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Abstracts
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Mechanism of ischaemic infarct in spontaneous carotid dissection

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Objective: It is unclear whether stroke in patients with spontaneous dissection of the cervical internal carotid artery (ICAD) is due to thromboembolism or impaired haemodynamics. This study investigated the mechanism of stroke in ICAD by examining brain imaging and cerebrovascular findings of such patients.

Methods: We retrospectively evaluated the prospectively collected brain CT, MR and ultrasound findings of 141 consecutive patients with 143 ICADs causing ischaemic stroke. Eleven patients were not included because they had an inappropriate temporal bone window (n = 6) or were treated with thrombolysis (n = 5). Thus, the data of 130 patients (76 men, 54 women) with 131 ICADs were analysed.

Results: All patients had territorial infarcts and 6 patients (5%) in addition border zone infarct patterns. Territorial infarcts affected the middle cerebral artery (MCA) in 130 of 131 cases (99%) and the anterior cerebral artery (ACA) in one case (1%). Additional vascular territories were affected in 8 patients with MCA infarcts (ACA, n = 5 [4%]; posterior cerebral artery, n = 3 [2%]). The pattern (haemodynamic versus thromboembolic) and extent of infarction were not influenced by vascular findings (MCA stenosis or occlusion, ACA occlusion, degree of obstruction in the dissected ICA, pattern of cross-flow in 115 patients with >80% ICA stenosis or occlusion).

Conclusions: This study suggests that thromboembolism and not haemodynamic infarction is the essential stroke mechanism in ICAD.

Reduction of ischaemic injury after transient focal ischaemia in transgenic tg21 mice overexpressing erythropoietin (EPO) in the brain

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It has been suggested that erythropoietin (Epo) protects against stroke. Based on this assumption, clinical trials have recently been initiated. In transgenic mice overexpressing Epo, unfortunately an increase in infarct size has been reported following focal ischaemia. Since these mice expressed Epo in the whole body, the increase of injury has been related to haemodynamic disturbances caused by polyglobulia. Thus, the question arose whether brain selective Epo overexpression may have beneficial effects in cerebral ischaemia. Here, we therefore examined injury development following 90 min of middle cerebral artery (MCA) thread occlusion in mice overexpressing Epo exclusively in the brain (so-called tg21 line). In our study, intraluminal thread occlusion led to a reproducible reduction of cerebral laser Doppler flow to ~10–20% of control values, which was followed by a restoration of blood flow immediately after thread retraction. Haemodynamic changes did not differ between control and Epo-overexpressing mice, and were similar in male and female animals. Both in male and female control mice, reproducible MCA infarcts were obtained after 24 hours of reperfusion (infarct volume: 61.5 ± 8.1 and 58.1 ± 15.2 mm^3, brain swelling: 28 ± 3 and 25 ± 8% of contralateral, respectively, $p < 0.05$, n = 5 animals/ group). Both the infarct size and brain swelling were significantly reduced in Epo-overexpressing male and female mice (infarct volume: 4.9 ± 3.0 and 23.5 ± 15.4 mm^3, brain swelling: 7 ± 6 and 8 ± 3%, respectively, $p < 0.05$, n = 5–6 animals/group). The neurological score was also improved in Epo overexpressing as compared with control mice ($p < 0.05$). Our data support the notion that Epo is protective in the brain. However, further studies are needed before this compound should more widely be used in human patients.

Acute ischaemic stroke and sleep apnoea: evolution of clinical findings, diffusion-weighted MRI and blood pressure in the first 3 days after stroke onset

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Background and objectives: Sleep apnoea (SA) is present in about 50% of patients with acute ischaemic stroke. Hypoxia and haemodynamic changes accompany SA. The aim of the study is to test the hypothesis that in the acute phase of stroke moderate–severe SA leads to an enlargement of the ischaemic volume that is more pronounced than in patients without SA.

Design/methods: We include patients with neuroradiologically proven ischaemic stroke and admission within 24 hours after stroke onset. Stroke severity is estimated by NIH and Scandinavian stroke scale (NIHSS, SSS) at admission (day 1) and day 3. Sleep breathing is assessed by an intelligent CPAP device (Autoset® Embletta pds, ResMed) the first night after admission. Moderate–severe SA is defined by an apnoea hypopnoea index >25. Blood pressure (BP) monitoring is performed at intervals of 30 minutes with an ambulatory device (bp one, Cardiette) from 8 p.m. of day 1 until 6 a.m. of day 3. MR imaging is performed on a 1.5 T MR system at 7 p.m. of day 1 and again at 7 a.m. of day 3. Stroke volumes are measured on DWI.

Results: We so far evaluated 12 patients with a mean age of 65 years (range 44–83). Sleep breathing and blood pressure recordings were performed in all patients, acute and follow-up MRI studies were completed in 5 patients. Moderate–severe SA was present in 6 patients. Three of these 6 patients had a clinical stroke progression which was accompanied in 2 patients by a clear-cut increase in stroke volume. In 6 patients SA was mild or absent. One of these patients had a clinical stroke progression and 2 of them had an increase in stroke volume. Mean values of blood pressure were not statistically different in patients with and without moderate–severe SA. A night-time BP dipping was absent in 3 of 6 patients with, and in 5 of 6 patients without moderate–severe SA.

Conclusions: Preliminary results of this ongoing project suggest that in patients with acute ischaemic stroke moderate–severe SA may lead to (1) clinical stroke progression and (2) increase in stroke volume on DWI within the first 3 days after stroke onset. These detrimental effects may not be related to blood pressure changes.

Evolution of blood pressure and clinical findings in the first 3 days after acute ischaemic stroke in patients with and without moderate–severe sleep apnoea

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Background/objectives: Sleep apnoea (SA) is recognised as cardiovascular risk factor and is present in about 50% of patients with acute ischaemic stroke. Aim of our study is to analyse the evolution of blood pressure (BP) values in patients with and without moderate–severe sleep apnoea and their correlations with the clinical evolution in the first three days after acute ischaemic stroke.

Patients/methods: We include patients with neuroradiologically proven ischaemic stroke and admission within 24 hours after stroke onset. Stroke severity is estimated by NIH and Scandinavian stroke scale (NIHSS, SSS) at admission (day 1) and day 3. Sleep breathing is assessed by an intelligent CPAP device (Autoset® Embletta pds, ResMed) the first night after admission. Moderate–severe SA (MSSA) is defined by an apnoea hypopnoea index >25. Blood pressure (BP) monitoring is performed at intervals of 30 minutes with an ambulatory device (bp one, Cardiette) from 8 p.m. of day 1 until 6 a.m. of day 3 and analysed for daytime and night-time. Night-time BP dipping is defined by a ratio of night-time/daytime mean systolic BP values of <0.9.

Results: We evaluated 15 patients with a mean age of 64 years (range 44–83). The mean AHI was 27 (range 6–101), in 12 patients AHI was >10, and 6 patients had MSSA (AHI >25) with a mean AHI of 47 (range 29–101). Clinical stroke progression was found in 4 patients, 3 of them with MSSA. Mean BP daytime was 166 (range 147–199)/105 (range 93–126) mm Hg in patients with MSSA, 147 (range 123–170)/94 (range 77–113) mm Hg in the non-MSSA group. Mean BP night-time was 156 (range 136–203)/97 (range 85–125) mm Hg in patients with MSSA, 143 (range 104–180)/90 (range 77–111) in patients with no or slight SA. 3 patients with MSSA and 8 patients with no or slight SA were non-dippers.

Conclusion: Preliminary results of this ongoing project show higher systolic and diastolic BP values in patients with MSSA after acute ischaemic stroke, especially in the second night. Moreover, MSSA may also favour clinical stroke progression. These differences are, however, not statistically significant at this point.

Multiple organ-specific autoantibodies in Lambert-Eaton myasthenic syndrome (LEMS) without associated cancer

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A 76-year-old man was hospitalised because of progressive generalised weakness involving trunk and proximal limb muscles, finally interfering with his gait. Furthermore, he complained of difficulties swallowing. On clinical examination muscle reflexes were absent, but could be evoked with short pre-activation. Contrast examination of the oesophagus showed diminished contractions with slow propulsion of contrast medium. There was hyperthyroidism, with an elevated free thyroxin level. The antibody pattern suggested definitely Grave's disease. However, normalisation of thyroid metabolism did not give any relief from muscle weakness, making thyreotoxic myopathy unlikely as the underlying cause. Testing of neuromuscular transmission revealed a 180% increment with high frequency stimulation at 50 Hz. Thus both clinical pattern, with muscle weakness and autonomic, i.e. enteric, dysfunction, and neurophysiological findings were characteristic of Lambert-Eaton myasthenic syndrome (LEMS). This could definitely be corroborated by the evidence of autoantibodies against presynaptic, voltage-gated calcium channels (VGCC). Antibodies against acetylcholine receptors were negative. The careful search for an underlying malignancy was not diagnostic. In summary, our observation suggests that LEMS without underlying tumour is an autoimmune disorder, which is accompanied by multiple organ-specific autoantibodies. The association with HLA class II alleles DRB1*0301 and DQB1*0201 is discussed.

Motor radiculopathy after intrathecal treatment with thiotepa

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Introduction: Thiotepa is a cytotoxic medication used for treatment of malignancies. It rarely causes neuropathy, but few cases with severe neuropathy have been reported. We report on a patient who developed a severe motor radiculopathy after intrathecal chemotherapy with thiotepa.

History and findings: This 37-year-old patient was diagnosed with rhabdomyosarcoma of the Sinus ethmoidalis. After systemic chemotherapy, radiotherapy and radical resection because of skull infiltration, he received 6 times thiotepa 15 mg intrathecally with systemic therapy (ifosfamide + adriamycine). Intrathecally no malignant cells were discovered. He developed progressive weakness of distal leg and hip muscles, resulting in a waddling and high stepping gait. Sensory deficits or pain were minor. On examination he presented with severe paresis and atrophy of foot dorsiflexors and foot flexors, sparing knee and hip flexors and extensors. Reflexes were absent with mild distal sensory loss. Electromyographic examination revealed a mild generalised sensomotor axonal neuropathy, but active denervation of paraspinal and distal muscles L5 and S1.

Conclusion: The disabling gait was caused by a severe motor radiculopathy of the L5 and S1 roots. Sporadic cases of axonal damage of lower limbs – often associated with intrathecal application of methotrexate – have been reported. This is the first reported case with electromyographic evidence of a motor radiculopathy induced by thiotepa. The timely association of intrathecal thiotepa administration and development of paresis and atrophy suggests that thiotepa can exert a severe neurotoxic effect on the motor roots next to its application site.

Bilateral reversible MRI – changes in non-convulsive status epilepticus

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Introduction: Nonconvulsive status epilepticus is relatively common in the elderly age group. So far, there exists no conclusive explanation regarding the cause of the epileptic status in most of these patients. At present, MRI is the most sensitive method for detection of abnormalities in epileptic seizures.

Case history: We report on a 77-year-old female patient with acute onset of somnolence and confusion on September 3, 2003. Neurological examination on admission demonstrated disorientation to time and place, aphasic symptoms as well as mild hemiparesis on the left side which resolved within 3 hours. Confusion persisted for several hours with amnesia for the acute event. Clinical status next day was completely normal.

EEG: Marked focal slowing bitemporally which resolved within 24 hours showing normal EEG next day.

MRI: Bilateral cortical signal intensities in the parietal regions on T_2-weighted images were more pronounced on the right side on initial MRI on the day of admission. These

signal intensities were not present any more on the follow-up MRI 2 weeks later.

Discussion: We interpret the transient confusional state with respect to the clinical and EEG findings as nonconvulsive status epilepticus which resolved within one day. MRI showed transient bilateral focal cortical hyperintensities on T_2-weighted images which completely resolved within two weeks. Excitatory cytotoxic oedema caused by excessive glutamate concentration and other noxious substances is the most likely cause for these transient findings. This is substantiated by the transient mild hemiparesis on neurological examination and the reversible focal slowing on EEG.

Quantitative analysis in multimodale imagery in presurgical exploration for epilepsy

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Pre-surgical evaluation for epilepsy is taking advantage of the development of all cerebral anatomical and functional imaging techniques. For this study, 3D electrical sources reconstruction based on 128 EEG channels, ictal and interictal SPECT and PET were compared in 15 patients with respect to the localisation precision of each in a quantitative way. For each modality, the distance between the abnormal area and the anatomic lesion was computed.

EEG source localisations were performed based on high spatial resolution EEG. A realistic head model and appropriate inverse algorithm were used to reconstruct the source from spike averages. The PET and SPECT volumes held more than 40 axial slices with a resolution of 128×128 pixels. The nuclear medicine images were aligned to the original MRI using the AIR software. For each modality we determined the most "abnormal" point (x, y, z) (i.e. the maximum of activity for the EEG source reconstruction and the strongest deviance in metabolism for interical/ictal SPECT and PET). For each patient, the lesion area was determined either by the postoperative MRI or by the contour of the lesion for the non-operated patients. Then the Euclidian distance from the most "abnormal" point to the anatomic lesion was calculated.

The results show that the EEG source reconstruction based on high electrode density and realistic head model performed in quantitative way as well as well-established tools in a presurgical workup for 77% of our patients. Consequently this technique should be used more intensively to localise epileptic foci in pharmaco-resistant patients.

Antiepileptic drug (AED) treatment before and after selective amygdalohippocampectomy

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Retrospectively, we analysed pre- and postoperative AED treatment in relation to long-term annual seizure outcome in the Zurich selective amygdalohippocampectomy (AHE) series, excluding "palliatively" operated patients and patients with normal histopathological findings. Study sample: 376 patients (hippocampal sclerosis ["HS"], n: 185; other lesions ["lesional"], n: 191) with a follow-up of >1 year (mean 7.5 ± 5.7 years).

Results: In the last available seizure outcome, 60% were seizure- and aura-free (ILAE Class 1). During the year prior to surgery, in the "HS" group a mean of 2.3 ± 0.8 AEDs were taken. The percentage of patients without AEDs increases to 36% in the postoperative years 1–5 (postoperative year 5: "HS" 28%; "lesional" 46%). In postoperative years 7–11 this percentage is between 40 and 43% (postoperative year 10: "HS" 30%; "lesional" 55%). In the ILAE Class 1a, at postoperative year 5, 74% of patients have discontinued AED intake. At the last available seizure outcome 36% of patients were off AEDs and additional 19% had a "substantial" reduction (i.e. from polytherapy to monotherapy, or a reduction of the existing monotherapy by at least 66% compared to the year before AHE). We conclude that the time of discontinuation of AEDs after AHE should be tailored based on the results of the presurgical evaluation, the early postoperative seizure outcome, the histopathological findings, the intraoperative ECoG findings and the postoperative EEG. In an optimal constellation, "substantial" AED reduction with the goal of a monotherapy can be advised one year and discontinuation 2 years after surgery.

Wieser HG, Häne A. Antiepileptic drug treatment before and after selective amygdalohippocampectomy. Epilepsy Res 2003;55:211–23.

Antiepileptic drug-compliance following selective amygdalohippocampectomy

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We evaluated antiepileptic drug(AED)-compliance by retrospectively assessing case records from 376 patients of the Zurich selective amygdalohippocampectomy (AHE) series, excluding "palliatively" operated patients and patients with normal histopathological findings. Advices for AED intake of the epileptologist were compared with the AED intake and serum concentrations at each control. In the case of non-compliance the patient and family doctor were asked to explain why the prescribed AED treatment was not followed. Reasons and time of deviation were recorded.

Results: The percentage of *patients free of "disabling" seizures who did not follow the medical advice to discontinue/reduce AEDs* increases with longer follow-up period. From postoperative year 7 on, the percentages amount from 12% to a peak of 35% at postoperative year 12. In the 15th postoperative year this figure is 28% and is 4.2 times higher for patients with hippocampal sclerosis than for patients with the histopathological diagnosis of a gross lesion. Reasons for not following the physician's advice to reduce/discontinue the AEDs are: (1) being afraid of the risk of a seizure relapse because seizure recurrence would heavily influence psychosocial functioning. (2) Being professionally dependent on the driving licence. The percentages of patients who were *free of "disabling" seizures and reduced/discontinued the AEDs against the advice of the treating physician* are low (4.0% in the first and 2.0% in the second postoperative year). After that, the number decreased steadily so that from the 8th postoperative year on, with one exception, no patient reduced/discontinued AEDs on her/his own.

Wieser HG, Häne A. Antiepileptic drug treatment before and after selective amygdalohippocampectomy. Epilepsy Res 2003;55:211–23.

Relapse rate, rate of re-gained seizure control and the "running down phenomenon" after selective amygdalohippocampectomy

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We analysed the relapse rate, the rate of re-gained seizure control, and the "running down phenomenon" of seizures in 376 patients of the Zurich selective amygdalohippocampectomy (AHE) series (with a follow-up of >1 year; mean 7.5 ± 5.7 years).

The relapse rate is similar for patients who were free of disabling seizures [a] for ≥1 year and without AEDs (17%), [b] immediately after surgery with or without AEDs (18%), and [c] for patients who had a "substantial" AED reduction (i.e. from polytherapy to monotherapy, or a reduction of the existing monotherapy by at least 66% compared to the year before AHE) over the entire follow-up period (19%). The rate of re-gained full seizure control, however, is significantly better for group [b] with 77%, compared to group [c] with 53%. 11% of patients showed the "running down phenomenon," i.e. had seizures during the first post-

operative year, but then became seizure-free for 1 or more years.

Wieser HG, Häne A. Antiepileptic drug treatment before and after selective amygdalohippocampectomy. Epilepsy Res 2003;55:211–23.

Amino acid composition of brain cysts: levels of excitatory amino acids in cyst fluid fail to predict seizures

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A recent study describing two epileptic patients with brain cysts has suggested that elevated concentrations of excitatory amino acids in cysts may play a role in induction and maintenance of epileptogenesis. We studied 22 consecutive patients with brain cysts undergoing neurosurgery at the Zurich University Hospital. Cyst fluid was harvested and kept at –80 °C. The free amino acids were analysed chromatographically. The analysis revealed that only in 3 out of 22 patients cyst fluids displayed highly increased amounts of the excitatory amino acids aspartate and/or glutamate. Two of these patients experienced epileptic seizures prior to neurosurgical intervention. Thus, highly increased excitatory amino acid levels are present only in a subset of patients with brain cysts. Our observation that one patient with highly increased glutamate and aspartate concentrations in the cyst did not display seizures or typical epileptiform potentials in the EEG questions that these excitatory amino acids in the cyst fluid are directly involved in epileptogenicity. This patient displayed an increased level of adenosine in the cyst fluid, which is known to have anticonvulsant properties and might provide protection from seizures. In summary, there is no evidence for a close correlation between excitatory amino acids in brain cysts and the occurrence of seizures.

Wieser HG, Rudolph U, Blau N, Boison D, Imhof HG, Bernays R, et al. Amino acid composition of brain cysts: levels of excitatory amino acids in cyst fluid fail to predict seizures. Epilepsy Res 2003;55:191–9.

Serial EEG findings in sporadic and iatrogenic Creutzfeldt-Jakob disease (CJD)

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In neuropathologically diagnosed CJD patients the EEG typically shows periodic sharp wave complexes (PSWC) of 1/s, but often in the later stages. Little is known on the EEG findings in early CJD stages and on the test-re-test reliability of serial EEGs under various conditions. We present the EEG courses of 6 patients with CJD (3 with sporadic CJD [sCJD]: # 1, 2, 3); one possible iatro-genic CJD [iCJD] (death 22 years[!] after lyodura graft: # 4); and 2 with proven iCJD (contaminated brain depth electrodes: # 5, 6; *see Bernoulli et al., Lancet 1977;26: 478–9*), who had serial EEGs and proven histological diagnoses.

The serial EEGs covered variable time spans: –53 to –3 (# 1), –30 to –16 (# 2), –234 to –57 (# 3), –33 to –15 (# 4), –726 to –134 (# 5; inoculation at day –724), and –1272 to –95 days before death (d.b.d.) (# 6; inoculation at day –1271).

Frontal intermittent rhythmic delta activity (FIRDA) was recorded in # 2, 3, 5 and 6 at –30, –57, –198 and –661 d.b.d. Prototypic PSWC were present in # 1, 4 and 6 at –53, –33 and at –587 d.b.d.

Conclusion: The EEG course depends on the form of CJD (sporadic, familiar, iatrogenic, new variant). In sCJD and iCJD the EEG shows a time-variable progressive slowing of background activity, followed by FIRDA, followed by the appearance of pseudoperiodic long-interval triphasic graphoelements with gradual appearance of the prototypic PSWC. In iCJD the mode and localisation of inoculation seems to correlate with the localisation of regionally accentuated EEG abnormalities.

Seizure-related respiratory patterns mimicking sleep-related breathing disorders

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Background and Rationale: Recognising respiratory patterns is an integral part of polysomnography (PSG), as specific disease entities often show stereotypical tracings. In our experience, typical findings in respiratory PSG may conceal comorbid or alternate diagnosis which can only be adequately recognised and diagnosed using full 10–20 EEG montages. These similarities are illustrated in a series of 5 patients.

Patients: B.P. male *1937 Dg: symptomatic generalised epilepsy with tonic seizures and atypical absences. PSG: seizures mimicking central apnoea/hypopnoea: frontal-central bilateral rapid rhythms with concomitant apnoea/hypopnoea without desaturation. When discharges are of extended duration, tonic seizure symptomatology is seen only on EMG tracing (not on video).

- S.G. male *1967 Dg: symptomatic epilepsy of frontal origin with complex partial seizures and secondary generalisation. PSG: seizures mimicking mixed apnoea: frontal-central bilateral rapid rhythms and spike series with concomitant apnoea/hypopnoea and desaturation when of extended duration (>1 sec); no seizure symptomatology seen on video.
- B.S. female *1967 Dg: idiopathic generalised epilepsy with absences and generalised tonic-clonic seizures. PSG: subtle seizures mimicking hypopnoea: bifrontal spike-wave series with concomitant hypopnoea, without desaturation; no evidence of seizure on video.
- M.R. female *1942 Dg: kryptogenic partial epilepsy with focal-tonic seizures. PSG: seizures mimicking arousal with tachypnoea: bifrontal rapid rhythms with occasional supplementary-motor seizure-symptoms. Tachypnoea for 2–4 seconds as seizure correlates also without SMA symptoms.
- B.St. male *1981 Dg: partial epilepsy with complex-patial and tonic-clonic seizures. PSG: seizures mimicking hypopnoea with desaturation: bifrontal spike wave and sharp wave series with concomitant apnoea/hypopnoea with desaturation. No evidence of seizure on video or EMG.

Discussion: All five patients show bifrontal EEG discharges that are accompanied by respiratory changes, the patterns of which resemble obstructive sleep apnoea, central sleep apnoea and/or central hypoventilation. In most cases, EEG characteristics (rapid rhythms) show only subtle signs of epileptogenicity and may be missed when using the 2- to 4-channel EEG which is standard for most polysomnographic investigations.

Valproic acid does not cause weight gain in the elderly

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Introduction: Weight gain is reported in about 50% of patients on valproic acid (VPA) therapy and can pose a considerable health risk. So far it was said that there are no predictive factors for weight gain such as age, gender, pre-treatment body weight or valproate dosage.

Methods: We studied all patients newly treated with VPA between May 2000 and May 2003 in our department. Investigated parameters included age, gender, body weight and body mass index (BMI) at beginning and at the end of therapy or in August 2003, respectively.

Results: Included were 23 consecutive patients (15 women, 8 men) with a mean age of 61.7 years (range 35–81 years). Mean body weight was 67.0 kg, mean BMI 24.4 (range 18–37) at beginning of therapy. After a mean observational period of 10.5 months (range 3–20 months) the mean body weight was 67.4 kg and the mean BMI 24.5. In the younger age group aged 55 or less 4 of 9 patients (44%) gained weight. None of the patients aged 55 or above had a weight gain, 6 patients in this age group even lost weight.

Conclusion: Contrary to previous reports without age as predictive factor we did not find any weight increase in patients newly treated with VPA at age 55 or above. The metabolic causes of valproate-induced weight gain remain still unclear. Considering our results age is a predictive factor for weight gain. This is of major importance for general health, especially in elderly patients.

Experimental evidence for smooth pursuit pathomechanism of cerebellar downbeat nystagmus

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Downbeat nystagmus (DBN) is a typical ocular motor sign in patients with lesions of the vestibulo-cerebellum. Why in those patients the eyes drift upwards, remains still unclear. The most widely accepted theory assumes an imbalance between anterior and posterior semicircular canal signals, which normally is counteracted by the vestibulo-cerebellum. Alternatively, asymmetric vertical smooth pursuit signals can be regarded as the main source of upward drift in patients with DBN. We investigated the latter hypothesis by exposing healthy subjects (N = 6) to continuous asymmetric smooth pursuit stimulation in the upward direction. Two minutes of stimulation elicited a short pursuit after-nystagmus in the upward direction. After 20 minutes of stimulation, however, an enduring DBN appeared with maximal upward drift velocity in down gaze, in accordance with Alexander's law. Since in patients with cerebellar DBN upward pursuit typically is better preserved than downward pursuit, we conclude that this pursuit asymmetry is the basis of DBN.

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High-acceleration vestibulo-ocular reflex in patients with Fabry disease

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Fabry disease (FD) is an X-linked lysosomal storage disorder due to a deficient activity of the enzyme α-galactosidase A. Resultant intracellular accumulation of glycosphingolipids leads to renal, cardiac and cerebrovascular manifestations. Due to random X-chromosomal inactivation, females may be affected too. We studied the prevalence of peripheral vestibular deficits in male and female patients with FD, as well as the effect of enzyme replacement therapy (ERT) on the peripheral vestibular function by quantitative head-impulse testing. The vestibulo-ocular reflex (VOR) during rapid rotational head thrusts to both sides (= head-impulse testing) was recorded with dual search coils in 21 patients before ERT (= base line examination). 9 patients (3 female) were tested around 12 months and 14 patients (3 female) around 24 months after ERT initiation. ERT consisted of gene-activated human α-Gal A infusions (Agalsidase alfa, Replagal®) every 2 weeks at doses of 0.2 mg/kg. At base line examination, 17 patients with Fabry disease (81%) showed reduced VOR gains. The deficit was unilateral in 9 patients (3 female) and bilateral in 8 patients (3 female). Gain reductions were not significantly different between male and female patients on both the better and weaker sides at base line as well as at ~12 and ~24 months (unpaired t-tests: $p > 0.05$). After 24 months of ERT, the average vestibular deficit on the weaker side for male and female patients tended to improve, but the change was not significant (paired t-test: $p = 0.59$). We conclude that Fabry disease affects peripheral vestibular function in both male and female patients. Female patients seem to be affected less frequently than male patients, but, on average, vestibular deficits are not different between the two groups. To confirm or reject the found tendency for vestibular improvement during ERT, more patients have to be tested and longer follow-up periods are required.

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Steroid-responsive bilateral vestibulo-cochlear syndrome: what is the evidence for autoimmune disease?

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To determine diagnostic criteria for autoimmune disease in patients with rapidly progressive bilateral vestibulo-cochlear syndrome we investigated 10 patients with bilateral vestibulo-cochlear hypofunction. All patients were examined for clinical and laboratory findings indicating autoimmune disease. Patients werde identified as clearly steroid-responsive by improved (= 8 patients) or stabilised (= 2 patients) hearing under steroid treatment. According to clinical spectrum, clinical course and laboratory findings patients were divided into three groups: (1) Cogan syndrome, (2) bilateral vestibulo-cochlear syndrome in association with multisystem and/or central nervous system manifestations ("extended clinical syndrome") including patients with "atypical Cogan syndrome", (3) isolated bilateral vestibulo-cochlear syndrome, "restricted AIED". Exclusion criteria were ototoxicity, Menière's disease, and infectious disease such as lues, borreliosis, HIV.

All patients, when examined prior to steroid treatment, had signs of systemic inflammatory disease, as evidenced by increased erythrocyte sedimentation rate, increased C-reactive protein, leucocytosis or meningitic cerebrospinal fluid.

Laboratory tests indicative of autoimmune disease were slightly abnormal in only 2 patients (ANA). The Anti-68 kDalton (hsp-70) Antibody was negative in all patients tested.

Clinical and laboratory data provided only indirect evidence of autoimmune-related bilateral vestibulo-cochlear hypofunction in the patients tested. In addition to steroid responsiveness, findings suggestive for autoimmune disease were: (1) laboratory signs of systemic inflammatory disease, (2) meningitic CSF without signs of infection.

Rapidly progressive bilateral vestibulo-cochlear hypofunction without findings of systemic inflammatory disease may still be autoimmune-related in some patients. Alternatives, however, such as mitochondrial cytopathy that also can be influenced by steroids have to be taken into consideration.

CSF hypocretin-1 (orexin A) in neurological disorders

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Objective: To evaluate if hypocretin neurotransmission is deficient in traumatic brain injury, Parkinson's disease and dementia with Lewy bodies.

Background: Hypocretin-1 (orexin A) is a recently discovered neurotransmitterwhich is involved in the pathophysiology of narcolepsy. In a few patients with posttraumatic hypersomnia, low CSF hypocretin-1 levels were observed months after trauma. Some authors reported a hypocretin neurotransmission deficiency in advanced Parkinson's disease, which shares with dementia with Lewy bodies and narcolepsy such symptoms as excessive daytime sleepiness, REM-sleep behaviour disorder and hallucinations.

Design/Methods: CSF hypocretin-1 levels of patients with moderate and severe acute traumatic brain injury (n = 18), Parkinson's disease (n = 5) and dementia with Lewy bodies (n = 10) were compared with those of a

healthy control group (n = 20). Hypocretin-1 determination was performed with a highly sensitive radioimmunoassay.

Results: In Parkinson's disease and dementia with Lewy bodies, CSF hypocretin-1 levels were normal (mean: 493 and 521, respectively, range: 307–654 and 382–667, respectively) compared to those of the healthy control group (mean: 497 pg/ml, range: 350–603 pg/ml), whereas 14 out of 18 patients with acute traumatic brain injury had hypocretin-1 levels below 200 pg/ml (mean: 161, range: undetectable –536).

Conclusions: We found a neurotransmission deficiency in a majority of patients with acute traumatic brain injury. Aetiology and clinical implications of this observation remain unclear at present. On the other hand, we could not confirm the hypothesis of a final common path-way in the pathophysiology of excessive daytime sleepiness and "REM-symptoms" in narcolepsy, Parkinson's disease and dementia with Lewy bodies.

Practice of immunomodulatory treatment of multiple sclerosis in Switzerland 1995–2003

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Background: Since the provisional approval of IFNB1b in spring 1995 about 90 percent of prescriptions of beta interferon and glatirameracetate in Switzerland are submitted to the Swiss Federation for Common Tasks of Health Insurances (SVK) for central approval of reimbursement. Structured documentation of disease characteristics has to be provided by the treating neurologists at baseline (BL) and every year thereafter for renewal of reimbursement approval.

Methods: From spring 1995 to July 31, 2003 reimbursement was granted for IFNB 1b (Betaferon® BET) in 2136 (1743 RR-MS, 406 SP-MS), for IFNB 1a (Avonex®, AVO) in 530 (516 RR-MS, 3 SP-MS), IFNB 1a (Rebif®, REB) in 1084 (986 RR-MS, 66 SP-MS) and for glatirameracetate (Copaxone®, COP) in 132 patients (130 RR-MS, 4 SP-MS). EDSS change was defined as a difference of at least 1.0 point (0.5 point for EDSS ≥6.0). Because of adaptations of the documentation form, comparable data on relapse rates are available for approvals after January 1, 1998.

Results: Mean age of *RR-patients at baseline* was 40.0 (BET), 39.1 (AVO), 39.9 (REB) and 39.2 (COP). Mean time since diagnosis in RR-MS was longest with BET (63.1 months), comparable for AVO (52.9 months) and REB (52.7 months), and shorter for COP (45.6 months). Mean EDSS at BL was 2.0 (BET), 1.9 (AVO), 2.1 (REB), 2.0 (COP). Mean number of relapses within two years prior to treatment was 2.4 (BET), 2.2 (AVO), 2.3 (REB), 2.5 (COP). 90% of patients starting on BET, 89% on AVO, 83% on REB and 88% on COP continued treatment in the 2nd year. The respective percentages of patients continuing for the 3rd, 4th and 5th year were 93, 94, 94 for BET; 92, 93, 94 for AVO; 90, 96, 94 for REB and 92, 95 (3rd, 4th year) for COP.

Mean age of *SP-patients at BL* was 49.8 (BET) and 50.7 (REB). Mean time since diagnosis was 112.7 months (BET), 131.8 months (REB). Mean EDSS at BL was 2.8 (BET) and 3.0 (REB). Mean number of relapses within 2 pre-treatment years was 1.0 for BET and 1.6 for REB. 82% of patients starting on BET, 78% on REB continued treatment in the 2nd year. The respective percentages of patients continuing for the 3rd, 4th and 5th year were 87, 93, 93 for BET and 78, 89, 95 for REB.

Conclusion: Patients were more prone to discontinue therapy within the first 1–2 years of treatment. Thereafter the rate of treatment adherence is higher and seems to stabilise after two years. Patients with higher EDSS scores before treatment and SP-MS patients were more likely to discontinue treatment.

Quality assessment in multiple sclerosis therapy quasims

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Introduction: Four different interferon beta preparations are currently available for the treatment of relapsing-remitting MS (RRMS): Interferon beta-1a (1×30 µg im/week [A], AVONEX®), Interferon beta-1b (3.5×250 µg sc/week [B], BETAFERON®) and Interferon beta-1a (3×22 µg sc/week [R22] or 3×44 µg sc/week [R44] REBIF®). A prospective trial comparing these four preparations, however, is not available.

Objective: To compare the efficacy and tolerability of all available interferon beta preparations in a four-arm, retrospective, open, international multicentre study.

Methods: MS-patients with RRMS who received interferon beta therapy for at least 2 years with continuous documentation of relapses, disease progression (EDSS) and adverse events were eligible for the survey.

Results: 4754 patients from 510 centres in Switzerland, Germany and Austria were included. Treatment allocation: A = 1728, B = 1706, R22 = 932, R44 = 388; average patient age at onset of the disease: 36.6 years; mean disease duration by start of therapy 5.0 years; mean duration of therapy 44.7 months. No relevant differences in patient characteristics were observed across treatment groups. R44 was significantly less often used as initial therapy.

Baseline EDSS in the four treatment arms: A 2.6, B 3.0, R22 2.4 and R44 2.8. Progression of disability (defined as mean EDSS change over 2 years): under treatment with A, B, R22 and R44 = 0.2, 0.3, 0.2 and 0.4, respectively. Annualised relapse rates for 2-year treatment were 0.52, 0.54, 0.5 and 0.7 for A, B, R22 and R44, respectively.

Conclusion: Demographics and patient characteristics were in line with data reported in previous phase-III trials. Disease progression and relapse rates over 2 years appeared to be comparable for A, B and R22. R44 was significantly more often follow-up therapy, had a significantly lower proportion of progression- and relapse-free patients.

These data suggest that there is no correlation between dose/frequency of IFN β treatment and efficacy. Switching between IFN β products does not appear to improve efficacy.

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Subacute sclerosing panencephalitis in a 31-year-old man

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Subacute sclerosing panencephalitis (SSPE) is a rare progressive and usually detrimental neurological disorder of childhood and early adolescence caused by persistent defective *measles* virus.

Here, we report a 31-year-old man with insidious progressive loss of memory and several episodes of necrotising retinitis during the course of several years. Upon admission, he presented with a severe amnesic syndrome and minor extrapyramidal signs. CSF examination revealed elevated IgG index and intrathecal production of *rubeola* antibodies. Repeated brain MR imaging showed generalised severe leukoencephalopathy. His EEG was unremarkable except for some unspecific alterations; in particular, it did not show periodic alternating complexes. Brain biopsy demonstrated diffuse microgliosis and demyelination compatible with post-infectious encephalitis. A diagnosis of subacute, stage-I SSPE was made and treatment with *Isoprinosine*® started.

In conclusion, we suggest that SSPE should be included in the differential diagnosis in younger patients with leukoencephalopathy even in the absence of myoclonus or typical EEG findings because therapy is most efficient in the early stages.

Hashimoto's encephalopathy: reversible MRI-findings after steroid treatment

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A 75-year-old woman exhibited a myoclonic syndrome involving the left leg and persisting for one week. Myoclonus ceased after a two-week treatment with primidone, when progressive change of personality with psychotic phenomena and two generalised epileptic seizures led to re-hospitalisation. At clinical examination psychiatric symptoms prevailed with desorientation, paranoid ideas and aggressive behaviour while no focal deficits could be found. Clinically suspected Hashimoto's encephalopathy could be corroborated by elevated anti-TPO (104.5 IU/ml, normal <12) and anti-thyreoglobulin antibodies (49.6 IU/ml, normal <30). CSF analysis revealed a mononuclear pleocytosis (37/µl). Extensive serological and microbiological investigations were negative. Only the rheumatoid factor was elevated (137 U/l, normal <40), known as associated autoantibody in Hashimoto's encephalopathy. In the literature neuroradiological findings in patients with Hashimoto's encephalopathy are often described as normal or non-specific (i.e. generalised brain atrophy, leukencephalopathy). However, in the present case cerebral MRI revealed frontal leptomeningeal gadolinium enhancement besides multiple bilateral subcortical hyperintensities on T_2-weighted images. Corticosteroid therapy resulted in improvement of the symptomatology as well as in reduction of MRI leptomeningeal enhancement, CSF pleocytosis (6/µl) and thyroid autoantibodies.

Hereditary transthyretin amyloidosis: a case report of a newly described TTR variant Ile 107Met

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The most common form of hereditary amyloidosis is associated with mutations of the transthyretin (TTR) gene and shows autosomal dominant inheritance. The TTR gene is located on chromosome 18 and more than 80 mutations have been identified so far with substantial differences in clinical presentation. The condition is characterised by progressive sensorimotor and autonomic neuropathy, although cardiovascular, renal, ocular and leptomeningeal involvement can be part of the clinical spectrum.

We report a 53-year-old Serb male with a new TTR variant, Ile 107Met, with no suggestive family history. He was first treated for carpal tunnel syndrome in 1991. Five years later he underwent vitrectomy on his right eye and three years later on his left eye due to vitreous opacities of unknown origin. He came to our neurological department in July 2002 with clinically and electrophysiologically evident sensorimotor axonal neuropathy with autonomic dysfunction. Deposits of amyloid were found in the subcutaneous fatty tissue of the abdominal wall. Diagnosis of TTR amyloidosis was finally made on the basis of sural nerve and rectal mucosa biopsy. Molecular genetic testing of the transthyretin gene detected a new methionine (Met) 107 variant. The clinical course of the disease was dominated by the rapidly progressive atrophic paresis and the patient became wheelchair-bound six months after definite diagnosis. Later on epileptic seizures as well as mild cognitive impairment occurred causing us to suspect leptomeningeal involvement. The highly increased protein level in cerebrospinal fluid supported this hypothesis, but brain MRI and repeated EEG were normal.

Blink reflex in stiff person syndrome

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Background: Stiff person syndrome is a rare disease characterised with progressive, fluctuating muscular rigidity and spasms prominent in axial and proximal limb muscles. It is probably an autoimmune disorder since antibodies against GABAergic neurons are present in about 60% and it is frequently associated with other autoimmune disorders such as insuline-dependent diabetes mellitus, thyreoiditis and pernicious anaemia. The typical neurophysiological finding is continuous firing of motor units that persists even during contraction of the antagonist muscle with good response to benzodiazepines. The blink reflex has rarely been used in the assessment of stiff person syndrome.

Case report: Blink reflex and simultaneous two-channel EMG recording of the tibialis anterior muscle and the musculus gastrocnemius of a 70-year-old female patient with stiff person syndrome were performed before and two months after initiation of therapy with clonazepam (3×0.5 mg/d). At the first visit, the blink reflex showed normal latencies of the R1, R2 and R2c responses but in addition a contralateral R1 response. The two-channel EMG revealed co-activation of the two muscles when the patient was asked to dorsiflect the right foot and slowly decreasing EMG activity after relaxation. Under treatment this phenomenon was nearly unchanged but the contralateral R1 response disappeared completely.

Conclusion/Discussion: The R1 response is thought to be elicited via a monosynaptic connection between V afferent und VII efferent fascicles. Our results suggest that
– monosynaptic excitation of the contralateral facial nucleus is due to hyperexcitability of brainstem circuits,
– the response is under GABAergic control,
– the blink reflex seems to be more sensitive to assess treatment effects than two-channel EMG recordings.

Differential effects on regional cerebral blood flow after slow and fast repetitive transcranial magnetic stimulation

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Introduction: rTMS is a powerful research tool to study neural connectivity at the systems level and is used therapeutically in a number of neuropsychiatric disorders. However, the neurophysiological effects of rTMS, particularly as a function of the stimulation parameters (e.g. frequency and intensity), remain unclear. The aim of this positron emission tomography (PET) study was to assess differential blood flow (CBF) responses to slow and fast rTMS applied to the left dorsolateral prefrontal cortex (DLPFC).

Method: 8 healthy right-handed men participated in a combined TMS/PET study. A T_1-weighted MRI was acquired for each subject to ensure the proper positioning of the TMS coil (center of the figure 8 coil over the left middle frontal gyrus). A total of 12 O^{15} water PET scans were performed in each subject (baseline, 1 Hz and 10 Hz rTMS, repeated 4 times each). For the 1 Hz condition, a continuous 60 s stimulation was applied, whereas in the 10 Hz condition, pairs of 5 s stimulation and 5 s rest were repeated 6 times. The stimulation intensity was set to 110% of the individual motor threshold. 90 s PET acquisitions started immediately after each cessation of TMS. PET data were analysed using statistical parametric mapping as well as an analysis of variance on predefined regions of interest.

Results: CBF was significantly increased in the stimulated area (left DLPFC) following slow and fast rTMS. In the homotopic contralateral area 1 Hz rTMS induced a significantly larger rCBF increase than 10 Hz rTMS.

Conclusions: Previous studies report a decrease in CBF in the stimulated area following 1 Hz and an increase in CBF following 10 Hz rTMS. In contrast, the present study demonstrates that slow and fast stimulation of the left DLPFC increases CBF bilaterally. More importantly, a stronger contralateral activation was observed following slow (1 Hz) rTMS compared to fast (10 Hz) rTMS.

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Orthostatic intolerance and syncope associated to Chiari type I malformation

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The Chiari type I malformation (CM1) is characterised by herniation of cerebellar tonsils at least 3 to 5 mm below the plane of the foramen magnum and can present a wide variety of clinical symptoms. Syncopal episodes are a rare symptom of CM1 and are attributed either to a compression of the brainstem structures or a vascular compromise of the vertebro-basilar artery. In the present case of a 42-year-old patient with syncopes, preceded by premonitory symptoms such as dizziness, pallor and nausea, blood pressure and heart rate measurements suggested postural orthostatic tachycardia syndrome secondary to CM1 which resolved completely after surgical decompression. Rarely, syncope and orthostatic intolerance can be associated to CM1 and successfully be treated by surgical intervention.

Childhood-onset schizophrenia in a patient with lipoma on the corpus callosum

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We present the case of a female 31-year-old lawyer who suffered from childhood-onset schizophrenia. Otherwise, her previous history was uneventful, there were no neurological or other psychiatric symptoms nor cognitive dysfunctions. Neurological examination and EEG between psychotic episodes were normal, however, brain imaging (MRI) revealed a lipoma on the splenium of the corpus callosum. Conducted after an episode, neuropsychological examination revealed a discrete functional asymmetry with better verbal than non-verbal functions. There were no indicators of motor, tactile or visual callosal dysfunctions. Considering normal intra- and interhemispheric transfers functions, we conjecture that our case, rather than supporting the hypothesis of a causal relationship between callosal abnormality and schizophrenia-like symptoms, more likely favours the notion that cerebral abnormalities constitute a risk factor to develop neuropsychiatric symptoms.

Swiss Society for Sleep Research, Sleep Medicine and Chronobiology (SGSSC)

Waking up properly: the role of thermoregulation in sleep inertia

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We have previously shown that induction of distal vasodilatation and body heat loss is associated with a rise in sleepiness and a rapid onset of sleep, suggesting a link between thermoregulatory and arousal systems. In two separate constant routine studies with healthy young subjects (age: 20–31 y), investigating a normal night's sleep (11 p.m. – 7 a.m.; N = 9 men) or an afternoon nap at a circadian phase with relatively stable core body temperature (CBT) levels (4–6 p.m.; N = 8 women, 8 men), we aimed to see whether the process of sleep inertia is associated with the converse thermoregulatory mechanisms. In both studies CBT, distal and proximal skin temperatures were continuously registered. The distal-proximal skin temperature gradient (DPG) provided a measure for the selectivity of distal vasodilatation, and the Karolinska Sleepiness Scale (KSS) assessed subjective sleepiness. In study 1, DPG rose rapidly at lights off and fell immediately at lights on. In addition to this rapid process, there was an underlying slow circadian modulation of DPG and CBT, previously described in a constant routine with sleep deprivation. During wakefulness KSS exhibited a very close parallel time course to DPG. In study 2, DPG rose rapidly at lights off whereas CBT declined marginally, indicating redistribution of core blood (and hence heat) to the extremities. After lights on, DPG and KSS declined in parallel with similar exponential cooling-out functions. The symmetry between the thermoregulatory processes initiating sleepiness and those dissipating it is striking and further supports the concept of a thermoregulatory input to the arousal systems.

Sleep inertia: state-specific performance changes after sleep, rest and waking

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Sleep inertia is a state of hypovigilance, confusion and impaired cognitive and behavioural performance at the transition from sleep to wakefulness. The aim of the study was to investigate sleep inertia in subjects who were not sleep deprived after a daytime nap compared with rest and wake control groups. The subjects (n = 50, 25 females) performed an addition and an auditory reaction time task and rated their subjective sleepiness 5 times at 12-minute intervals after an afternoon experimental phase of 2 hours with polysomnography. The wake group watched a film and the rest group lay in the dark without sleeping. Immediately after the nap the sleep group calculated fewer sums and had longer reaction times than the other groups. Individuals who slept longer showed greater performance decrements. On the addition task, the rest group showed inertia that was less pronounced than in the sleep group, suggesting that darkness and a supine position may be sufficient to impair performance. Speed of calculation recovered within an hour, whereas auditory reaction speeds showed significant but not complete recovery up to an hour after the experimental period. Subjective sleepiness changed across sessions, but the groups did not differ from each other. This is the first study that demonstrates sleep inertia after daytime sleep compared with waking and rest controls, which control for changes in performance independent of sleep inertia. In addition, our study provides the first evidence for "rest inertia".

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Napping and resting promote auditory learning

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Compared with waking, sleep augments improvements or prevents decrements in performance that occur between training sessions in visual perceptual, motor and other types of learning tasks. Additional investigations are needed to determine which features of sleep promote learning. According to the "interference hypothesis", sleep benefits learning because it prevents interference from ongoing sensory input, learning or other cognitive activities that normally occur during waking. We tested this hypothesis by comparing the effects of sleep, waking and resting on auditory learning. Participants (n = 48; 16 per group) completed an auditory tone sequence learning task before and one hour after a 2-hour afternoon experimental period with polysomnography. During this period, the wake group watched a film under constant supervision and the rest group lay in the dark with constant polysomnographic monitoring to prevent sleep. The sleep group slept for a mean of 83 min (range: 41–111 min). The sleep and rest groups showed significant performance improvements between sessions, whereas the wake group did not. These performance improvements in the sleep and rest groups were significantly larger than in the wake group. Thus, consistent with recent findings for human language learning, sleep facilitated

learning of complex tone sequences compared with waking. Resting in the dark for an equivalent period provided similar benefits, as predicted by the interference hypothesis. These findings suggest that a dark, quiet environment, reduced sensory and cognitive interference, and physiological changes that accompany rest are sufficient to account for the facilitation of auditory learning that occurs during sleep.

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Age-related attenuation of the circadian arousal signal in the late evening

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The human circadian pacemaker in the suprachiasmatic nuclei generates an arousal signal which peaks in the late evening at 22 h (the "wake maintenance zone"). It maintains timing and consolidation of sleep-wake behaviour by opposing the increase in homoeostatic sleep need associated with sustained wakefulness. In the absence of this circadian arousal signal, sleep-wake consolidation is lost, and the sleep-wake cycle changes from monophasic to polyphasic. We hypothesised a weaker circadian arousal signal in older subjects, resulting in a less distinct wake maintenance zone in the evening. To test this assumption, circadian rhythms and spectral components of the sleep EEG were investigated in 17 young (20–31 y) and 14 older volunteers (57–74 y) during a controlled 40-h protocol under constant semi-recumbent body posture and lighting conditions (<8 lux), whereby they were scheduled to alternating cycles of 150 min of wakefulness and 75 min of sleep. The circadian rhythm of salivary melatonin and time spent asleep during the naps was significantly attenuated in the older subjects. They slept more during the wake maintenance zone and less during the biological night. In addition, the day-night difference in EEG sleep spindle activity and theta power was significantly reduced in the elderly. This decrease in the circadian arousal signal led to an increasing trend in subjective sleepiness during the 40-nap protocol compared with younger volunteers. Our data corroborate previous findings of an age-related reduction in circadian amplitude for several neurophysiological variables leading to dominance of homoeostatic processes in the regulation of sleep and sleepiness in the elderly.

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1 Hz resolution spectral analysis defines a NREM-specific fast frequency band 15–18 Hz in sleep EEG

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Spectral power time-courses over the ultradian cycle of the sleep electroencephalogram (EEG) provide a useful window for exploring the temporal correlation between cortical EEG and sub-cortical neuronal activities. Precision in the measurement of these time-courses is thus important but is hampered by lacunae in the definition of the frequency band limits that are in the main based on wake EEG conventions. A frequently seen discordance between the shape of the beta power time-course across the ultradian cycle and that reported for the sequential mean firing rate of brainstem-thalamic activating neurons, invites a closer examination of these band limits. Sleep EEG literature indicates an intriguing non-uniformity of time-course comportment across the traditional beta band. Here therefore, using data from 18 healthy subjects, we apply several criteria based on changes in power time-course comportment in order to examine this non-uniformity as we move in 1 Hz bins through the frequency range 14–30 Hz. The results show a striking discontinuity of shape at around 18 Hz, with only the upper 18–30 Hz band displaying a time-course similar to that of the firing-rate changes measured in brainstem activating neurons and acknowledged to engender states of brain activation. Fast frequencies in the lower 15–18 Hz band, on the other hand, are shown to be specific to non-rapid-eye-movement sleep. Splitting the beta band at 18 Hz may there-fore permit a significant improvement in EEG measurement and a more precise correlation with cellular activity.

Human sleep spindle characteristics after sleep deprivation

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Sleep spindles (12–15 Hz oscillations) are one of the hallmarks of the electroencephalogram (EEG) during human non-rapid eye movement (non-REM) sleep. We have investigated the effect of enhanced homoeostatic sleep pressure after a 40-h sleep deprivation (SD) under constant routine conditions on spindle characteristics along the antero-posterior axis. EEGs during non-REM sleep in 16 healthy young volunteers (8 female, 8 male, age range 20–31 years) were analysed with a new method for instantaneous spectral analysis, based on the Fast Time Frequency Transform (FTFT), which yields high-resolution spindle parameters in the combined time and frequency domain. FTFT revealed that after SD, mean spindle amplitude was enhanced, while spindle density was reduced. The reduction in spindle density was most prominent in the frontal derivation (Fz), while spindle amplitude was increased in all derivations except in Fz. Spindle frequency and its variability within a spindle were reduced after SD. When analysed per 0.25-Hz frequency bin, amplitude was increased in the lower spindle frequency range (12–13.75 Hz), whereas density was reduced in the high spindle frequency range (13.5–14.75 Hz). The observed reduction in spindle density after SD confirms the inverse homoeostatic relationship between sleep spindles and slow waves. The increase in spindle amplitude and the reduction in intra-spindle frequency variability support the hypothesis of a higher level of synchronisation in thalamocortical cells when homoeostatic sleep pressure is enhanced.

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EEG spectral analysis: respiratory induced sleep EEG-changes in healthy young subjects

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Objectives: To use spectral analysis (Fast Fourier Transformation, FFT) as a tool to investigate respiratory induced EEG-changes.

Methods: In 16 healthy men 2 undisturbed nights (UN) with sham loading and 2 nights with repetitive respiratory loading (LN) were analysed. An FFT of the sleep EEG was performed for 9 frequency bands. An EEG-change was defined as a 2 SD power change during intervention (2 min) compared to 2 min before intervention.

Results: EEG-changes occurred in >80% of all interventions already in UN. There were significantly more EEG-changes in LN than UN. LN: EEG-changes occurred significantly earlier in the frequencies ≥9 Hz in stage 2 (except for 13 Hz) and REM sleep. In slow-wave sleep (SWS) the changes were significantly delayed in high alpha.

Conclusions: EEG-changes after respiratory loading occur more frequently and faster than in undisturbed nights. These changes occur mainly in REM sleep. In addition FFT analysis shows not only different timing, but also that EEG-changes occur in different frequency bands in stage 2, SWS and REM sleep.

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The fixed valerian-hop extract combination Ze 91019 interacts with the adenosine receptor and neutralises the effect of caffeine

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Dietary supplements containing valerian are used as mild sleep-inducing agents. In an *in vitro* radioligand binding assay the fixed extract combination of valerian and hops (Ze 91019) and the valerian extract therein exhibited partial agonistic activity at the human recombinant A_1 adenosine receptor (AR) [1].

In another placebo-controlled study with 48 volunteers the EEG profiles were recorded before and after the subjects consumed a dose of 200 mg caffeine and subsequently either placebo or 2 or 6 tablets of Ze 91019. Ze 91019 was shown to neutralise the pharmacodynamic effects of caffeine dose-dependently. The pharmacodynamic effects of caffeine were measurable as a decrease in alpha-1-power after 30 minutes, whereas the effect of six tablets Ze 91019 resulted in an increase in alpha-1-power already after 60 minutes of oral intake. This pilot study demonstrated that a single dose of Ze 91019 has a measurable effect in the CNS in subjects who displayed pharmacodynamic characteristics similar to a nervous state [2].

In conclusion, the partial adenosine agonist Ze 91019 acts via the central adenosine mechanism and this might be the reason for its sleep aid activity.

Due to the variability of plant material and manufacturing procedures, the exhibited effect of Ze 91019 may be neither qualitatively nor quantitatively similar to those of other valerian-based products.

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Subjective caffeine sensitivity, sleep quality and polymorphisms of the adenosinergic system

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Caffeine promotes alertness via antagonism at adenosine A_1 and A_{2A} receptors ($A_{2A}R$). Adenosine possibly plays an important role in homoeostatic sleep regulation. A quantitative trait locus (QTL) analysis in mice suggested that several genes modify the rate at which non-REM sleep pressure accumulates in wakefulness. One of the proposed genomic regions included the gene for adenosine deaminase (ADA), an adenosine-metabolising enzyme. Furthermore, a polymorphism on the $A_{2A}R$ gene was recently associated with self-reported anxiety in response to an acute dose of caffeine. We hypothesised that the high variability in the subjectively perceived sleep-disrupting effects of caffeine is also genetically determined. To study the relationships among subjective caffeine sensitivity, sleep quality and polymorphisms in the adenosinergic system, we distributed an internet-questionnaire about the subjective sleep-disrupting effects of caffeine to 20 343 students of ETH and University of Zurich. Analyses of the 4329 responses suggested that high subjective caffeine sensitivity is associated with prolonged sleep latency and reduced sleep maintenance. Moreover, caffeine consumption may disturb sleep in subjectively caffeine-sensitive persons, yet not in caffeine-insensitive persons. We identified 116 respondents with very low or very high subjective caffeine sensitivity and determined previously described polymorphisms on the ADA and $A_{2A}R$ genes by allele specific PCR. These polymorphisms were equally distributed in caffeine-sensitive and -insensitive subjects. However, subjects with the ADA-GA genotype (n = 12) reported less frequent night-time awakenings than subjects with the ADAGG genotype (n = 104). In ongoing sleep deprivation studies, we are now investigating possible relationships between subjective caffeine sensitivity and sleep homoeostasis.

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Caffeine attenuates the effects of sleep deprivation on the sleep EEG

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In previous studies we have hypothesised that the adenosine receptor *antagonist* caffeine reduces the progressive increase in sleep propensity associated with wakefulness. To test this hypothesis we investigated the combined effects of 40 h wakefulness (one night of sleep deprivation) and caffeine on EEG power spectra in waking and sleep. Twelve healthy men aged 20–26 received caffeine (200 mg) or placebo after 11 and 23 h of waking according to a randomised, double-blind, cross-over design. After both treatments EEG power values in non-REM sleep were increased after sleep deprivation when compared with baseline in the 0.75–8.0 Hz band and reduced in the frequency range of sleep spindles (13.25–16.0 Hz). Comparison with placebo, however, revealed that non-REM sleep power in the recovery night was attenuated after caffeine in the 0.75–1.5 Hz band and enhanced in the 12.25–20.0 Hz range. The saliva level of the stimulant decreased from a peak value of 15.7 µmol/l after the second caffeine administration, to 1.8 µmol/l one hour before recovery sleep. At the peak caffeine concentration power values in a 5-min waking EEG were reduced in most bins between 0.75 and 9.0 Hz and in the 13.25–14.0 Hz band. In contrast, no differences between caffeine and placebo were found in the wake EEG one hour before the recovery night. These findings indicate that the caffeine-induced changes in non-REM sleep are unlikely to be due to residual caffeine. The data also suggest that 2×200 mg caffeine intake during sleep deprivation attenuates the increase in sleep propensity during wakefulness.

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Electrophysiological correlates in adult sleepwalking and sleep terrors: a spectral EEG study

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Sleep terrors (ST) and sleepwalking (SW) are defined as arousal disorders implying occurrence during sleep and no dysfunction in neuronal excitability. The study of dynamic changes in electroencephalographic (EEG) activity preceding ST and SW may allow characterisation of the neural changes required to trigger the motor event. We

performed a quantitative EEG analysis to determine whether specific changes in EEG activity occur prior to the paroxysmal motor attacks and whether they differ from those of physiological awakenings.

Polysomnography was performed in 10 patients having ST and/or SW. Motor attacks were classified as minimal, minor or major according to videopolygraphic analysis and compared to physiological awakenings in patients and in 10 controls. Spectral EEG activity was measured 10 minutes and 20 seconds before the awakenings and the different types of motor events.

Ten minutes before the motor attack onset, a progressive and significant rise was found for delta activity associated with a gradual decline in sigma. This pattern was not different from that occurring before physiological awakenings. In the 20-second period before the event onset a significant rise in delta and beta activity was noted, peaking in the first second before the event onset, affecting all cerebral areas, without difference with physiological awakenings.

Spectral EEG activity before ST and SW paralleled the changes in brain activity found during physiological arousal with a progressive rise in slow and fast activities peaking just before the event onset. These findings suggest that parasomnias may be expression of a dysfunction of arousal mechanisms from NREM sleep.

A monozygotic twin pair concordant for narcolepsy-cataplexy without any detectable abnormality in the hypocretin (orexin) pathway

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Background/objectives: Narcolepsy with cataplexy (NC) is currently considered as an hypocretin-1 (orexin-A) deficiency syndrome caused by genetic and environmental factors. We report a monozygotic HLA-DQB1*0602 positive twin pair that is concordant for NC but had normal cerebrospinal fluid (CSF) hypocretin-1 levels and no mutation either in hypocretin receptor genes or hypocretin gene.

Methods: Clinical history, polysomnography, MSLT, cranial MRI scanning, HLA-typing, CSF hypocretin-1 levels, genomic sequencing of prepro-hypocretin gene and both hypocretin receptor genes.

Results: In both 37-year-old sisters (ID and JD) narcolepsy started in childhood with sleep paralysis and hypnagogic hallucinations. Full narcoleptic tetrad appeared in both sisters during adolescence with excessive daytime sleepiness (EDS) and clear-cut cataplexy provoked by emotions. Mean sleep latency on MSLT was 4 min (ID) and 5 min (JD), respectively. ID had two sleep onset REM periods on MSLT. Both sisters bear the narcoleptic HLA-markers DQB1*0602, DQA1*0102, DRB1*15, DRB5* and had normal CSF hypocretin-1 levels (546 pg/ml and 530 pg/ml, respectively). No mutation or known polymorphism was found in genomic sequencing of prepro-hypocretin gene and both hypocretin receptor genes including exon-intron junctions.

Conclusions: Our observation is exceptional for two reasons. (1) This is the first report of a simultaneous onset of narcoleptic symptoms in early childhood suggesting that NC was predominantly genetic in nature. (2) Our report proves the existence of a genetic form of NC that is linked to the disorder's genetic marker (DQB1*0602) but not to a demonstrable deficiency in hypocretin transmission.

Affective startle reflex modulation in patients with narcolepsy-cataplexy

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Background/objectives: Cataplexy is typically triggered by sudden emotions suggesting the possibility of an abnormal emotional motor control in narcolepsy-cataplexy (NC). To assess emotional control of efferent motor pathways in NC patients we test bulbospinal response patterns of acoustic startle reflex (ASR). In healthy subjects ASR covaries with valence and anticipation of stimulus perception.

Patients/methods: In 3 NC-patients and 2 healthy matched controls (HS) we measured the magnitude (area under the curve) of acoustic elicited OOR (orbicularis oculi reflex) during the view and anticipation of positive, neutral and negative pictures. Subjects rated the valence of the pictures taken from the standardised International Affective Picture System (IAPS) on a standardised Self-Assessment Manikin-Scale.

Results: Emotional modulation of ASR was similar in NC when compared to normal controls. During pleasant pictures responses were attenuated (HS: 89% of neutral pictures response, range: 76–101%; NC: 94% of neutral picture response, range: 89–99%) and during unpleasant stimuli responses were enhanced (HS: 159% of neutral pictures, range: 138–179%; NC: 107% of neutral pictures, range 104–110%). While anticipating an unpleasant stimulus, controls showed a clear physiological enhancement (201% of neutral responses, range 197–205%) whereas NC-patients even had an attenuated response (82% of neutral response, range 49–129%).

Conclusions: Preliminary results suggest that anticipation of emotional stimuli is abnormal in NC. Assessment of emotional modulation of ASR in NC may represent a useful tool for the diagnosis of cataplexy.

Influence of sleep stage and wakefulness on spectral EEG activity and heart rate variations around periodic leg movements

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Periodic leg movements (PLM) are short-lasting movements of the lower limbs occurring periodically every 20 to 40 seconds during sleep and wakefulness. Typical changes in spectral EEG activity and heart rate (HR) have been described in PLM associated with microarousals. We aimed to determine the effect of sleep stage and wakefulness on these responses to assess whether a common pattern of EEG and HR activation takes place.

The time-course of EEG spectral activity and HR variability around the onset of PLM with MA and PLM during wakefulness was analysed in 13 patients during light NREM sleep, REM sleep and wakefulness.

An EEG activation was found around PLM during sleep, wakefulness having little effect. While in NREM sleep an increase in delta and theta bands was detected before the PLM onset, in REM sleep and wakefulness the EEG activation occurred simultaneously to the PLM onset. A rise in all EEG bands was noted around the PLM similar in all sleep stages, but not during wakefulness. Thereafter, while in stage 2 all frequency bands power returned to baseline values, during stages 1 and REM, alpha and fast frequencies tended to remain sustained. The pattern of cardiac activation was similar in all sleep stages and wakefulness starting before the PLM onset and followed during sleep by bradycardia.

We conclude that the EEG and HR responses to PLM differ between sleep stages and wakefulness with differences occurring before and after the PLM. These differences open discussion on the hypothesis of a common generator of PLM during sleep and wakefulness.

Restless-legs symptoms and psychiatric co-morbidity

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There is controversy about treatment of patients with restless legs syndrome (RLS) and psychiatric co-morbidity because of potential worsening of RLS as well as periodic limb movement in sleep (PLMS) after use of antidepressants.

We report 4 patients with severe RLS-like symptoms in whom standard RLS drug treatment with dopaminergic agents, benzodiazepines, opiates and anticonvulsants was

not effective, rejected or accompanied by intolerable side effects.

- Patient J. E., 56 years, international RLS Study Group severity scale (IRLSSG-score) 28/40, PSG (untreated): PLMS-index of 39/h, sleep efficiency 93%. Anticipating side effects the patient denied all treatments. No psychiatric assessment was done but the patient complained of depressive and anxious symptoms.
- Patient H. R., 59 years, IRLSSG-score 31/40, PSG (while on clonazepam, tramadol, zolpidem): PLMS-index of 44/h, sleep efficiency 45%; psychiatric assessment: anxiety and depression. Five dopaminergic drugs and gabapentin were ineffective and/or had intolerable side effects. Treatment with paroxetine has now been started.
- Patient L. I., 78 years, IRLSSG-score 30/40, PSG (untreated): PLMS-index 9/h, sleep efficiency of 75%. The psychiatric assessment confirmed a chronic panic disorder. Four dopaminergic drugs and mirtazapine were ineffective and/or had intolerable side effects.
- Patient T. R., 41 years, IRLSSG-score 29/40; first PSG (untreated): PLMS-index 1/h, sleep efficiency of 68%; second PSG (while on paroxetine): PLMS-index 38/h, sleep efficiency 72%. The patient has been diagnosed with depression and put on several antidepressants. RLS-like symptoms were relieved best only when a combination of pramipexole with paroxetine was used.

We suggest the existence of an RLS-like syndrome with psychiatric co-morbidity, typically affecting elderly females who may not respond to and/or do not tolerate standard RLS drug treatment. Awareness and treatment of psychiatric co-morbidities represent a challenge in what may turn out to be a distinct subgroup of RLS patients.

Randomised cross-over trial of two autoCPAP devices versus fixed CPAP for the treatment of sleep apnoea

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We evaluated efficacy of two different continuous positive airway pressure devices with automatic mask pressure adjustment (auto CPAP) in comparison to fixed CPAP in treating obstructive sleep apnoea syndrome in 29 patients. Mean (± SE) apnoea/hypopnoea index was 46 ± 4 per hour, Epworth score 14.2 ± 0.7. Patients were treated over 3 consecutive 1-month periods with 3 regimens in random order: an autoCPAP device responding to apnoea/hypopnoea and snoring (DeVilbiss AutoAdjustLT™, Sunrise), another auto-CPAP device responding to the latter and changes in flow contour (Auto SetT™, ResMed) and fixed CPAP at the 90th pressure percentile titrated by auto CPAP over 2 weeks. Allowed pressure in auto CPAP mode was 4 to 15 cm H_2O. At the end of each treatment period, symptoms, quality of life, vigilance and nocturnal breathing disturbances were evaluated. All 3 treatment modalities improved symptoms, quality of life domains and apnoea/hypopnoea index significantly and to a similar degree. Mean (± SE) maintenance-of-wakefulness time increased by 4.5 ±1.8, 6.0 ± 1.5 and 6.1 ± 1.4 minutes with DeVilbiss AutoAdjustLT™, AutoSetT™ and fixed pressure CPAP, respectively ($P < 0.001$ versus baseline, P = NS for comparisons among the 3 modalities). We conclude that both autoCPAP devices were equally effective as fixed pressure CPAP in improving major outcomes of sleep apnoea therapy.

Sleep fragmentation induced by frequently interacting cardiac pacemaker? A case report

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We present the case of a 61-year-old male patient, who presented in our sleep centre suffering from excessive daytime sleepiness with 10 points according to Epworth Sleepiness Scale (ESS). After a syncopal episode four months earlier a cardiac pacemaker has been implanted following the diagnosis of a sick sinus syndrome. Polysomnography (PSG) showed a high index of arousals (43 per hour) correlated by an equal number of pacemaker onsets (number of onsets per hour of sleep). Analysis of heart rate and EEG showed that the overwhelming majority of arousals was associated with pacemaker onsets, i.e. heart rate showed a rapid alternation between the 80/minute rate set by the pacemaker and frequencies of 42 to 46/min, which was the patient's endogenous heart rate. Deceleration to 40/min caused a pacemaker response to 80/min which was maintained for approximately 40 seconds before the endogenous rate reappeared. Polysomnographic EEG revealed a high percentage of REM sleep with early onset REM (REM latency = 43 minutes) and a missing circadian REM progression which suggested an additional affective disorder. In conclusion, adjustment of pacemaker setting was recommended presuming that pacemaker induced arousals were contributing to the subjective complaints of EDS. After adjustment of pacemaker (heart frequency: 70 Hz during daytime, 50 Hz during sleep) arousals were no longer triggered by pacemaker onset in the polysomnography.

Conclusion: Pacemaker impulses might cause arousals in patients with wide pace/no-pace margins leading to severe sleep fragmentation. However, the consequence of interfering bradycardia alone has to be differentiated carefully. Or bradycardia may herald impending arousals.

Polysomnography (PSG) in patients with mild traumatic brain injury (MTBI) and excessive daytime somnolence (EDS)

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Study Objectives: After mild MTBI patients may suffer from EDS. Are there any specific polysomnographic features which could explain posttraumatic EDS?

Design: Prospective study in 25 patients with MTBI and Epworth Sleepiness Scale (ESS) >10 pt matched with 30 patients without MTBI and ESS >10 pt. Comparison of standard polysomnographic data with regard to arousability (arousal-spectrum*).

Setting: Random sample of outpatients admitted to the sleepcentre because of EDS and dyssomnia. Patients for diagnostic polysomnography with EDS-onset immediately after MTBI but EDS lasting > than 1 year.

Exclusion criterias: Patients under medications, apnoea/hypopnoea-index >10/h (AHI), myoclony-index (MI >5/h), PSG-study night worse than usual, EDS lasting <1 year, no unconsciousness at trauma in the MTBI-group, unconsciousness in the control-group without MTBI or epilepsy in the history.

Method: Audiovideo-controlled PSG, standard scoring-criteria, Cheshire-definition for arousal-scoring, scorer blinded to medical history, statistical significance assessed by t-Test, arousal-spectrum defined as arousal-index per hour sleep induced by: apnoea/hypopnoea (ARI) myoclony (PRI), spontaneous cortical (EEI) and respiratory events related (RERA).

Results: 55 patients (males 33 : females 22) matched for group 1 with MTBI (n = 25 / m:f = 13:12) group 2 without MTBI (n = 30 / m:f = 20:10). There are no statistical significant group-differences for body mass index (BMI), age and ESS between the groups. Assessing the arousability within MTBI group 1, two subgroups could be identified: group 1A with posttraumatic spontaneous cortical hyperarousability in contrast to subgroup 1B with posttraumatic cortical hypoarousability. Between groups 1A/1B, 1A/2 and 1B/2 highly significant differences in respect to EEI could be detected: 1A/1B EEI = 15.1 ± 6.1 vs 5.4 ± 2.5 ($p = 0.0006$), 1A/2 EEI = 15.1 ± 6.1 vs 9.9 ± 3.9 ($p = 0.001$) and 1B/2 EEI = 5.4 ± 2.4 vs 9.9 ± 3.9 ($p = 0.01$). No statistical significant group-differences were found in other arousal-parameters.

Discussion: Patients with EDS and MTBI are sometimes labelled as suffering from posttraumatic psychosomatic syndrome. However, in these disordered patients PSG shows a pathological cortical arousability. Further studies may additionally include unphysiological EEG-frequencies / potentials to explore the posttraumatic EDS in more detail.

Conclusions: PSG focussed on arousal-spectrum is able to discriminate patients with *posttraumatic EDS due to spontaneous corti-*

cal hyperarousability vs patients with *post-traumatic EDS due to spontaneous cortical hypoarousability* compared with EDS-patients without MTBI. In patients with post-traumatic EDS a polysomnographic evaluation is mandatory to differentiate the aetiology of EDS, which may result in substantial therapeutical consequences: i.e. daytime stimulants or night-time sedatives respectively.

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Cognitive performance, behavioural and psychological symptoms and circadian rhythm disturbances in Alzheimer's disease patients treated with quetiapine or haloperidol

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Alzheimer's disease (AD) is characterised by cognitive decline, behavioural problems (BPSD) and sleep-wake cycle disturbances: the latter decrease the quality of life of patients and caregivers and result in earlier institutionalisation. 16 AD patients (10 women, 6 men, age: 80 ± 2 y, MMSE: 19 ± 1) were enrolled in this 6-week, open, comparative study and randomly assigned to quetiapine or haloperidol. Before treatment period and in the 5th week of treatment, we assessed cognitive performance with CERAD, BPSD with NPI and NOSGER, and the circadian rest-activity cycle with actimetry for one week. Some cognitive functions (delayed word recall) improved with quetiapine ($p < 0.05$). Haloperidol worsened depression scores ($p < 0.05$) and increased abnormal motor activity as well as augmenting difficulties in self-care, whereas quetiapine improved both symptoms of depression and anxiety ($p < 0.05$). A significant fragmentation of the circadian rest-activity cycle was found after haloperidol, whereas quetiapine tended to consolidate circadian rhythm organisation. Overall, these results show a tendency for quetiapine to improve not only cognitive performance, but also BPSD and circadian rhythm disturbances, in contrast to haloperidol.

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Role of alpha2-GABA(A) receptor subtypes in the effect of diazepam on the sleep and waking EEG

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The inhibitory neurotransmitter gamma-aminobutyric acid (GABA) is involved in the generation of various brain rhythmic activities, which can be modulated by the benzodiazepines. Benzodiazepines potentiate GABAergic neurotransmission through alpha1-, alpha2-, alpha3- and alpha5-containing GABA(A) receptors. Despite their expression in the corticothalamic system, alpha1- and alpha3-GABA(A) receptors do not mediate benzodiazepine effects on the sleep EEG. Here we assessed the contribution of alpha2-GABA(A) receptors to these effects by combining pharmacological and genetic tools. The effects of diazepam on the sleep and waking EEG was compared between point-mutated knock-in mice in which the alpha2-GABA(A) receptor was rendered diazepam-insensitive and their wild-type controls. The suppression of delta activity typically induced by diazepam in non-REM sleep was significantly smaller in the mutant mice compared to the wild-type. Moreover, the EEG frequency activity above 16–18 Hz was enhanced in wild-type mice both in non-REM sleep and waking. This effect was absent in the mutant mice. Theta activity was enhanced in both REM sleep and waking in the wild-type mice. In the mutants the effect on REM sleep was markedly reduced while it persisted in waking. These findings suggest that alpha2-GABA(A) receptors, which are expressed in hypothalamic and pontine nuclei and in thehippocampus, represent markers for distinct neural circuits relevant for the modulation of rhythmic brain activities in sleep and in waking. Furthermore, diazepam-induced changes in theta activity are mediated by different GABA(A) receptor subtypes depending on the vigilance state.

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A major gene regulates the generation of slow-wave activity during sleep

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We have previously shown in mice that several sleep EEG characteristics are strongly affected by genotype, with heritability estimates similar to the human EEG. We also noticed in some inbred mouse strains that during slow-wave sleep (SWS), when the EEG is normally dominated by delta activity (1–4 Hz), substantial activity is also present in the theta frequency range (5–8 Hz). In DBA/2J (D2) strain this activity actually exceeds delta activity during SWS. Sleep is abnormally fragmented in D2 mice and the rate at which SWS need accumulates is significantly reduced in this strain. To understand the mechanisms, by which this dramatic change in the SWS EEG activity occurs in D2 mice, we undertook a systematic quantitative genetic analysis. Here we show that the ratio of the EEG spectral powers in the theta and delta range (θ ratio) can be used for mapping the underlying genes. Mapping analysis revealed the presence of a major gene on chromosome 14. Candidate gene analysis suggests that the retinoic acid receptor beta (*Rarb*) might be the best candidate. We show that *Rarb* cDNA contains several polymorphisms in D2 mice, which may interfere with *Rarb* expression. We also show that retinoic acid treatment in non-D2 mice dose-dependently reduces θ ratio. Our results therefore indicate that the *Rarb* gene, known to be critically involved in the CNS development, could also be involved in the regulation of slow-wave activity during sleep.

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Interhemispheric EEG coherence in sleep and waking in mice with congenital callosal dysgenesis

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Regional variations in changes in the sleep EEG under increased sleep pressure may arise from differences in EEG synchronisation within or between the hemispheres. To investigate the role of the corpus callosum in interhemispheric EEG synchronisation, spectra of EEG coherence between the hemispheres were computed in mice with congenital callosal dysgenesis (B1, total dysgenesis, n = 3; partial dysgenesis, n = 6). EEG recordings were performed under baseline conditions and after 6-h sleep deprivation and compared with the coherence spectra of a control strain (C57BL/6, n = 7).

In B1 mice interhemispheric coherence was lower than in controls in all vigilance states. The level of coherence in each of the three totally acallosal mice was lower than in the mice with only partial callosal dysgenesis. The difference between B1 and control mice was present over the entire 0.5–25 Hz frequency range in NREM sleep, and in all frequencies except for the high delta-low theta band (3–7 Hz) in REM sleep and waking. In control mice, sleep deprivation led to a rise of coherence in the delta band of

NREM sleep in the first 2 hours of recovery. This effect was absent in B1 mice with total callosal dysgenesis and attenuated in mice with partial callosal dysgenesis. In both strains the effect of sleep deprivation dissipated within 4 hours.

Daily torpor decreased performance in an object recognition task in the Djungarian hamster

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Daily torpor is a hypometabolic state that in contrast to hibernation typically lasts only several hours and is characterised by major physiological changes including a decrease in metabolism and body temperature. We examined whether daily torpor affects memory consolidation in an object recognition task in the Djungarian hamster, *Phodopus sungorus,* which repeatedly exhibits daily torpor in a short photoperiod.

In experiment 1 the response to object novelty was assessed in a 3-object, two trial paradigm in a T-maze. The animals were assigned to a control group (n = 33) and a torpor group (n = 11, animals had an episode of daily torpor between two trials). While both groups recognised the familiar object in trial 2, the torpor group remembered the familiar object less well. Experiment 2 was performed to examine whether spatial cues contributed to the performance. Naïve hamsters were exposed to a single object in the T-maze and in trial 2, the familiar and one novel object were presented in a 6-compartment box. No difference in performance was found between the two groups (torpor, n = 11; controls, n = 19), i.e. object recognition was not impaired. Experiment 3 was performed to test whether performance depends on the difficulty of the task. Group 1 (n = 16) was exposed to 3 objects, while group 2 (n = 29) to only 2 objects. Only group 2 recognised the familiar object. The failure of group 1 to recognise the familiar object was due to the increasing age of the animals ($r = -0.49$, $p < 0.0005$, Pearson product-moment correlation, age vs "discrimination index").

The decreased performance after a torpor episode indicates that processes are inhibited during torpor that contribute to memory consolidation.

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