a marker for vascular pathology and memory performance and they suggested that functional abnormalities induced by WMAs do not produce impairments in memory.

Due to the highly variable cognitive profiles in patients with beginning VaD, the cognitive profile does not necessarily discriminate between VaD and that of certain idiopathic and focal epilepsies.

2.4.4 Multiple sclerosis (MS)

Long-term memory is impaired in 40-65% of Multiple Sclerosis (MS) patients and is one of the leading cognitive symptoms of the disorder. Earlier studies suggested that the primary cause of memory deficits was difficulty in retrieving information from long-term memory. More recent studies have shown that the primary deficit lies in the initial learning of information. Patients with MS require more repetitions to reach a learning criterion. Recall and recognition of acquired information, however, is apparently unimpaired. Autobiographical episodic memory was found to be affected in 60% of patients, whereas autobiographical semantic memory appeared to be unaffected [80]. Many factors have been considered to be responsible for the observed memory deficits including slow processing speed, susceptibility to interference, executive dysfunction, and perceptual deficits [81]. Recent findings, however, provide evidence for selective and progressive hippocampal atrophy in MS localized initially to the CA1 subregion that is associated with deficits in memory encoding and retrieval [82]. In MS patients, semantic memory is less affected than episodic memory [80, 83].

Finally, multiple sclerosis may mimic the memory profile of epilepsy patients, especially of patients with MTLE. Epilepsy itself, with a prevalence of 3-4%, is an infrequent but not rare consequence of multiple sclerosis [84].

2.4.5 Huntington's disease (HD)

Memory impairment in patients with Huntington's Disease (HD) appears to be mainly characterized by a retrieval deficit. Their difficulties in initiating and monitoring retrieval processes reflect the predominant pathology in subcortical frontal circuits. It has been shown that HD patients and AD patients exhibit comparable deficits in immediate and delayed free recall. In contrast, retention and recognition performance

are almost normal in HD, showing that storage is only minimally affected by the disease. In general, semantic memory is preserved in HD. Nevertheless, performance in semantic memory tests may be impaired due to the general retrieval deficit if the testing procedure requires efficient and flexible retrieval of information from semantic stores, e.g. in category fluency tasks.

HD's memory profile, which is characterized by a clear benefit from recognition procedures which minimize the need for effortful, strategic retrieval, can be regarded as prototypical for subcortical neurodegenerative disorders [85].

2.4.6 Dementia with Lewy bodies (DLB), Parkinson's Disease Dementia (PDD)

In concordance with their subcortical pathology and relative sparing of the medial temporal lobe, DLB and PDD show a pattern of memory impairment with a prominent retrieval deficit while retention and recognition are less affected [86]. Although there is considerable overlap between DLB and PDD [87], memory performance in these disorders seems to be rather variable and the pattern is less salient than that seen in HD [85]. In particular, there seems to be a less clear advantage of recognition procedures over free recall. A

Table 1: Impairment of long term memory processes in different cerebral affections.
IGE, idiopathic generalized epilepsy with absence seizure or GTCS; MTLE, medial temporal lobe epilepsy; FLE, frontal lobe epilepsy; ADHD, attention deficit hyperactivity disorder; MD, major depression; AD, Alzheimer's disease; FTD, frontotemporal dementia (frontal variant); VaD, vascular dementia; MS, multiple sclerosis; HD, Huntington's disease; PDD, Parkinson's disease dementia; DLB, dementia with Lewy bodies.

	Episodic Memory				Semantic Memory
	Encoding	Retention	Retrieval	Recognition	
Normal aging	*	=	*	*	=
Epilepsy					
IGE	*	=	*	=	?
MTLE	**	**	**	**	*§
FLE	*§	=	*	*§	*
Psychiatric					
ADHD	*	=	*		
Schizophrenia	**		**	*	
MD	*	=	*	*	
Degenerative					
AD	***	***	***	***	*/**
FTD	*	=/*	*/**	*	=
VaD	**	**	**	**	**
MS	***	*	*	=	*
HD	*	=	***	*	=
DLB, PDD	***	** §	**	**	

= - no impairment
* - mild impairment
** - moderate impairment
*** - severe impairment
=/* - variable
§ - verbal vs visual-nonverbal asymmetry

consistent finding, however, is that DLB patients benefit to a high degree from contextual information (such as that which is provided in story recall) which helps them compensate for their executive deficit [88]. Also, a disadvantage in encoding visual-nonverbal versus verbal material has been suggested, possibly indicating abnormal function of visual cortical areas [87].

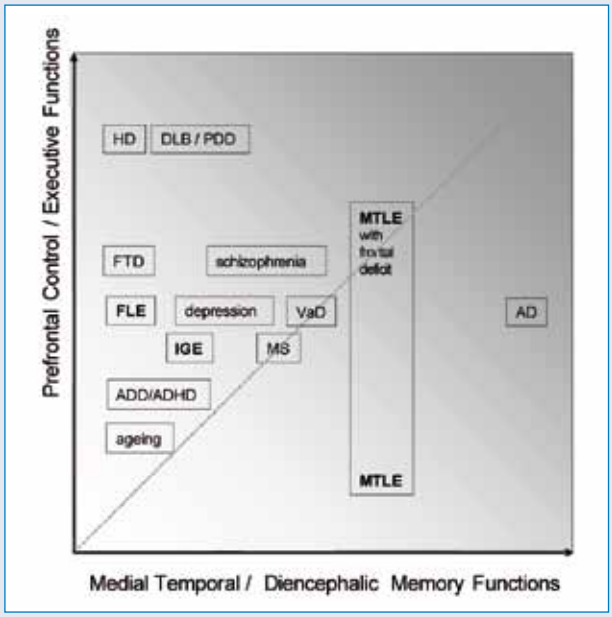

Figure 3 illustrates that the majority of disorders have a spectrum of memory impairments along prefrontal and medial temporal /diencephalic memory functions. Increased impairment is in the direction of the arrow.

3. Discussion

The analysis of the patterns of memory impairment in a representative selection of neurological and psychiatric disorders and normal aging suggests that episodic memory encoding and retrieval are affected in all conditions (**Table 2**). Encoding and retrieval processes are reliant on both the integrity of prefrontal functional systems and on functions associated with the hippocampal formation [89]. Prefrontal functions are more or less affected in all selected disorders as well as in aging, with the end result that the majority of memory failures in those patients may arise from transient or chronic prefrontal dysfunction.

Retention, in contrast, seems exclusively to be affected in some degenerative disorders, particularly in Alzheimer's dementia (AD) and to a lesser degree and less consistently in patients with vascular dementia, multiple sclerosis, and mesial temporal lobe epilepsy (MTLE). Retention is almost entirely determined by the functional integrity of the hippocampal formation and anterior diencephalic structures serving as "bottleneck" structures of memory formation [89, 90].

In the highlighted disorders the extent of prefrontal and mesial-temporal impairment is variable. Hence, we found it useful to organize disorders along dimensions of relative involvement of prefrontal and mesial-temporal functioning. In **Figure 3** we aimed to assign each disorder on a prefrontal and mesial-temporal axis based on the overview we provided in **Table 2**.

Regarding the epilepsies, we conclude that IGE and FLE share similar aspects of memory impairment, namely weaknesses in encoding and retrieval. Although IGE and FLE usually differ in aetiology, pathology, seizure type, and course of epilepsy both demonstrate neuropsychological impairment of various prefrontal functions. Because retention is usually not impaired in FLE and IGE, their memory profile resembles those of ADHD, FTD, schizophrenia, depression, and aging. From a neuropsychological point of view, it is not possible to discriminate FLE and IGE on individual memory test performance, nor can a memory profile help to exclude the presence of comorbidities such as ADHD or depression.

In contrast, the memory profiles of MTLE, MS and VaD have more in common with regard to impaired retention than the epilepsy memory profiles within themselves. We propose that MTLE and probably also multiple sclerosis may serve as neuropsychological prototypes that can be characterized by a memory impairment of a fronto-temporal spectrum. Prefrontal metabolic disturbances have been repeatedly reported in patients with MTLE [91-93]. In accordance with these findings, impaired cognitive functions associated with the frontal lobes have been well documented in patients with MTLE [16, 35, 94]. The intra- and inter-individual differences in the degree of prefrontal impairment are probably a significant factor in the observed performance variability seen in patients with MTLE.

In addition, the cognitive side-effects of anti-epileptic drugs, particularly in polytherapy and with the use of higher dosages as administered in patients with refractory epilepsy, are prone to affect prefrontal executive functions, attention, and working memory [96]. Therefore, the memory phenotype of patients with MTLE probably results from a combination of mesial temporal structural and functional impairments, seizure related temporo-lateral and prefrontal impairments and impairment of prefrontal functions due to high dose AED polytherapy.

Consequently, seizure-free status, low dose or no AEDs could help preserve the memory capacities of patients with epilepsies. Beyond that, there are therapeutic measures to improve prefrontal functions in neurological and psychiatric patients. Behavioural therapy, consideration of the cognitive and psychiatric profiles of AEDs, the use of external memory aids, cognitive enhancers as well as future memory enhancing drugs may help preserve or improve memory performance of affected patients with epilepsy. Finally, we suggest that the comparison and integration of knowledge and ex-

perience gained from disorders other than epilepsies stimulates and widens our perspective on memory impairments in epilepsies. This in turn can only improve our consideration and treatment of our patients' memory complaints.

Regardless of disorder and independent of the individual degree of impairment, one should not forget that memory is more than an instrumental cognitive function. Its loss can have grave effects on the awareness, integrity and perception of self.

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