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The mesial temporal lobe epilepsies
Posters presented at the 1st International Epilepsy Colloquium, Marburg, Germany, June 2008

ABSTRACT

Temporal lobe epilepsy is the most frequent type of focal epilepsy and is especially likely to become medication resistant. Mesial temporal lobe epilepsy (MTLE) is one of the epilepsy syndromes best characterized by clinical and basic science research.

The 1st International Epilepsy Colloquium was the first of a series of annual meetings that will be hosted in alternating years in Marburg (Germany), IDEE-Lyon (France) and UH Cleveland (USA). The Marburg Colloquium, directed by Prs. Rosenow, Hamer and Knake covered all aspects of the mesial temporal lobe epilepsies including the influence of genetics, psychosocial sequelae, novel imaging techniques and alternative surgical strategies used. The extensive body of knowledge that has accumulated over the recent years was made available to interested adult and pediatric epileptologists, neurologists, neurosurgeons and neuropsychologists. The Proceedings of the 1st International Epilepsy Colloquium will soon be published in the format of a book dedicated to Temporal Lobe Epilepsies.

Abstracts of the posters presented for discussion are published in the present issue of *Epileptic Disorders*.

Histology/pathophysiology of MTLE and TLE subsyndromes

Hippocampal mossy fibres form new connections with inhibitory interneurons in patients with temporal lobe epilepsy

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Objective. Temporal lobe epilepsy is frequently associated with Ammon's horn sclerosis which is characterised by neuronal death and sclerosis in the hippocampal regions CA1 and hilus. Additionally, there is a reorganisation of mossy fibres in the dentate gyrus, known as mossy fibre sprouting. This sprouting is characterised by an abnormal projection of granule cell axon collaterals backwards to the granule cell layer. It has been proposed that sprouting contributes to seizure generation by forming a local excitatory feedback circuit of granule cells. However, data obtained in animal models point to increased connections of sprouted mossy fibres with inhibitory basket cells.

Methods. We examined the connectivity of mossy fibres in neurosurgical specimens of patients with temporal lobe epilepsy using a novel tracing technique. In addition, double immunolabeling and electron microscopy were applied to identify putative target cells of the sprouting mossy fibres.

Results. We show that excitatory granule cell axons (mossy fibres) impinge both on excitatory granule cells and inhibitory interneurons. Granule cells were identified by direct tracer application and synaptoporin immunohistochemistry (IHC). Inhibitory interneurons were identified by parvalbumin IHC and GABA-postembedding immunogold electron microscopy.

Conclusion. These results suggest that sprouted mossy fibres do not only lead to an excitatory feedback circuit but also innervate inhibitory basket cells. We hypothesise that this aberrant innervation of interneurons not only results in an increased inhibition of dentate granule cells, but may contribute to the synchronisation of seizures in this network.

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Increase in the number of postsynaptic spines on granule cells in the hippocampus in different mouse models and in patients with temporal lobe epilepsy

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Objective. The most common form of pharmacoresistant epilepsy is the temporal lobe epilepsy (TLE). Its pathology is characterised by a sclerosis of the hippocampus, including a specific loss of neurons in the pyramidal layer of CA 1 and in the hilus. In contrast,

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granule cells of the dentate gyrus survive but show a widening of the usually tightly packed granule cell layer (GCL) and a reorganisation of their connections with the granule cell axons (mossy fibres) sprouting backwards to the inner molecular layer.

Methods. To examine a potential effect of sprouting, recurrent mossy fibres on granule cell dendrites, we have estimated the number of postsynaptic spines in two TLE mouse models, p35-knock-out mice and mice with intrahippocampal kainate injections. In addition, we studied reeler mice which exhibit a neuronal lamination defect, and tissue samples of patients with TLE. Granule cells were stained by Golgi impregnation and analysed by a computer-based camera lucida system.

Results. The most striking result was an increase in spine density in the GCL in p35 mutants and in kainate-injected mice as well as in patients with TLE. In reeler mice, which lack a distinct GCL due to a lamination defect, there was an elevated spine density on all dendritic segments.

Conclusion. We conclude that granule cells develop more postsynaptic spines under conditions of increased neuronal activity, probably associated with a granule cell lamination defect and recurrent mossy fibre sprouting.

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Increased postictal IL-6 release in patients with temporal lobe epilepsy and hippocampal sclerosis

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Objective. Inflammatory mechanisms appear to be involved in the pathogenesis and course of epilepsy. Vice versa, immune functions are regulated by the brain. We, therefore, measured prospectively postictal changes in serum levels of the proinflammatory cytokines IL-1beta, IL-6 and TNFalpha in patients with temporal lobe epilepsy (TLE) and determined the influence of possible modifying factors.

Methods. Using a sandwich ELISA, serum levels of IL-1beta, IL-6 and TNFalpha were quantified at baseline as well as immediately, 1 h and 24 h after a complex partial (CPS) or secondary generalized tonic-clonic seizure (GTCS) during video-EEG monitoring in 25 patients suffering from temporal epilepsy. Non-parametric statistics were applied.

Results. IL-6 increased in average by 51% immediately after the seizure ($p < 0.01$) and remained elevated for 24 hours. This increase lacked in patients with hippocampal sclerosis (HS; $n = 16$, mean increase 28%, $p > 0.5$ *vs* 112%, $p < 0.01$ in patients without HS). IL-6 levels were higher after right-sided seizures as compared to left-sided seizures 24 h after the seizure (8.7 pg/mL *vs* 3.4 pg/mL, $p < 0.05$). In patients taking valproate (VPA), the levels of IL-1beta were higher as compared to patients not treated with VPA. Seizure semiology (CPS *vs* GTCS), gender, duration of epilepsy, past seizure frequency or intake of anticonvulsants other than VPA did not influence cytokine levels.

Conclusion. The results suggest a relationship between the cytokine system and characteristics of TLE such as side and pathology. The lack of postictal IL-6 increase in patients with hippocampal sclerosis suggests a possible role of this cytokine in the pathogenesis of HS.

Phenotypic characteristics of temporal lobe epilepsy with hippocampal sclerosis

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Background. Mesial Temporal Lobe Epilepsy with Hippocampal sclerosis (MTLE-HS) is considered as an epileptic condition different from other Temporal Lobe Epilepsies (TLEs). However, the question whether it has a unique biological background is not yet answered. We compared phenotypic characteristics of MTLE-HS patients with TLE patients without HS.

Material and method. 218 patients from seven Norwegian University Hospitals were diagnosed with TLE using the ILAE criteria. Patients with MLTE-HS were identified by MRI. Only patients of Caucasian race and age over 18 year's were included. The patients completed a standardized evaluation form, and a case record form was completed by a doctor or nurse. Epidemiological data and clinical features were compared.

Results. 56 (25.7%) patients were diagnosed with HS versus 162 patients (74.3%) without HS. Age at epilepsy onset was lower in patients with MTLE-HS ($p = 0.002$), with 50% onset before age of 6 years, in contrast to 23.4% in other TLE patients. Incidence of simple partial seizures ($p = 0.006$) and complex partial seizures ($p = 0.001$) was significantly higher in MTLE-HS. There was no difference in generalized tonic-clonic seizures. Incidence of ictal psychiatric symptoms ($p = 0.015$) as well as autonomic symptoms ($p < 0.001$) were higher in MTLE-HS. Interictal psychiatric symptoms, included depression, were more common in TLE patients without HS. There was a higher appearance of childhood febrile seizures in patients with HS ($p = 0.043$). In contrast, TLE patients without HS appeared to have more frequently first grade family members with febrile seizures in childhood ($p = 0.019$).

Conclusion. Our study identified significant differences in patients with MTLE-HS regarding epidemiological, clinical and diagnostic aspects supporting that MTLE-HS is a unique biological entity. A proper classification of subgroups in TLE and a clear definition of "key features" in TLE with HS are important in diagnostic-, treatment- and prognostic terms, and deliver crucial information to future phenotype-genotype studies.

Temporal lobe epilepsy with and without mesial temporal sclerosis a comparative study between video- electroencephalographic and magnetic resonance image findings

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Temporal lobe epilepsy (TLE) is a condition characterized by recurrent unprovoked seizures originating from the medial or lateral temporal lobe. The seizures associated are varied in clinical manifestations. Hippocampal sclerosis is the most common pathologic finding in TLE and its clinical relevance is associated to refractory epileptic activity despite of antiepileptic drugs.

Objectives. To compare Video-electyroencephalographic (VEEG) interictal and ictal findings in patients with temporal lobe epilepsy with and without mesial temporal sclerosis and correlate this with magnetic resonance image (MRI) findings.
To identify the electroencephalographic patterns in these patients.

Methods. Comparative, descriptive and transversal study.

Results. We analyzed 79 patients with temporal lobe epilepsy from January to November of 2007, in all patients were performance studies of VEEG and MRI. The main findings were mesial temporal epilepsy in 48 (60.76%) and lateral temporal epilepsy in 31 (39.24%) by clinical and electroencephalographic findings. In 13 patients of the group of lateral epilepsy (16.4%) the MRI findings corresponded to focal lesions like vascular malformations, cortical dysplasia and neurocysticercosis).
The VEEG showed bilateral lesion in 59 patients (46.83%), left side was more affected in 50 (39.25%) *vs* 18 (13.92%) in the right side, without statistical differences (p = 0.5).
In the group of mesial temporal epilepsy there was a true concordance between VEEG and MRI findings only in 15 patients (31,25%).

Conclusions. The evaluation of patients with TLE is an important challenge because it needs an exhaustive evaluation, clinical, VEEG and imaging studies such as MRI and SPECT in order to locate the epileptic zone and to make success the surgical procedures. Previous studies have shown the importance of VEEG in the localization of epileptic activity lateralization with a predictor grade of 85%, in our study this grade was much lower (60%). Others studies are in course in order to confirm and complete these results.

Clinical significance of cortical dysplasia in mesial temporal lobe epilepsy

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Objectives. Mesial temporal lobe epilepsy (MTLE) constitutes a distinct clinical syndrome with variable etiopathogenesis. Extrahippocampal regions may be affected, association with cortical dysplasia is common, and temporal polar cortex is frequently involved in seizure onset. The aim of the study was to review clinical variables of TLE patients with histopathologically proven cortical dysplasia and to compare these data with MTLE patients with isolated hippocampal sclerosis (HS).

Methods. From 123 patients who underwent temporal lobe resection for refractory epilepsy in our centre, 55 cases with cortical dysplasia (CD) were identified (19 patients with isolated CD, 36 patients with CD and associated HS, *i.e.* group CD+HS). Both subgroups were compared to 32 cases of isolated HS. Demographic, clinical, electrographic and seizure semiology variables were obtained and their prevalence compared between the groups.

Results. Groups did not differ significantly in the age of surgery, frequency of seizures, occurrence of epigastric aura, interictal and ictal EEG findings.
Isolated FCD patients had less frequently early childhood injury (26%) and never had febrile seizures. The average seizure onset was 17,8 years. Psychic aura was more frequent (32%) and early oroalimentary automatisms less frequent (53%) in this group. The side of surgery was more often on the right (74%) and FCD of type 2 was found more frequently (42%) than in CD + HS group.
History of early childhood injury was more frequent in the group of isolated HS patients (84%) and meningitis/encephalitis was the most common (54%). The average age at seizure onset was 11,1 years. Early oroalimentary automatisms were frequent (88%) in this group.
CD + HS patients had the history of an insult in 61% and the most frequent was febrile seizures, only rarely they had meningitis (6%). The average seizure onset

was 11,4 years. FCD type 2 was found only in one patient of this group.

Conclusions. Cortical dysplasia may be difficult to distinguish preoperatively on the basis of electrographic features or ictal clinical semiology. Detailed information regarding possible precipitating insult seems to be of critical importance.

Mesial temporal lobe epilepsy in Iran

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Purpose. Mesial temporal sclerosis (MTS) is one of the leading causes of medically intractable complex partial seizures. To our knowledge, this is the first report of Magnetic resonance imaging (MRI) and clinical findings in 21 Iranian patients who had medically intractable mesial temporal lobe epilepsy (MTLE).

Methods. Twenty-one patients (8 females, 13 males) aged 16-68 years with clinically and EEG proven MTLE were included in this pilot study. Age at seizure onset was 3 months to 35 years, Median of seizures attack frequency was once a week. Six patients had history of febrile convulsion. All MRI were performed on a 1.5T GE (signa) and 3D coronal FSPGR, T2W and Flair sequences were obtained. Volumetric measurements of the hippocampus in patients with TLE was performed and compared with control group.

Results. Hippocampal atrophy was seen in 7 patients, in 3 in both hippocamp, 3 in the right and 1 in the left side. Seven patients had extra hippocampal gliosis (3 in right and 4 in left), 2 patients had tumor and 1 patient had migration disorder. Nine patients had normal MRI findings.
Additionally, volumetric measurement results in left side were 1.94 ± 0.49 and 2.19 ± 0.24 ($p = 0.070$) and in right side were 1.94 ± 0.49 and 2.30 ± 0.26 ($p = 0.01$) in patients and control groups, respectively. There was a strong association between Febrile convulsion and hippocampal volume loss ($p = 0.006$ in left side, $p = 0.026$ in right side). However, there was no association between hippocampal volume loss and history of trauma as well as frequency of seizure attack. There was a moderate correlation between right hippocampal volume loss and age of seizure onset ($r = 0.589$, $p = 0.006$). There was a statistically poor correlation between extra-hippocampal gliosis and history of trauma.

Conclusion. To our knowledge, this is the first report of temporal lobe MRI and clinical findings in 21 Iranian patients with MTLE. The occurrence of MTS following febrile convulsion was a common finding in our study which requires further studies with larger sample volumes.

Neuropsychology and psychiatric comorbidity

Pre-surgical language deficits distinguish left temporal lobe epilepsy from right temporal lobe epilepsy

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Objective. Temporal Lobe Epilepsy (TLE) is often a chronic neurological condition that disrupts daily functioning and frequently is associated with neuropsychological comorbidity. About one third of patients with focal epilepsies are refractory to medication, and are candidates for surgical treatment. Surgery presents with risks for post-surgical language deficits, particularly for patients with left temporal lobe epilepsy (LTLE). This study explored the magnitude of language deficits in patients with LTLE and right temporal lobe epilepsy (RTLE), and evaluate post-operative changes in language function.

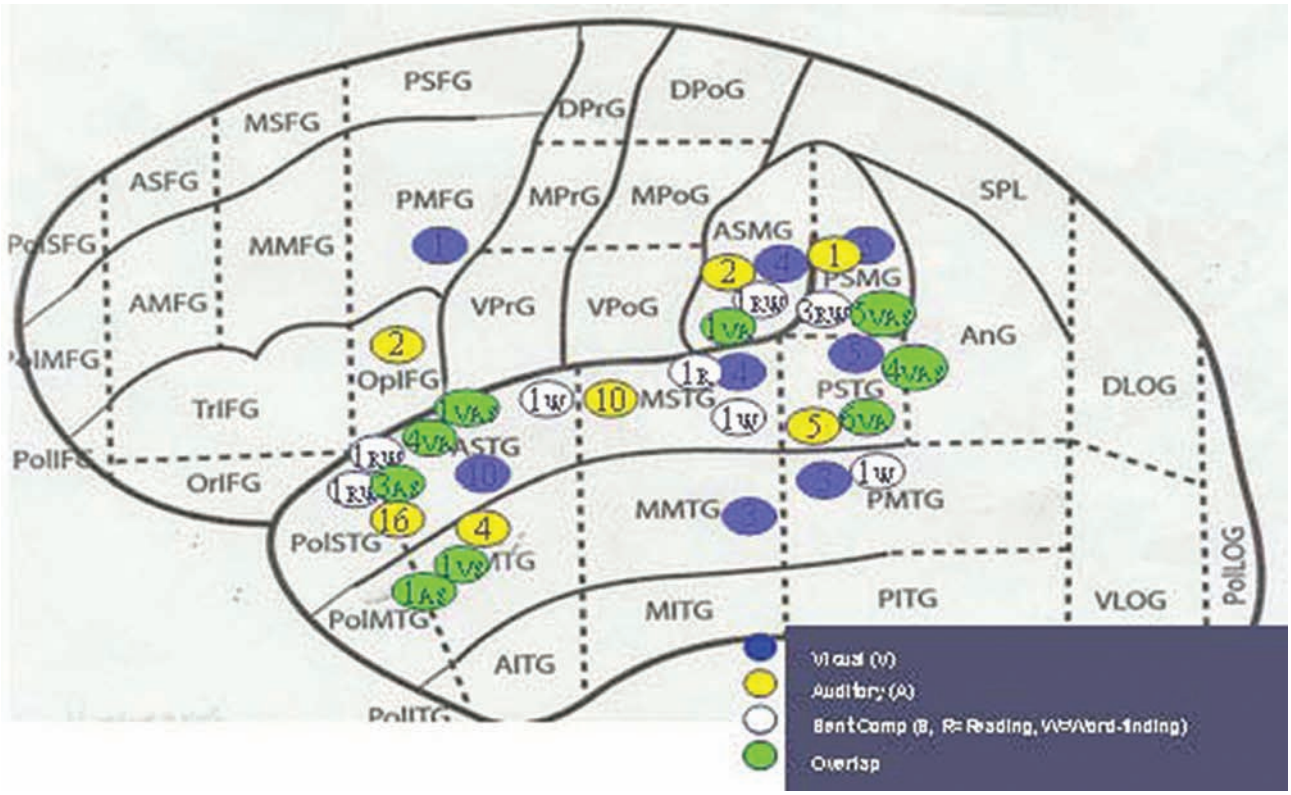
Method. Sixty-six patients with medically refractory TLE who underwent a pre-surgical neuropsychological assessment and met inclusion and exclusion criteria were included in the study. Thirty participants had LTLE while 36 subjects were diagnosed with RTLE.

Measures. Boston Naming Test (BNT) and verbal fluency tests.

Procedure. Presurgical language test scores were standardized and compared using education and FSIQ as covariates in analysis of variance. Post-operative changes will be evaluated with MANOVA.

Results. The LTLE sample's average age was 40 years old. The RTLE average age was 38 years old. Presurgically, the RTLE group was significantly better educated (14.4 years of education) and had a higher FSIQ (FSIQ = 100.9) than the LTLE group (mean years of education = 13.4, FSIQ = 90.4). Education and FSIQ were used as covariates in subsequent analsyses. MANCOVA found subjects with LTLE performed significantly worse on the BNT and semantic and phonemic verbal fluency than participants with RTLE ($p < 0.01$). Increasing duration of epilepsy decreased BNT and verbal fluency scores in both LTLE and RTLE groups. As expected, left anterior lobectomy more significantly affected language function than right anterior lobectomy.

Conclusion. These data further support previous studies in which pre-operative neuropsychological language measures can be helpful indices of lateralized epilepsy. Left TLE scored significantly lower on both indices than right TLE. Comparisons with lesion on MRI and Wada's test scores will be presented, along with individual analysis of change in BNT scores using RCI scores.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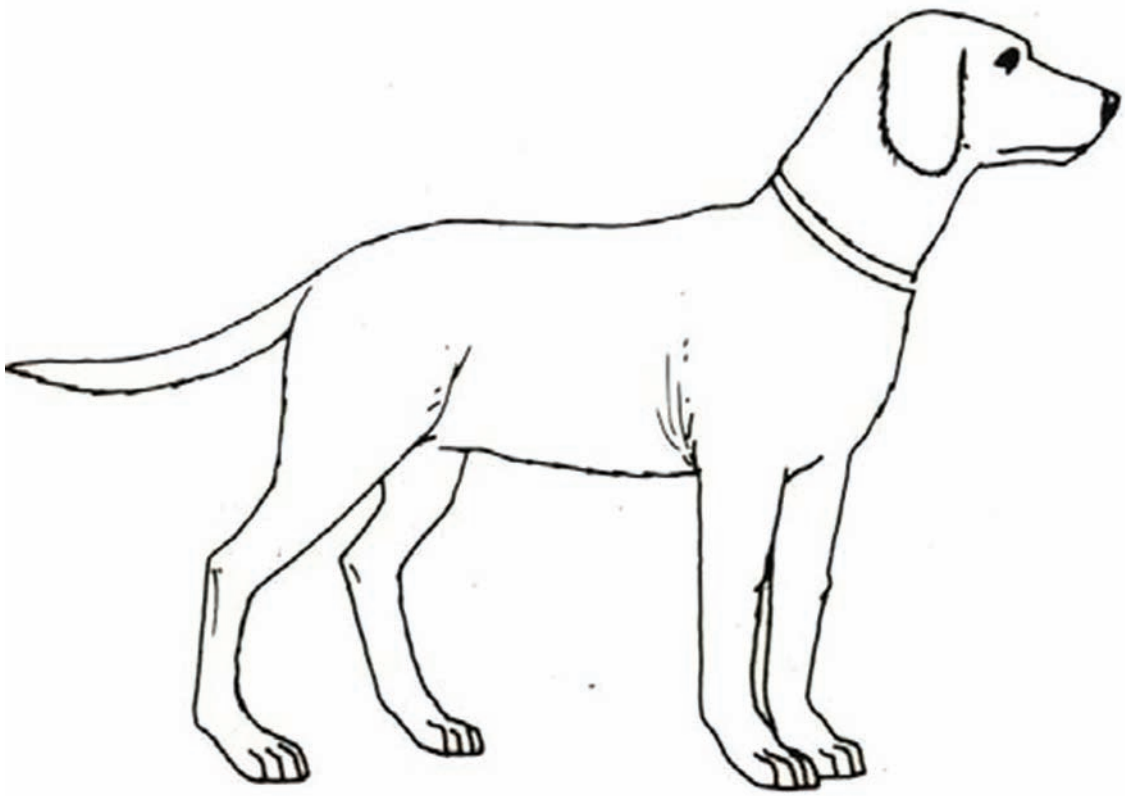

Cortical distinctions in visual, auditory, and sentence-completion word-finding

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Objective. Visual naming is used extensively in cortical stimulation mapping (CSM) to determine language-sparing resection margins. However, many patients have word finding difficulties severe enough to interfere with both speech and reading, but show few deficits on visual naming tasks (Hamberger and Tamny, 1999). We have previously demonstrated cortical distinctions in visual and auditory naming tasks (Serafini and Haglund, 2004). Using a sentence-completion paradigm we developed, we further demonstrate that there are cortical distinctions in reading-based word finding in left temporal epilepsy (LTE) patients during CSM (*figure 1*, p. 377).

Methods. Twenty-one LTE patients (11 fm, ages 21-60) scheduled to undergo awake temporal lobe resection with CSM for epilepsy treatment participated in the study. Line drawings were shown every 4 seconds for the visual naming task. Auditory naming involved listening to short (3-7 words) definitions. Sentence-completion (n = 9) had patients reading and completing a sentence-stem. Patients responded in each paradigm with a carrier phrase ("This is a … ") before the object name. Fisher's Exact tests ($p < 0.05$), compared the error rate for each task at a specific site with the error rate of all non-stimulated trials.

Results. 65% of patients had distinct visual sites, while 90% had distinct auditory sites and 44% had distinct sentence-completion sites. 83% of patients showed overlapping sites for visual/auditory, visual/auditory/sentence, or auditory/sentence tasks. Overlapping sites with visual naming were always found in posterior areas but only 60% of overlapping sites with visual naming occurred in anterior areas, the remainder being accounted for by auditory/sentence tasks. The overall pattern shows visual sites in relatively superior/posterior areas such as supramarginal areas, and posterior STG. The majority of auditory naming sites appear in anterior areas such as the anterior/middle STG and MTG. Sentence-completion sites are clustered in supramarginal areas and along the edge of the Sylvian fissure in the STG.

Conclusions. There are distinct cortical areas found in patients during CSM between visual and auditory naming and sentence-completion tasks. Including auditory and sentence-completions tasks in the language mapping procedure provides a more comprehensive language map, particularly in anterior and inferior areas, and sparing these sites may prove significant in reducing post-operative language deficits in patients.

Naming famous persons in patients with temporal lobe epilepsy

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Objectives. Previous studies assigned a special role to the temporal lobes in naming known persons. From these studies, it is unclear whether patients with temporal lobe epilepsy (TLE) have naming impairments only or also suffer from defective semantic knowledge. The present study assesses separately recognition of famous persons (FPs), retrieval of biographical information, retrieval of proper names and, in the case of failed word retrieval, recognition of proper names, on both visual confrontation (face naming) and verbal definition in patients with left- or right-sided TLE.

Method. LTLE and RTLE patients (all right-handed; Table 1) were compared with age- and education-matched healthy controls on visual confrontation and verbal definition tasks.

Visual confrontation: (a) recognition, the FP's photograph was presented with 3 distractors, participants had to point to the FP (FPs were known from politics, cinema and sports, and were all contemporaries); (b) confrontation naming, participants had to name the FP; (c) semantic questions (n = 2 per FP); (d) cues in case of failed name retrieval (initial letter, first name, multiple-choice).

Verbal definition: (a) definition naming, a short definition of a FP was provided, participants had to name the FP; (b) semantic questions; (c) cues (same procedure as in visual confrontation).

Results. Visual confrontation: (a) no group difference in recognition scores *(table)*; (b) LTLE but not RTLE differed from controls in naming scores (even when adjusted for correct recognition); (c) both LTLE and RTLE performed poorer than controls on semantic questions (even when scores were adjusted).

Verbal definition: differences between patient groups and controls in (a) naming scores and (b) semantic scores. No other relevant result emerged.

Conclusions. The present study shows that TLE patients are familiar with famous faces, but have difficulties in naming as well as in retrieving the person's specific semantic knowledge. Both LTLE and RTLE patients differ from healthy controls in semantic tasks and in naming to definition. Thus, lack of semantic information seems to be a characterising feature of proper name anomia in TLE. LTLE patients, but not RTLE patients perform poorer than controls in assigning proper names to famous faces, even when scores are adjusted for correct recognition. This finding suggests that the dominant temporal lobe plays an essential role in assigning the lexical word form to correctly identified faces.

	Max score	LTLE (n = 17) M (SD)	RTLE (n =9) M (SD)	Controls (n =16) M (SD)
Ages (years)		35.8 (8.7)	46.9 (12.0)	41.7 (14.9)
Education (years)		10.8 (1.9)	9.4 (1.8)	10.8 (1.3)
Gender (f:m)		7:10	5:4	9:7
Disease onset (years)		14.5 (9.6)	21.0 (18.4)	
Disease duration (years)		21.3 (15.5)	25.0 (13.0)	
Naming on visual confrontation				
Recognition	18	14.5 (3.0)	14.1 (3.2)	15.1 (2.9)
Confrontation naming	18	8.6 (4.4)*	9.4 (4.7)	12.6 (3.7)
Adjusted naming score#	1	0.60 (.30)*	0.65 (.24)	.82 (.15)
Semantic questions	36	21.9 (9.0)*	21.8 (8.3)*	28.6 (6.3)
Adjusted semantic score##	2	1.5 (.4)*	1.6 (.4)*	1.9 (.2)
Naming on definition				
Naming on definition	18	9.1 (4.7)*	8.4 (4.7)*	13.4 (3.3)
Semantic questions	36	17.9 (8.3)*	17.6 (7.9)*	26.6 (5.0)

= naming/recognition; ## = semantic score/(2 x recognition); * = significant difference between the patient group and the healthy control group (Mann-Whitney U-test, one-sided $p < 0.05$). No significant difference emerged between patient groups.

Memory for public events in patients with TLE compared to extra TLE patients, generalized epilepsy patients and healthy volunteers

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Objective. Remote memory deficits have been previously described in Temporal Lobe Epilepsy (TLE). The aim of this study was to determine memory for public events as a marker of remote memory function in patients with different epilepsy syndromes. Considering the important role of temporal lobe structures for learning and memory, we hypothesized deficits to be predominantly apparent in TLE.

Methods. 23 healthy volunteers (age: 34 ± 9 yrs), 36 TLE patients (34 ± 8 yrs), 19 extra TLE (ETLE) patients (31 ± 8 yrs) and 18 patients (31 ± 8 years) with generalized epilepsy (GE) were included. Knowledge about public events that happened in the 1970's, 80's, 90's and up to 2004 was obtained *via* interview. Additionally, premorbid IQ (German vocabulary test; WST), depressive symptoms (Beck Depression Inventory; BDI) and handedness (Edinburgh Handedness Inventory; EHI) were assessed.

For comparison between patients and healthy controls raw scores were used. To adjust for item difficulty comparison between patient groups was conducted with individual Z-scores (relative to the control group). Additionally, the difference in Z-scores for public events of decades before and after onset of illness (Z-scorepost-pre) were computed for each patient and compared between the epilepsy groups.

Results. The TLE and the GE patients showed a trend towards lower premorbid IQ compared to controls (T-Test; $p < 0.1$). Furthermore, a trend towards younger mean age in the GE group compared to the TLE group could be observed (T-Test; $p < 0.1$).

ANOVA with the within-subject factor ''decade'' and the between-subject factor ''group'' revealed main effects for both factors ($p<.05$) and a trend towards an interaction effect ($p < 0.1$). Controlling for premorbid IQ the group effect remained significant, while the interaction effect did not. Post hoc T-Tests disclosed that overall performance was lower in all patient groups than in controls ($p < 0.05$). Furthermore, TLE patients knew significantly less events than ETLE patients. With respect to the GE group, TLE patients only showed a trend towards lower overall performance ($p < 0.1$).

Analysing Z-scores for the patient groups, ANCOVA with age as a covariate again revealed main effects for the factor ''decade'' and ''group'' as well as a significant interaction effect ($p < 0.05$).

Regarding the interaction effect, TLE patients knew less public events from the two recent decades (1990's; 2000-2004) than the ETLE and GE group (T-Tests; $p < 0.05$).

Regarding onset of illness ANOVA for the Z-scorepost-pre indicated significant group differences. However, when controlling for age only a trend remained. Post-hoc T-Tests pointed towards a superior decline in knowledge for public events after onset of illness in TLE patients compared with ETLE and GE patients.

Conclusion. In this study patients with TLE showed a pronounced deficit in remote memory for public events compared to patients with ETLE and with GE. In TLE the observed deficit was predominantly apparent for events from the more recent decades, indicating a time gradient in memory dysfunction. With TLE patients remembering less public events of the time period after onset of illness, the remote memory deficits can be partly attributed to the well known intended learning deficit in this syndrome.

Memory, WADA and temporal lobe epilepsy

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Purpose. Temporal lobe epilepsy (TLE) is the most frequent pharmacoresistant epilepsy in adults. Epilepsy surgery is an important treatment option to reduce or even stop seizures. Negative side effects of this treatment can include cognitive deficits such as memory impairment or naming difficulties. Predicting the postoperative memory outcome is of crucial importance for patients. Different predictors like presurgical episodic memory or WADA memory scores have actually been used. However, as different epilepsy centres use different parameters, no gold standard has been defined yet. We present data from our neuropsychological epilepsy program and memory scores which can help predict postoperative memory outcome.

Methods. 49 consecutive patients (mean age = 37.7; 22 female, 27 male) with drug resistant unilateral temporal lobe epilepsy (26 left and 23 right sided) were evaluated for epilepsy surgery in the comprehensive Innsbruck Epilepsy Surgery Program (INES) and finally underwent resective surgery with a minimum follow up of one year. All patients underwent 3 neuropsychological evaluations (before, 3 and 12 months after surgery) and a WADA test (assessment of language and memory). Left hemisphere was the dominant hemisphere for language in all patients. Patients with right lateralized language or bilateral representation were not included in the study.

Results. At the group level only the left TLE group showed significant memory loss after surgery. Good pre-surgery memory scores lead to relatively good post-surgery memory scores; however, they were also associated to greater memory loss compared to cases with low pre-surgery memory scores. This was the case for both left- and right-sided TLE. For left TLE WADA memory scores (from both left and right hemispheres) correlated with one year post-surgery memory scores (ROC = 0.816). By using a combination of WADA memory scores and an episodic memory test (long delay free recall) a positive predictive value of 0.86 and an negative predictive value of 0.66 was found.

Conclusions. A combination of pre-surgical neuropsychological memory data and WADA-memory scores helps to predict postoperative mnesic performance). Results derived from the WADA test imply that both hemispheres account for good post-surgery memory. Thus, contralateral compensation as well as ipsilateral functional reserve seem to contribute to good memory outcome.

Visual and verbal memory of selected patients with right or left temporal lobe epilepsy after selective temporal lobectomy

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Objective. Temporal lobe epilepsy (TLE) is the most commonly diagnosed focal epilepsy. Temporal lobe resection successfully controls medically intractable seizures in 60 to 85% of patients. However, post-surgical memory loss remains a significant risk. Risk of memory loss is increased among patients with intact pre-surgical verbal memory and absence of ipsilateral hippocampal abnormality. Despite continued efforts to predict outcome, significant decline in memory continues to occur. The purpose of this study was to further evaluate the magnitude in change scores among selected patients with right or left TLE.

Method. The study included review of epilepsy patients completing pre and post-surgical evaluations for medically refractory epilepsy.

Participants. Seventeen patients were identified that met study inclusion and exclusion criteria. There were 8 participants with LTLE and 9 participants with RTLE.

Measure(s). Comprehensive neuropsychological evaluations pre-surgically and an average of 10.2 months after selective anterior temporal lobectomy (ATL). Results from MRI, V-EEG, Intracarotid Amytal (Wada's) test, and neuropathology will be included.

Results. The mean age of the LTLE sample was 39 years old (SD = 10.7) with 13.6 years of education. The mean age of the RTLE group was 35 years old (SD = 12.4) with 14.3 years of education. Education and FSIQ differed between groups ($p < 0.05$) and were used as covariates in subsequent analyses. Prior to surgery, there was a significant interaction in which subjects with LTLE scored worse on verbal memory scores than patients with RTLE. Alternatively, patients with RTLE scored better than subjects with LTLE. MANCOVA found a significant decline in verbal memory for patients status-post right ATL while patients status-post left ATL exhibited a trend decline. Conversely, visual memory significantly improved following left ATL while there was no change

in visual memory scores for the right ATL group. Performance on Wada's test and pre-surgical memory scores were independent predictors of post-surgical memory outcome.

Conclusion(s). These data further support observations that presurgical neuropsychological data are valuable in predicting post-surgical memory outcome. Presurgially, the LTLE group performed worse on verbal memory tests than subjecs with RTLE, but post operative decline was greater for the RTLE group. The RTLE group performed worse than the LTLE group on visual memory scores.

Decision making after unilateral temporal lobe epilepsy surgery

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Objectives. The present study focuses on two different types of decision making in patients who underwent unilateral temporal lobe epilepsy (TLE) surgery – decision under ambiguity (information is missing) and decision under risk (probabilities are well-defined). It has been suggested that the amygdala is a critical structure in decision making since it is involved in emotional arousal associated with the anticipation of rewards and punishments (Phelps and LeDoux, 2005). To the best of our knowledge no study so far compared different types of decision making in patients affected by TLE. Impairments in decision making may have severe consequences in everyday life.

Methods. Epileptic patients who underwent unilateral amygdala and hippocampal resection matched with healthy controls were tested with a detailed neuropsychological test battery. To assess decision making two decision tasks were used. One decision task tested decision making under ambiguity (Iowa Gambling Task, IGT; Bechara *et al.* 1994), the other decision making under risk (Probability-Associated Gambling task, PAG; Sinz *et al.* 2008).

Results. In the IGT, TLE patients selected more disadvantageously than healthy controls and failed to develop an advantageous strategy over time. Moreover, TLE patients showed reduced flexibility (switching between strategies) as well as reduced stability (maintaining an advantageous strategy). Patient and control group performed similarly in the PAG task and no significant differences were detected. Importantly, our results indicate that participants' performance on both decision tasks correlated with executive functions.

Conclusion. Our study shows that TLE patients have difficulties in decision under ambiguity, but not in decision under risk with explicit rules. Difficulties in the IGT may be attributed to deficient learning from feedback.

Psychological impacts on quality of life among Saudi patients with epilepsy

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Background. Depression and anxiety are common psychological symptoms in patients with epilepsy, exerting a profound negative effect on health-related quality of life. Studies have estimated that up to 50% of patients with epilepsy develop psychological dysfunctions; the most common are depression and anxiety disorders.

Objectives. This study aims to:
1. estimate the prevalence of anxiety and depression in Saudi patients with newly-diagnosed and chronic epilepsy;
2. evaluate the effect of depression and anxiety on quality of life of epilepsy patents;
3. correlate the prevalence of these psychological disorders with the type of epilepsy.

Methods. We will investigate 200 patients with epilepsy (age 16 years and above) who attend Epilepsy Out-Patient Clinics at King Fahad Medical City in Riyadh. All subjects will complete:
1. an identification card and epilepsy data;
2. hospital Anxiety and Depression Scale (HADS);
3. QOLIE 31.

Statistical considerations. The collected data will be analyzed through using SPSS computer software. Analysis of variance (ANOVA) and correlation/ regression test will be performed. Statistical significance will be considered at ($p < 0.05$).

Expected results. Our study will shed light on the prevalence of psychological dysfunction among Saudi patients and the way it affects quality of life. Moreover, we will highlight on the prevalence of these psychological problems in TLE versus generalized epilepsies. That will have a great impact on patient care and management plans.

Kindled "limbic psychotic trigger reaction", analogous to primates

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Twenty-four "feloms" remembered their our-of-character, motiveless, unplanned, nonvoluntary crimes, typically toward strangers, without emotional involvement. The otherwise unexplainable symptomatology was proposed as a new kind of limbic seizures: "Limbic Psychotic Trigger Reaction" (LPTR) (Pontius). LPTRs symptoms are basically analogous to "unilateral mesial

temporobasal limbic seizures" experimentally evoked in presurgery patients by direct electrical stimulation (Wieser1983 and 1998, Pontius and Wieser 2004). The obviously richer context of LPTR occurrence revealed an additional analogy to nonconvulsive behavioral seizures with indications of visual hallucinations in kindled primates (Wada 1978 and 1998). The neurophysiological mechanism of seizure kindling, requires no morphological brain damage, merely intermittent exposure to subthreshold stimuli. Congruent with experimental kindling, LPTR is not typically associated with changes in objective brain tests, although brain injury might facilitate LPTR. Thus, half of the so far 24 LPTR patients had a remembered history of closed head injury and half had some abnormal brain test (EEG, CT, MRI) at some time during their lives.

LPTR consists of 12 symptoms and signs, emerging in three seizure-like phases (aura, ictus, post-ictus). LPTR is apparently elicited by a chance encounter with a highly individualized trigger stimulus that suddenly revives the memory of past merely mild to moderate stressful experiences. Aside from the bizarre and remembered acts, the symptoms include sudden autonomic arousal, a fleeting *de novo* psychosis (of any sensory modality, formed or unformed hallucinations, mostly visual; and/or delusions (frequently of grandeur) or depersonalization).

LPTR is strictly determined by 16 inclusion- and 13 exclusion criteria (Pontius & Wieser, 2004). LPTR may not be restricted to felonious acts. There may be a reservoir of many more undetected (and untreated) "sleeper" cases among the general population, who commit "merely" bizarre social misbehavior, deleterious to both patient and victim alike (see Marcel Proust: M. Swann).

Implicated in LPTR is a transient fronto-limbic dysbalance, during which limbic seizure (?)- based hyperactivation temporarily overwhelms prefrontal monitoring. A fleeting state of limbic level functioning with "paleo-consciousness" is proposed that could explain the preservation of memory, the flat affect and bizarre changes of drive motivation, intent, planning and volitional action.

Epilepsy surgery: diagnosis, techniques, outcome

The added value of invasive video-EEG monitoring at Ghent University Hospital

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Introduction. At Ghent University Hospital, invasive video-EEG monitoring (IVEM) is performed in patients with refractory epilepsy in whom the non-invasive presurgical evaluation is insufficient to localise the ictal onset zone prior to resective surgery (RS). The aim of this retrospective study was to evaluate the role of the IVEM in the presurgical evaluation in a large group of patients.

Methods. Data from patients who underwent IVEM between 1992 and 2007 was reviewed. Following IVEM, the ictal onset zone was classified as focal (F), regional (R), multiple (M) or undefined.
Suitable patients for RS were identified. Suitability was defined as the identification of a unique focus without overlap of the ictal onset zone and functional cortex. The number of seizure free patients following RS was evaluated.

Results. Over the past 16 years, 68 refractory epilepsy patients (M/F 41/27), aged between 10 and 50 with a mean age of 32, underwent IVEM. In 56/68 patients (82%) the ictal onset zone was defined following IVEM (42/56 patients were classified F, 5/56 were classified R and 9/56 were classified M). 20/56 patients (36%) were considered unsuitable candidates for RS following IVEM, 36/56 patients (64%) were considered suitable. 8/36 suitable patients (22%) preferred deep brain stimulation or vagus nerve stimulation to RS. 28/36 patients (78%) eventually underwent RS. 22 of them (79%) have remained seizure free for a mean duration of follow-up of 63 months (range: 12-120 months).

Conclusion. RS became a treatment option in about half of patients following identification of the ictal onset zone using IVEM. One third of patients, in whom the ictal onset was undefined on the basis of non-invasive tests, became seizure free following RS after IVEM. For these patients IVEM is indispensable to make them eligible for RS.

Selective amygdalohippocampectomy in temporal lobe epilepsy: impact of hypometabolism in FDG-PET on postoperative seizure outcome?

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Objectives. In mesial temporal lobe epilepsy (mTLE) with hippocampal pathology (HCP), the impact of hypometabolism in preoperative FDG-PET on postoperative seizure outcome after selective amygdalohippocampectomy (SAHE) is not celar. In this study, a possible predictive value of the extent of hypometabolism in FDG-PET for postoperative outcome after SAHE was investigated.

Methods. All patients with mTLE and HCP undergoing SAHE between February 1999 und February 2007 were retrospectively included in this study. We examined

the extent of hypometabolism in preoperative FDG-PET (mesial vs. mesial and lateral).

Results. Twenty-five patients (17 women, 8 men, mean age 40 ± 12 years) underwent SAHE between 1999 and 2007. In all patients, MRT scan revealed HCP (19 hippocampal sclerosis, 3 dysplasia, 2 cavernoma, 1 tumor WHO II). Presurgical evaluation elicited in all patients temporo-mesial seizure onset. In 21/24 patients, preoperative FDG-PET showed hypometabolism exclusively temporo-mesial, in 4/25 hypometabolism was obvious in the whole temporal lobe (temporo-mesial, -polar and -lateral). Outcome: In the group with temporo-mesial hypometabolism, 13/21 patients had postoperative Engel outcome class IA (1 IB, 2 IC, 1 II A, 2 IIB, 1 IID, 1 IIIA). In the group with PET-hypometabolism involving the whole temporal lobe, 3/4 were seizure free (Engel outcome class IA; 1 IIB).

Conclusion. In this series, the extent of hypometabolism in preoperative FDG-PET has no predictive value for postoperative seizure outcome in patients with mTLE and HCP undergoing SAHE.

Changes in seizure semiology of temporal lobe epilepsy - a longitudinal video-EEG study

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Objective. In this longitudinal study, we investigated whether seizure semiology in temporal lobe epilepsy (TLE) changed over time and whether surgery had an effect on this change.

Methods. We included 30 patients (19 men, mean age: 29) with pharmacoresistant TLE and complex partial seizures and who had at least two separate ictal video recordings in a time span of > 5 years. Epilepsy surgery after the first monitoring was performed in 24 patients.

Results. Psychic aura became less frequent over time. The odds ratio (OR) was 0.89 with an 0.86-0.91 confidence interval (CI). Similarly, oral automatism occurred less often over time (OR = 0.74, CI: 0.57-0.91). We found significant effects of surgery for psychic aura, cloni, and head version. That is, in patients with temporal lobe resections, there was a relative increase in psychic auras compared to the non-surgical patients. In the surgical group both cloni (OR = 0.80, CI: 0.64-0.99) and head version (OR = 0.75, CI: 0.60-0.95) decreased relatively compared to the non-surgical group.

Conclusion. Seizure semiology may show some changes over time: psychic aura and oral automatisms became less frequent over time. In patients who underwent surgery, ictal version and ictal unilateral limb cloni occurred less frequently, while psychic aura appeared more frequently over time. We suggest that the clinical picture of epilepsy and epileptic seizures is not static over time even in adult epilepsy, especially if the patient undergoes epilepsy surgery where the changed seizue semiology can be explained by having cut off the pathways for extratemporal seizure spread.

Disconnection in temporal lobe epilepsy surgery: seizure outcome and safety

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Objectives. To assess the efficacy and safety of temporal lobe disconnection in patients suffering from intractable Temporal Lobe Epilepsy (TLE) associated with hippocampal sclerosis or with normal MRI.

Methods. This retrospective analysis includes 54 consecutive TLE patients treated by temporal lobe disconnection at Grenoble University Hospital between 1999 and 2005. Seizure outcome was evaluated according to based on the modified Engel's classification

Results. There were 30 women (55%) and 24 men, whose mean age at surgery was 30.9 years (range 3-50). Age at seizure onset ranged from 3 months to 39 years (mean 10.3 years) with a mean duration of epilepsy of 20 ± 1.4 years. Twenty four patients (45%) had a history of febrile seizure, which were complex in 15 (28%). MRI showed a unilateral hippocampal sclerosis in 82.7% of cases. VideoEEG monitoring was performed in all cases, additional stereotactic intracererbral EEG (SEEG) recordings were performed in 29 patients in whom non invasive data were insufficiently concordant or discordant. The mean duration of postoperative follow up was 46 months (range 14-80 years). The probability of Class I outcome for the overall patient group was 93% at 3 months, 87% at 1 year, 88% at 2 years, 91% at 3 years, and 88% at 5 years postoperatively. The probability Class Ia outcome was 80% at 3 months, 70% at 1 year, 68% at 2 years, 73% at 3 years, and 64% at 5 years postoperatively. Post-operative persistent morbidity included mild hemiparesia (n = 1), mild facial paresia (n = 1), quadranopia (n = 23), hemianopia (n = 3). Verbal memory was worsened in 13% of cases when the disconnection was performed in the dominant lobe. MRI control showed 2 non symptomatic thalamic or pallidal limited ischemias, 2 temporal horn cystic dilatation, one requiring surgical reoperation without sequellae. There was one case of post-operative phlebitis. A post operative depression was reported in 26 patients.

Conclusion. Temporal lobe disconnection surgery appears to be as safe and effective as temporal lobe resection. It prevents the occurrence of subdural cyst

and of hematomas in the temporal cavity, prevents the occurrence of oculomotor palsy and limits the occurrence of quadranopia. However, comparative studies are required to evaluate the temporal disconnection as an alternative to lobectomy in non-lesional TLE.

Surgical treatment of temporal lobe epilepsy with structural lesions

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Objective. To evaluate the effect of surgical techniques, presurgical evaluation, intraoperational ECoG on resection of lesions and control of seizures in patients with temporal lobe epilepsy (TLE) and structural lesions.

Methods. Presurgical evaluation was performed in 74 patients with TLE and structural lesions who underwent resection of lesion plus epileptogenic focus tailored by intraoperative ECoG. All patients were followed up from 6 to 48 months.

Results. Epilepsy was found as main symptom in 39 cases (53%), while increased intracranial pressure dominated in 35 cases (47%). 51 cases were in Engel I (70%), 13 cases in Engel II (18%), 5 cases in Engel III (7%), 5 cases in Engel IV (7%).

Conclusion. Neuroimaging associated with V-EEG, analysis of clinical history as well as other methods may play an important role in localization of lesions and epileptogenic focus. Resection of lesion plus epileptogenic focus under the guidance of neuroimaging and electrophysiology might be more effective for the patients with TLE and structural lesions.

Surgical treatment for Intractable epilepsy secondary to paraneoplastic limbic encephalitis

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Background and aims. Adult-onset temporal lobe epilepsy may have an autoimmune etiology, and be associated to non paraneoplastic or paraneoplastic limbic encephalitis. This condition is usually responsive to treatment of the corresponding tumor, corticosteroids and intravenous immunoglobulins. Same patients do not respond and go on to develop refractory TLE, usually secondary to mesial temporal sclerosis. We report a patient with intractable mesial temporal lobe epilepsy secondary to paraneoplastic encephalitis who underwent surgical treatment.

Material and methods. We report a 37 year old man with drug resistant partial simple and complex seizures, which started one year after removal of a testicular tumor (seminoma). Seizures consisted of different auras (piloerection, rising epigastric sensation, intense fear, etc.), followed at times by partial lose of awareness and subtle oral automatisms. He used to have aura status lasting for up to 48 hours. MRI showed increased size of the right amygdala and hippocampus; anti MA2 antibodies were present in serum. He was diagnosed with paraneoplastic limbic encephalitis. Inmunoglobulins and steroids were tried, with only transient responses. Several anticonvulsivants were given in different combinations (valproate, oxcarbacepine, levetiracetam, topiramate and gabapentine) without success. In 2004, he underwent presurgical evaluation. Several auras were recorded; the patient showed impairment of consciousness only in one seizure. Surface EEG showed either no EEG change or rhythmic theta over the temporal right temporal region. MRI at that time showed right hippocampal atrophy and ictal SPECT showed right mesial temporal hyperperfusion. He underwent right anteriomesial temporal lobectomy. After surgery he continued to have auras, mainly psychic (fear); he is not currently having impairment of awareness during the seizures, but we have not been able to reduce his medications due to increased frequency of auras.

Conclusion. Seizures accompanying to limbic encephalitis are usually responsive to immunosuppressive treatment. However, some cases evolving to mesial temporal sclerosis may result in intractable seizures. Resective surgery may be offered to these patients, although likelihood of seizure freedom may be lowered by active and extensive underlying inflammatory process.

Left temporal cavernoma and right temporal seizure onset zone: a remediable epilepsy?

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We present the case of a twenty-four-years-old, right-handed male. Family history was negative for epilepsy. Delivery and psychomotor development were carried out normally. Since 10 years of age he had been experiencing diurnal and nocturnal seizures.

Nocturnal seizures were characterized by sudden eyes opening, left arm and leg hypertonus, often followed by eyes and head turning towards the left side and "pedalage" automatisms. During these seizures, lasting one minute, the patient could talk and understand what people were saying and at the end he was able to remember. Nocturnal seizures occurred weekly.

During the diurnal seizures, the patient rapidly cut himself from the enviroment: he forgot what he was doing and the meaning of what he was doing and he repeated stereotyped phrases. He could answer to simple questions and he remembered his seizures. The frequency of these seizures was monthly.

Pre-surgical evaluation protocol included: history, neurological examination, neuro-psycological assessment, prolonged video-EEG monitoring, high-resolution MRI and fMRI, visual field evaluation, interictal and ictal SPET (the latter obtained during seizures pharmacologically provoked by pentylenetetrazol, a central and respiratory stimulant).

Neurological examination was fully normal. MRI put in evidence a cavernoma in the left anterior temporal lobe. fMRI demonstrated left dominance for language. Scalp video-EEG allowed to record two brief seizures, not conclusive. We decided to perform bilateral foramen ovale exploration which demonstrated that the seizure onset zone was located in the right temporal lobe.

Considering the bilateral involvement of temporal lobes (lesion in the left side and seizure-onset zone in the right side) we decided firstly to remove the cavernous angioma.

After 1-year follow-up the patient continued to have seizures. Should we propose a right temporal lobectomy?

Selective resection of the uncus and amygdala in a patient with bilateral mesial temporal sclerosis: case report

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Temporal lobe epilepsy due to bilateral mesial temporal sclerosis is a challenging situation of the clinical practice. The pharmacological therapy is rarely able to reach a seizure control and the indication for the surgical treatment is limited. We present the case of a 41-year old woman whose clinical features were compatible with temporal lobe epilepsy. She presented psychomotor seizures preceded by fear auras (3-4 per week) and depression with paranoid symptoms. The first epileptic episodes occurred in the childhood and during the clinical treatment the patient developed pharmacoresistance. Clinical and neurological examination was normal with right-hand dominance. The neuropsychological evaluation revealed progressive bilateral cognitive deficit with the verbal memory worse than the figurative one. MR showed signs of sclerosis and atrophy of both hippocampi. WADA test and Functional MR demonstrated right hemisphere language dominance. Due to a left mesial dominant focus observed in the video-EEG the patient underwent the stereotaxic implantation of 6 deep brain electrodes – 1 amygdalian and 2 hippocampal electrodes on each side. The invasive EEG recording revealed a dominant epileptic focus the left amygdala. On the following step she was submitted to the selective resection of the left amygdala and uncus with preservation of the ipsilateral hippocampus. The histological analysis showed no signs of neoplasic or dysplasic changes. In the follow-up period she presented no more psychomotor seizures, however the fear auras persisted (Engel I). The post-operative neuropsychological assessment demonstrated an improvement of the verbal tasks and no more depression. Invasive EEG recording guided by stereotaxic techniques is a valorous co-adjuvant on the diagnostic investigation because they permit a detailed electrophysiological study and a more precise determination of the epileptic focus. We highlight the importance of highly selective surgical procedures in selected patients with bilateral mesial temporal sclerosis aiming a better seizure control. Further studies are nevertheless required to determine the role of these promising strategies in the management of the bilateral temporal lobe epilepsy.

Intracranial cerebrospinal fluid and epileptogenicity: a new rheological proposal

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Purpose. The aim of this study are to know whether the intracranial cyst flow will contribute to develop epileptogenic focus.

Patients and methods. Two cases with post hemorrhagic porencephalic cyst in their left temporo-occipital region were the subject of this study.
– Case 1: a 22-year-old woman suffered from intractable seizures 15 years after the removal of the arteriovenous malformation (AVM) with hemorrhagic insult.
– Case 2: a 71-year-old woman developed an intracerebral hemorrhage 5 years ago but has remained seizure free.
Physiological studies with the conventional EEG, EEG dipole analysis were performed to estimate the localization of the epileptic focus. Neuroradiological studies with MRI including FLAIR imaging, fiber tractography using Diffusion tensor imaging (DTI) and cine MRI that visualize intracranial cerebrospinal fluid (CSF) flow were performed to clarify anatomical structure of the lesions and to investigate rheological activities inside the cystic lesion. These acquired data were visualized into fusion images.

Results.
– Case 1: dipole analysis of interictal EEG suggested that the epileptic foci were located both on her mesial temporal region and her left temporo-occipital gliotic lesion neighboring to the porencephalic cyst. Cine

MRI demonstrated the CSF flow by heart pulsation struck the gliotic lesion continuously. Moreover, the fiber connection between these foci was suggested by DTI tractography.
– Case 2: neither CSF flow relating to cystic lesions or obvious electrophysiological focus was detected.

Conclusion. The results of electrophysiological and neuroimaging studies suggested that the intracranial CSF flow and it's hydrodynamic stress play an important role in epileptogenecity and secondary kindling. We neurosurgeon need to pay deep attention not only to ordinal surgery but to post-operative CSF flow and remaining neuronal fiber connections.

Antiepileptic drug withdrawal after temporal lobectomy

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Objective. To investigate the rate, timing and speed of antiepileptic drug withdrawal after successful temporal lobectomy. Furthermore, to assess the rate of relapses and the prognosis after a relapse.

Methods. Retrospective analysis of 102 patients who underwent a temporal lobectomy between 1995 and February 2007 in the Netherlands. Postoperative follow-up was at least one year and was executed in Kempenhaeghe, location Hans Berger Clinic.
The postoperative data were taken from the medical records; the following data were analyzed: Engel-score after 1, 2, 3, 4, 5, 10 years and during the last follow-up; timing and speed of tapering the antiepileptic drugs (AEDs); total or partial withdrawal; number of AEDs; rate of relapses; outcome after a relapse.

Results. The mean duration of the postoperative follow-up was 5.8 years (median 4.5 years). After one year 75.5% of the patients had an Engel-score of 1 (68.6% Engel 1A), which remained quite stable during the following years.
During last follow-up, 21 patients (20.6%) successfully stopped their medication. Before any drug withdrawal, 28 patients had a relapse (27.5%). Only 34 patients (33.3%) did not taper the medication. Of the remaining 68 patients, during or after drug withdrawal 12 patients had a relapse (17.6%). The mean onset of drug tapering was at 26.1 months. The mean duration from onset to a total withdrawal was 30.2 months. 59 patients stopped at least one drug with a mean duration of 5.9 months, 25 patients stopped a second drug (mean duration 7.4 months) and 6 patients stopped a third drug (mean duration 12.5 months).
Of the 12 patients with a relapse during or after drug withdrawal, the mean time between changing the medication and relapse was 3.4 months. After adjustment of the medication 6 patients became seizure-free (Engel 1). The remaining patients had an Engel-score of 2A (5 patients) or 2D (1 patient).

Conclusion. After successful temporal lobe surgery only a minority of the patients did not taper the antiepileptic drugs. In contrast with a previous report the relapse rate after tapering the medication was lower than with unchanged medication. A proposal for a prospective controlled trial will be made.

Table 1. Medication withdrawal and Engel score during last follow-up. Number of patients (%).

Engel score AED postop.	1A	1B	1C	1D	2A	2B	2D	3A	4A	Total
No withdrawal	12 (11.8%)	5 (4.9%)	4 (3.9%)	0	1 (1.0%)	3 (2.9%)	4 (3.9%)	3 (2.9%)	2 (2.0%)	34 (33.3%)
Partial withdrawal[1]	27 (26.5%)	1 (1.0%)	4 (3.9%)	1 (1.0%)	1 (1.0%)	1 (1.0%)	0	1 (1.0%)	0	36 (35.3%)
Total withdrawal[1]	17 (16.7%)	0	3 (2.9%)	0	0	0	0	0	0	20 (19.6%)
After relapse[2] AED > initial AED	0	0	1 (1.0%)	0	0	0	0	0	0	1 (1.0%)
After relapse[2] AED = initial AED	0	0	1 (1.0%)	0	3 (2.9%)	0	0	0	0	4 (3.9%)
After relapse[2] AED < initial AED	0	1 (1.0%)	1 (1.0%)	1 (1.0%)	2 (2.0%)	0	1 (1.0%)	0	0	6 (5.9%)
After relapse[2] AED stop	0	0	1 (1.0%)	0	0	0	0	0	0	1 (1.0%)
Total	56 (54.9%)	7 (6.9%)	15 (14.7%)	2 (2.0%)	7 (6.9%)	4 (3.9%)	5 (4.9%)	4 (3.9%)	2 (2.0%)	102 (100%)

[1] In case of relapse: relapse before drug withdrawal.
[2] Relapse after drug withdrawal (partial or total).

Table 2. Follow-up, postoperative Engel-score and AEDs.

Follow-up (years post-op)	1	2	3	4	5	10	Last follow-up[1]
Number of patients	102	90	73	58	49	12	102
Engel score							
1	77 (75.5%)	63 (70.0%)	51 (70.0%)	43 (74.1%)	38 (77.6%)	10 (90.9%)	80 (78.4%)
1A	70 (68.6%)	52 (57.8%)	39 (53.4%)	28 (48.3%)	25 (51.0%)	7 (63.6%)	56 (54.9%)
1B	6	8	4	3	2	0	7
1C	-	2	6	11	11	3	15
1D	1	1	2	1	0	0	2
2A	5	10	8	3	2	0	7
2B	7	4	3	2	1	1	4
2D	5	5	4	3	3	0	5
3A	6	6	4	6	4	0	4
4A	2	2	3	1	1	0	2
no. of AEDs							
Average	2.15	1.92	1.71	1.59	1.32	0.50	1.54
Range	1-4	1-4	0-3	0-4	0-3	0-2	0-4
SD	0.71	0.71	0.79	0.88	0.87	0.67	1.09
Change of AEDs[2]							
Initial monotherapy							
Unchanged	14	8	3	4	2	0	3
Other monotherapy	0	0	3	3	2	1	1
Increased[2]	5	5	5	3	2	1	4
Decreased	0	4	3	3	4	1	3
Stopped	0	0	2	2	5	4	9
Initial polytherapy							
Unchanged	64	37	18	10	6	0	21
Other polytherapy	3	2	3	3	3	0	3
Increased[3]	7	8	7	5	4	0	9
Decreased[4]	9	26	26	23	18	2	37
Stopped	0	0	3	2	4	3	12

[1] Range last follow-up 13-144 months (1.1-12.0 years) SD 3.0 years.
[2] Change of AEDs: in relation to initial therapy at time of surgery.
[3] Increase of AEDs: dosage or number of AEDs.
[4] Decrease of AEDs: dosage or number of AEDs.

Medical treatment: human and animal studies

Lamotrigine in patients submitted to video-electroencephalographic monitoring: effect of co-medication in temporal and extratemporal epilepsy

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Objectives. Despite current pharmacological arsenal more than 30% of epileptic people remain without seizure remission. These refractory patients, characterized mostly by polytherapy, are often submitted to video-electroencephalographic (VEEG) monitoring, for presurgical evaluation or diagnosis of epilepsy. The main goal of this study was to perform a pharmacodynamic evaluation based on eventual correlations between seizures and plasma levels, considering the: 1) co-medication profile and 2) localization of epileptogenic focus (temporal *vs*. extratemporal).

Methods. The analysis was performed in 142 consecutive adult epileptic patients receiving lamotrigine [LTG] as add-on therapy, associated to carbamazepine (CBZ) or valproic acid [VPA], submitted to VEEG monitoring in the Epilepsy Monitoring Unit of Coimbra University Hospital (CUH). Drug reduction was used as a seizure precipitation technique in order to record patient

typical seizures (local Ethics Committee of CUH approved this study and written informed consent was obtained from all patients). LTG was quantified by high-performance liquid chromatography (Castel-Branco *et al.* 2001), and CBZ and VPA were analyzed by fluorescence polarization immunoassay. PKS program (Abbott Diagnostics) was used to estimate ictal LTG, CBZ and VPA serum levels.

Results. Only 76 patients exhibited partial epilepsy. Two groups were established according to the presence of CBZ (LTG+CBZ group, n = 33) and VPA (LTG + VPA group, n = 18). Temporal epilepsy lobe was observed in 21 and 13 patients in LTG + CBZ and LTG + VPA groups, respectively. The first seizure occurrence seems to be related to CBZ/VPA levels (or CBZ/VPA tapering), since no significant change was observed in LTG serum levels, before (basal) and after drug withdrawal protocol application. Basal LTG serum levels observed in LTG + CBZ and LTG+VPA groups were the following: 1.9 ± 1.3 mg/L and 7.6 ± 4.0 mg/L, respectively. Furthermore, time to reach first seizure was longer in LTG + VPA group (76.4 ± 49.3 h) than that of LTG + CBZ group (48.6 ± 27.8 h) ($p \leq 0.05$).

Conclusion. The present results suggest that a more favourable pharmacodynamic interaction could be attributable to the LTG + VPA association.

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Secondary generalization in patients receiving lamotrigine during video-electroencephalographic monitoring

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Objectives. Drug reduction is often used as a seizure precipitation technique in order to record patient seizures during video-electroencephalographic (VEEG) monitoring. Nevertheless, this procedure presents obvious associated risks. Lamotrigine (LTG) is a new generation antiepileptic drug used in Portugal since 1994 for add-on therapy. Although, and besides more than a decade of clinical experience, clinical studies and publications, much of the pharmacokinetic-pharmacodynamic relationship of LTG remains unknown, especially regarding its application in the VEEG monitoring. The aim of the present study was to perform a pharmacodynamic evaluation based on eventual correlations between seizures (secondary generalization) and LTG plasma levels.

Methods. The study has been conducted in 142 consecutive adult epileptic patients submitted to VEEG monitoring in the Epilepsy Monitoring Unit of Coimbra University Hospital (CUH), from October 1998 to June 2005 [the local Ethics Committee of CUH approved this study and written informed consent was obtained from all patients]. LTG was quantified by high-performance liquid chromatography (Castel-Branco *et al.* 2001. PKS program (PKS® System, Abbott Diagnostics) was used to estimate ictal LTG serum levels. Four treatment groups were established as follows: Group 1 (LTG + inducer agents); Group 2 (LTG + valproic acid [VPA]); Group 3 (LTG + inducers and VPA); and Group 4 (LTG alone).

Results. Simple partial seizures seem to be associated to higher LTG levels, whereas lower LTG concentrations were mainly related to complex and generalized seizures ($p < 0.05$). Also, a large number of secondary generalizations were associated to patients with extratemporal epilepsy (mean number 1.3 *vs* 0.5, in extratemporal and temporal group, respectively). Furthermore, the percentage of patients with secondary generalization was 42% and 28% when analyzing in detail LTG + CBZ group (n = 33) and LTG+VPA group (n = 18), respectively (LTG + CBZ group: 33% *vs* 58% in temporal and extratemporal group, respectively; LTG + VPA group: 16% *vs* 60% in temporal and extratemporal group, respectively).

Conclusion. Our results suggested that secondary generalizations may be associated to the presence of an inducer such CBZ and to extratemporal epilepsy.

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Anticonvulsive effects of intracerebroventricular administration of rutin in a rat model of absence seizure: a novel compound to treat seizure

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Objectives. Various synthetic derivatives of natural flavonoids are known to have neuroactive properties. The aim of the present study was to investigate the anticonvulsant effects of rutin (3,3',4',5,7 - pentahydrohyflavone-3-rhamnoglucoside), a flavonoid which is an important dietary constituent of food and plant-based beverages.

Methods. To this end, we assessed the anticonvulsant effects of rutin in rats treated with pentylenetetrazole (PTZ) (90 mg/kg, i.p.) and sought to clarify this mechanism.

Results. Intracerebroventricular (i.c.v.) injection of rutin dose-dependently affected minimal clonic seizures (MCS) and generalized tonic clonic seizures (GTCS) induced by PTZ, through increments in seizure onset. Additionally, pretreatment with flumazenil (5 nM, i.c.v.) abolished the anticonvulsant effects of rutin during the onset of both seizures.

Conclusion. These results indicate that rutin has anticonvulsant effects in the brain, possibly through positive allosteric modulation of the GABAA receptor complex *via* interaction at the benzodiazepine site.

Local anti-epileptic therapy with valproate in a mouse model of pharmacoresistant temporal lobe epilepsy

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Objective. In patients with pharmacoresistant epilepsy caused by an epileptogenic focus in an eloquent brain area, operative resection may result in severe neurological deficits. Therefore we have developed a novel experimental technique by implanting valproate-containing osmotic minipumps with catheter (1) or a gel of controllable release (2) into (1) or on the surface of (2) the epileptic mouse hippocampus in an animal model of pharmacoresistant temporal lobe epilepsy.

Methods. The well described mouse model of unilateral intrahippocampal kainate injection, reflecting pharmacoresistant temporal lobe epilepsy, was used. In a first operation 50 nL (1 nmol) kainate was injected stereotactically into the left dorsal hippocampus followed by the development of limbic seizures within a period of four weeks. In these mice osmotic mini pumps with catheter tips within the left hippocampus were implanted, delivering either saline or 10 mg valproate within 7 days. In a second group (2) valproate gel or placebo was applied on the surface of the hippocampus after corticotomy. Subsequently, intrahippocampal encephalography electrodes (EEG) were implanted in all mice and long term EEG recordings were performed. Anticonvulsant effects were measured by mathematical counting paradigm of high frequency oscillation (fast ripples).

Results. Clear antiepileptic effects of valproate micro pumps and gels, compared to the placebo groups, were observed. Valproate micropumps decreased the fast ripple activity from 100% to 37.7%. This effect, however, did not reach the level of significance due to a too small sample size. Valproate gels decreased the fast ripple activity from 100% to 5% ($p < 0.05$). The antiepileptic effect disappeared after 14 days in both groups and the previous epileptic activity was restored. After this local antiepileptic treatment, 10 mg valproate was given intraperitoneally in a single dose in both the verum and the placebo groups to test whether the used animal model was pharmacoresistant to conventional application of valproate (as described in the literature). Intraperitoneal valproate application, however, did not decrease fast ripple activity. All hippocampal specimens showed Ammon's horn sclerosis, the neuropathological correlate of temporal lobe epilepsy.

Conclusion. We have demonstrated that local, but not systemic application of valproate has antiepileptic effects in a conventionally pharmacoresistant epilepsy model.

Intracerebroventricular administration of pasipay suppresses epileptic seizures in rats: a novel antiepileptic drug

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Objectives. Passion flower is used in traditional medicine of Europe and South America to treat anxiety, insomnia and seizure. Its hydro-alcoholic extract, Pasipay has been established in treating the physical symptoms of opioid withdrawal in human and anxiety disorder. It has also shown anticonvulsant effects in mice.

Methods. The anticonvulsant effects of Pasipay were investigated using the pentylenetetrazole (PTZ) model in rats. The latency to minimal clonic seizure (MCS), generalized tonic-clonic seizure (GTCS) and percent of mortality protection were recorded, as well as the percentages of protection against the mortality.

Results. In this study, the intracerebroventricular injection of Pasipay dose dependently prolonged the onset of MCS and GTCS. Flumazenil reversed the anticonvulsant activity of Pasipay.

Conclusion. These results indicate that Pasipay has anticonvulsant effects which may be related to effect of it on GABAergic. More studies are needed in order to investigate its exact mechanism.

Bi-directional chiral inversion of S- and R-licarbazepine in CD-1 mice

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Objectives. Licarbazepine is the active metabolite of oxcarbazepine (OXC). It is a chiral compound and it exists as two chemically different entities, S-licarbazepine (S-Lic) and R-licarbazepine (R-Lic). In humans, OXC is metabolised in the liver to both active metabolites S-Lic and R-Lic. However, in spite of the use of OXC in clinical practice for almost ten years few studies have explored the occurrence of chiral inversion of licarbazepine enantiomers. Therefore, the present study was carried out to investigate the possibility of bi-directional chiral inversion of S-Lic and R-Lic after their oral administration separately to CD-1 mice.

Methods. Single doses of S-Lic or R-Lic (350 mg/kg) were administered to groups of adult male CD-1 mice by oral gavage (n = 8). Blood and liver tissue were taken at 0.25, 0.5, 0.75, 1, 2, 4, 6, 10, 16, 24 h post-dose. Plasma and liver concentrations of licarbazepine enantiomers were assessed by a chiral HPLC-UV assay previously validated. The mean concentration-time profiles obtained were analysed by a non-compartmental model using WinNonlin® version 4.1. All experimental procedures were approved by the Portuguese Veterinary General Division.

Results. After S-Lic administration, the corresponding Cmax was attained at 0.25 h in both liver (71.13 mcg/g) and plasma (49.47 mcg/mL) and the AUC0-∞ was 446.40 mcg.h/g and 310.49 mcg.h/mL respectively. In these conditions, plasma R-Lic concentrations were below the limit of quantification, but it was quantified in liver with the Cmax of 0.87 mcg/g (Tmax = 0.25 h) and the AUC0-∞ of 1.16 mcg.h/g. By treatment with R-Lic, its Cmax was also achieved in liver (74.96 mcg/g) and in plasma (74.55 mcg/mL) at 0.25 h and the corresponding AUC0-∞ were 263.44 mcg.h/g and 282.68 mcg.h/mL respectively. In this case, S-Lic appeared in measurable amounts in liver (Cmax = 5.24 mcg/g; Tmax = 0.25 h; AUC0-∞ = 46.25 mcgh/g) and in plasma (Cmax = 1.09 mcg/mL; Tmax = 0.25 h; AUC0-∞ = 11.67 mcg.h/mL).

Conclusion. The bi-directional chiral inversion of licarbazepine was herein demonstrated in adult male CD-1 mice and it occurred preferentially in the direction R → S.

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Kidney pharmacokinetic profiles of S- and R-licarbazepine in mice

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Objectives. Pharmacokinetic studies in humans have demonstrated the extensive presystemic metabolic conversion of oxcarbazepine (OXC) to licarbazepine. Licarbazepine contains an asymmetric centre, existing as two chemically different entities, S-licarbazepine (S-Lic) and R-Licarbazepine (R-Lic). Taking into account that kidneys are the main responsible for licarbazepine excretion, the present study characterized the kidney pharmacokinetics of S-Lic and R-Lic following their oral administration to mice separately.

Methods. Single doses of S-Lic or R-Lic (350 mg/kg) were administered to groups of adult male CD-1 mice (n = 8) by oral gavage. Kidneys were taken at 0.25, 0.5, 0.75, 1, 2, 4, 6, 10, 16, 24 h post-dose. The kidney concentrations of licarbazepine enantiomers and of their metabolites were assessed by a validated enantioselective HPLC-UV assay. The mean concentration-time profiles obtained were analysed by a non-compartmental model using WinNonlin® version 4.1. To investigate in mice the enantioselective kidney exposure to S-Lic and R-Lic after equivalent dose regimes, the S/R enantiomeric ratios were calculated for the Cmax and AUC0-∞ pharmacokinetic parameters. All experimental procedures were approved by the Portuguese Veterinary General Division.

Results. The mean kidney pharmacokinetic profiles obtained after S-Lic and R-Lic administration showed that these parent compounds accounted for most of the kidney drug exposure, being metabolised to a small extent to oxcarbazepine (OXC) and to their complementary enantiomer. After R-Lic administration an extra metabolite was found in kidney tissue, but it was not quantified since the analytical method was not validated for that purpose. The main pharmacokinetic parameters estimated are presented *(table)*. On the other hand, the values calculated for the Cmax and AUC0-∞ S/R enantiomeric ratios were 0.95 and 1.65 respectively.

Table. Kidney pharmacokinetics of S-Lic in mice after single oral doses (350 mg/kg).

Parameters	S-Lic administration			R-Lic administration		
	S-Lic	R-Lic	OXC	R-Lic	S-Lic	OXC
Tmax (h)	0.25	0.25	1.00	0.25	0.25	0.75
Cmax (mcg/g)	51.71	0.55	3.01	54.62	2.52	3.66
AUC0-∞ (mcg.h/g)	375.37	NC	31.79	227.96	15.43	16.28
T1/2 (h)	7.26	NC	7.08	9.18	4.16	4.56

NC: not calculated.

Conclusion. These results indicate the presence of differences in the pharmacokinetics of licarbazepine enantiomers in mouse kidney tissue and support that the extent of exposure to S-Lic was higher than that to R-Lic after an equivalent dose.

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Plasma protein binding of licarbazepine enantiomers in human and mouse species

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Objectives. Eslicarbazepine acetate (ESL), the next generation voltage-gated sodium channel blocker, is a prodrug of S-licarbazepine (S-Lic). Together with R-licarbazepine (R-Lic), they compose the asymmetric centre of licarbazepine (Lic). It is well known that

plasma protein binding (PPB) is enantioselective for many chiral drugs and some differences in the pharmacokinetic profiles between enantiomers may be due to differences in their PPB. This study aimed to determine in vitro PPB of S- and R-Lic in human and mouse over the therapeutic range of Lic to investigate the enantioselectivity in that process.

Methods. Pooled blank plasma samples were obtained from plasma of healthy humans after their written informed consent and from adult male CD-1 mice. Aliquots of human and mouse plasma were spiked at 10, 25 and 50 mcg/mL with S- or R-Lic solutions in Sorënsen buffer (pH 7.4) and were incubated at 37ºC for 30 min (n = 3). After that, plasma samples were transferred to Microcon Ultracel YM-30 ultrafiltration units and centrifuged at 14000 rpm for 30 min (37ºC). Lic enantiomers were measured in plasma (Cp) and in the ultrafiltrate (Cu) by HPLC-UV. The extent of PPB was calculated (mean ± standard deviation) according to% binding = (1-Cu/Cp) x 100. Non-specific binding of S-Lic and R-Lic to the ultrafiltrate apparatus was also assessed. The binding of S- and R-Lic to the filtrate apparatus was not considered to be significant (~1%) and the ultrafiltration was confirmed as a suitable method for the determination of PPB for Lic enantiomers.

Results. Human PPB was found to be 30.5 ± 5.6, 30.3 ± 1.3 and 28.9 ± 0.7% for S-Lic, and 32.1 ± 1.5, 27.5 ± 1.0 and 30.4 ± 2.7% for R-Lic at 10, 25 and 50 mcg/mL respectively. On the other hand, in mouse, the PPB was shown to be 30.5 ± 0.5, 28.7 ± 1.1 and 28.3 ± 1.1% for S-Lic and 30.3 ± 0.7, 31.5 ± 1.6 and 31.3 ± 1.5% for R-Lic at the same concentration levels. Accordingly, over the concentration range tested, differences were not observed in PPB for both Lic enantiomers either intra or interspecies ($p > 0.05$, ANOVA).

Conclusion. The extent of PPB of S- and R-Lic was low (~30%) and non-enantioselective in human and mouse. Therefore, differences in the disposition of Lic enantiomers in these species are not dependent of their affinity to plasma proteins. Moreover, the PPB of S-Lic and R-Lic was concentration independent, indicating a non-saturable process in the therapeutic range.

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