

*Dr. med. Günter Krämer*



Im vorliegenden Sonderheft der Zeitschrift „Epileptologie“ der Schweizerischen Liga gegen Epilepsie finden Sie die Abstracts der freien Vorträge und Posterbeiträge für die inzwischen schon achte seit 1999 alle zwei Jahre im Wechsel in Deutschland, Österreich und der Schweiz stattfindenden gemeinsamen Jahrestagungen der deutschsprachigen Epilepsiegesellschaften bzw. -ligen.

Nach 2001 in Zürich und 2007 in Basel treffen wir uns diesmal etwas mehr im Landesinneren der Schweiz. Ich bin sicher, dass die wunderbare Umgebung die Teilnehmer aus Deutschland und Österreich für die Mühen der Anreise entschädigen wird.

Auch im Namen von Herrn Professor Holger Lerche und Herrn Professor Eugen Trinka, den Vorsitzenden der Deutschen bzw. Österreichischen Gesellschaften für Epileptologie, bedanke ich mich bei den Autoren für ihre Beiträge und wünsche den Lesern eine spannende Lektüre

A handwritten signature in blue ink, which appears to read 'G. Krämer'. The signature is fluid and cursive.

*Günter Krämer*  
*Präsident der Schweizerischen Liga gegen Epilepsie.*

P 1

### Acute angioedema of the tongue after oral monotherapy with levetiracetam

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#### Aims:

We report the case of a 86-year-old woman who was admitted to the hospital with the first generalized tonic-clonic seizure due to a subcortical vascular dementia. In the last six months, several focal clonic seizures of the right extremities were reported. A treatment was not started yet.

#### Method:

On admission, neurological examination was unremarkable and the EEG showed epileptic activity bihemispheric frontocentral. Twenty minutes after the first oral dose of 500 mg levetiracetam (LEV), the patient developed an increasingly swelling tongue and neck due to an acute angioedema. Arterial blood pressure and oxygen saturation remained normal. LEV was stopped and she was treated with prednisolon and antihistaminic drugs.

#### Result:

Within two hours, the swelling of the tongue and neck disappeared. Topiramate in a dosage of 100 mg daily was started and well tolerated without any side effects.

#### Conclusion:

To our knowledge, we here present the first case of acute angioedema of the tongue due to treatment with a monotherapy of LEV. Hypersensitivity reaction of LEV is a very rare event with an incidence of 0,3%. Angioedema is caused by mast cell degranulation and release of inflammatory mediators. The occurrence of an angioedema is only described in one patient as a cross sensitivity between phenytoin, lamotrigine and LEV.

P 2

### Addressing adverse events in epilepsy treatment: a systematic approach

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#### Aim:

To systematically assess adverse events (AEs) in patients with epilepsy and antiepileptic drug (AED) treatment.

#### Method:

To screen outpatients of a large tertiary epilepsy centre for potential AEs, we employed a questionnaire based on the Liverpool Adverse Events Profile (LAEP). In this 19-item self-report instrument, frequency of occurrence of potential AEs 4 weeks prior to index visit is quantified by 4-point Likert scales (1="never" to 4="always or often") resulting in a total score ranging from 19 to 76. Cut-off for high frequency of AEs was a total score of >44. In addition, overall health status and quality of life were assessed by 11-point numerical rating scales (0="worst" and 10="best"). Data on patients' age, sex, age at epilepsy onset, epilepsy duration, epilepsy syndrome, aetiology, seizure freedom >12 months, and number of AEDs were obtained from a database at the index visit when the questionnaire was completed.

#### Results:

Inclusion criteria were met by 665 patients (46.8% male; mean age 45.4±16.6 years). Mean age at epilepsy onset was 25.4±19.7 years; mean epilepsy duration was 20.8±16.8 years. Partial epilepsy was diagnosed in 70.8%, generalised epilepsy in 22.1%, and unclassified epilepsy in 7.1%. Aetiology was symptomatic in 44.4%, idiopathic in 20.6%, and cryptogenic in 35.1%. Prior to their index visit, 33.5% of patients were seizure-free for at least 12 months. At index visit, 58.9% were treated with 1 AED and 40.2% had 2 or more AEDs; 0.9% of patients were not treated at the index visit. Median total LAEP score was 37, with 26.6% of cases scoring >44 points. Independent predictors of LAEP scores >44 were partial epilepsy (OR 1.786; 95% CI 1.164-2.739; p=0.008), female sex (OR 1.918, 95% CI 1.328-2.771; p=0.001), and number of current AEDs (OR 1.327, 95% CI 1.05-1.676; p=0.018). Seizure freedom was a negative predictor for severe AEs (OR 0.503, 95% CI 0.332-0.761-2.3; p=0.001). Median scores for overall health

status were 6 and for quality of life 7; these were negatively correlated with LAEP scores ( $r=-0.577$  and  $r=-0.546$ , resp.;  $p<0.01$ ).

#### Conclusions:

This questionnaire is a reliable screening tool for AEs in AED treatment. Partial epilepsy, female sex, persisting seizures, and higher number of AEDs were independent predictors of more frequent AEs. Overall health status and quality of life were negatively correlated with frequency of AEs. Further analyses are required to address further variables such as impact of individual AEDs.

P 3

#### Advantages and disadvantages in the use of generic versions of Levetiracetam

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#### Background:

The antiepileptic substance Levetiracetam (LEV), approved in Germany in 2000, effective in the treatment of focal and generalized seizures, has ideal pharmacodynamic and pharmacokinetic qualities. Thus, it is not astonishing that many generic versions of LEV (26 up to now in Germany) became available after patent protection for the brand drug (Keppra® by UCB) expired.

#### Purpose:

The aim is to describe possible advantages and disadvantages in the therapeutic use of some of those generic versions of LEV.

#### Methods:

Information on the costs of generic versions of LEV is given, as well as the effects of switching from branded to generic LEV respectively between different generics of LEV are described in 4 patients, based on a retrospective file review.

#### Results:

Keppra® and the identical Levetiracetam UCB® are available in dosages of 250, 500, 750 and 1000mg as divisible tablets, oral and injectable dilutions. Not all generic versions of LEV are offered in all of these dosages and administration forms. Whereas 200 tablets of Keppra® à 1000mg cost 724,94 EUR, Levetiracetam UCB® (same dosage and administration form) cost only 554,53 EUR, and the cheapest generic LEV at the moment 136,86 EUR. Different names, colours and flavours tend to lead to confusion, especially in elderly or mentally handicapped patients. Effectiveness or side effects have been different depending on the generic version in our 4 reported patients.

#### Conclusion:

To start therapy with a generic version of LEV is unproblematic and certainly recommendable, given the high costs of a potentially lifelong therapy. But substitution of a generic version of LEV for the brand drug, or for another generic version of LEV, should only be undertaken after careful consideration, and in the case of seizure freedom without (severe) side effects it should be strictly avoided, because seizure freedom is of great value for both the patient and the national economy and should not be jeopardized.

P 4

#### Bidirectional interactions between progestins and Valproate, Lamotrigine and Carbamazepine monotherapy in women with epilepsy

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Hormonal contraceptives in combination with antiepileptic drugs in women with epilepsy can lower the efficiency in both ways such as seizure susceptibility and unintended pregnancies

#### Methods and Materials:

Ninety-one women on hormonal contraception were included. 61 women with epilepsy treated with LTG (n=33), VPA (n=23) and CBZ (n=5) and 30 healthy women. Blood samples were drawn during menstruation and between day 14 and 21 of the menstrual cycle. The technique used for quantitative simultaneous determination of 6 progestins in human plasma was online solid-phase extraction-high performance liquid chromatography-tandem mass spectrometry (online SPELC-MS/MS). Since most variables were not normally distributed, results were calculated with non-parametric tests using Kruskal-Wallis-Test and Wilcoxon-Test.

#### Results:

LTG serum levels were decreased significantly during on-phase compared to offphase (4.7 [1.1-21.3] vs. 1.8 [0-22.9] µg/ml,  $p=0.002$ ). On distribution of HC into progestins following differences occurred: LTG serum level decreased on drospirenon significantly (2.9[1.6-4.8] vs. 1.4[0.9-2.8] µg/ml,  $p=0.018$ ) and on levonorgestrel was a tendency for reduction (7.1[3.5-17.1] vs. 2.1[0-10.6] µg/ml,  $p=0.068$ ) during on-phase compared to off-phase. On gestoden there was no change in LTG serum level (6.3[1.1-21.3] vs. 1.9[1-22.9] µg/ml,  $p=0.59$ ).

#### Discussion:

The study shows an inhibiting effect of particular progestins on AEDserum levels which might increase seizure risks. In part the results for LTG serum concentra-

tion varied with different progestins. Of note, gestoden does not seem to interact with LTG and therefore could be a suitable progestin for WWE. Drospirenon and presumably levonorgestrel could increase seizure susceptibility and the risk of contraceptive failure due to reduction of LTG and their own serum concentrations.

P 5

### **Dose dependent adverse effects of Sodium channel blocking antiepileptic drugs: A comparison of Oxcarbazepine and Lacosamide**

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#### **Aims:**

The entity of available antiepileptic drugs has increased in the last 20 years, some implementing new mechanisms of actions, others offering a variation of well-known mechanisms, for example blocking of sodium channels. The purpose of this work was to compare the tolerability of oxcarbazepine (OXC) and lacosamide (LCM), two second generation sodium channel blocking antiepileptic drugs.

#### **Methods:**

Retrospective data from 60 electronic patient charts are evaluated based on inclusion criteria of a) focal epilepsy, b) uncontrolled seizures with prior medication, c) new introduction of either unretarded OXC (n1=21) or LCM (n2=39). Data analyzed are dosages at titration, maximal tolerated dosages, types of adverse effects occurring during titration in dependence on dosage and adverse effects leading to drug withdrawal. We divided both groups of patients in a high-dose and a low-dose subgroup. The limit for low-dose subgroups was 200mg/d in LCM-treatment and 1200mg in OXC-treatment.

#### **Results:**

Overall occurrence of adverse effects was in OXC treatment with 76% considerably higher than in LCM treatment (33%), the rate of withdrawal due to adverse effects was 23% OXC-treatment versus 12% in LCM-treatment.

Especially low-dose treatment with LCM showed a good tolerability, adverse effects occurred in 11%, mainly CNS-related adverse effects like dizziness in 6%, drowsiness, unsteady gait and impaired vision in 3% each. However, in 77% of all treatments, a dose of 200mg/d did not prove sufficient to achieve seizure freedom. In the LCM high-dose treatment group, adverse effects occurred in 30%, cardinal effects were dizziness and tremor, each in 13%. Drowsiness and impaired vision occurred in 3% each.

In low-dose treatment with OXC, 24% of patients

suffered from adverse effects, namely drowsiness, 5% of them also stated unsteady gait. In 56%, the dose needed to be increased above 1200mg/d. In this group, adverse effects occurred in 85%, especially impaired vision (54%), followed by dizziness (23%), rarely, drowsiness, dysarthria and hyponatraemia appeared in 8% each.

#### **Conclusion:**

LCM shows as predictable a profile of adverse effects, which qualitatively resembles those of OXC, with the exception of tremor which is not a side effect of OXC, and of hyponatriemia which is found only with use of OXC. This retrospective comparison suggests better tolerability of LCM when comparing unretarded formulations of both drugs.

P 6

### **Effectiveness and side effects of perampanel: a first utilization study**

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#### **Aims:**

Perampanel(PER) is a highly selective, non-competitive AMPA receptor antagonist that recently received approval from the European Medicines Agency as an adjunctive treatment in patients aged  $\geq 12$  years with partial-onset seizures, with or without secondarily generalized. The aim of our study was both to investigate dose-related effectiveness and potential side effects of PER in patients with refractory partial-onset epilepsy.

#### **Methods:**

We retrospectively analyzed data of 19 patients (4 women) with refractory partial-onset epilepsy who initially received 2mg PER as an inpatient treatment since September 2012. Two mg dose increase was carried out every 2 weeks. We assessed outcome data by a direct telephone interview after a mean follow-up of 3.7 months.

#### **Results:**

Details of all patients included in the study are given in **table**. The mean age was 37.7 +/- 13.4 years (range 20-60), mean duration of epilepsy was 23.7 +/- 13.6 years (range 8-56). Ten patients (52.6%) suffered from temporal lobe epilepsy, two patients (10.5%) had the diagnosis of Lennox-Gastaut syndrome. Eighteen patients (94.7%) had a history of secondarily generalized seizures. Mean number of previous antiepileptic drugs (AED) was 9 +/- 3.7 (range 2-15). Mean number of concurrent AEDs was 1.9 +/- 0.7 (range 1-4), seven patients (36.8%) had a co-medication with lamotrigine. Nine patients (47.4%) already received 8-12mg PER per day

at time of follow-up. Four patients (21.1%) had to stop PER, two of them (10.5%) due to side effects such as depression, ataxia, dizziness, aggressiveness or agitation. These two patients reached doses of 4 and 12mg, before they discontinued. One patient had to decrease dose from 10 to 8mg because of dizziness. Side effects did not persist after discontinuation or reduction of PER. Twelve patients (63.2%) reported any side effects at all. No patient became seizure free, but 26.6% of patients who continued PER had a decrease of seizure frequency > 50%. They sustained a dose between 4 and 8mg. 33.3% of the patients had a decrease of seizures frequency < 50%, but still observed an effect. Only one patient reported an increase of seizure frequency.

### Conclusions:

Despite a small sample size our study shows a clear therapeutic benefit of a new AED even in patients with a large number of previous AED. PER might be effective in these difficult-to-treat patients and should be considered as therapeutic option. Side effects seem to be rare but might cause discontinuation

P 7

### Eslicarbazepinacetate instead of levetiracetam in patients with symptomatic epilepsy due to glioblastoma

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### Aim:

Patients with glioblastoma multiforme suffer in 20-50% of cases from symptomatic epilepsy. The choice of anticonvulsant medication heavily influences the patient's quality of life mainly due to tolerability, in addition to control of seizure frequency. In patients with glioblastoma and symptomatic epilepsy, we switched anticonvulsant medication due to adverse effects from first-line levetiracetam to eslicarbazepineacetate and monitored accompanying subjective changes in quality of life.

**Table:** Details of all patients included

NO.	AGE	SEX	ES	E0	ED	ST	GTC	PAED	Follow-up (month)	Co-AED	SEF	EF	PER (mg)	VNS	MR	DIS
1	54	1	1	6	48	3	1	10	10	1	1	1	10	2	2	2
2	20	2	2	9	11	3	1	11	11	2	2	3	4	2	2	2
3	26	1	2	15	11	3	1	06	06	2	1	2	4	2	2	2
4	50	2	2	38	12	3	2	04	04	2	1	u.	8	2	2	2
5	37	2	1	7	30	3	1	10	10	2	2	0	12	1	2	1
6	24	1	2	10	14	3	1	10	10	3	1	1	10	1	2	2
7	49	1	1	5	44	3	1	14	14	1	1	2	8	2	2	2
8	27	1	1	1	26	3	1	10	10	2	2	u.	2	2	2	1
9	49	1	1	33	16	2	1	03	03	1	2	3	2	2	2	2
10	22	1	1	14	08	3	1	09	09	2	2	u.	4	2	2	2
11	64	1	2	8	56	3	1	13	13	2	2	u.	4	2	2	2
12	47	1	1	16	31	3	1	10	10	2	2	1	6	2	2	2
13	50	1	1	27	23	2	1	02	02	1	2	3	10	2	2	2
14	35	2	1	17	18	3	1	12	12	1	1	3	4	2	2	1
15	40	1	2	23	17	2	1	08	08	3	2	1	4	2	1	2
16	32	1	1	14	18	3	1	02	02	2	2	2	8	2	2	2
17	23	1	3	8	15	3	1	15	15	3	2	1	8	1	1	2
18	21	1	3	7	14	5	1	09	09	2	2	2	6	1	1	2
19	46	1	3	7	39	5	1	07	07	3	1	3	12	1	1	1

Sex: 1=male, 2=female; ES=epilepsy syndrom, 1=TLE, 2=ETLE, 3=others; E0=epilepsy onset; ED=duration of epilepsy; ST=seizure types; GTC=generalized tonic clonic, 1=yes, 2=no; PAED=previous AED; SEF=side effects, 1=yes, 2=no; EF=effect, 1=<50%, 2=>50%, 3= no effect on seizure frequency, 0=increase of frequency, u= unknown; PER=Perampanel in mg; VNS= Vagus-Nerve-Stimulator, 1=yes, 2=no; MR=mentally retarded; DIS=Discontinuation of PER.

### Methods:

In seven patients initially treated with levetiracetam suffering from severe fatigue, daytime sleepiness, depressive episodes and/or emotional incontinence, we switched the anticonvulsant medication. We changed to eslicarbazepineacetate in individual end doses of 800-1200mg/day. We controlled changes in quality of life (QOL) before and after drug switching using an adapted questionnaire based on the Liverpool Adverse Events Profile consisting of 19 items that could be al-

located to seldom (1 point i.e. never a problem), rare (2 points), sometimes (3 points), and always (4 points i.e. always a problem) and two rating scores (0 means extremely bad – 10 means extremely good) concerning health-related quality of life and health status.

#### Results:

No changes of seizure frequency or, respectively, seizure freedom rates were observed. We found significant (Wilcoxon signed rank test,  $p < 0.05$ ) improvement both in scores of the Liverpool Adverse Events Profile (especially in items concerning excitability, fatigue and mood) and of health-related quality of life and health status.

#### Conclusions:

In this open-label pilot study on patients with glioblastoma suffering from symptomatic epilepsy, second line eslicarbazepineacetate administered after prior levetiracetam was found equally effective but with significantly less side-effects. Though off-label in monotherapy, the current data indicate that eslicarbazepineacetate may be a reasonable alternative to levetiracetam in patients with highly severe brain disorders.

P 8

#### First clinical experiences with perampanel

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#### Aims:

To assess data from patients at the Kork Epilepsy Centre, who were treated with add-on perampanel (PER) after the launch in September of 2012.

#### Methods:

Patients on add-on PER were consecutively collected and followed. Seizure outcome and tolerability were assessed. Only patients with a history of at least three months since the initiation of PER were considered. If data were not complete or patient contact was not successful, patients were excluded.

#### Results:

At cut-off in January of 2013, 79 patients had been registered, 41 could be analyzed. The observation period comprised a mean of 3.8 months (range 3 – 5 months). Mean age was 36.2 years (15 – 71 years). PER dosages ranged from 4 to 14 mg (mean 9.2 mg). All patients had PER once daily at bedtime. Thirty-eight patients had focal epileptic seizures, the remaining three patients suffered from Lennox-Gastaut syndrome. The monthly rate of generalized tonic-clonic seizures dropped by 30%. Other seizures were reduced by 36%. Eight patients were seizure-free for at least one month

(19.5%), 13 more cases were responders (32%). Adverse events were reported in 23 patients (56%), in 5 patients two adverse effects were seen simultaneously. Side effects comprised fatigue ( $n = 16$ , 39%), dizziness ( $n = 8$ , 19.5%), ataxia ( $n = 3$ , 7%) and irritability ( $n = 1$ , 2%). PER dosages in patients with adverse events ranged between 4 mg and 14 mg (mean 9 mg) compared with 4 mg to 12 mg (mean 9.6 mg) in patients without tolerability problems.

#### Conclusions:

Our first clinical experiences with add-on PER in a highly selected group of difficult-to-treat epilepsies are promising.

P 9

#### GRAP – The German registry of antiepileptic drugs and pregnancy – an explorative interim report

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#### Aims:

The German Registry of Antiepileptic Drugs and Pregnancy investigates pregnancies with exposition to anti-epileptic drugs (AED). The prospective study collects data of epilepsy-specific and general teratogenic risk factors, and aims at the registration of possible infantine major congenital malformations too.

#### Methods:

All women taking AED at the time of conception are included until the 16th week of gestation and are observed until 1 year post partum. The present study concentrates on the cross-sectional comparison between central variables in the years of 2000 until 2012. The sample comprises all registered women ( $N = 819$ ). Recording to scale level the central variables point-biserial correlations were calculated for the identification of possible bivariate relationships. The logistic regression and discriminant analyses were used for detecting a possible predictive contribution of the inclusion year.

#### Results:

The correlative results featured a negative relation between inclusion year and the rate of malformations ( $rpb = -.322$ ,  $p < .01$ ). Furthermore, we found a small significant positive relationship between inclusion year and folic acid prophylaxis ( $rpb = .200$ ,  $p < .01$ ) as well as the breastfeeding rates ( $rpb = .196$ ,  $p < .001$ ). Regarding the anticonvulsant therapy there was no significant relation ( $rpb = -.004$ ,  $p > 0.05$ ). The regression analyzes showed that the predictive contribution of the variable inclusion year was marginally failed regarding to the variable rates of malformations ( $B = -.087$ ,  $p > .05$ ). However, the results of the discriminant analyses emphasize the need of more investigation in regard of the

relationship between inclusion year and rates of malformations ( $\lambda = .885$ ,  $p < .05$ ). The small positive relation of inclusion year and breastfeeding rate was not confirmed ( $B = .05$ ,  $p > .05$ ;  $\lambda = .997$ ,  $p > .05$ ). The inclusion year was not significantly related to the folic acid prophylaxis ( $B = .048$ ,  $p > .05$ ;  $\lambda = .997$ ,  $p > .05$ ) as well as to the anticonvulsant therapy ( $B = -.021$ ,  $p > .05$ ;  $\lambda = .999$ ,  $p > .05$ ).

#### Conclusions:

Our explorative investigation represents a first orientation for further analyzes, although it is subject to certain restrictions. Additional factors (for example, etiology of epilepsy, age and educational grade of the patient) should be considered. However, we conclude that the education of pregnant women with epilepsy develops in a positive direction.

P 10

#### Hepato- and encephalopathy under therapy with retigabine

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#### Aims:

Description of hepato- and encephalopathy with excessive increase of liver enzymes after initial and re-exposure to retigabine (RTG)

#### Case Report:

In a 21-year-old patient with therapy-resistant temporal lobe epilepsy due to bilateral hippocampal sclerosis after non-paraneoplastic, VGKC and GAD-Ab positive limbic encephalitis in 2004, therapy with RTG 300 mg/day was started in March 2012 (add-on to LTG 550, PGB 600 CLB 15 and sertraline 50 mg/day). In view of good tolerability, normal laboratory results and satisfying anticonvulsant effect (seizure frequency halved), the dose was increased to 400 mg/day 3 months later. Clinical symptoms appeared approx. 3-4 weeks later, with headache, dizziness, dysarthria, cognitive disturbances, and finally confusion, nausea and recurrent vomiting. Given massively elevated liver enzymes (AST 1006, 1321 ALT, GGT 254 U/l) and bioptic evidence for destruction of hepatocytes, drug-induced hepatopathy was suspected and RTG and sertraline were discontinued. In the following, however, hepatitis E infection was diagnosed because of the detection of slightly elevated corresponding IgM antibodies. Clinical symptoms disappeared and liver enzymes turned normal. Since the seizure situation worsened again after discontinuation of RTG, a re-exposure with 300 mg/day was started on Oct 20, 2012, assuming that the former symptoms did not result from the medication but from hepatitis E infection. After 2 weeks, however, an increase of liver enzymes was again recognized (AST 56, ALT 59, GGT 76

U/l). In the same time, the Dept. of Hepatology revised their judgement. Following a new assessment of antibodies (which now came out normal) they diagnosed again a drug-induced hepatopathy as the most probable cause. RTG was therefore finally discontinued on Nov 6, 2012. The patient was clinically asymptomatic, but liver enzymes still increased until mid-November (AST 407, ALT 833, GGT 76 U/l) before they returned to normal by December.

#### Conclusions:

1) RTG most likely caused the hepatopathy; this is supported by its recurrence after re-exposure. 2) Hepato- and encephalopathy may manifest even 3 months after initial exposure at hitherto unremarkable laboratory results and apparently well tolerated RTG medication. 3) This latency, the early increase of liver enzyme after re-exposure and the further rise after discontinuation of RTG speak against a direct toxic effect and indicate a rather idiosyncratic effect.

P 11

#### Lacosamid in childhood – results of a retrospective analysis

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<sup>1</sup> Münster, <sup>2</sup> Köln, <sup>3</sup> Hannover, <sup>4</sup> Düren, <sup>5</sup> Klein-Wachau, <sup>6</sup> Bonn, <sup>7</sup> Heidelberg, <sup>8</sup> Kiel, <sup>9</sup> Herdecke, <sup>10</sup> Traunstein, Germany*

#### Subject:

Effectiveness and toleration of Lacosamid (LCM) in children with epilepsy under 16 years of age.

#### Methods:

110 children undergoing treatment with Lacosamid were selected from 10 epilepsy outpatient clinics in Germany and data was evaluated for a retrospective analysis of the above subject.

#### Results:

61 boys; age at onset of LCM treatment: 3 months – 15.3 years, median age 9.1 years. 49 girls: age at onset of LCM treatment: 3 months – 15.9 years, median age 10.2 years.

The following forms of epilepsy were present: symptomatic focal (n=56); LGS (n=13); GM (n=8); CSWS (n=6); metabolic disorder (n=5); chromosome defect (n=9); Doose Syndrome (n=1); BECTS (n=1); absence epilepsy (n=1); focal motor (n=1); non-classifiable (n=10). All children had previously been treated unsuccessfully with all AED as a monotherapy or combination therapy. LCM initial dosage: 0.5 mg/kg body weight (bw) – 8 mg/kg bw, 3.25 mg/kg bw on average. Dosage increase: dosage was increased weekly by the amount of the initial dosage (2-30 days). LCM final dosage: 4 mg/

kg bw – 20 mg/kg bw, 9.6 mg/kg bw on average.

#### **Side effects:**

73 children tolerated the LCM therapy at the described dosages with no side effects; the remaining children showed no specific conspicuous side effects.

An ECG conducted before (n=45) and during LCM therapy (n=34) was normal. Co-medication: differed considerably; co-medication acting on sodium channels: n=78. 10 children received LCM as a monotherapy; the co-medication was reduced for 25 children and at least one AED was discontinued for 36 children.

#### **Therapy effect:**

26 children were seizure free (24.3 %); 75 % seizure reduction in 14 children (13.0 %); 50 % seizure reduction in 21 children (19.6 %); 32 children experienced no benefit (29.9 %). The EEG was normalized in 11/110 children, 29 improved and 67 children showed no change on the EEG.

Seizure-free children (n=26): symptomatic focal epilepsy (n=11), the remaining children different epilepsy syndroms. 6 seizure-free children had a LCM serum level of 2.3 µg/ml – 18.8 µg/ml (average: 10.3 µg/ml).

#### **Co-medication:**

Primary monotherapy (n=3); 10 children undergoing combination therapy received an additional AED acting on the sodium channels (OXC, LTG, DPH).

#### **Summary:**

LCM is also very well tolerated by children under 16 years of age both in monotherapy and in combination therapy. 24.3 % of our group were subsequently without seizures, 13 % showed a seizure reduction of 75 % on LCM. The therapeutic effect appears to be enhanced without increasing side effects when LCM is combined with another AED affecting sodium channels.

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#### **Lacosamide-induced ictal asystole: a case report**

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#### **Introduction:**

Ictal asystole is defined as the transient cessation of cardiac electrical activity during an epileptic seizure. A predisposition to falls has been reported in many cases. It might be mistaken for convulsive syncope with possible fatal implications. It is best identified by long-term-EEG recording with simultaneous ECG. Treatment needs to consider both careful anticonvulsant therapy as anticonvulsant drugs can affect cardiac conductive tissue, and the implantation of a cardiac demand pacemaker. We describe a patient with prior asymptomatic ictal bradycardia who developed ictal asystole after initiation of lacosamide.

#### **Clinical case:**

A 45 year old woman with a history of a cryptogenic pharmacoresistant epilepsy was admitted to the Neurology Department after an unobserved fall. Her husband found his wife unconscious at the floor. After a few seconds she was already awake and oriented, but she suffered from emesis and headache. She remembered that she had vertigo just before loss of consciousness.

On admission she was taking levetiracetam 1500mg/day and lacosamide 400mg/day, the latter since some months. After onset of lacosamide she experienced repeated falls with preceding vertigo.

Neurological examination was normal except for a right hearing attenuation, Weber test lateralized to the left and an anosmia. The CCT showed acute minor traumatic coup- and contre-coup lesions in the right occipital and left frontal pole and a right transversal petrosal bone fracture. The emergency 12 lead ECG was normal. Repeated asystole of more than 20 s were registered in the cardiac telemetry, otherwise no intrinsic cardiac disease was detected. The interictal longterm-EEG indicated bilateral foci in the temporo-posterior region. An epileptic seizure was registered with left temporo-posterior onset, which was followed by an asystole of a duration of 22 s. Therapy with lacosamide was stopped. During the remaining hospitalisation no more epileptic seizures occurred under levetiracetam monotherapy. Because of the prior known seizures associated with bradycardia, the established pharmacoresistance, the lack of options for epilepsy surgery, and the increased risk of falls and risk of SUDEP, a pacemaker was implanted.

#### **Conclusion:**

In this case, the asystole was epileptic and lead to recurrent falls, the last one with traumatic brain injury. The transformation of ictal bradycardia to asystole was probably due to therapy with lacosamide. This has been described for other antiepileptic drugs before, but to our knowledge this has not been described for lacosamide. Cardiac side effects of lacosamide are rare. In the literature, patients with diabetic neuropathy and one patient with epilepsy have been reported. Our case demonstrates the need for careful use of lacosamide in patients with known cardiac dysrhythmia.



P 13

### Long term treatment with oral methylprednisolone pulse therapy in a 9 year old boy with Landau-Kleffner syndrome – a case report

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#### Aim:

We present a 9 year old boy with Landau-Kleffner syndrome. At 4 years of age, the patient developed clinically significant symptoms whereby he failed to respond to requests and showed worsening of expressive speech and ESES in sleep-EEG. After initial effective treatment with sulthiame and clobazam the eeg worsened and symptoms reappeared. Further treatment with valproate and levetiracetam showed no success, so that we started oral methylprednisolone pulse therapy (20mg/kg/d on three consecutive days with intervals between 1-5 weeks) at the age of nearly 7 years, with immediate clinical and electrophysiological effect. We report on the course of the therapy taking into account electrophysiological and neuropsychological data and potential side-effects.

#### Methods:

Case report with documentation of electrophysiological (overnight eeg), clinical (weight, height, blood pressure, laboratory results, ophthalmologic and cardiologic examination) and neuropsychological data at regular intervals over a treatment course of 30 months (39 pulses of methylprednisolone).

#### Results:

Treatment with repetitive high-dose oral methylprednisolone pulse therapy showed an immediate and sustained clinical and electrophysiological effect. Temporary dose reduction or enlargement of the treatment interval over 5 weeks led to electrophysiological and clinical impairment, thus the treatment remained unchanged. Until now (after 30 months of treatment) the patient has not shown any side effects regarding weight gain, growth, glaucoma, hypertension, cardiac hypertrophy or endocrinological problems. Neuropsychological data improved (SON-R IQ 69 --> 88) and the sleep eeg remained widely normal without signs of ESES.

#### Conclusion:

In our presented case long term high-dose oral methylprednisolone pulse therapy (20mg/kg/d on three consecutive days per pulse) with a treatment interval of 4-5 weeks was well tolerated and highly effective in a case of difficult-to-treat Landau-Kleffner syn-

drome. Oral methylprednisolone pulse therapy could be an efficient and safe treatment option in the long-term treatment of Landau-Kleffner syndrome.

P 14

### Perampanel-Intoxikation mit der 25,5-fachen Tagesdosis

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Perampanel ist eine neue Substanz mit Zulassung als Antikonvulsivum für Patienten mit fokalen Epilepsien. Häufige Nebenwirkungen sind Schwindel, Müdigkeit, Zephalgien und zerebelläre Symptome. Wir berichten über einen Fall eines Suizidversuchs mit Perampanel mit der 25,5-fachen Tagesdosis (204mg).

Eine 34-jährige Patientin mit pharmakoresistenter symptomatischer Epilepsie bei genetisch gesicherter Tuberöser Sklerose, die mit LEV, TPM und LTG nicht anfallsfrei wurde, erhielt im Rahmen einer offenen Phase-III-Studie 8 mg Perampanel. In suizidaler Absicht ingestierte die Patientin 204 mg der Studiensubstanz und entwickelte binnen 2 Stunden eine quantitative Bewusstseinsstörung mit Somnolenz und dann eine qualitative Bewusstseinsstörung mit psychomotorischem Erregungszustand und situativer Verknennung für die Dauer von 2 Tagen. EKG-Veränderungen (QTc-Zeit) wurden nicht beobachtet. Im EEG zeigte sich eine generalisierte Verlangsamung. Das EKG zeigte eine normwertige QTc-Zeit. Das Labor zeigte normwertige Befunde bzgl. Blutbild, Leber-/Nierenwerte, CK, LDH, CRP. Die Bewusstseinsstörung bildete sich nach 2 Tagen vollständig zurück. Im Verlauf wurde psychiatrisch die Diagnose einer depressiven Störung gestellt. Mögliche Auslöser der depressiven Symptomatik, Interaktion von Perampanel mit der Komedikation sowie das therapeutische Vorgehen bei einer Intoxikation mit Perampanel werden diskutiert.

P 15

### Severe epilepsy in children – is pulsatile methylprednisolone an effective treatment?

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#### Aim:

There is limited data on corticosteroid therapy in severe paediatric epilepsy, other than West syndrome. This multicentre retrospective study aims to evaluate the efficacy of pulsatile methylprednisolone treatment in this challenging group.

**Methods:**

Patients were treated with oral methylprednisolone pulses between 1999-2011 at the University children's hospital in Heidelberg, Germany, and the Centre for Epilepsy in Kork, Germany. A single dose of 20 mg/kg/day was given for 3 consecutive days weekly for at least 4 weeks and intervals between pulses were increased thereafter. In order to evaluate efficacy, response, relapse rate, and adverse effects were assessed. Response to treatment was defined as cessation or clear improvement of EEG status in combination with a significant seizure reduction.

**Results:**

59 patients (29 female, aged 0,3 - 13 years, median 5,2) were included. Epilepsy aetiology was structural-metabolic in 27%, genetic in 20% and unknown in 53%. 47/59 (80%) patients suffered from encephalopathy. A total of 1 to 52 pulses (mean 12) were applied with a treatment period from 1 to 150 weeks (mean 23). Follow-up ranged from 0 to 10 years (mean 2).

21/59 (36%) patients responded to pulsatile methylprednisolone therapy, while 38/59 (64%) patients did not respond. 14/31 (45%) of patients with epilepsy of unknown aetiology responded, while only 3/16 (19%) with structural-metabolic cause and 4/12 (33%) with a genetic cause responded. 16/47 (34%) patients with encephalopathy responded to therapy. In particular, 6/17 (35%) patients with electrical status epilepticus during slow sleep (ESES) responded to therapy.

Of those who responded, 7/21 (33%) patients relapsed in EEG or clinically after 1 to 35 months (mean 11) following termination of treatment.

At the end of therapy 73% of patients had experienced adverse effects. 19/59 had recurrent infections, 25/59 had unspecific symptoms (i.e. tiredness, unstable mood), 6/59 had metabolic side effects (i.e. weight gain), 4/59 had cardio-vascular side effects (i.e. transient bradycardia). 10/59 had severe adverse reactions, such as Cushing's disease, osteoporosis, nephrocalcinosis, or premature puberty.

**Conclusion:**

The value of oral pulsatile methylprednisolone in the treatment of severe epilepsies in children still remains unclear, considering response rate (21/59 = 36%) and relapse rate (7/21 = 33%) vs. rate of adverse effects (43/59 = 73%). However, some individuals had a clear and safe benefit from therapy.

P 16

**Sex differences in anticonvulsant therapy and side effects in patients with epilepsy – a cross-sectional study**

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**Aim:**

Sex differences have been found in many pharmacodynamic and -kinetic aspects. Furthermore, men (M) and women (W) differ in quantity and quality of reporting adverse events. Concerning antiepileptic drugs (AED), women experience cutaneous reactions on lamotrigine (LTG) or carbamazepine and weight gain on valproate more often. The aim of this study was to systematically evaluate differences in AED dosage, plasma concentration and adverse events in men and women with epilepsy.

**Methods:**

Using a semistructured interview, we obtained data regarding epilepsy syndrome, AED and side effects in epilepsy outpatients from a large academic institution. Additionally, plasma levels of the patients' current AED were routinely determined.

**Results:**

302 patients were included into the study (161 W, 53.3%). The amount of patients with idiopathic generalized epilepsy (IGE) was higher among women (W: 32.3%; M: 10.6%,  $p < 0.001$ ). Partial epilepsies were more frequent in men (M: 85.1%; F: 58.4%;  $p < 0.001$ ). More women than men were treated with monotherapy ( $p = 0.008$ ). On average, men took 1.62 ( $\pm 0.98$ ) AED while women took 1.41 ( $\pm 0.75$ ),  $p = 0.022$ . Considering mono- and polytherapy, no sex difference in choice of substances was found. In monotherapy, more women were treated with LTG (W:  $n = 36$ , 36.4%; M:  $n = 13$ , 20%;  $p = 0.036$ ) and more men received oxcarbazepine (W: 3, 3%; M: 8, 12.3%;  $p = 0.027$ ). There were no differences in dosage and plasma concentration of any AED in monotherapy. 69.2% of all patients (W:  $n = 119$ , 74.4%; M:  $n = 90$ , 63.9%) ever experienced adverse events, 40.1% within the last 3 months (W:  $n = 70$ , 43.5%; M:  $n = 51$ , 36.2%). Women and men reported different adverse events: men mentioned gait disturbances more frequently ( $p < 0.001$ ). Women more often complained about tiredness ( $p = 0.049$ ), impaired vision ( $p = 0.016$ ), skin reactions ( $p = 0.004$ ) and weight gain ( $p = 0.025$ ).

**Conclusions:**

IGE is more frequent in women, as partial epilepsy is in men. Epilepsy syndrome influences the choice of AED, this could explain the substance differences in monotherapy and the finding that men took more AED than women. We found significant differences in adverse events between men and women with epilepsy. Some are congruent with literature (skin reactions,

weight gain), while others have not yet been described and require further systematic research to be confirmed and explained. These findings encourage to take patient's sex into further account when choosing the appropriate AED and evaluating reported side effects.

P 17

### Stiripentol in adults with SMEI or other epilepsy-syndromes

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#### Aim:

Stiripentol has been approved by the EMEA in 2007 as an orphan drug for add on-treatment of Severe Myoclonic Epilepsy of Infancy (SMEI/Dravet-syndrome). In Germany it is available since January 2008.

Stiripentol modulates GABAergic neurotransmission and has pharmacokinetic interactions with several antiepileptic drugs (clobazam, carbamazepine, valproate, phenytoin), raising their serum-levels by inhibiting their hepatic clearance.

There is little experience with stiripentol in adult patients with SMEI or other epilepsy-syndromes. As the treatment of seizures in SMEI is challenging, we report our observations in those patients.

#### Patients and methods:

Since 2008 we treated 14 pats. (6 women, 8 men; age 20-50 years; follow up 6-40 months, median 24 months). 8 pats. showed typical clinical features of SMEI (up to now SCN1A-mutation is proved in 5 of them). 6 pats. had pharmaco-resistant multi-/focal epilepsies with daily seizures (median 8 previous unsuccessful AED-treatments). The severity of these epilepsies and lack of treatment options justified off label-use.

Dosage of stiripentol was 750-3000 mg (median 2000 mg) /d, antiepileptic comedication predominantly consisted of clobazam, valproate and topiramate.

#### Results:

In the SMEI-group all 8 pats. responded to stiripentol (reduction of seizure-frequency > 50%), 4 pats. had a reduction >75%. 3 of 6 pats. with other epilepsy-syndromes responded to stiripentol. The success was stable over the whole follow up-period.

The tolerability of stiripentol was good in general, it had to be withdrawn in two pats. due to interactions with comedication (bromide, carbamazepine).

#### Discussion and conclusion:

In our small group effectiveness of stiripentol in adult SMEI is very good and comparable to previous results in children. Tolerability was good and there was no trend of developing tolerance. Stiripentol seems to be a

good option in focal epilepsies as well, but off label use has to be justified carefully.

Further studies are necessary to evaluate stiripentol in different epilepsy-syndromes.

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### Sustained seizure remission on perampanel in progressive myoclonic epilepsy (Lafora disease)

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#### Aim:

To provide initial evidence that add-on treatment with perampanel might be highly effective in progressive myoclonic epilepsy (PME) such as Lafora disease.

#### Case report:

Initially this female patient presented in 2005 at the age of 14 years with myoclonus and generalized tonic-clonic seizures. During a video-EEG-monitoring interictal generalized spikes and polyspikes as well as three seizures with a generalized onset were recorded. There was no evidence for a focal EEG seizure onset. Throughout the last seven years no seizure remission could be achieved on various combinations of anticonvulsant drugs. Furthermore, disturbance in gait (ataxia) and a cognitive decline were rapidly progressing in this patient. Subsequently a mutation in the EPM2A gene and thus a diagnosis of Lafora disease was established.

Since a generalized, convulsive status epilepticus in April 2012 the anticonvulsive medication was switched to valproate 2,000mg/d, levetiracetam 4,000mg/d, clonazepam 9mg/d, piracetam 12,000mg/d, zonisamide 600mg/d and a ketogenic diet. The patient continued to suffer from daily myoclonus and daily to weekly generalized tonic-clonic seizures. In September 2012 the patient was admitted due to a seizure exacerbation and was started on an adjunctive therapy with perampanel, which was titrated up to 8mg/d. Other anticonvulsants were not changed at this point in time. On follow-up in January 2013 the parents reported a sustained seizure remission without myoclonus and generalized tonic-clonic seizures for more than 3 months.

#### Conclusions:

Perampanel is a selective, non-competitive antagonist of AMPA-type glutamate receptors and recently licensed as adjunctive therapy for the treatment of refractory focal onset seizures. There is evidence for effectiveness in generalized epilepsies and phase III studies for this indication are on the way. Our case illustrates that perampanel might be a valuable option for treatment in PME. Considering the impressive efficacy we suggest a prospective, multicenter study evaluating perampanel in PME.

## Valproat Induced Hyperammonemic Encephalopathy (VHE)– case vignette and review of the literature

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### Introduction:

VHE was first described by Coulter in 1980 [1]. Recent data have shown an incidence rate of 0.13% (11/8.372) [2].

### Patient:

A 35-year-old female patient suffering from non-lesional intractable left sided epilepsy with simple partial seizures with motor and aphatic symptoms, complex partial seizures, rare secondary generalized tonic clonic seizures and repetitive status epileptic since the age of 28 years was admitted to the epilepsy monitoring unit due to a new series of simple partial seizures with aphatic symptoms. On admission, her regular antiepileptic drug (AED) treatment included Levetiracetam 3000 mg/d, Primidone 1125 mg/d, Pregabalin 300 mg/d and Lacosamide 200 mg/d respectively. Due to well video-EEG-documented series of simple partial seizures additional therapeutic steps were needed.

Lorazepam 4 mg IV followed by Phenytoin 750 mg IV (maintenance dose of 2250 mg per day) was initiated. After failure to control seizures, 2000 mg Valproic acid (VPA) IV (maintenance dose of 2500 mg per day) was started. The patient remained seizure free for 3 days but developed clinical deterioration with psychomotor slowing, perseverations and somnolence. EEG exhibited slowing of the background and high amplitude generalized delta activity. Liver function tests were normal. Serum ammonia was moderately elevated (186 µmol/l; normal 11- 48 µmol/l). The diagnosis of VHE was made. Due to withdrawal of VPA, the patient improved clinically, unfortunately, seizure frequency increased again. Consecutively, the patient was transferred to the intensive care unit and anaesthetic therapy was initiated.

### Discussion:

The patient developed moderate encephalopathic features on a combination of VPA, Phenytoin, Levetiracetam and Primidone. VHE occurs more often in combination with multiple AEDs [3]. Other possible risk factors include urea cycle disorders, carnitine deficiency or protein rich diet [4]. VHE is generally characterized by an acute onset of impaired consciousness, focal neurologic symptoms and increased seizure frequency [5]. The exact mechanisms are unclear, but relate to the accumulation of toxic VPA metabolites and elevated ammonia levels [6]. Treatment of VHE includes discontinuation of VPA and supplementation of L-Carnitine [7]. In general, complete recovery is common.

### Conclusion:

VHE requires early diagnosis via clinical assessment and EEG monitoring as well as timely management. Discontinuation of VPA usually leads to complete resolution of VHE.

### References:

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7. Lheureux et al., 2009.

P 20

**Bilateral cortical representation of orgasmic ecstasy localized by depth electrodes**

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**Introduction:**

Traditional studies on the brain basis of human sexual arousal and orgasm are mainly based on patients presenting epileptic seizures with sexual auras (SA). The latter are strongly associated with temporal lobe epilepsy (TLE) of the right hemisphere. However, direct electrical stimulation (DES) of cortical regions remains the gold standard for localization of brain functions. While sexual arousal, in one case resulting in an orgasm, had been evoked during DES of the right mesial temporal lobe, and the septal region, isolated orgasmic ecstasy evoked by DES are not reported in the literature. We report the first case of isolated bihemispheric reproduction of orgasmic ecstasy by stimulation via depth electrode in a patient implanted for epilepsy.

**Case Report:**

To better define the epileptogenic zone(s), an invasive electrode study was performed in a 49 year-old, right-handed woman. In the course of DES for cortical mapping the patient reported an orgasmic ecstasy following the stimulation of the left hippocampus at 3mA. This stimulation was followed by an 18-second afterdischarge over the left hippocampus, the parahippocampal gyrus and the anterior-inferior insula. Stimulation of the right hippocampus at 1mA generated the same orgasmic sensation and triggered a 45-second seizure discharge over the right hippocampus, parahippocampal gyrus, temporal pole and anterior insula.

**Discussion:**

This observation provides further insight into the generation of orgasmic ecstasy. For one, such a response can be evoked bilaterally. Second, activation of a large network (hippocampus, parahippocampal gyrus, temporal pole and anterior insula) appears to be necessary in order to generate such sensations, conciliating past observations and more recent ones .

**Conclusion:**

Observation from this case study and previously reported cases suggest that SA, or at least isolated orgasmic ecstasy involve the activation of a network comprising the amygdala, the hippocampus, the parahippocampal gyrus, the temporal pole, the anterior inferior insula and the septal area.

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**Impaired neuronal recovery during sleep in “continuous spike waves during slow wave sleep”**

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**Aims:**

Continuous spike waves during slow wave sleep (CSWS) is characterised by the electrophysiological pattern of electrical status epilepticus during slow wave sleep and multimodal neuropsychological deficits. A spike waves density of more than 50% seems to be necessary for causing the neuropsychological deficits, and the localisation of the spike wave focus was related to specific neuropsychological deficits. A causal relationship between the spike waves and the neuropsychological deficits is generally accepted, but its pathophysiological mechanisms are still largely unknown.

The synaptic homeostasis hypothesis predicts that the strength of cortico-cortical synapses is downscaled during slow wave sleep. In the EEG, this synaptic downscaling is best reflected by the overnight decrease of the slope of slow waves and has been linked to recovery and higher cognitive functions. In a previous study, we have shown that the slope (at a central derivation) did not decline over night in CSWS patients. Here, we investigate whether this impairment of the slope decrease is related to (1) the density of spike waves and (2) their localisation.

**Methods:**

In a retrospective study, we calculated the slope of slow waves (<2 Hz) in the first and the last hour of sleep (19 EEG electrodes) in 14 patients with CSWS (age 3.1-13.5 y). (1) The density of spike waves was determined in a spike wave index (SWI) for the first 30 minutes of sleep (% of seconds affected by spike waves). (2) The spike wave focus was defined as the localisation of the electrodes with the highest amplitude spike waves (measured in the source derivation).

**Results:**

(1) The SWI was positively correlated ( $p < 0.05$ ) with the impairment of the slope decrease over night. Hence the higher the SWI, the less the slope decreased. (2) There was no slope decrease in the electrodes over the spike wave focus. In contrast, there was a significant decrease in the remaining electrodes ( $p < 0.05$ ). As a consequence, the slope of slow waves was steeper in the focus during the last hour of sleep ( $p < 0.01$ ).

**Conclusions:**

In CSWS-EEGs the density and localisation of spike waves are related to the impairment of the physiological decrease of the slope of slow waves. The decrease of the slope, reflecting synaptic downscaling, has been linked to recovery and higher cognitive functions. Thus, the impairment of this process by spike waves could be a potential mechanism for the neuropsychological deficits in CSWS.

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**Impaired slow wave sleep downscaling in infantile spasms with hypsarrhythmia**

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The epileptic encephalopathy West Syndrome is characterized in the EEG by multifocal spike waves and high amplitude slow frequency activity (hypsarrhythmia), that is most pronounced during non-REM (NREM) sleep, and is often accompanied by developmental regression. The underlying pathophysiology of the encephalopathy is unknown and it can be effectively treated with corticosteroids. In the epileptic encephalopathy ESES (electrical status epilepticus in slow wave sleep) it was recently shown that the pathological changes in the sleep EEG impair sleep dependent renormalization of network synchronisation. In healthy individuals, neuronal synchronisation increases during the day, which is reflected in steep slow waves during initial NREM sleep, and decreases back to baseline level in the course of sleep. This renormalization of neuronal synchronicity is thought to be important for

efficient learning the next day. We hypothesised that hypsarrhythmia may also impair the renormalization of neuronal synchronicity in patients with West Syndrome. We analysed retrospectively the overnight EEG of 14 patients (mean age  $6 \pm 2.4$  months) before treatment. In 7 patients we also analysed a follow-up afternoon nap after treatment (after  $3.9 \pm 1.5$  months). The results were compared to 13 (overnight), respectively 5 (nap) healthy age and gender matched control subjects. Overall, the slope of slow waves was significantly steeper in patients compared to control subjects ( $p < 0.05$ ). Furthermore the overnight decrease of the slope from the first to the last hour of NREM sleep was significantly reduced in patients ( $4.6 \pm 2\%$ ) compared to control subjects ( $12.8 \pm 1.7\%$ ,  $p=0.01$ ). Interestingly, the steeper the slope at the beginning of the night, the less the slope decreased overnight ( $R = -0.63$ ,  $p = 0.01$ ). In the control subjects no such correlation was found ( $R = 0.26$ ,  $p = 0.4$ ). After treatment the slope of sleep slow waves did not differ between the patients and the control group. In conclusion, our results show evidence for a hyper synchronisation of neuronal activity in West Syndrome patients, which might be due to a diminished overnight reduction of neuronal synchronisation. Such impaired sleep dependent renormalization of network synchronization may contribute to the developmental regression seen in these patients. Moreover, after treatment with corticosteroids, we found a normalization of the neuronal synchronicity. This work was supported by the Swiss League against Epilepsy (SLgE).

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**Low prevalence of epileptiform discharges after the first seizure**

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**Background:**

EEG provides essential information for the management of patients in whom a first epileptic seizure is suspected because of transient alteration of consciousness. An early EEG may help in the localization of the epileptogenic zone and the syndrome classification, which is important for therapy and prognosis. In adult studies at epilepsy centers, the yield of the first EEG varied between 29% and 55%. We studied whether it is possible to diagnose specific epilepsy syndromes promptly by use of standard clinical methods, electroencephalography (EEG), and magnetic resonance imaging (MRI).

**Methods:**

We investigated 111 patients (male: 72 [64.9%], female: 39 [35.1%]), aged from 19 to 92 years (mean:

50±21), who were referred to our epilepsy centre from 08/2002 till 10/2012 due to the first epileptic seizure (age range at seizure onset: 17 to 90 years, mean: 49±22).

#### Results:

33 patients had normal EEGs (29.7%), in 61 abnormal but non-epileptiform EEG pattern like focal or generalized slow waves were recorded (55%), and 17 showed IED (15.3%). Among the 17 EEGs with detected IED 7 were performed within 12 hours, 3 within 12 to 24 hours, 1 within 24 to 36 hours, and 6 later than 48 hours after the seizure (range: 2 to 14 days, mean: 4). The IED were found in patients who suffered from alcohol withdrawal seizures (EEG > 48h [14d]), symptomatic focal epilepsies due to ischemia (EEG < = 12h), bacterial meningitis (EEG > 48h [2d]), cortical malformation (EEG > 48h [3d]), brain trauma (EEG < = 12h, 24-36h), cerebral neoplasias (EEG < = 12h, > 48h [5d]), and chronic cerebral-vascular disease (EEG 12-24h), cryptogenic focal epilepsies (EEG > 48h [4d]), idiopathic (EEG < = 12 h, > 48h [3d], 12 - 24h, < = 12h, 12 - 24 h) and cryptogenic (EEG < = 12h) generalized epilepsy with grand mal seizures, and from actually non-classifiable grand mal seizures (EEG < = 12h).

#### Conclusion:

In our study population of 111 first seizure patients there was only a 15.3% prevalence rate of IED recorded with the first EEG in a time interval between < = 12 hours and 14 days after the seizure. According to the literature it is recommended to perform an EEG within 24 hours after the first epileptic seizure. But also the duration of the EEG monitoring, the number of repeated EEG recordings, activation methods, and additional electrodes should be considered for an increased detection of IED.

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#### Multizentrische Studie zur Evaluierung einer automatischen Anfallsdetektion für Langzeit-EEG-Ableitungen

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#### Fragestellung:

Langzeit-EEG Ableitungen finden weite Verbreitung etwa in der prächirurgischen Epilepsiediagnostik und der Differenzialdiagnose. Ein hoher Zeitaufwand für das Personal verbunden mit einem hohen Anfallsrisiko für die Patienten fordern neue Ansätze in der Methodik. EpiScan ist ein Echtzeitsystem zur automatischen Erkennung von epileptischen Anfällen in Langzeit-EEG Ableitungen. In einer prospektiven, multizentrischen Studie wurde die Anfallsdetektion unter dem Gesichtspunkt der Verbesserung der Patientensicherheit sowie der Effektivitätssteigerung bei der Analyse des EEGs evaluiert. Parameter wie Sensitivität und Spezifität der Detektionen wurden ermittelt und dienen als Bewertungsgrundlage.

#### Methodik:

Die Studie umfasst 180 konsekutive Patienten aus drei Epilepsie-Monitoring-Units die einem Video-EEG-Monitoring unterzogen wurden. EpiScan bewertet die digitalen Daten des Oberflächen-EEGs in Echtzeit ohne Benutzerinteraktion oder Konfiguration und erzeugt akustische Anfallsalarne sowie EEG-Markierungen für die spätere Auswertung. Ein Anfall wird als „erkannter Anfall“ gezählt, falls sich eine automatisch erzeugte EEG-Markierung innerhalb der Zeitspanne des elektrographisch sichtbaren Anfallsbeginns bis drei Minuten nach Anfallsbeginn befindet. Jede automatisch generierte EEG-Markierung ausserhalb des Anfallszeitraums wird als Fehlalarm gewertet. Fehlalarme, die länger als 30 Sekunden andauern, werden mehrfach gezählt. Sensitivität ist als Quotient aus der Anzahl der erkannten Anfälle zur Anzahl aller Anfälle definiert und wird patientenweise ermittelt. Die Spezifität wird als mittlere Dauer zwischen zwei Fehlalarmen angegeben.

#### Ergebnisse:

Bisher wurden 11'453 Stunden EEG von 149 Patienten aufgezeichnet, bei 64 Patienten wurden Anfälle registriert. Bei 33 Patienten wurde eine Sensitivität von 100 % erreicht, 19 Patienten hatten eine Sensitivität zwischen 99 und 33 %, nur 12 Patienten lagen unter 33 %. Die mittlere Sensitivität über alle Patienten betrug 70 %. Der mittlere Abstand zwischen Fehlalarmen betrug 3,4 Stunden, wodurch sich im Mittel 7 Marker pro Tag ergaben.

#### Schlussfolgerungen:

Die hohe Sensitivität und niedrige Fehlalarmrate von EpiScan erlauben den Einsatz als Unterstützungssystem für die Patientenüberwachung. Die gespeicherten Anfallsmarkierungen geben eine rasche Übersicht über das Langzeit-EEG. Der prospektive, multizentrische Aufbau der Studie zeigt die Anwendbarkeit eines Anfallsdetektionssystems im klinischen Alltag.

P 25

### Onset of ictal tachycardia in relation to intracranial and scalp EEG recordings

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#### Aims:

Ictal tachycardia (ITC) is a well-known phenomenon occurring in 32.9-100% of partial-onset seizures depending on the patient population studied. Leutmezer et al (2003) showed that on average, ITC preceded EEG seizure onset in surface-EEG recordings by 14 s in temporal lobe seizures and by 8 s in seizures with extratemporal origin. We report here the occurrence of ITC in relation to intracranial and scalp EEG onset.

#### Methods:

We screened long-term video-EEG-recordings at the Epilepsy Center Freiburg from the past years for patients with ITC. We retrospectively analyzed the recordings and marked the EEG-onset, the clinical onset and the EEG-end of seizures. An R-Wave detecting algorithm was applied for the calculation of time-differences between the heart rate increase and the seizure onset in the EEG (scalp and intracranial) and the clinical onset. The three thresholds defined for ITC were 100 bpm in patients with a baseline below 90 bpm, and an increase of 20% or 35% above baseline obtained 1 min prior to intracranial EEG onset.

#### Results:

12 patients (9 female; mean age 34.2 years) with 49 seizures with ITC were analyzed. In 24 seizures only intracranial recordings, and in 25 seizures simultaneous scalp and intracranial EEG recordings were available. The mean latency between intracranial and scalp EEG onset was 26.0 s. Latencies between intracranial EEG onset and tachycardia were 23.6 s for a threshold of 100/min (n=41), for a 20% increase in HR 16.2 s (n=49), and for a 35% increase in HR 20.5 s (n=49). The mean latency for other clinical signs was 16.8 s. HR increase preceded scalp EEG seizure onset in 68%. In 46 seizures (52.2 %) HR increase was the first clinical sign; in these cases other clinical signs followed after a mean latency of 6.3 s.

#### Conclusions:

These preliminary results show that seizure-related tachycardia is an ictal rather than a preictal phenomenon following intracranial EEG onset, but usually preceding scalp EEG onset. Since ITC constitutes the first clinical sign in a large proportion of analyzed seizures, its detection is of interest for therapeutic intervention. Furthermore, our data shows that the time lag between intracranial EEG onset and ITC is substantially longer

than the period between tachycardia and other clinical signs when tachycardia occurs first. Thus seizure detection based on intracranial EEG may offer advantages over HR-detection with regard to the therapeutic window available before clinical onset.

P 26

### Seizure propagation analysis via segmentation-based classification of ictal electrocorticography

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#### Aims:

Surface electroencephalography (EEG) is often limited by movement artifacts, suppression of high frequencies and low spatial resolution. Therefore non-invasive recordings do not always reveal a precise identification of the seizure onset zone especially in patients with non-lesional epilepsy. Invasive subdural strip electrodes allow for a better identification of the seizure onset zone. A semi-automatic evaluation of ictal activity and propagation may support clinicians performing video EEG monitoring.

#### Methods:

Invasive subdural strip electrodes were implanted to record electrocorticograms (ECoGs) during video EEG monitoring in a drug-resistant patient with focal epilepsy. The patient suffered from four seizures during invasive recording. A novel software was designed for automatic segmentation of individual ECoG channels on the basis of power changes in the physiological frequency bands. Each segment was then evaluated automatically by a three-step algorithm which is based on a rule set for classification of epileptic activity. This rule set is inspired by the procedure of visual analysis, focusing on rhythmic activity and high amplitudes in a first step and refined criteria in the two subsequent steps. Segments representing ictal activity were marked by this program.

#### Results:

Three seizures were analyzed using this novel segmentation-based classification method. Seizure onset on individual channels as detected with this method was well correlated with the visual analysis of ECoGs. In addition, time spread of rhythmic activity on individual channels allowed an evaluation of seizure propagation.



**Conclusion:**

Our ECoG segmentation method may allow for a faster and more objective seizure onset detection and description of ictal activity propagation in ECoG. Knowledge of ictal activity propagation may be useful for a better prediction of seizure outcome after epilepsy surgery.

P 27

**Value of ECG changes and response to Benzodiazepine treatment as predictors for survival in nonconvulsive status epilepticus**

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**Aims:**

Nonconvulsive status epilepticus (NCSE) is diagnosed increasingly. Simple clinical predictors of outcome in this frequent clinical situation are not well established. The relevance of basic changes in electrocardiograms (ECG) in patients with NCSE is questionable. The relevance of electroencephalograph (EEG) changes, which are frequently seen as effect of benzodiazepine (BDZ) treatment is unclear. This study explores the value of basic ECG parameters as well as the response to BDZ treatment as predictive factors for outcome in patients with NCSE.

**Methods:**

On our Stroke Unit 62 Patients with NCSE were included from 01/2010 – 12/2011. In 26 cases ECG parameters were recorded with Holter-ECG until discharge from hospital. End of NCSE was determined by daily EEGs. Further EEGs were performed on clinical request. The 62 Patients underwent BDZ treatment (Lorazepam 2 mg) during EEGs as part of our clinical routine. EEGs were analysed by a board-certified electroencephalographer and a resident in neurology. Patients were followed up from diagnosis until exitus or discharge from hospital. Data was analysed descriptively. Fisher's exact test was used to explore the statistical significance of changes of ECG parameters and response to BDZ-treatment on outcome.

**Results:**

In the 20 patients with 26 episodes of NCSE of whom ECG parameters were obtained, median heart rate decreased minimally after end of NCSE (89 versus 88/min). The ratio of heart rate after to during NCSE was slightly lower in surviving patients than in non-survivors (0,97 versus 0,99). This difference was not considered to be significant ( $p = 0.4$ ).

82% (51/62) of patients who received BDZ treatment survived. Stratified by location of the epileptiform pattern, patients with focal patterns of NCSE were more likely to survive than those with a generalized

pattern (91% versus 77%,  $p = 0.3$ ). In patients with focal NCSE, there was no significant difference in survival between responders (12/14) and non-responders (9/9) ( $p = 0.5$ ). Patients with generalized NCSE responding to BDZ treatment did survive significantly more often than non-responders. 87% (21/24) of responders compared to only 43% (3/7) of non-responders survived ( $p = 0.03$ ).

**Conclusion:**

Response to BDZ treatment in patients with generalized NCSE was associated with a higher rate of survival and might therefore be a valuable predictor for outcome. Basic ECG parameters were not identified as potential predictive factors to determine outcome in NCSE.

P 28

**Video-EEG Monitoring in children: Retrospective data analysis of 237 video-EEGs**

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**Aims:**

This is a retrospective data analysis to assess results in long term video EEG monitoring for diagnostic and therapeutic purposes!

**Methods:**

Patients admitted to our video EEG (vEEG) unit between 1.6.2010 and 1.7.2011 were included (202 patients, 237 vEEG analysis, 435 monitoring days). Continuous EEG with video was performed using Schwarzer Harmony System with electrodes placed in accordance with the international 10-20 system with additional electrodes ranging from 21-64 electrodes.

In 106 (44.7%) vEEGs it was the first analysis for diagnostic proposes (= group 1), 41 (17.3%) analysis were for reconfirming the diagnoses from outpatient department (= group 2) and 90 (38%) analysis due to reevaluation for refractory epilepsy (= group 3).

**Results:**

In group 1 49 patients (46.2 %) were found to have a new pathology. In 44 cases (= 41.5 %) therapy was initiated. In group 2 65.9 % ( $n = 27$ ) were started on therapy and in group 3 51.1 % ( $n = 46$ ) had therapy modification after vEEG.

**Conclusion:**

Video-EEG is an important tool for diagnostic work up as well as therapy modification.

P 29

### Automated detection of periventricular nodular heterotopia by morphometric MRI analysis

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#### Aims:

To evaluate the diagnostic benefit of a new MRI postprocessing technique for the detection of periventricular nodular heterotopia (PNH). The method is a further development of voxel-based morphometric analysis with focus on a region of interest around the lateral ventricles in order to increase the sensitivity and specificity for automated detection of abnormally located gray matter in this area.

#### Methods:

T1-weighted MRI volume data sets were normalized and segmented in SPM5, and the distribution of gray matter was compared to a normal database. As a new approach, individual masks derived from segmentation of the lateral ventricles of the investigated patient were used to restrict the search for ectopic gray matter to the periventricular area. PNH were automatically detected by localizing the maximum deviation to the normal database in this area, provided that the z-score at this position exceeded a certain threshold. The optimal z-score threshold for maximum sensitivity and specificity was determined by a receiver operating characteristic (ROC) analysis. The method was applied in 40 patients with PNH and 400 healthy controls.

#### Results:

PNH were detected in 37/40 patients, false-positives were found in 34/400 controls, amounting to 92.5% sensitivity and 91.5% specificity. In 17 of the patients in whom PNH could be identified, these lesions had been overlooked in the past, in 8 patients even in the high-resolution MRI subsequently used for the postprocessing presented here.

#### Conclusions:

The results of this study suggest that automated morphometric MRI analysis with focus on ectopic gray matter in the periventricular areas facilitates the evaluation of MRI data and increases the sensitivity for the detection of PNH.

(This study has been accepted for publication in *Epilepsia*.)

P 30

### Comparison of morphometric analysis based on T1- and T2-weighted MRI data for visualization of focal cortical dysplasia

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#### Aim:

Focal cortical dysplasias (FCD) are highly epileptogenic lesions frequently accounting for pharmacoresistant focal epilepsy. Visual MRI analysis combined with morphometric analysis of T1-weighted MRI data was shown to be of higher diagnostic sensitivity in detecting and delineating FCD than conventional visual analysis alone. So far it is unknown whether morphometric analysis of T2-weighted MRI volume data sets is of equal benefit or perhaps more helpful for visualizing FCD.

#### Methods:

Morphometric analysis was applied to T1- and T2-weighted MRI volume data sets of 20 epilepsy patients with FCD using a fully automated MATLAB script with scanner- and sequence-specific normal databases for T1 and T2 images. For each modality, a new feature map (i.e., 'junction image') highlighting the FCD-typical blurring of the grey-white matter junction and quantifying this feature in comparison to the normal database in terms of z-scores was calculated. The resulting T1 and T2 'junction images' were compared for conspicuity and recognizability of the FCD both qualitatively by visual assessment and quantitatively by analysis of the mean z-scores inside and outside the lesions.

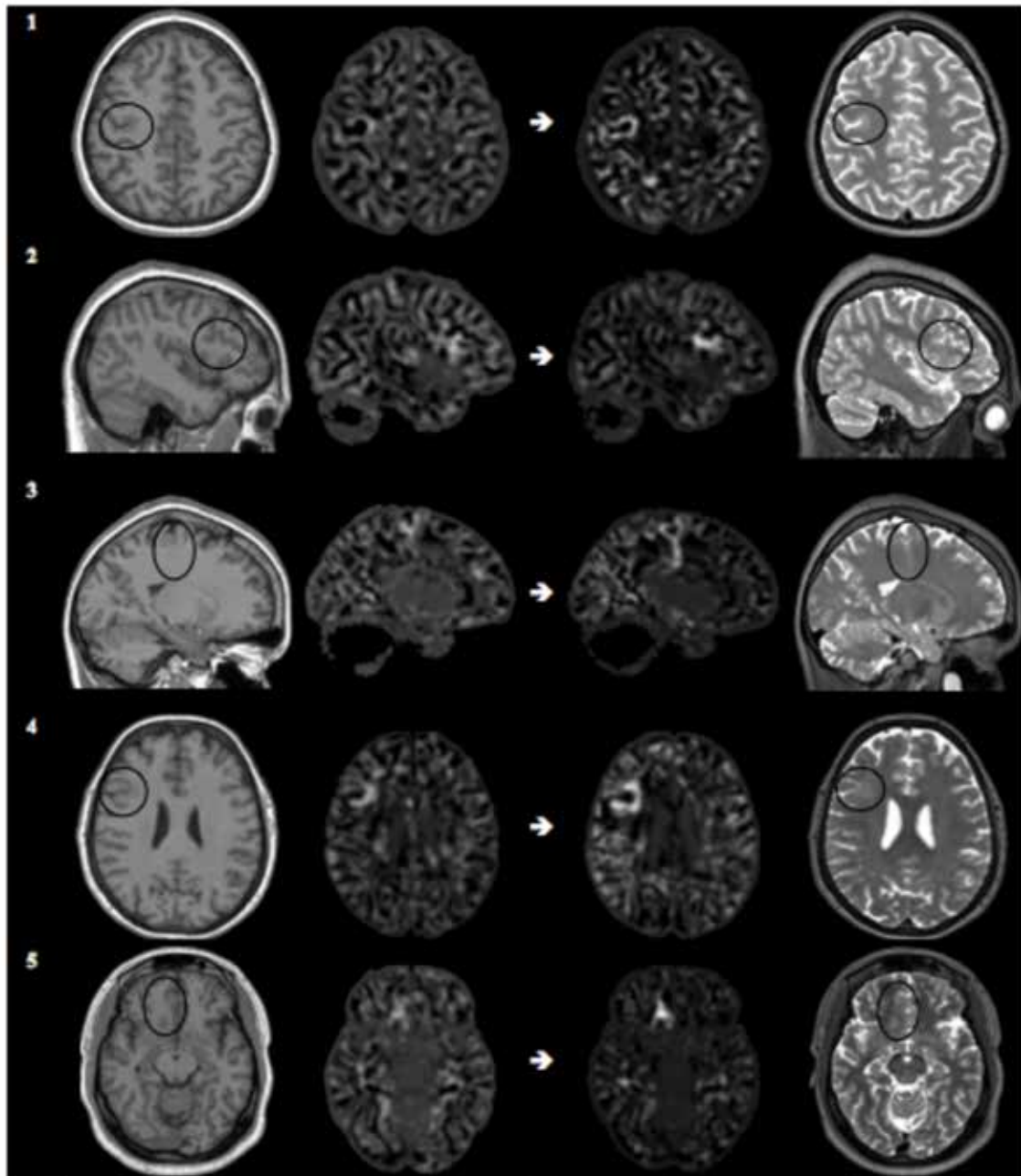
#### Results:

In 80% of the cases, the FCD presented with higher contrast and/or clearer delineation in the T2 than in the T1 'junction images' and were thus easier to recognize in these images. The quantitative analysis supported this impression: in 95% of cases, the ratio of mean z-scores inside and outside the FCD was higher in T2- than in T1-based 'junction images'. For the T2 'junction images', this ratio amounted to 8.7 on average and was thus more than twice as high as the corresponding T1 result of 3.7 ( $p < .003$ ).

#### Conclusions:

Concerning visualization of FCD by highlighting blurring of the grey-white matter junction, the results of the present study indicate that morphometric analy-

sis of T2-weighted MRI data on average is superior to T1-based morphometry. With improved detection and delineation of FCD, morphometric analysis of T2 data could contribute to better outcomes in epilepsy surgery.



**Notes:** T1 and T2 'junction images' resulting from morphometric analysis are aligned together with their corresponding normalised 3D T1-weighted image to the left and T2-weighted image to the right. Each line shows the results of one patient. For each patient, all images are presented in the same orientation and in the same slice, which best depicts the FCD. The results of qualitative assessment are indicated by arrows pointing to the 'junction image' with better lesion conspicuity.

Figure 1: Examples of the results of morphometric of T1 and T2 data

P 31

### MRI postprocessing in patients with hypermotor seizures: benefit in a case series

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#### Aim:

Focal cortical dysplasias (FCD) are highly epileptogenic and a frequent cause of drug-resistant focal epilepsy. By complete surgical resection seizure freedom can often be achieved. However, presurgical evaluation of patients with hypermotor seizures with marked agitation is still challenging. Surface EEG is often not helpful to lateralize and localize seizure onset, and even in high resolution 3-Tesla MRI subtle FCD may remain undetected. Morphometric MRI analysis (MRI postprocessing) can increase diagnostic sensitivity, but does it really lead to a better clinical outcome in patients with formerly classified cryptogenic epilepsy?

#### Methods:

We identified five patients with drug-resistant focal epilepsy suffering from hypermotor seizures with marked agitation in our database, which had either been classified as cryptogenic or where conventional MRI analysis had been ambiguous. In all cases morphometric MRI analysis was performed.

#### Results:

MRI postprocessing detected abnormalities congruent to seizure semiology in all patients. Three patients were originally MRI negative, and in two cases conventional MRI reports with suspicion of FCD were confirmed. The preoperative seizure frequency ranged from several times a month up to several times a night. Epilepsy surgery was planned based on MRI data. Histopathology revealed FCD Ia in one patient, and Ib in four patients. Complete seizure freedom was achieved in three patients (60% Engel Ia), Engel II and Engel IV each in one case. The average latency of surgery was 17.6 years (range 5 to 29 years).

#### Conclusions:

Morphometric MRI analysis should be routinely used in presurgical evaluation of patients with "MRI-negative" focal epilepsy with hypermotor seizures of possible frontal origin. Patients with long lasting pharmaco-resistant "cryptogenic" focal epilepsy should undergo a re-evaluation. The individual benefit of an MRI-postprocessing driven surgical approach can be tremendous.

P 32

### PET-Imaging in limbic encephalitis with faciobrachial-dystonic seizures

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Limbic encephalitis (LE) is increasingly recognized as non-paraneoplastic disorder with distinct autoantibodies to neuronal proteins. We report on serial FDG-PET findings of a 72-year old man with a recently described particular subtype of non-paraneoplastic LE with faciobrachial-dystonic seizures (FBDS) associated with antibodies to Lgl1. FDG-PET revealed circumscribed hypermetabolism of basal ganglia and right temporal lobe in the acute phase with more than 50 FBDS/d. After high-dose corticosteroid pulse-therapy, significant clinical improvement of memory and FBDS occurring now only in strong emotional context, the follow up FDG-PET yielded a normalization of temporal lobe and almost normalized metabolism of basal ganglia. PET identifies the affected brain regions of this peculiar autoimmune pathology – while neither MRI nor CSF revealed any abnormality.

P 33

### Structural changes of the white matter and neuropsychological findings in patients with juvenile myoclonic epilepsy

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#### Aim:

Juvenile myoclonic epilepsy (JME) is a common type of generalized epilepsy.

Amongst others it is characterized by the absence of structural brain abnormalities using magnetic resonance imaging (MRI) in the clinical routine. Recent findings in MRI studies however suggest regional changes of the brain in patients with JME. Albeit those findings are partly inconsistent, there is a tendency towards changes in the frontal lobe.

Certain personality traits considered as frontal lobe pathology have repeatedly been described with JME

patients, identifying deficits regarding executive functions, mental flexibility and cognitive speed. We studied neuropsychological measures, personality traits and MRI parameters of the brains of JME patients vs healthy volunteers to complete the picture of neuropsychological and behavioral deficits and find correlations with structural changes.

**Methods:**

20 JME patients and 20 healthy controls, matched for sex, age and education had a 3 Tesla MRI scan including a diffusion MRI scan (DTI). DTI images were analysed using Tract-Based Spatial Statistics (TBSS) and fractional anisotropy (FA) as a measure of white matter integrity was computed. The subjects also underwent a battery of standardized neuropsychological tests and personality trait questionnaires.

**Results:**

We found a significant reduction in FA within the corpus callosum (CC), especially in the anterior region, in JME patients. Patients performed significantly less well in tests specific for attention ( $p = 0.01$ ), executive functions ( $p = 0.04$ ), verbal abstraction ( $p = 0.04$ ), figurative memory ( $p = 0.02$ ) and short term memory ( $p = 0.02$ ) whereas both groups performed similar in the working memory paradigm. Concerning the personality traits patients displayed a higher degree of alexithymia ( $p = 0.01$ ) which is characterized by difficulties identifying and describing emotions in the self.

**Conclusions:**

The reduced FA within the CC suggests an impaired structural connectivity concerning the frontal lobe. Similar findings have been published by O'Muircheartaigh et al in 2011, so this may be considered as a robust result. We also found neuropsychological and personality changes associated with a frontal lobe dysfunction. Thus our findings are further evidence that regional changes of the brain might exist in generalized epilepsy as well and support the hypothesis of an impaired frontal network in JME patients.

P 34

**An fMRI study of autobiographical memory in patients with temporal lobe epilepsy using SenseCam**

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**Aims:**

Using functional magnetic resonance imaging (fMRI) we examined the neural correlates of autobiographical memory in patients with temporal lobe epilepsy (TLE) compared to healthy controls.

**Methods:**

In this study, autobiographical memory was assessed in five patients with unilateral left TLE (4 female, age mean = 35 yrs) and fourteen right-handed normal controls (7 female, age mean = 30 yrs) using a novel automatic camera, SenseCam. Participants carried a SenseCam around the neck on an excursion to local attractions in Freiburg. The SenseCam automatically captured pictures of the surrounding area approximately every 30 s using a fish eye lens. During the scanning session images of the excursion were presented. We adapted a remember-know paradigm. The participants should rate if they could remember the situation shown in the picture in detail (remember), vague (know) or not at all (unknown). In the following the results for the contrasts remember vs. unknown will be illustrated. For the group of healthy subjects as well as for patients one sample t-tests of the main contrast were calculated. In addition we realized a group comparison of the patient group with an age- and gender matched control group calculating a two sample t-test. In order to compare behavioral data of the groups, t-tests were evaluated (response behavior: remember vs. unknown, remember vs. know, number of errors).

**Results:**

Concerning the recall of autobiographical memories healthy controls showed bilateral activations in the precuneus, the prefrontal cortex, the left middle temporal gyrus and the left inferior parietal cortex. In patients, activations could also be seen bilaterally in the precuneus and the inferior parietal lobe as well as in the left calcarine gyrus. A direct comparison of the patient group with the healthy controls showed stronger activations of the right middle frontal gyrus, the right

precuneus and the right hippocampus. Concerning the performance we could not find a statistical significant difference between both groups.

**Discussion:**

In summary, our results of healthy controls showed patterns of activation, which are comparable with the autobiographical network. Furthermore the stronger activation of the patients in the right hippocampus may reflect a compensatory mechanism.

P 35

**Cognition and quality of life one year after stereotactic interstitial radiosurgery in epilepsy patients with hypothalamic hamartoma**

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**Introduction:**

Hypothalamic hamartomas (HH) are rare congenital lesions often presented with epileptic seizures which can be treated with interstitial radiosurgery. The proximity of the HH to memory related structures like the fornix bears a risk for mnemonic disturbances after treatment. We report on cognitive and psychosocial outcome one year after surgery.

**Patients and Methods:**

Twenty-four patients (9 female, age mean  $\pm$ sd = 26.2  $\pm$ 11.8 yrs, age at disease onset mean  $\pm$ sd = 4.5  $\pm$ 3.7 yrs) were evaluated before stereotactic implantation of 125-I-seed implants into the target volume of the HH and after a mean of 15.7  $\pm$ 6.1 months. Standardized neuropsychological assessment comprised IQ, memory and attentional functions, as well as quality of life (QOL) and psychiatric symptoms using questionnaires. Furthermore, seizure outcome was evaluated. In order to calculate changes across time, Wilcoxon signed-rank tests were computed.

**Results:**

The preoperative neuropsychological examination resulted in below average performance in a number of patients. Performance improved significantly in selective attention after radiosurgery ( $p < 0.05$ ). There was a trend towards decline in verbal recognition ( $p = 0.07$ )

and visuospatial learning performance ( $p = 0.06$ ).

Nevertheless, evaluation of QOL showed a significant increase in subjective rating of work and activities ( $p < 0.05$ ), and a trend towards gain in the subscale concerning physical abilities ( $p = 0.069$ ). Evaluation of psychological distress revealed a trend towards decline in anxiety ( $p = 0.082$ ) and paranoia ( $p = 0.091$ ) at one-year follow-up. Furthermore, screening for depressive symptoms showed a group mean below cut-off, and that the number of patients above cut-off score ( $N = 2$ ) remained unchanged.

All patients continued to have seizures at the time of follow-up, however, 10 patients (41.7 %) experienced significant seizure reduction as compared to the preoperative seizure frequency and strength (Engel I to III).

#### Discussion:

Mnemonic functions were impaired prior to surgery in 30 to 50 % of the patients, irrespective of intelligence. Thus, the syndrome of epilepsy due to HH already caused memory dysfunctions. Interstitial radiosurgery led to improvements in attentional functions and seizure frequency, and in a few cases to decreased memory performance. Seizure reduction may have induced improvements in attentional functions and work and activities as well as reduced feelings of anxiety.

P 36

#### Cognitive functions and quality of life in school-aged children with newly diagnosed epilepsy: Course and relevant predictors

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#### Aim:

Children with epilepsy are at a higher risk for cognitive impairment or school problems than healthy children or children with other chronic diseases. The present study aimed to analyze the course of cognitive functions in children with newly diagnosed epilepsy.

#### Methods:

Thirty four children, diagnosed with new-onset epilepsy and treated in the Children's University Hospital of Heidelberg, were investigated in an explorative, descriptive, non-interventional, prospective study. A neuropsychological test battery on executive functions, memory and cognition was performed before the start of antiepileptic medication (T1), three months after titration (T2) and at least three months after T2 (T3). Disease-related and socio-demographic information were gathered from parents in a structured interview and with questionnaires. One-sample t-tests, paired t-tests and non-parametric tests were used for the statistical analysis of the results.

#### Results:

Cognitive performance of children with epilepsy did not differ from the normal population, except for non-verbal memory. Parents reported subjective cognitive and behavioral problems. No significant differences were found between performance at T1, T2 and T3.

#### Conclusion:

Despite the fact that, except for non-verbal memory, all examined cognitive functions were normal at the onset of epilepsy and remained stable after the start of antiepileptic drugs, parents increasingly report subjective problems, which indicate the importance of taking notice of the subjective perception of parents.

P 37

#### Implications of "enhanced learning" versus "accelerated forgetting" in lateralizing temporal lobe epilepsy

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#### Aims:

At present there is ongoing debate about the lateralizing validity of visual memory tests in pre-surgical epilepsy diagnostics. The concept of "accelerated forgetting" suggests that certain mnemonic dysfunctions may only appear after prolonged recall intervals in temporal lobe epilepsy (TLE). We therefore wanted to determine the clinical usefulness of applying prolonged delays to both verbal and visual memory tasks in order to lateralize the epileptogenic zone.

#### Methods:

Fourteen left TLE and thirteen right TLE patients were given two matching-to-sample memory tasks for faces and words redesigned and adapted after the Recognition Memory Test (RMT), previously established by Warrington (1984). Two recognition time points were included, one immediately and the second three days after presentation. Patients were under stable medical conditions and did not experience seizure episodes during the time interval. Additionally, twelve control subjects were assessed.

#### Results:

For the immediate word recognition trial no significant differences were found between the three groups. The repeated measures analysis showed that all participants significantly forgot the verbal material after three days, without a lateralization effect. Concerning, the recognition for faces, the immediate trial did not show any group differences, nevertheless after the

three-day delay, the right TLE group performed significantly worse in this task as compared the left TLE patients or the control subjects. Further post-hoc analysis revealed that the difference was not due to accelerated forgetting of the right TLE sample, but rather an amelioration of recognition performance in the left TLE group.

#### **Conclusion:**

These findings suggest that the application of long-term delays may be useful for lateralizing right TLE foci during the preoperative cognitive evaluation. Importantly, this demonstrates that clinicians should not focus solely on “accelerated forgetting” in patients with right TLE, but additionally on “enhanced learning” for visual recognition memory tasks in patients with left TLE.

P 38

#### **Is there an influence of subclinical epileptic EEG patterns on reaction time of epilepsy patients? A pilot study**

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#### **Aim:**

In patients with subclinical seizure patterns in electroencephalography (EEG) it is assumed that reaction times are negatively influenced. The aim of our work was to evaluate this hypothesis in a first pilot study.

#### **Methods:**

Several measurements of the response time were performed during a standard 10/20 EEG recording in two patients and two healthy volunteers. Upon hearing an acoustical signal, test subjects were instructed to press a button as quickly as possible. The reaction time was recorded and the interval from acoustic signal to reaction (pressing a button) was marked in the corresponding EEG recordings. In the patient group there were subclinical seizure patterns in parts of the EEG recordings, whereas healthy volunteers showed normal EEGs.

For evaluation, the response times of the control group compared to the patient group during normal EEG portions were analyzed (Wilcoxon-Mann-Whitney-Test). Additionally, in the patients the values during the normal EEG parts were compared with those of the pathological sections.

#### **Results:**

Comparing reaction times during normal EEG sections patients performed equally or better than controls. Comparing normal and pathological EEG sections within each patient reaction times were not significantly different ( $p = 0.54$ ,  $p = 0.28$ ).

#### **Conclusions:**

In patients with subclinical epileptic patterns in EEG lasting longer than 4 seconds fitness to drive is subject of strong discussions. In our pilot study it could, however, be shown that reaction times are not influenced by subclinical seizure patterns in EEG in general and suspending of driving license is not justified in all patients. This yields further studies on dependency of reaction times and subclinical seizure patterns in EEG.

P 39

#### **Neurocognitive changes and quality of life after bilateral electrical stimulation of the anterior thalamic nuclei in 11 patients with refractory epilepsy**

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#### **Aims:**

A previous study reported memory problems and depression as possible adverse events of bilateral electrical deep brain stimulation (DBS) of the anterior nuclei of the thalamus (ANT). One explanation might be the participation of the mesial temporal lobe along with the ANT in the limbic circuit of Papez. We assessed changes in neurocognition, mood and quality of life (QoL) after bilateral DBS of the ANT in patients with refractory epilepsy.

#### **Methods:**

Eleven adult epilepsy patients (6 female, 5 male) with a mean age of  $31.4 \pm 10.9$  years underwent detailed neuropsychological testing and completed QoL and psychiatric inventories before DBS surgery. Seven patients were re-evaluated 4 weeks after implantation of electrodes, but before onset of stimulation, 10 patients after 4 months of stimulation, one patient also after an additional 4 months of unilateral (right) stimulation, and 3 after 16 months of stimulation.

#### **Results:**

One month after implantation, before turning on the stimulator, we observed a significant decline of nonverbal short-term memory (i. e. encoding), but improvement in several scales of the psychopathological inventory (i. e. obsessive-compulsive, anxiety, hostility, paranoid ideation) and a tendency towards improvement of mood. We named this psychological effect after implantation „relief effect“, when patients feel relieved and hope for seizure reduction. Four months after stimulation onset we noticed a significant decrease of nonverbal short-term memory and a tendency towards verbal long-term memory (i. e. retention) decline. There were no changes in general cognitive abili-



ties (IQ), attention, executive and language functions, and visuospatial abilities. In general, mood, QoL and psychiatric profile also remained unchanged. There was only a slight tendency towards improved general health perceptions. In one patient where left-sided stimulation was turned off due to verbal memory decline, we observed a recovery of verbal memory 4 months after deactivation of the left electrode. Long-term follow-up tests of 3 patients 16 months after stimulation onset did not show any consistent changes.

#### Conclusions:

In the present sample we were able to demonstrate (reversible) verbal and nonverbal memory changes as a medium-term effect of DBS of the ANT in epilepsy patients. Stimulation had no effect on other cognitive functions, mood, QoL and psychiatric scales. Further investigations are scheduled.

P 40

#### Language localisation from the MRI confirmed by invasive deep brain electrodes

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#### Introduction:

During presurgical evaluation, a precise localization of the eloquent cortex is essential. Language is one of the most important functions that should be preserved and presurgically characterized as well as possible.

Usually, language is lateralized by history of handedness, neuropsychological assessment, fMRI (functional Magnet Resonance Imaging), or fTCD (functional Transcranial Doppler Sonography).

The gold standard for language lateralization is the Wada test which is, however, not routinely applied in every patient because it is invasive. All these methods, except fMRI, give information about lateralization, but not about localisation. However, the validity of the fMRI in language localization is under debate.

Here we report on a patient, who had fTCD, neuropsychology and Wada test as well as fMRI for language lateralization. Results were validated by invasive sEEG (stereo Electroencephalography) using a novel coregistration approach.

#### Material and methods:

A 22 y old left handed man with medically refractory right temporal lobe epilepsy underwent comprehensive presurgical evaluation including a multimodal approach for language localisation with neuropsychological assessment, fMRI, fTCD and Wada test. For clinical reasons, sEEG electrodes were placed in the right temporal pole, amygdala, hippocampal head and body as well as in the posterior temporal region. We coregistered the position of the sEEG electrodes, as well as the fMRI activity on a presurgical T1 weighted anatomical image. One electrode was placed in the region defined as Wernicke's area by fMRI.

#### Results:

Medical history, neuropsychological testing, fTCD and Wada test pointed to an atypical right hemispheric language localisation. fMRI also suggested right hemispheric language dominance and clearly identified Broca's and Wernicke's areas. Cortical stimulation inducing speech arrest confirmed right hemispheric language lateralisation and the identification of Wernicke's area suggested by fMRI.

#### Discussion:

Localization of Wernicke's area by the fMRI could be verified by stimulation of the sEEG electrodes as a Gold Standard.

Our findings show that fMRI may help to localized language relevant regions in selected patients and supports the use of fMRI in the presurgical evaluation.

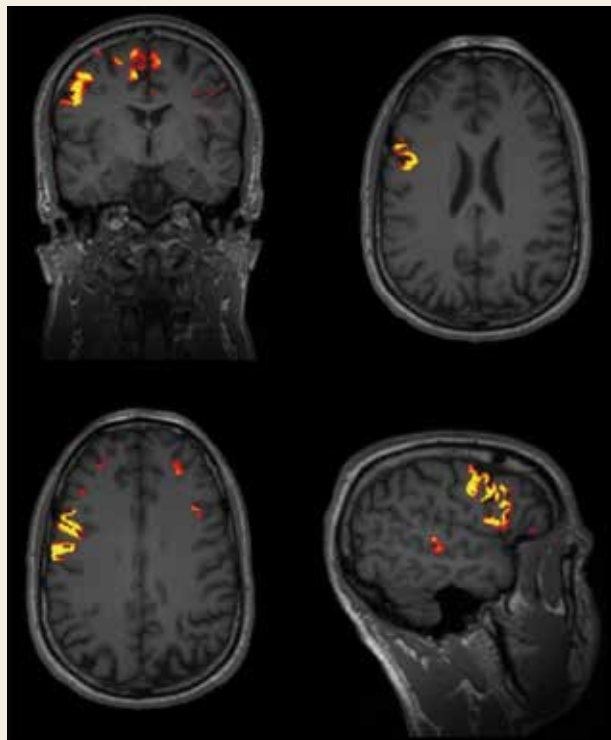


Figure 1: Results from the presurgical fMRI

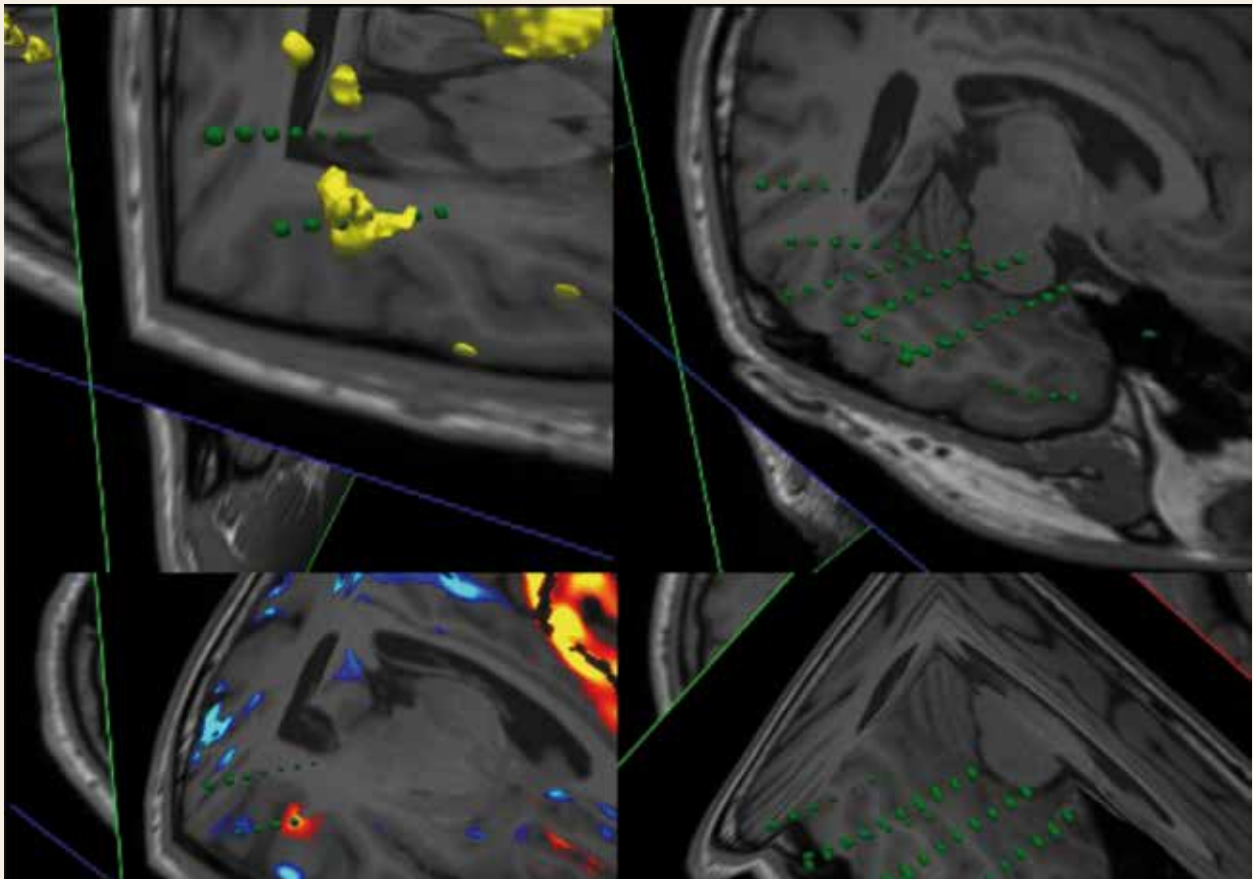


Figure 2: Position of SEEG deep brain electrodes and the results of the fMRI

P 41

**The camera walk: first experiences with a new visual memory fMRI paradigm in patients with temporal lobe epilepsy**

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**Aims:**

In the current study, we aimed to investigate whether the recall of episodic and semantic information is associated with differential mesiotemporal brain activations in patients with mesial temporal lobe epilepsy (TLE). Therefore, we used a new fMRI task in TLE patients and healthy subjects.

**Methods:**

To date, 7 TLE patients (5 with left-sided TLE, 2 with right-sided TLE) and 10 healthy subjects were investigated with the so-called camera walk fMRI paradigm: Twenty-four hours prior to scanning, the participants went for a walk and took pictures at predefined spots. During the fMRI investigation these pictures (episodic recall condition) and pictures of famous spots (semantic recall condition) were presented. Blocks of both con-

ditions were shown alternately, interrupted by an un-specific resting condition.

**Results:**

Compared to the resting condition, the episodic recall elicited mesiotemporal activations in both groups (beyond parieto-temporal and frontal activations). In healthy subjects, these mesiotemporal activations were significantly stronger on the right side compared to the patients (two-sample t-test, peak:  $x = 38, y = -12, z = -24, k = 408, p = .03$ ). The semantic recall also lead to mesiotemporal activations in both groups. These were significantly stronger within the left hemisphere in healthy subjects than in the patients (two-sample t-test, peak:  $x = -38, y = -40, z = -4, k = 188, p = .04$ ). In the healthy group, we observed stronger bilateral mesiotemporal activations during the episodic compared to the semantic recall condition (one-sample t-test, peak:  $x = -32, y = -38, z = -14, k = 154$  und  $x = 32, y = -38, z = -14, k = 183, p < .002$ ). This between condition differences was not found in the patient group.

**Conclusion:**

Our preliminary results indicate differential, i.e. type of recall specific, mesiotemporal activations in healthy subject, but not in TLE patients: Stronger mesiotemporal activations in the episodic compared to the se-

semantic condition did not occur in the TLE patients. We currently enlarge the patient sample in order to study whether or not the reported activation patterns are affected by the side of seizure onset.

P 42

### The impact of anxiety, seizure severity, executive dysfunction, subjectively perceived psychological deficits and depression on social function in patients with epilepsy. Preliminary results

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#### Aim:

The impact of measures of anxiety, seizure severity, executive dysfunction, subjectively perceived psychological deficits and depression on social function in patients with epilepsy (PWE) will be analyzed. Here we present the preliminary results of a study, which is proposed to include 40 PWE.

#### Method:

A brief cognitive screening test (Epi-Track) and an estimation of the last 6 months cumulative seizure severity (Chalfont seizure severity scale) are performed and questionnaires on subjectively perceived cognitive deficits (c.I.-Skala), anxiety (State-Trait Anxiety Inventory STAIX1 and STAIX2), depression (Self Rating Depression Scale, SDS) and social function (Soziale Aktivität Selbstbeurteilungsskala, SASS) are filled in.

#### Results:

25 PWE (age 43.3 years, SD 18; 14 female, 11 male) have been analyzed by now. 48% had a score signifying depression in the SDS, 28% had a pathological result in at least one of the anxiety scores. Symptoms of depression were significantly correlated with anxiety as a trait (STAIX2) ( $r = 0.68$ ,  $p = 0.0001$ ). Partial correlation coefficients showed that symptoms of anxiety as a trait had a significant influence on social functioning apart from depressive symptoms ( $r = -0.46$ ,  $p < 0.02$ ), cognitive deficits ( $r = -0.07$ ,  $p < 0.0001$ ) and seizure severity ( $r = -0.55$ ,  $p < 0.005$ ).

#### Conclusion:

Symptoms of anxiety impair the social function of patients with epilepsy apart from depression, cognitive function and seizure severity. They should be taken into account in the treatment of patients with epilepsy.

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### Unilateral mesial temporal epilepsy impairs remote brain activation and social cognition

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#### Aim:

Unilateral mesial temporal lobe epilepsy (MTLE) has been associated with impaired social cognition and ipsilateral amygdala dysfunction. Due to the high prevalence of functional alterations in structures remote from the mesial temporal lobe, deficits in social cognition may not merely be attributable to amygdala dysfunction. Whether a dysfunctional amygdala causes functional changes in remote regions underlying social cognition has yet to be thoroughly investigated. Therefore, in this multiple case study, the frequencies and topographic distributions of cortical and subcortical BOLD-responses to animated fearful faces were described in patients with unilateral MTLE.

#### Methods:

A previously validated fearful face paradigm with proven reliability to evoke amygdala activation in single cases (Schacher, 2006a) was used in 50 patients with unilateral MTLE (24 right-sided) and 25 healthy controls. Single-subject fMRI analyses were applied. At the behavioral level, both affective and cognitive aspects of self-reported empathy and theory of mind (ToM) were assessed.

#### Results:

Right and left MTLE was associated with functional alterations in remote frontal and limbic-paralimbic regions. Notably, these functional modulations were more prominent in patients with right- than left-sided seizure onset. Consistent with these findings, both affective and cognitive aspects of self-reported empathy and ToM were more severely impaired in patients with right than left MTLE.

#### Conclusions:

These results indicate that impaired social cognition in MTLE is associated with predominantly right frontal lobe dysfunctions attributable to remote influences of the primary epileptogenic zone. These findings shed further light on the etiopathogenesis of impaired social cognition in patients with unilateral MTLE.

## Validation of a German version of the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)

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Depression is a frequent concomitant disorder in epilepsy, has a severe impact on the patients' quality of life and increases the risk of suicide. Therefore, it is important to detect depressive disorders in epilepsy patients and to initiate the required therapy. Gilliam and colleagues developed the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), a six-item screening tool that is easy to administer even in a busy setting [1]. An important advantage of this instrument is that the assessed symptoms can be differentiated from common adverse effects of antiepileptic drugs. The aim of this study was to make the instrument accessible for use in German.

The NDDI-E was translated into German, translated back into English by a native speaker and approved by the group that had developed the original instrument. 144 in-patients (52.8% female, mean age 34.1 years, 68.1% focal epilepsies) of Bethel Epilepsy Centre were examined using the German versions of the NDDI-E, the Beck Depression Inventory II (BDI II), the symptom check-list SCL-90-R, and the Mini International Neuropsychiatric Interview Plus (MINI Plus).

25 (17.4%) out of the 144 patients had a diagnosis of depression according to the MINI Plus. Internal consistency reliability (Cronbach's Alpha) of the NDDI-E was 0.83; explorative and confirmative factor analyses indicated unidimensionality. NDDI-E was significantly correlated with BDI II ( $r=0.77$ ) and the depressiveness subscale of the SCL-90-R ( $r=0.75$ ). The AUC of Receiver Operating Curve of the NDDI-E with MINI Plus-defined current major depression was 0.85 (95% CI: 0.77-0.94).

An NDDI-E score of  $> 15$  had a sensitivity of 0.68, a specificity of 0.82, a negative predictive value (NPV) of 0.82 and positive predictive value (PPV) of 0.45; a score of  $> 16$  had the same sensitivity, but a specificity of 0.90, a NPV=0.93 and PPV=0.59.

The German version of the NDDI-E is valid and reliable for the detection of depression in epilepsy patients. A cut-off score of  $> 16$  might be more suitable than one of  $> 15$  as used in the original version.

1. Gilliam FG, Barry JJ, Hermann BP, Meador KJ, Vahle V, Kanner AM. Rapid detection of major depression in epilepsy: a multicentre study. *Lancet Neurol* 2006; 5: 399-405

P 45

**Effects of levetiracetam, lamotrigine and carbamazepine on contraction properties of murine cardiomyocytes**

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**Aims:**

Most anticonvulsant drugs inhibit seizure generation by acting on voltage-dependent ionic channels. Voltage-dependent sodium and calcium channels are commonly expressed in both brain and heart, suggesting that anticonvulsants may have considerable cardiodepressive effects. Here, we investigated the effects of levetiracetam (LEV), lamotrigine (LTG) and carbamazepine (CBZ) alone and in combination on the contraction properties of isolated ventricular cardiomyocytes of wild type mice.

**Methods:**

Properties of murine cardiomyocytes were determined by recording the sarcomere shortening with a video imaging system before, during and after administration of anticonvulsants at different concentrations and combinations. We assessed (i) the number of successful contractions following individual electrical stimulations (stimulation-contraction coupling) and (ii) the contraction amplitude upon repetitive electrical stimulation at 4 Hz. Summary data are given as mean (+/-SEM).

**Results:**

At 100  $\mu$ M, LEV (14 cells), LTG (12 cells) and CBZ (16 cells) alone had no effect on the stimulation-contraction coupling, but reversibly reduced contraction amplitudes by 10.6% (+/-2.7), 20.7% (+/-4.1) and 10.2% (+/-3.1), respectively. Increasing the LTG concentration to 250  $\mu$ M (22 cells) and 500  $\mu$ M (4 cells) reversibly inhibited the stimulation-contraction coupling in 59% and 100% of the experiments. Importantly, simultaneous application of LEV, LTG and CBZ at 100  $\mu$ M also impaired the stimulation-contraction coupling in 5 of 16 cardiomyocytes (31%).

**Conclusions:**

Anticonvulsant drugs reversibly suppress cardiac excitation and contraction in a concentration-dependent manner. Importantly, these effects appear to be additive when anticonvulsants are simultaneously applied. Our experimental findings underscore the importance

of rationale anticonvulsant drug therapy and the potential facilitation of serious cardiac dysfunction when anticonvulsant drugs are used in combination.

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**Effects of oxygen insufflation during pilocarpine-induced status epilepticus on mortality, tissue damage and seizures**

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**Aim:**

The aim of this prospective, randomized study was to test the effect of O<sub>2</sub> insufflation during pilocarpine-induced status epilepticus (SE) in rats. This in vivo model of temporal lobe epilepsy potentially reflects the human pathology with respect to a potential life-threatening condition. In patients, oxygen (O<sub>2</sub>) is commonly supplied during SE and believed to attenuate energy depletion since a hypermetabolic area is commonly seen within the epileptic seizure onset zone. Available data on rodent models have also pointed to interictal hypometabolism and ictally increased glucose consumption. Therefore, it appears conceivable to offer O<sub>2</sub> to animals during pilocarpine-induced SE with the aim of reducing SE-related mortality.

**Methods:**

Status epilepticus (SE) was induced by intraperitoneal injection of 340 mg/kg pilocarpine, and terminated by diazepam after 40 min. During SE, rats were randomized to O<sub>2</sub> treatment (insufflation rate of 1.5 l/min O<sub>2</sub>) during SE or normal air conditions. Outcome measures were SE-related mortality, seizure occurrence, mossy fiber sprouting, neuronal cell loss and expression of 27-kDa heat-shock protein (Hsp27).

**Results:**

O<sub>2</sub>-treated and O<sub>2</sub>-untreated animals did not differ with respect to SE latency, diazepam dose required to stop SE. While 4/27 rats died during SE in the O<sub>2</sub>-untreated group, no mortality (0/28) occurred in the O<sub>2</sub>-treated group (P < 0.05). However, within one hour after SE termination, five O<sub>2</sub>-treated rats died which was not observed in the O<sub>2</sub>-untreated group indicating no significant difference in overall mortality. There was a tendency towards lower seizure rate in the O<sub>2</sub>-treated group at one month after pilocarpine-induced

SE. However, mossy fiber sprouting, neuronal cell loss and Hsp27 expression did not differ between O2-treated and O2-untreated groups.

#### Conclusions:

The major finding of the present study is that O2 supply failed to reduce overall mortality, and did not show any improvement in aberrant mossy fiber sprouting, neuronal cell loss and Hsp27 protein expression. On the other hand, occurrence of spontaneous seizures following one month after SE was significantly less in O2-treated animals. This indicates that O2 treatment might reduce the relative risk of epileptic seizures following an initial brain injury, but it may also lead to a rather unfavorably increased heterogeneity of epileptogenesis in experimental studies. We therefore do no longer offer O2 during SE in the attempt of improving SE survival.

P 47

#### Gene expression profiling and morphological analysis of mild focal cortical dysplasias (FCD)

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Focal cortical dysplasias (FCD) are malformations of the human neocortex and a common cause of pharmaco-resistant focal epilepsy. The histological characteristics of FCD extend from mild laminar disorganization with hypertrophic neurons to severe dislamination with the appearance of dysmorphic neurons and cytomegaly cells. To date little is known about the pathomechanisms leading to the architectural abnormalities associated with FCD.

In order to investigate how the dysplastic cortex differs from normally developed neocortex, we used a combined morphological and molecular approach to compare FCD and non-dysplastic specimens from the temporal lobe. In each FCD sample the degree of dislamination and neuronal cytoarchitecture was visualized by immunolabeling for NeuN and non-phosphorylated neurofilament H (SMI32), a marker for pyramidal cell layers 3 and 5. For gene expression profiling we performed microarray analysis of FCD IB, IIA and IIIA type cases and controls. The samples were hybridized to Human Gene 1.0 ST arrays (Affymetrix). Microarray results were verified by reverse transcription qPCR analysis.

We found that in all dysplastic specimen lamination was radially disturbed. The samples differed strongly with respect to lamina width; in some cases layers were even blurred. Our microarray data showed a strong het-

erogeneity of gene expression pattern in the FCD cases and the control group. However, statistical analysis revealed that the transcriptome of the FCD phenotype showed approximately 0.1% differentially expressed genes when compared to non-dysplastic neocortex. Furthermore we observed that most differentially expressed genes were down-regulated in dysplastic tissue. Both, microarray and quantitative PCR analyses reveal a down-regulation of genes associated with myelin sheath formation and maintenance.

Taken together, our data indicate that FCD show a heterogeneous gene expression profile corroborating the morphological and neuropathological phenotype. Furthermore we can assume that myelination disturbances may contribute to the dysplastic phenotype in FCD.

Supported by the Deutsche Forschungsgemeinschaft (DFG FA 775/2-1)

P 48

#### Tissue inhibitor of matrix metalloproteases-1 impairs Reelin processing in experimental epilepsy

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The extracellular matrix protein Reelin is an important regulator of neuronal migration and positioning in the developing and mature brain. Reelin is synthesized and secreted by Cajal-Retzius cells and GABAergic interneurons and its function depends on proteolytic cleavage after secretion. Lack of Reelin causes severe disturbances in cerebral layering such as the reeler phenotype and granule cell dispersion (GCD) in temporal lobe epilepsy. We have recently shown that epileptic conditions not only decrease Reelin levels, but also impair extracellular processing of Reelin by inhibition of matrix metalloprotease (MMP) activity. As a consequence, uncleaved Reelin accumulates in the extracellular matrix as a functionally inactive form and thereby contributes to the development of GCD (Tinnes et al., FASEB J 25, 2011).

In the present study, we used organotypic hippocampal slice cultures (OHC) to investigate the exact mechanism of MMP inhibition. When epileptic conditions were mimicked by KA treatment of OHC, we found significantly increased levels of tissue inhibitor of metalloproteases 1 (TIMP-1) levels in tissue extracts and supernatants indicating enhanced TIMP-1 synthesis and secretion upon hyperexcitation. TIMPs are endogenous inhibitors known to control MMP activity. Moreover we found that KA treatment strongly enhanced TIMP-1 immunolabeling in hippocampal neurons. Application of TIMP-1 alone was sufficient to inhibit proteolytic processing of Reelin and to induce a significant widen-

ing of the granule cell layer as observed after KA treatment. In contrast, by functional inhibition of TIMP-1 we could prevent the impairment of Reelin cleavage induced by KA, indicating that an increase in TIMP-1 expression is involved in impaired Reelin processing under epileptic conditions. In summary, we present evidence that epileptiform activity inhibits MMP activity by up-regulation of endogenous TIMP-1 which in turn leads to extracellular accumulation of uncleaved Reelin and to GCD.

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### Novel mutation in the sodium channel SCN8A in a family with BFIS, PKD and idiopathic generalized epilepsy

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#### Aims:

Mutations in PRRT2 are known to be the major cause of BFIS (benign familial infantile seizures) and PKD (paroxysmal kinesigenic dyskinesia). Here we examined a PRRT2 negative family with 7 affected members. 4 patients showed a BFIS phenotype with clusters of generalized tonic-clonic seizures with an onset between 5-12 months, which responded well to antiepileptic drugs. These patients are now all seizure free without anticonvulsive treatment. The other three patients have an epilepsy with primary generalized tonic-clonic seizures since childhood which might be classified as idiopathic generalized epilepsy. These patients became seizure free in adulthood and are still on antiepileptic treatment. The index-patient also had a PKD and a migraine with aura which occurred in early adulthood.

#### Methods:

We performed exome sequencing in two index-patients in this family negative for a PRRT2 mutation. We searched for novel variations in both exomes. Variations were considered to be novel if they are absent in the databases db135, the 1000 Genomes Project and the National Heart, Lung and Blood Institute (NHLBI) Exome Sequencing Project. For co-segregation, Sanger sequencing was used.

#### Results:

We detected a novel variation in the SCN8A gene, which was previously described in rare cases with epi-

leptic encephalopathy but not in patients with a paroxysmal movement disorder. The mutation co-segregated in all available affected family members.

#### Conclusions:

We detected in a family with BFIS, PKD and idiopathic generalized epilepsy a novel mutation in the sodium channel SCN8A. The mutation is located in a functional relevant region and therefore could alter the biophysical properties of the channel. Functional studies are planned in the near future. Our findings enlarge the phenotypic spectrum of mutations associated to SCN8A mutations.

P 50

### Epilepsy in adult patients with Down syndrome

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#### Aims:

Patients with Down syndrome (DS) have an increased risk to suffer from concomitant epilepsy, but this risk seems to be lower compared to other patients with intellectual disability. The aim of this retrospective study was to address the question whether the extent of intellectual impairment and severity of epilepsy in DS patients is comparable to control subjects (CS) with intellectual disability other than DS.

#### Methods:

Patients with DS were compared with age- and sex-matched control patients with intellectual disability of other causes regarding the extent of intellectual impairment, emergency admittances, total time of inpatient treatment, and number of anticonvulsant drugs in medical history and at discharge. Statistics were performed with SPSS 19, categorical variables were calculated by Chi-square test and continuous variables by Student's t-test. Differences were regarded as significant with  $p < 0.05$ .

#### Results:

Out of 2,024 patients with intellectual disability and epilepsy admitted to our ward for patients with special needs (1999-2012), we identified 35 subjects with DS (1.7%). Compared to 35 CS, DS patients did not differ with regard to sex distribution and age at first admittance (DS,  $47 \pm 13$  y; CS,  $43 \pm 10$  y). However, patients with DS were less likely to suffer from mild forms of intellectual disability (6% vs. 29% in CS,  $p = 0.023$ ). So far, DS patients had been treated with fewer antiepileptic drugs ( $2.2 \pm 2$ ) compared to CS ( $4.5 \pm 3.4$ ;  $p < 0.001$ ). At discharge, the number of antiepileptic drugs did not differ between groups (DS,  $1.6 \pm 0.7$ ; CS,  $1.7 \pm 0.8$ ). The total number of admittances was significantly lower in pa-

tients with DS ( $1.5 \pm 0.9$ ) than in CS ( $2.2 \pm 1.5$ ;  $p=0.033$ ). Emergency admittances were not different between groups (DS, 23%; CS, 26%). There was a trend for a shorter length of inpatient treatment in DS patients ( $39 \pm 33$  days) compared to CS ( $54 \pm 50$  days), but differences did not reach a significant level ( $p=0.13$ ).

#### Conclusions:

Though in patients with Down syndrome the degree of intellectual disability was more severe than in age- and sex-matched controls, lower number of hospital admittances and lower number of prior antiepileptic drugs point to less severe forms of epilepsy. These findings argue against a simple correlation between extent of intellectual disability and severity of epilepsy. The pathophysiological mechanisms of epilepsy in patients with DS seem to differ from those in patients with other acquired or genetic causes of intellectual disability.

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#### Epilepsy in elderly patients – clinical data from an outpatient seizure clinic

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#### Background:

Epilepsy is a frequent problem in elderly people with an annual incidence rate of  $\sim 80/100.000$ . As the number of elderly people in the population is rising, diagnostic and treatment challenges have to be faced in elderly people with epilepsy.

#### Aim:

To evaluate epidemiology, diagnosis and treatment in elderly patients with epilepsy in a tertiary epilepsy center.

#### Methods:

We retrospectively analyzed patients older than 60 years who were diagnosed with epilepsy or had acute symptomatic seizures between October 1977 and December 2011 at the epilepsy outpatient clinic at the Department of Neurology, Medical University Hospital Innsbruck. We included patients with a minimum follow up of one year.

#### Results:

Five hundred and eight patients (287 M/221 F) with a mean age of 82.7 years ( $SD \pm 10.6$  y) were included. The mean follow up (FU) was 4.6 years ( $SD \pm 4.0$  y). Seizure onset was between 60 and 91 years (mean: 69.3 y;  $SD \pm 6.9$  y). The underlying etiology was idiopathic in 2/508 (0.4 %), unknown in 52/508 (10.2%) and symptomatic in 545/508 (89.4%), respectively. Among pa-

tients with a symptomatic etiology cerebrovascular disease was the most frequent attributable cause. Simple partial seizures were observed in 79/508 (15.6 %), complex partial seizures in 157/508 (30.9 %) and secondary generalized tonic-clonic seizures in 336/508 (66.1%) of patients, representing the most common seizure type. Status epilepticus was documented in two patients with idiopathic generalized epilepsy and in 57/508 (11.2%) patients with other etiologies. Comorbidities, mainly internistic diseases, were found in 318/508 (58.1%) patients. About one third of the patients (158/508) were partly or fully dependent on support in their daily routine. Antiepileptic treatment was started either immediately or up to 15.8 y (mean: 1.4 y;  $SD \pm 28.0$  y) after the first seizure manifestation. Three hundred and eight patients (60%) were seizure free for at least one year. Adverse events (AEs) were reported in 110/450 patients (24.4 %) with fatigue followed by dizziness representing the most frequently reported AE.

#### Conclusion:

Elderly patients with epilepsy represent a distinct subgroup of patients treated in an outpatient seizure clinic. Importantly, seizure freedom may be achieved in the majority of patients. Closely monitoring of AEs is recommended to avoid further physical and/or mental impairments.

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#### Focal epilepsy associated with a Glucose Transporter Type 1 (Glut1) defect

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#### Aims:

Mutations in SLC2A1, encoding the glucose transporter type 1 (GLUT1), underlie a wide range of neurological disorders such as the classic GLUT1 deficiency syndrome, paroxysmal exercised-induced dyskinesia (PED) and different forms of idiopathic generalized epilepsy. We tested two non-related individuals with the phenotype of PED and focal epilepsy whether their syndrome was related to SLC2A1 mutations.

#### Methods:

The two patients were clinically examined. SLC2A1 was sequenced in both cases including the exon/intron



boundaries and the functional effects were tested in glucose uptake measurements and protein expression assays.

#### Results:

Clinically, the patients suffered from focal epilepsy, in one patient suspected to be symptomatic in origin associated with PED. We were able to identify causative mutations in both individuals resulting in a decreased glucose uptake in functional assays and altered protein expression. In individual A we found a missense mutation (c.A661G, p.Q161R) and in individual B two missense mutations (c.G405c, p.G76S and c.A10124F, p.Q282R). In individual B both mutations caused functional effects independently.

#### Conclusion:

This study shows that the syndrome of PED and focal epilepsy may rely on SLC2A1 mutations and thus enlarges the spectrum of disorders associated with GLUT1 defects. Patients with this phenotype ought to undergo genetic testing and may benefit from a ketogenic diet.

P 53

### „Idiomatic“ Epilepsy: Combination of genetic and structural epilepsy in a pediatric patient

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#### Introduction:

Mutations in the KCNQ3-gene are well known to be responsible for different kinds of epilepsies like benign neonatal familial convulsions, idiopathic focal and idiopathic generalised (IGE) epilepsies. Epigenetic factors and other conditions are considered to be relevant in terms of pathogenesis in some mutations of this gene though.

#### Methods:

To investigate the etiology of a drug-resistant epilepsy in a 2.5 year old boy, we performed a next generation sequencing (NGS) of an epilepsy gene panel, covering 319 genes.

A Video-EEG-monitoring was performed as well as a high resolution MRI of the brain.

#### Results:

NGS revealed the previously published mutation c.1720C>T; p.P574S in the KCNQ3-gene in a heterozygous state. The pathogenicity of the mutation is uncertain and incomplete penetrance has been suggested.

Video-EEG-monitoring documented an EEG-status

bitemporooccipital and bifrontal as well as numerous seizures of different semiological types.

High resolution-MRI showed a clear focal cortical dysplasia right frontal.

There was no good correlation between the right frontal lesion and the EEG, both ictal and interictal.

The patient's asymptomatic father carries the same heterozygous mutation.

The EEG of the healthy sister is pathological. A genetic testing of the patient's sister was refused by the parents.

#### Conclusions:

Our case report presents a young boy suffering from a severe drug resistant epilepsy with a mutation in the KCNQ3-gene and an additional focal cortical dysplasia.

According to the classification of the International League Against Epilepsy, epilepsy syndromes are classified as either "genetic", "structural" or "unknown".

It is a longtime experience of our pediatric epilepsy surgery program though, that there may exist a coincidence of different etiologies in one epilepsy patient.

For the first time we now could genetically proof such a coexistence of a heterozygous mutation in a gene encoding a potassium channel and a structural lesion in the same patient.

This combination possibly explains the aggravated phenotype compared to previously described patients with the same mutation and to the other family members of our patient. The relevance of these findings and their interpretation in the clinical and electrophysiological context will be discussed.

P 54

### Long-term outcome in epilepsy with grand mal on awakening

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#### Method:

Based on charts of outpatients with IGE, patients with a clear syndrome of awakening epilepsy were identified and included into the study when follow-up was  $\geq 20$  years. Diagnostic allocation was made on the basis of clinical and EEG data as documented in patient charts. Data were derived from direct patient interviews or from detailed outpatient charts. Terminal remission was defined as seizure freedom in the last 5 years.

#### Results:

Forty-two patients (29 males, 69%) were included into the study (mean age,  $60 \pm 13$  years). Age at onset was  $21 \pm 9$  years. Eleven patients had died, age of death was  $74 \pm 11$  years. After follow-up of  $40 \pm 13$  years, 26

patients (62%) were seizure free, 5 without antiepileptic drugs (AED). Following multivariate analysis, age at investigation (OR 0.939; CI95% 0.887-0.994;  $p = 0.029$ ) was an independent predictor for lack of remission. Twenty patients (48%) had withdrawn AED at least once, 12 of those (60%) suffered from seizure relapse.

#### **Conclusion:**

Four decades after onset of awakening epilepsy, more than 60% of patients were seizure free in the last 5 years. Lack of remission was a function of patients' age, the younger patients were, the less likely they were seizure free. Antiepileptic drug withdrawal was associated with significant relapse risk. Awakening epilepsy is not associated with premature mortality.

P 55

#### **Occurrence of cavernomas not related to seizure generation**

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#### **Aims:**

Cavernomas (CAV) have a high epileptogenic potential of 40 – 70% of the affected patients, presumably due to micro hemorrhage in the surrounding cerebral tissue. In general they are identified during the diagnostic work-up of the seizures and consecutively operated on.

#### **Methods:**

To identify patients in whom the cavernoma was not the cause of the seizures we reviewed the diagnostic work-up including MR imaging and video-EEG-monitoring (VEM) of all patients with these two disease entities. If MRI and the seizure onset zone in VEM were discordant with respect to the side or the affected lobe, the cavernoma was classified as non-causative. We included patients before surgery as well as patients who had been operated in other institutions but were not free of their typical seizures and requested another diagnostic work-up.

#### **Results:**

We identified nine out of 95 patients who met the above mentioned criteria: 5 women, 3 men, age 22 – 67 y, 4 CAV left frontal, 4 CAV right temporal.

Two patients with right temporal CAV showed clearly independent left and right temporal seizure onset zones (SOZ), one patient with left frontal CAV had bitemporal and right temporal SOZ, and one patient with left frontal CAV had left and right frontal SOZ. One patient with left frontal CAV showed unequivocal pattern of idiopathic generalized epilepsy (Janz syndrome). One patient with left frontal CAV did not show seizures

during monitoring but had a specific interictal focus contralateral. Two patients with right temporal CAV had been operated on without presurgical diagnostic work-up in an other institution. One of them had further seizures of the same semiology after temporo-polar resection followed by a temporo-lateral resection. VEM surface electrodes and with intracranial electrodes subsequently showed independent SOZ predominantly in the left fronto-mesial lobe and in both hippocampi. The other patient presented an unchanged high number of non-epileptic seizures with the typical semiology indicating dissociative disorder.

#### **Conclusion:**

About 8% of cavernoma patients presenting with seizures do not have structural epilepsy due to these lesions. This number suggests that these patients should undergo a specialized presurgical diagnostic procedure before the CAV is treated surgically with the aim to cure the epilepsy.

P 56

#### **Panic attacks in girls with double cortex syndrome: ictal amaurosis?**

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Within the last 3 years we saw 7 inpatients with double cortex syndrome at our Department in Kork. Five out of 7 girls had a history of visual auras which were accompanied by panic attacks in two. We report of a girl with impressive transient MRI findings supporting the hypothesis of visual auras.

The 15 year old girl with mild to moderate cognitive impairment presented with a typical double cortex syndrome in MRI. There were no other affected relatives and her development was primarily retarded. At the age 4 years a first generalized tonic-clonic seizure occurred. In the following year she suffered from repetitive grand-mal and by the age of 7 years increasing and more discognitive seizures with staring and cyanosis appeared. Attacks with complete loss of vision for several minutes were reported. However, no prophylaxis with anticonvulsive drugs was started and seizures were treated with acute benzodiazepine administration. At age 13/8 years she had a day with several seizures with confusion and repetitive eye deviation. Because of panic attacks she was hospitalized for the first time. Prolonged discognitive seizures (atypical absences), headaches, vertigo and eye deviations to the left were recognized. A MRI five days after admission showed a marked oedema on T2 images in the right parietooccipital region. Control after 8 days revealed a complete recovery in MRI. After six months she was

again admitted to hospital with an episode of several days with repetitive visual auras, with suspected amaurosis and vertigo. An acute MRI demonstrated again an oedema in the identical right parietooccipital area.

**Conclusion:**

Auras are a common seizure manifestation in lissencephaly. To our experience, visual auras are frequent. They may lead to panic attacks that can be falsely interpreted as behavioural problems, especially in mentally handicapped patients.

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**Pediatric SUDEP in a boy with a novel SCN1A-mutation and co-existing cortical temporal-lobe dysplasia**

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**Aim:**

To report observational informations about the co-occurrence of a SCN1A-mutation and a focal temporal lobe dysplasia in a pediatric SUDEP-case.

**Methods:**

Case report from a population-based regional pediatric epilepsy facility.

**Results:**

A male patient presented in the first year of life with prolonged febrile and afebrile seizures. He developed epilepsy with recurrent generalized and partial seizures not responding to standard anticonvulsants and showed a dementia-like cognitive decline. At the age of 11 years, he was found dead after having fallen asleep. After forensic work-up his death was classified as SUDEP. Post-mortem molecular analysis revealed a c.504 frameshift mutation in exon 4 of the SCN1A gene. Neuropathological examination detected a multifocal micronodular cortical dysplasia in the left temporal cortex and bilateral gliosis of hippocampal CA 4 region.

**Conclusions:**

Focal cortical temporal lobe dysplasias can be observed in DRAVET-syndrome – usually classified as generalized pediatric epilepsy syndrome with a high SUDEP-risk. They may play a role in the pathophysiology of this event.

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**Retrospective evaluation of antiepileptic drugs in patients with CDKL5 mutations**

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**Rationale:**

Mutations in the X-linked cyclin-dependent kinase-like 5 gene (CDKL5) cause an epileptic encephalopathy with early-onset severe neurological impairment and intractable seizures. Currently, there is no concept how to treat these rare patients.

**Methods:**

In this retrospective study we evaluated the efficacy of antiepileptic drugs in 34 patients with CDKL5 muta-

tions (29 female; mean age 7.1) after 3 and 6 months after the introduction of each drug. Drug response was defined as a 50% seizure reduction.

#### Results:

The patients were treated with 4 to 21 (mean: 9) different AED. 31 patients (91%) showed initial response to at least one AED for several weeks. In most of them, loss of efficacy occurred in the following weeks. One patient became seizure free with CBZ for 9 years. In the other patients seizures recurred after weeks to months. The responder rate to at least one AED after 3 months was 68% (23/34) and 32% (11/34) after 6 months. The highest rate of seizure reduction after 3 months was reported during treatment with FBM (2/3), CLB (4/17), steroids (5/24), VPA (8/31) and LEV (7/33). 12 patients (35%) experienced a seizure aggravation to at least one AED. LEV (5/33), CBZ (4/14) and LTG (3/19) were described most frequently as aggravating, which led to discontinuation. One patient (1/1) responded to intravenous immunoglobulines and 2/11 to ketogenic diet.

#### Discussion:

Most patients showed some but only initial response to various AEDs with different modes of actions. Seizure aggravation was frequently reported. Because of age-related and spontaneous fluctuation in seizure frequency and types, overall benefit of different antiepileptic drugs remains unclear. Collaborated clinical long-term observations might help clinicians to define treatment strategies in patients with this rare and refractory epileptic encephalopathy.

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#### Continuous motor impairment in young children due to highly active focal epileptiform discharges in the interictal EEG

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#### Introduction

We report on 3 children with the onset of focal-motor seizures manifesting at the age of 3. All 3 children showed a permanent motor impairment related to frequent interictal spike wave activity in the right resp. left central region. An ictal or postictal cause (e.g. postictal Todd's paresis) for these deficits could be excluded. Before the onset of first seizures none of the children had a known neurological or motor deficit.

#### Case reports:

Patient A presented with focal-motor seizure with tonic resp. clonic movements of the right hand and arm. In the course of his illness he developed a weakness in fine motor skills and loss of function of the right

hand with neglect. This was so disturbing that he, during the first year, changed handedness. The fine motor deficit of the right hand persisted even after achieving seizure freedom and normalization of the EEG.

Patient B presented with myoclonic seizure and cloni of the left corner of her mouth. In the course of her illness she developed loss of fine motor competence of the left hand, dysphagia and dysfunction of articulation. Even after achieving seizure freedom and EEG normalization the fine motor deficit and minimal loss of power of the left hand and arm persisted.

Patientin C presented with sleep-associated focal-motor seizure with cloni of left corner of her mouth and tonic-clonic movement of left arm and leg. In the course recurrent buckling and weakness of the left leg with a tendency to falls occurred.

#### Conclusion

Transient cognitive impairment is a well-known phenomenon in patients with epilepsy and frequent interictal spike wave activity. We report on 3 patients with continuous motor impairment as a possible equivalent phenomenon. No patient showed motor or neurological deficit before the onset of epilepsy, no epileptogenic lesion, focal atrophy or other brain structure pathology could be found by repeated cMRIs. All EEGs showed highly frequent interictal spike waves in the left resp. right central region that clearly could be distinguished from seizure activity. During the phase with highly active interictal discharges a causal relation between motor deficit and interictal EEG can be assumed as it has been shown experimentally that epicortical spikes in superficial cortical layers cause a hyperpolarization in deeper layers disrupting descending neuronal activity. The reason for the residual symptoms after the EEG became normal remains unclear.

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#### Drug resistant epilepsy caused by oligodendroglial hyperplasia: presurgical findings and postoperative outcome

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#### Aim:

Oligodendroglial hyperplasia is a benign disorder, which is considered to be part of the spectrum of cortical migrational abnormalities. It has been found to be associated with drug resistant focal epilepsy. However, until now only single cases have been reported in the literature. In this study we present a case series consisting of five patients suffering from refractory epilepsy caused by histologically proven oligodendroglial hyperplasia.

## Methods:

We analysed all patients with histologically proven oligodendroglial hyperplasia who were operated on for drug resistant epilepsy at the University Hospital Bonn between 2010 and 2012. All patients underwent an extended lesionectomy after a comprehensive presurgical workup. Postoperative outcome was determined according to Engel's classification.

## Results:

The study group consisted of three females and two males. The median age at epilepsy onset was 11.8 years (range 1.1 - 30.0 years), the median age at surgery was 21.9 years (4.6 - 52.9 years), the median number of failed drug trials prior surgery was 5 (4 - 8), and the median seizure frequency prior surgery was 30 seizures per month (5 - 600). All oligodendroglial hyperplasias were discernible on the preoperative MRI. In three cases the lesion was located in the frontal lobe, in the remaining two cases it was located in the temporal lobe. Blurring of the grey-white matter junction was the main MRI feature in three patients; in the remaining two cases a cystic lesion was present. Seizure semiology, surface-EEG and localization of the lesion on MRI were concordant in all cases, so that four patients were operated after a noninvasive workup only. In the remaining case invasive diagnostics with implantation of a grid electrode were necessary primarily to delineate the lesion from eloquent cortical areas. A postoperative follow-up of at least 12 months was available in four patients. Three out of these achieved a favourable Engel class I outcome (2 x Ia, 1 x Id) and one patient achieved an Engel class III outcome.

## Conclusions:

To our knowledge this is the first case series reporting about refractory epilepsy caused by oligodendroglial hyperplasia. Our results indicate that this entity leads to a severe epilepsy with a high seizure frequency. On high quality MRI all lesions could be detected and surgical resection offers an effective therapeutic option when seizures cannot be controlled by antiepileptic drugs.

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### Posterior cortex epilepsies: successful tailored resection after intracranial invasive EEG recording in three patients

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## Purpose:

Posterior cortex epilepsy (PCE) is difficult to assess due to rapid seizure propagation, misleading scalp EEG and sz semiology. We present three patients (pt) with successful tailored resection after invasive video-EEG-monitoring.

## Case Report:

Pt1: male, 62, hemianopic to the right, sz since age 10 (3/mo) with visual aura, orolimentary automatisms (OAA), aphasia, secondary generalized tonic clonic seizures (sGTCS). Interictal (ii) EEG showed spikes right > left temporal, ictal (i) EEG onset was over left posterior. MRI (1.5T) showed atrophy and hyperintense lesion left temporo-occipital, [18]FDG-PET hypometabolism left occipital (occ) and right temporal (temp). Neuropsychology (NPSY) revealed reduced verbal and figural memory. Subdural strip and bilateral hippocampal (hc) depth electrodes were implanted. Sz onset was localized to temporo-occipital left, cortical mapping identified adjacent eloquent cortex. Tailored resection resulted in outcome Engel IC (FU 9 ys) without any postoperative deficit.

Pt2: male, 35, hemianopic to the left, sz since age 12 (10/mo) with unspecific aura, OAA, verbalization, and sGTCS with version left, **figure4** left, asymmetric seizure termination right, postictal hemiparesis left. iiEEG showed spikes right temp, iEEG onset was right temporal MRI showed right occ mesial ulegyria, [18]FDG-PET hypometabolism right temporal and parietal, [99mTc]iSPECT hyperperfusion temporo-occipital right. NPSY was normal. After implantation of subdural grid/strip and right hc depth electrodes sz onset was located in mesial occ region. Tailored resection resulted in seizure freedom (Engel IA, FU 2 ys) without any deficit.

Pt3: male, 22, without clinical deficit, sz since age 9 (2/mo), with micropsia/metamorphopsia, vertigo, visual hallucinations, headache right, ictal hemianopsia, rare cGTCS. iiEEG showed periodic spikes right occ, iEEG onset was right occ. MRI showed focal cortical dysplasia in right lateral occipito-temporal gyrus, [18]FDG-PET hypometabolism right temp and occ, [99mTc]iSPECT hyperperfusion right occipital and right amygdala. NPSY found minor deficits. Subdural grid/strip and 2 perilesional depths electrodes localized sz onset adjacent to MRI lesion. Pt is 6 month sz free after tailored resection without visual deficit.

### Conclusion:

Favorable postoperative outcome can be achieved in PCE when intracranial EEG recording identifies distinct seizure zone and seizure spread. Cortical stimulation successfully delineates eloquent regions.

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### Seizure control and developmental trajectories after hemispherotomy for refractory epilepsy in childhood and adolescence

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### Aims:

To evaluate the seizure control and developmental outcomes after hemispherotomy for refractory epilepsy in childhood and to identify their predictive factors.

### Methods:

We retrospectively studied the clinical courses and outcomes of 52 children with refractory epilepsy who underwent hemispherotomy in the Epilepsy Center Freiburg between 2002 and 2011.

### Results:

Mean age at epilepsy onset was 1.8 years (range 0 - 8) and mean age at surgery was 6.7 years (range 6 months - 18 years). The underlying etiology was congenital in 22 (42%) children, acquired in 24 (46%) and progressive in 6 (12%). At final follow-up of 1 - 9.8 years (mean 3.3), 43 (83%) children were seizure free. Seizure outcome was not correlated to etiology, with the exception of hemimegalencephaly that was linked to poor seizure control. Presurgical development was impaired in all but one child. Postsurgical development highly correlated with presurgical development. Patients with acquired or progressive etiology, later epilepsy onset and subsequent later surgery exhibited higher presurgical developmental status that substantially determined postoperative developmental outcome. Improved postsurgical development was determined by acquired etiology and seizure freedom off antiepileptic drugs.

### Conclusions:

In our study, the vast majority of selected children and adolescents achieved seizure freedom, including those with congenital etiology. Developmental outcomes, however, were superior in patients with acquired etiology and older age at surgery, underlining that it is never too late to reap the benefits of this procedure in terms of both epilepsy and development.

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### Enduring impact of social work counselling in the comprehensive care of people with epilepsy

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### Aim(s):

One of the cornerstones of comprehensive care of people with epilepsy is counselling by specifically trained social workers. However, studies investigating the enduring effects of counselling are lacking. The aim of this study is to analyse the long-term outcome of social work counselling of patients in the short stay department of the Saxon Epilepsy Centre at Radeberg. The study is focussing on consultations on the subject of severe disability, based on Book IX of the Social Code (Sozialgesetzbuch/SGB IX). SGB IX has the purpose of promoting self-determination and equal participation in society for people with disabilities and at risk of disability and to counteract or prevent discrimination.

### Methods:

In-patients with seizure disorders admitted to the Department of Neurology in 2011 were included in this interview study. Main inclusion criteria were: patients with epilepsy or psychogenic non-epileptic seizures, age of 18 or older, and counselling about the law of the severely disabled. At baseline, socio-demographic and clinical data were recorded together with key data of the severely handicapped pass of the patients. About 13 to 15 months after discharge, the outcome of the social work counselling was assessed by structured telephone interviews, focusing on post-discharge changes of the legal status as a severely disabled person.

### Results:

Counselling about the law of the severely disabled took place in 83 patients (35 female, 48 male; mean age 39.2 years (range: 20 to 74 years). 78 (94%) patients had epilepsy, 4 patients (5%) psychogenic non-epileptic seizures and 3 patients (4%) had dual diagnosis. At baseline, 35 (42%) of the patients had recognized severe disabilities, severely disabled pass with codes (Merkzeichen) was assigned to 15 (18%) patients. 14 (17%) patients applied for recognition as a disabled person. Post-counselling interviews will be performed between February 2013 and March 2013.

### Conclusions:

To the knowledge of the authors, this is the first study exploring the enduring impact of specialized social counselling of patients with seizure disorders. The design of the study enables us to investigate the relationship between counselling, legal status as a severely disabled person, and factors threatening an adequate assignment of legal status. This research will result in a methodological framework that will contribute to significant improvement in outcomes of social work counselling in patients with epilepsy.

P 64

### Should patients with epilepsy be allowed to drink alcohol?

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### Aims:

To identify independent risk factors for alcohol-related seizures in epilepsy patients, and to analyse physicians' advice on the use of alcohol.

### Methods:

At a tertiary epilepsy center, a standardised questionnaire was used to collect the data and logistic regression analysis was performed to identify independent predictors.

### Results:

Overall 310 subjects were included. Alcohol-related seizures were reported by 17.4% of alcohol-experienced patients. Seizures were generally preceded by heavy alcohol intake, equivalent to at least 1.4 liters of beer. Idiopathic generalized epilepsy (IGE) (OR 6.028, 95% CI 2.871–12.659), antiepileptic drug (AED) polytherapy (OR 2.400, 95% CI 1.236–4.660), and male sex (OR 2.005, 95% CI 1.027–3.916) were identified as independent predictors for alcohol-related seizures. Notably, physicians' advice on the use of alcohol was generally given across-the-board regardless of individual risk factors for alcohol-related seizures.

### Conclusions:

Light to moderate alcohol intake does not increase epilepsy patients' risk of seizure occurrence. In the present study, IGE was identified as the strongest independent predictor for the occurrence of alcohol-related seizures. In subjects with IGE, matutinally increased brain excitability may be potentiated by the hyperexcitable post-alcohol state that commonly occurs in the

early morning after consuming alcohol the night before. AED polytherapy reflects a more severe course of the disease, and patients affected may be more prone to external seizure triggering mechanisms. As men in general practice heavier alcohol consumption, male gender likely is a socio-cultural risk factor for alcohol-related seizures. The present study's findings should be taken into account by physicians counseling epilepsy patients on alcohol consumption.

P 65

### The Epilepsy and Work Network: Factors for remaining in employment

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### Aims:

The number of professional possibilities for people who are suffering from epilepsy is often rated as inadequate. An interdisciplinary company advisory and risk assessment service needs to be implemented in conjunction with the BGI 585 Risk Assessment Guidelines in view of protection against unfair dismissal framework and assistance. In order to be able to establish the above mentioned consulting services locally, the Epilepsy and Work Network has set up 23 multi disciplinary professional teams all over the German states with more than 300 experts. The teams will consist of neurologists, industrial physicians, rehabilitation consultants and consultants of epilepsy information centres. These teams will be able to advise and help people suffering from epilepsy.

The ultimate aim of the Epilepsy and Work Network is to prevent employees suffering from epilepsy from facing unfair dismissal and analyse the factors for remaining in employment.

### Methods:

The analyses are based on client-centred data sent by the teams from all over the German states to the Epilepsy and Work Network Bureau. Specific survey instruments have been developed including detailed questions about socio-demographic, epilepsy-specific and job-related information. The data set includes 135 persons suffering from epilepsy who have been advised by the members of the professional teams. The participants mean age is 36 years (range: 14 to 60 years), the majority is male (64%).

### Results:

The most often mentioned type of seizures is tonic-clonic (85%), followed by complex partial (32%). Only 10% of the participants have been seizure free for at least one year, the majority report of less than three seizures in one year (38%). Over 75% of the participants refer to risks at work. After consultation of the profes-

sional team 70% of the persons with epilepsy is (still) employed, 8% participates in a rehabilitation program, 5% is unemployed and 4% is in receipt of a disability pension. Of the persons who have less than three seizures in one year 84% are (still) employed. Of those having three or more seizures 71% are (still) employed. Further analyses will be presented.

**Conclusions:**

Although no causality can be proofed, there are strong hints that most employees with epilepsy benefit from being supported by multi disciplinary professional teams as part of the Epilepsy and Work Network.



FV 66

### 3T versus 1.5T MRI in the routine clinical setting

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#### Aims:

MRI is one of the major diagnostic tools in the pre-surgical evaluation. The detection and precise characterization of the epileptogenic lesion is crucial for the postsurgical outcome.

Previous studies in small patient populations have suggested that high-field MRI may help to identify, delineate, and characterize epileptogenic lesions in more patients. We describe the diagnostic gain in using 3T MRI compared to 1.5T MRI in 201 patients in a routine clinical setting.

#### Methods:

201 consecutive patients with medically refractory focal epilepsy who were referred for presurgical evaluation were included: All patients had a 1.5T MRI and a 3 T MRI with protocols optimized for the detection of epileptogenic lesions. MRI scans were read by an experienced neuroradiologist and an experienced epileptologist with access to all clinical information.

#### Results:

75/201 (37%) lesions were identified using 1.5 T MRI and 144/201 lesions (71%) were described using 3T MRI ( $p < 0.001$ ). Seventeen percent of the patients who were already MRI positive on 1.5T MRI had an additional lesion in the 3T MRI, an previously suspicious

lesions at 1.5T could be clarified using 3T in 40.3 %. Most of the lesions described at 1.5T were hippocampal sclerosis or other brain lesions (53 %), malformation of cortical development (MCD) were described in 30 %. At 3T, most of the described lesions were MCD (56 %) and hippocampal sclerosis (31 %) 84% of all newly detected lesions in the MCD-group were diagnosed as focal cortical dysplasia. 3T results were in better accordance with surface EEG (1.5T = 30.8%; 3T = 57.24%), invasive EEG (1.5T = 33.3%; 3T = 66.6%) or histopathological results (1.5T = 30.8%; 3T = 65.4%).

#### Conclusions:

In clinical routine, 3T MRI is superior to 1.5T MRI. All patients with medically refractory epilepsy should have a 3T MRI to minimize the amount of MRI-negative patients and to optimize lesion detection, extension and characterization.

#### Acknowledgement:

The study was supported by a grant of the Behring Roentgen Stiftung to SK.

Calculated with chi-quadrat-T.

FV 67

### A common SCN1A splice site polymorphism modifies the effect of carbamazepine on cortical excitability – a pharmacogenetic TMS-study

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#### Aims:

SCN1A encodes for the alpha subunit of the voltage-gated sodium channel Nav1.1 and plays a crucial role in several epilepsy syndromes, including genetic epilepsy with febrile seizures plus (GEFS+) and Dravet syndrome. Recent evidence suggests that the common SCN1A splice site polymorphism rs3812718 (IVS5N+5 G>A) might contribute to the pathophysiology underlying genetic generalized epilepsies. The polymorphism is associated with electrophysiological properties of the channel and the effect of sodium-channel blocking antiepileptic drugs in vivo and in vitro. In order to further

investigate the association between rs3812718 and genetic generalized epilepsies and pharmacoresponse, we assessed the effects of the rs3812718 genotype on cortical excitability at baseline and after administration of carbamazepine.

#### Methods:

Paired-pulse transcranial magnetic stimulation (TMS) was applied in 92 healthy volunteers with the homozygous genotypes AA or GG of rs3812718 at baseline and after application of 400mg of carbamazepine or placebo in a double-blind, randomized, cross-over design. The TMS parameters investigated included resting motor threshold (RMT), short interval intracortical inhibition (SICI) and facilitation (SICF) as well as cortical silent period (CSP).

#### Results:

The main finding was a higher carbamazepine-induced increase in CSP duration in subjects with genotype GG as compared to AA and the placebo induced changes (MANCOVA,  $p = 0.013$ ). An expected significant increase in RMT was genotype independent. At baseline there was no significant difference in any TMS parameter.

#### Conclusions:

We found that the rs3812718 genotype modifies the effect of carbamazepine on CSP duration, a TMS parameter mainly reflecting modulation of GABA-ergic inhibition. This provides clear evidence that rs3812718 affects the pharmacoresponse to carbamazepine via an effect on GABA-ergic cortical interneurons and supports earlier studies which showed that changes in the SCN1A gene lead to reduced function of these interneurons, possibly due to selective expression of NAV1.1.

FV 68

#### Allocation of new onset epileptic seizures and epilepsies based on semiology and additional investigations

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#### Aims:

For most patients, new onset epileptic seizures mark a major life event, and clinicians are challenged by making correct diagnoses and treatment decisions. This retrospective study evaluates the contribution of detailed history and further investigations for early diagnostic allocation of seizures and epilepsies.

#### Methods:

The database of a large academic neurological department was searched for patients  $\geq 18$  years admitted for new onset seizures and epilepsies between

01/2008 and 12/2010. Based on information from discharge and emergency room reports on semiology and further details of history as well as EEG and neuroimaging, all cases were allocated to one of 6 groups: acute symptomatic seizures, isolated unprovoked seizures, partial, generalized and undetermined epilepsy, and uncertain diagnosis. Furthermore, antiepileptic treatment strategies were assessed.

#### Results:

A total of 296 patients were included (59.5% male, mean age 56.6 $\pm$ 19.1 years). In 272 patients (91.9%), history alone was sufficient to diagnose a definite epileptic seizure, while in the remaining patients, additional investigations were necessary. For allocation to one of the 6 groups, pathological findings in standard EEG were helpful in 18.2% and in sleep deprivation EEG in 4.7%. Imaging studies were performed in 98% of patients; of these, 26.9% had MRI only, 34.1% CT scan only, and 39% both modes. For group allocation, neuroimaging results were helpful in 48.6% of all cases. In all patients with MRI, the most frequent pathological findings were cerebrovascular (30.4%) or neoplastic (6.8%) lesions. Based on history and test results, allocation to the 6 groups was as follows: acute symptomatic seizures 12.5%, isolated unprovoked seizures 20.6%, partial epilepsy 53.4%, generalized epilepsy 1.7% and undetermined epilepsy 2.4%; in the remaining 9.5% of cases the diagnosis remained uncertain. Treatment was initiated in 21.3% of patients with isolated seizures and in 84.9% of patients with partial epilepsy ( $p < 0.001$ ). In both groups, levetiracetam was the most frequently used AED (53.8% and 50.7%, resp.).

#### Conclusions:

The vast majority of new onset epileptic seizures can be diagnosed on the basis of detailed history alone. For correct group allocation, neuroimaging is more helpful than EEG ( $p < 0.001$ ). To determine prognosis of new onset seizures and epilepsies and follow treatment decisions, we plan to collect long-term data in a prospective manner employing a large-scale register.

FV 69

#### Application of volume rendering for localization of implanted electrodes in invasive evaluation of epilepsy surgery

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Supported by DFG STE 380/14-1, 15-1

**Aims:**

For invasive video-EEG monitoring in evaluation of epilepsy surgery, subdural and depth electrodes are implanted. Their localization is documented using X-ray in two planes, as well as MRI and CT. Especially the spatial relation to functional and anatomic cortex areas is however hard to determine by inspection of these slice data. Datasets are coregistered and displayed as surfaces for better spatial overview. We present a visualization technique using volume rendering and coregistration of atlas data for improved identification of epileptic and functional areas.

**Methods:**

Data from presurgical evaluation from a patient suffering from pharmacoresistant epilepsy due to focal cortical dysplasia (FCD) were processed. VBM-maps (voxel-based morphometry, MAP07-software) were calculated for segmentation of the FCD. After implantation of subdural grids for invasive video-EEG monitoring (6 and 4 contact strip, 64 contact grid), MRI and CT were acquired. Electrodes were segmented in the CT dataset and coregistered with MRI. In addition, the cortex surface was segmented. The Talairach-Tournoux atlas was coregistered for identification of the precentral gyrus (Curry 7, Compumedics Neuroscan, Singen, Germany). All datasets were overlaid and visualized using custom volume rendering software (VolumeLab).

**Results:**

Video-EEG monitoring results were concordant with the visualization: ictal and interictal activity was detected in contacts over the FCD. Electrical cortical

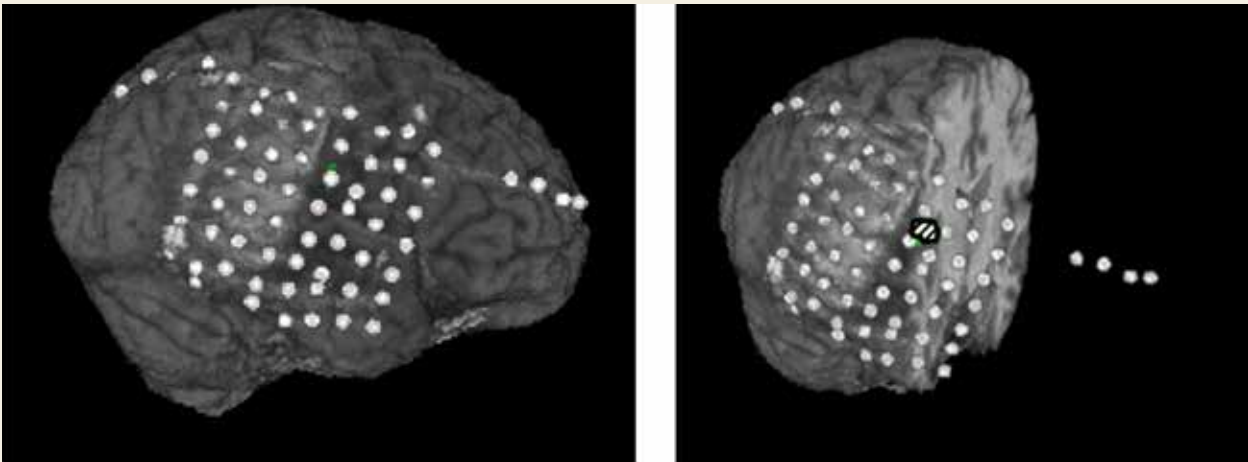


Figure 1: Electrode positions and FCD localization.

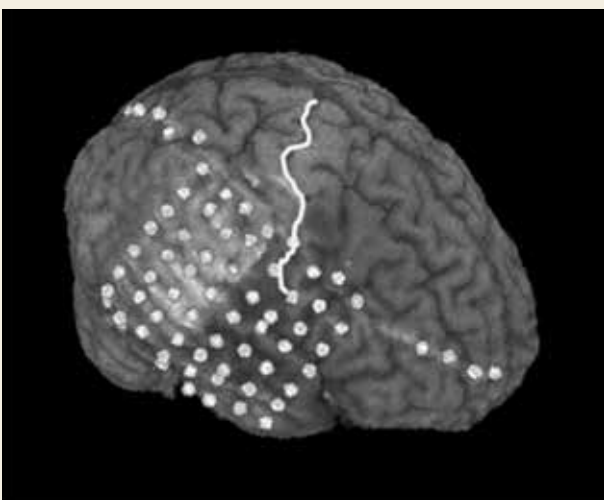


Figure 2: Location of the central sulcus from coregistered atlas data.

stimulation identified pre- and postcentral gyri, as well as the auditory cortex exactly under the predicted electrodes. The volume rendering technique allowed a more detailed visualization of sulci and gyri in comparison to the segmented cortical surface. Epilepsy surgery was planned using the coregistered 3D-visualization of epileptic and functional information, deliberately included parts of the facial motor cortex and did not lead to any unexpected deficits.

**Conclusions:**

Segmentation and coregistration of pre- and post-implantation data, as well as visualization using volume rendering enable an accurate estimation of electrode positions. Coregistered atlas data facilitate identification of eloquent cortex and spatial relation to implanted electrodes.

FV 70

### **Autosomal dominant vasovagal syncope: Clinical features and linkage to chromosome 15q26**

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#### **Aims:**

Vasovagal syncope (VVS) is the most frequent type of syncope and a common differential diagnosis of epilepsy. Using a twin-family design, we recently showed that VVS has a genetic etiology and complex inheritance is usual (Klein et al. *Neurology* 2012;79:561-565). Here, we establish the occurrence of an autosomal dominant form of VVS by detailed phenotyping of multiplex families and identification of the causative locus.

#### **Methods:**

We recruited patients with VVS and a family history of syncope. A standardized questionnaire addressing features differentiating syncope from epilepsy was administered to all available family members. Medical records were obtained and additional diagnostic tests performed in selected individuals. Six of 44 recruited families were suggestive of autosomal dominant inheritance. Linkage analysis was performed in family A using SNP genotyping microarrays and in four other families with microsatellite markers for chromosome 15q26. One family was too small for analysis. Candidate genes within the linkage interval were analyzed by sequence analysis.

#### **Results:**

The largest family A contained 30 affected individuals over three generations with a median onset of 8-9 years. The other families comprised 4-14 affected individuals. The affected family members reported typical triggers of VVS such as sight of blood, injury, medical procedures, prolonged standing, pain and frightening thoughts. There was considerable variation of the triggers within the families. Linkage analysis revealed significant linkage to chromosome 15q26 in family A (LOD score 3.28) with two peaks, one at chromosome

15q26.1 spanning 6.28 cM or 1.7 Mb, and the other at chromosome 15q26.2 spanning 1.19 cM or 0.5 Mb. Linkage to chromosome 15q26 was excluded in two medium-sized families but not in two smaller families. Sequence analysis did not identify mutations in the candidate genes *SLCO3A1*, *ST8SIA2* and *NR2F2*.

#### **Conclusions:**

The presented families demonstrate that familial VVS, inherited in an autosomal dominant manner, is not rare and has similar features to sporadic VVS. The chromosome 15q26 locus in family A increases the susceptibility to fainting but does not predispose to a particular vasovagal trigger. Genetic heterogeneity was established by linkage analyses in the other families. Identification of the causal mutations will help to further understanding of pathophysiology and guide further genetic research.

FV 71

### **Chronic stimulation of the nucleus accumbens in patients with intractable partial epilepsy**

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#### **Aims:**

In patients with intractable partial epilepsy, electrical stimulation of the anterior thalamus results in a significant reduction of seizure frequency. Unfortunately, a significant number of patients also reported depressive symptoms. The nucleus accumbens (NAC) has a relay function both for the frontal lobe and for the Papez circuit. Thus, it becomes a putative target to suppress ictal connectivity in these areas. Also, patients with major depression have been successfully treated with DBS of the NAC. The following observational study on patients with intractable epilepsy summarizes clinical outcome after 6 months of DBS in the NAC.

## Method:

Patients with intractable partial epilepsy underwent electrical stimulation of the NAC for 6 months. They were operated by a single surgeon (J.V.), and stimulation parameters and sites remained unaltered for each target. Patients underwent video-EEG-monitoring before surgery and after the stimulation period. The antiepileptic drug regimen remained unchanged, starting 6 months before surgery. Changes of seizure frequency, Liverpool-Seizure-Severity-Scale (LSSS) and Beck-test-score were assessed after 6 months of NAC stimulation and compared to baseline values. Due to pronounced interindividual heterogeneity in the baseline period, clinical variables were related to the individual baseline values and expressed as fraction of 1.

## Results:

Four patients were included into this study. Generalized tonic-clonic and complex-partial seizures were summarized as disabling seizures and simple partial seizures as non-disabling seizures, resp. In comparison to the 6 months before surgery, after 6 months of NAC stimulation the LSSS score was significantly reduced to  $0.81 \pm 0.11$  ( $p = 0.014$ ) and there was a tendency to reduction of the relative number of disabling seizures (to  $0.66 \pm 0.34$ ;  $p = 0.091$ ). In comparison to baseline, two subjects experienced a reduction in frequency of disabling seizures down to 58% and to 21%, resp. From all four patients only the patient with a 21% seizure reduction showed a diffuse electroencephalographic seizure onset pattern. The number of non-disabling seizures and the Beck score remained unchanged.

## Conclusion:

In four patients with intractable partial epilepsy, 6 months of bilateral NAC stimulation significantly reduced the seizure severity score. A larger cohort may show reduction in seizure frequency to be significant and reveal specific electrophysiological characteristics for responders.

FV 72

## Direct costs of epilepsy among children and adolescents in Germany

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## Aim:

Epilepsy is a common neurological disorder and imposes a substantial burden on patients, their caregivers and society as a whole. Only few studies worldwide and none in Germany examined the costs of epilepsy in children and adolescents. Therefore, we performed a cross-sectional cohort study in children and adolescents with epilepsy in the states of Hesse and Schleswig-Holstein. Patients seeking outpatient treatment from neuropaediatricians (NP), at centers for social paediatrics ("Sozialpädiatrische Zentren", SPZ) and at epilepsy centers (EC) were evaluated in 2011.

## Methods:

Patients and their treating physicians provided data on socioeconomic status, course of epilepsy and direct as well as indirect costs. Questionnaires over a 3-month period were used and evaluated according to German recommendations for health economic evaluations (IQWiG). Patients under 18 years of age were included irrespective of seizure severity, duration of illness and epilepsy syndrome. Five prognostic groups were used for classification: patients with newly diagnosed epilepsy (NDE), seizure remission for more than one year (SR), occasional seizures (OCS), non-drug-resistant seizures (NDRE) and drug-resistant seizures (DRE).

## Results:

Among the  $n=489$  patients with epilepsy (age  $10.4 \pm 4.2$  years, range 0.5-17.8 years, 264 male) 253 were treated by NP, 110 at SPZ and 126 at EC. We calculated total direct costs of  $\text{€}1631.9 \pm \text{€}4376.2$  per patient for a 3-month period. Direct medical costs were mainly due to hospitalization (47.4% of total direct costs,  $\text{€}773.8 \pm \text{€}3594.5$  per three months), anticonvulsants (13.8%,  $\text{€}225.7 \pm \text{€}402.9$ ) and ancillary treatment (9.0%,  $\text{€}147.3 \pm \text{€}344.1$ ). The mean duration of hospitalization was  $11.4 \pm 18.5$  days. Predominantly prescribed anticonvulsants were valproate (35.6%), lamotrigine (19.0%), levetiracetam (15.1%), oxcarbazepine (14.5%) and sultiame (11.2%). Within the prognostic groups, the lowest direct costs were associated with

patients in SR (n=204, €641.1±€1373.4 per patient and 3-month period) followed by patients with OCS (n=69, €1726.6±€5824.8), NDRE (n= 122, €1939.6±€3227.5), NDE (n=17, €2631.8±€5130.8) and DRE (n= 77, €3463.7±€7683.0).

#### Conclusion:

We could demonstrate that hospitalization, antiepileptic drugs and ancillary treatment are the main direct cost factors among children and adolescents with epilepsy. Mean direct costs of epilepsy in this German study were lower than in previous studies conducted at European epilepsy centers.

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#### Early detection of bone metabolism changes under different antiepileptic drugs (ED-BoM-AED) – a prospective multicenter study

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#### Aims:

To determine early changes in bone turnover markers induced by treatment with oxcarbazepine or valproate.

#### Methods:

In this prospective study, 31 adults (with newly diagnosed epilepsy) were included who were started on therapy with either oxcarbazepine (OXC, n=16, mean age 45.6 years, 37.5% female) or valproate (VPA, n=15, mean age 42.2 years, 33.3% female). Clinical characteristics were obtained at baseline, after 2 weeks and 3 months. In addition, blood samples were drawn at each visit. Calcium, phosphate, alkaline phosphatase (AP), receptor activator of NF-κB ligand (RANKL), osteoprotegerin (OPG), osteocalcin (OC) and cathepsin K were determined.

#### Results:

In OXC treated patients, OPG increased by 0.6 pmol/L (p = 0.0004) after 2 weeks and remained elevated by 0.5 pmol/L (p = 0.02) after 3 months. Between 2 weeks and 3 months of OXC treatment, OC increased by 1.98 ng/mL (p = 0.02). During the first 3 months of OXC treatment, total serum AP increased by 11% ± 9 % (p = 0.02). Compared to baseline, serum calcium raised by 0.06 mmol/L (p = 0.04) after 2 weeks and by 0.071 mmol/L (p = 0.004) after 3 months of OXC treatment. In VPA treated patients, a late OPG increase by 0.7 pmol/L (p = 0.007) occurred after 3 months. Dur-

ing the first 3 months of OXC treatment, total serum AP decreased by 7% ± 15% (p = 0.03). No changes in OC or calcium were seen. RANKL was below detection limit in 16 out of 31 patients (52 %) and did not change significantly during treatment. Cathepsin K was below detection limit at baseline in 27 out of 31 patients (87 %) and was therefore not further evaluated. Phosphate did not change during treatment.

#### Conclusion:

Increased bone turnover can be measured within few weeks of newly started treatment with OXC, while significant changes under VPA treatment occurred only after 3 months. Our data suggest distinct mechanisms of increased bone turnover in different anticonvulsants. These variable mechanisms may require individual prevention and treatment strategies.

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#### Functional MRI network modularity in temporal lobe epilepsy

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#### Aim:

Temporal lobe epilepsy (TLE) often can be much improved by the surgical removal of a localized structural pathology. Still, evidence has accumulated that this epilepsy syndrome (as well as others) need to be conceptualized as network disease (Laufs 2012) in which the interplay is disturbed between brain regions immediately affected by the structural pathology (e.g. the hippocampus) and those remote to them (e.g. the posterior cingulate, (Laufs, Hamandi et al. 2007)). We hypothesized that the network architecture in patients with temporal lobe epilepsy is significantly different to that of healthy volunteers reflecting semiological features of the epilepsy syndrome, i.e. memory impairment and compromised consciousness.

#### Methods:

We used graph theoretical methods based on fMRI functional connectivity to study in detail the modular network structure in 20 patients with TLE in comparison to 20 healthy controls with special reference to the vigilance state.

ten observed in TLE. The higher node degree in the posterior cingulate, an integral part of the “default mode” network, indicates an “over connection”, which might reflect an increased susceptibility of the DMN in TLE for its suspension observed with impaired consciousness.

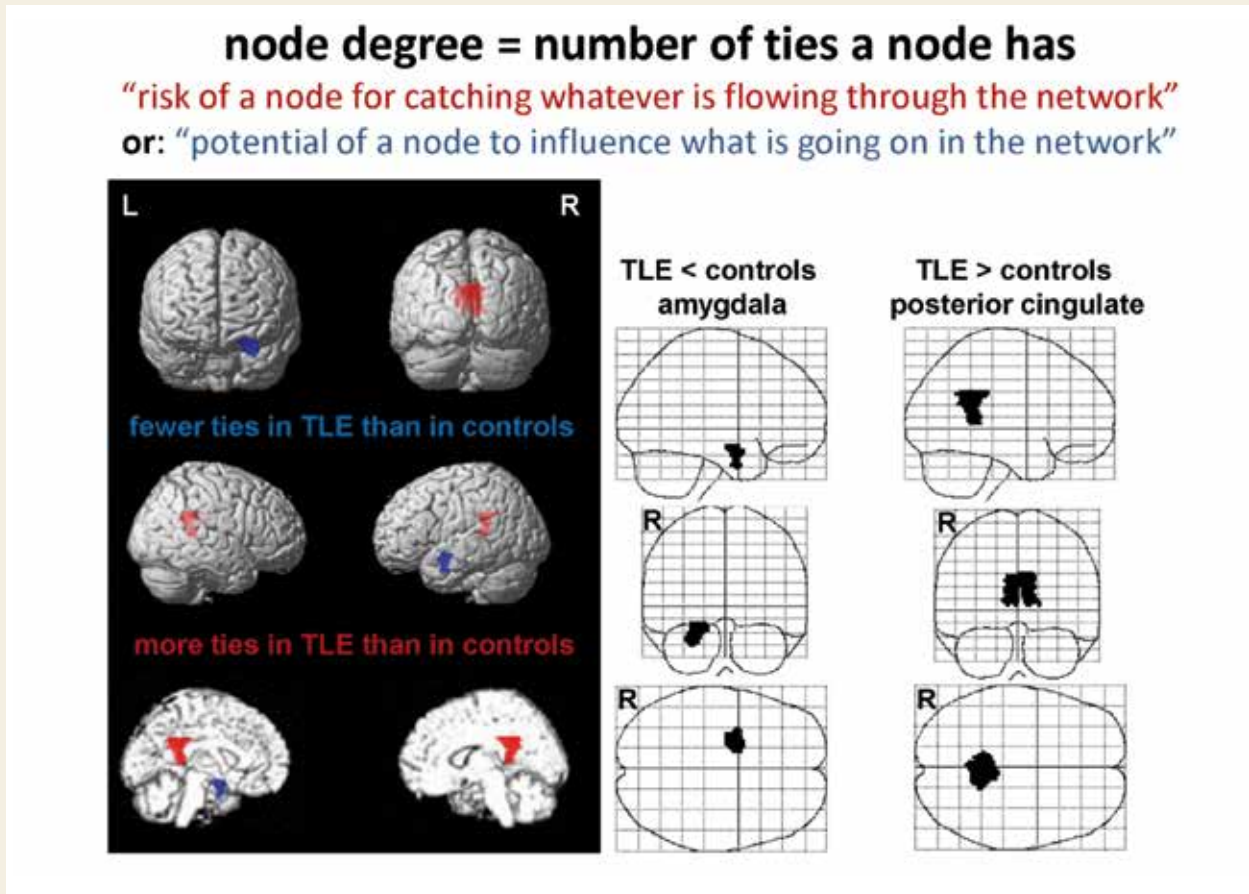


Figure 1

**Results:**

Compared to healthy controls, link density was reduced in TLE (= higher modularity in TLE). Node degree (= number of ties, a node has) in the amygdala was reduced in TLE compared to controls while in the posterior cingulate, it was higher in TLE than in controls.

**Conclusions:**

Network modularity quantifies the strength of interaction between functional modules. It was decreased in TLE compared to controls paralleling our findings in healthy subjects with deepening sleep (Tagliazucchi, von Wegner et al. 2013). Sleep is an example of a physiological condition with features similar to TLE: reduced consciousness and limited cognitive functioning. The decreased node degree in the amygdala can be interpreted as reduced connectivity to other network nodes, possibly linked to memory dysfunction of-

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### Improving semiological seizure classification through structured interviews and video tutorials

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#### Aim:

The analysis of seizure semiology is well established in presurgical epilepsy monitoring. Classifying seizure semiology from patient history may be more difficult, because the recollection by the patient and next of kin may be inconsistent and flawed by subjectivity. Possibly, though, seizure semiology could be an important piece of information to triage patients whether to undergo epilepsy monitoring or not. We therefore studied whether history taking of seizure semiology can be improved by structured interviews and by demonstrating seizure semiology through video examples.

#### Methods:

In a first step, we compared the seizure semiology of 208 consecutive patients as described in the patients' history and compared it to the seizure semiology recorded in our epilepsy monitoring unit. In a second step we compared the yield of seizure semiology information of 72 patients, when taken from patients' records, after structured interviews and after showing seizure videos to patients and their next of kin.

#### Results:

Of the 208 patients of the first part of the study, 138 (66.3%) could correctly report signs for focal epilepsy as compared to 54 patients (26.0%) that did not report any signs of focal epilepsy but had them recorded in the epilepsy monitoring unit. Six patients had generalized epilepsies and five of them had incorrectly reported focal semiology. Lateralizing signs could correctly be reported by 15.3% of patients. 7.4% reported lateralizing signs, but we could not reproduce them in the epilepsy monitoring unit and 44.1% of patients did not report lateralizing signs but we recorded them in epilepsy monitoring.

In the second part of the study, only 6 patients out of 56 (10.7%) with focal epilepsy had lateralizing signs on record (4 with localizing signs). After a structured interview, these numbers increased to 31 (55.4%) for lateralizing signs and 28 (50.0%) for localizing signs. After showing exemplary videos to the patients, these numbers increased even more, to 49 patients (87.5%) for lateralizing signs and 33 patients (58.9%) for localizing signs.

#### Conclusions:

Our study demonstrates that the analysis of seizure semiology from patient history may be incomplete, but that it may be improved by structured interviews and even more so by demonstrating video examples of typical semiology to patients. Taken together with other information, this may improve the triage of patients towards presurgical epilepsy monitoring.

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### Proximity between fMRI activation and structural language pathways predicts verbal fluency performance in left frontal lobe epilepsy

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#### Aims:

Language function is frequently reorganized in epilepsy patients, particularly in left frontal lobe epilepsy (FLE). Not only is the right frontal lobe increasingly recruited, there is also a significant reorganization within the left hemisphere. The degree of functional MRI (fMRI) activation, or measures such as the laterality index are often not correlated with the neuropsychologically measured language capabilities of patients. We hypothesize, that the proximity of functional cortex to the underlying language pathways is crucial for the language performance in left frontal lobe epilepsy. We investigate this with a combined fMRI and diffusion tensor imaging (DTI) pilot study in 16 patients with FLE.

#### Methods:

Patients were examined on a 3T MRI scanner. They performed a verbal fluency fMRI paradigm, comprising 5 blocks of 30 seconds covert word generation, alternating with rest. fMRI was recorded using a whole brain acquisition of 50 axial slices, 2.5 mm slice thickness with a TR of 2.5 sec. DTI was acquired with a total of 52 diffusion directions, a slice thickness of 2.5 mm and 2.5 mm in plane resolution. DTI data was normalized to standard space and probabilistic tracking of the arcuate fasciculus was performed. The resulting tracts were superimposed with the coregistered fMRI statistical parametric maps. Both images were smoothed and thresholded, and the overlapping volume was determined.

#### Results:

One patient failed to activate during the fMRI paradigm, two showed right language dominance and were also excluded. For the remaining patients, the peak



fMRI z-score ranged from 3.2 to 7.4. The volume of overlap between arcuate fasciculus and fMRI activation ranged from 0.8 to 31.4 ml, not normally distributed. The Verbal fluency score from neuropsychological assessment ranged from 4 to 22 words per minute. This was not in correlation with peak fMRI activation (Spearman correlation 0.22, but it was correlated with the overlapping volume of fMRI and DTI (Spearman correlation 0.81).

**Conclusions:**

We present a processing pipeline for combined analysis of functional activation in relation to underlying structural pathways. In patients with left FLE, this measure correlated with their neuropsychological verbal fluency scores, whereas the fMRI activation alone showed no relation to cognitive performance. This provides evidence, that the efficiency of cortical reorganization of language depends on the proximity to major structural pathways.

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**Caesarean section in women with epilepsy – current data from the German Registry of Antiepileptic drugs and Pregnancy**

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**Aims:**

Women with epilepsy are more likely to have a primary caesarean section than the general population. Main medical indications for a primary caesarean section in women with epilepsy are seizures during delivery and a known fetal malformation. However, seizures during delivery are relatively rare (3.6 %), and in most fetuses with abnormalities, caesarean section is not required. Thus, we wondered whether too many caesarean sections may be performed in epilepsy patients. During the last 12 years, we established a nationwide free internet and e-mail consultation service for epilepsy patients and their physicians. They can contact an epileptologist regarding pregnancy, delivery or child-care related questions. Here, we addressed whether the number of caesarean sections in women with epilepsy decreased over a period of 8 years due to the internet service, and compared this to demographic data of

**Table:**

Year of birth	Number of births*,	Caeserean sections*,	%	Number of births*,	Caeserean sections*,	%
	GRAP	GRAP		Germany	Germany	
2004	124	52	41.9	682767	183122	26.8
2005	145	47	32.4	664597	183346	27.6
2006	150	61	40.7	652642	186884	28.6
2007	141	51	36.2	664454	194526	29.3
2008	126	49	38.8	662783	200452	30.2
2009	123	56	45.5	644274	201480	31.3
2010	101	35	34.7	656390	209441	31.9
2011	111	48	43.2	642197	206012	32.1

\*in hospitals

women in Germany. Furthermore, we analysed the influence of education on the probability for a caesarean section in women with epilepsy.

**Methods:**

We retrospectively analyzed data from the German Registry of Antiepileptic drugs and Pregnancy (GRAP) from 2001 to 2012. Frequencies were analyzed by Pearson Chi square tests.

**Results:**

Women with epilepsy in Germany are more likely to have a caesarean section than women in general. The percentage of caesarean sections in epilepsy patients did not change significantly between 2004 and 2011 ( $p = 0.46$ ), while caesarean sections increase in the general population. In epilepsy patients, only 33.3% of 258 women with tertiary education had a caesarean section, while 41.0 % of 879 women with secondary or primary education did ( $p = 0.02$ ). Education and seizure frequency did not correlate. This makes it less likely that the lower number of caesarean sections in higher educated women is due to less severe epilepsy.

**Conclusions:**

The clearly elevated percentage of caesarean sections in epilepsy patients suggests that a high number is performed without medical indication. The reduced number of caesarean sections in higher educated women suggests a more information based decision in this subgroup. Future studies should collect more specific data on reasons for caesarean sections in epilepsy patients. If a relevant number should be due to non-medical reasons, better targeted information about the respective benefits and risks of the modes of delivery in women with epilepsy may be necessary.

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